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Botulinum toxin type A for facial wrinkles (Review)

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[Intervention Review]

Botulinum toxin type A for facial wrinkles

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ABSTRACT

Background

Botulinum toxin type A (BontA) is the most frequent treatment for facial wrinkles, but its effectiveness and safety have not previously been assessed in a Cochrane Review.

Objectives

To assess the effects of all commercially available botulinum toxin type A products for the treatment of any type of facial wrinkles.

Search methods

We searched the following databases up to May 2020: the Cochrane Skin Specialised Register, CENTRAL, MEDLINE, Embase, and LILACS. We also searched five trials registers, and checked the reference lists of included studies for further references to relevant randomised controlled trials (RCTs).

Selection criteria

We included RCTs with over 50 participants, comparing BontA versus placebo, other types of BontA, or fillers (hyaluronic acid), for treating facial wrinkles in adults.

Data collection and analysis

We used standard methodological procedures expected by Cochrane. Primary outcomes were participant assessment of success and major adverse events (AEs) (eyelid ptosis, eyelid sensory disorder, strabismus). Secondary outcomes included physician assessment of success; proportion of participants with at least one AE and duration of treatment effect. We used GRADE to assess the certainty of the evidence for each outcome.

Main results

We included 65 RCTs, involving 14,919 randomised participants. Most participants were female, aged 18 to 65 years. All participants were outpatients (private office or day clinic). Study duration was between one week and one year. No studies were assessed as low risk of bias in all domains; the overall risk of bias was unclear for most studies.

The most common comparator was placebo (36 studies). An active control was used in 19 studies. There were eight dose-ranging studies of onabotulinumtoxinA, and a small number of studies compared against fillers. Treatment was given in one cycle (54 studies), two cycles (three studies), or three or more cycles (eight studies).

The treated regions were glabella (43 studies), crow's feet (seven studies), forehead (two studies), perioral (two studies), full face (one study), or more than two regions (nine studies). Most studies analysed moderate to severe wrinkles; mean duration of treatment was 20 weeks.

The following results summarise the main comparisons, based on studies of one treatment cycle for the glabella. AEs were collected over the duration of these studies (over four to 24 weeks).

Compared to placebo, onabotulinumtoxinA-20 U probably has a higher success rate when assessed by participants (risk ratio (RR) 19.45, 95% confidence interval (CI) 8.60 to 43.99; 575 participants; 4 studies; moderate-certainty evidence) or physicians (RR 17.10, 95% CI 10.07 to 29.05; 1339 participants; 7 studies; moderate-certainty evidence) at week four. Major AEs are probably higher with onabotulinumtoxinA-20 U (Peto OR 3.62, 95% CI 1.50 to 8.74; 1390 participants; 8 studies; moderate-certainty evidence), but there may be no difference in any AEs (RR 1.14, 95% CI 0.89 to 1.45; 1388 participants; 8 studies; low-certainty evidence).

Compared to placebo, abobotulinumtoxinA-50 U has a higher participant-assessed success rate at week four (RR 21.22, 95% CI 7.40 to 60.56; 915 participants; 6 studies; high-certainty evidence); and probably has a higher physician-assessed success rate (RR 14.93, 95% CI 8.09 to 27.55; 1059 participants; 7 studies; moderate-certainty evidence). There are probably more major AEs with abobotulinumtoxinA-50 U (Peto OR 3.36, 95% CI 0.88 to 12.87; 1294 participants; 7 studies; moderate-certainty evidence). Any AE may be more common with abobotulinumtoxinA-50 U (RR 1.25, 95% CI 1.05 to 1.49; 1471 participants; 8 studies; low-certainty evidence).

Compared to placebo, incobotulinumtoxinA-20 U probably has a higher participant-assessed success rate at week four (RR 66.57, 95% CI 13.50 to 328.28; 547 participants; 2 studies; moderate-certainty evidence), and physician-assessed success rate (RR 134.62, 95% CI 19.05 to 951.45; 547 participants; 2 studies; moderate-certainty evidence). Major AEs were not observed (547 participants; 2 studies; moderate-certainty evidence). There may be no difference between groups in any AEs (RR 1.17, 95% CI 0.90 to 1.53; 547 participants; 2 studies; low-certainty evidence).

AbobotulinumtoxinA-50 U is no different to onabotulinumtoxinA-20 U in participant-assessed success rate (RR 1.00, 95% CI 0.92 to 1.08, 388 participants, 1 study, high-certainty evidence) and physician-assessed success rate (RR 1.01, 95% CI 0.95 to 1.06; 388 participants; 1 study; high-certainty evidence) at week four. Major AEs are probably more likely in the abobotulinumtoxinA-50 U group than the onabotulinumtoxinA-20 U group (Peto OR 2.65, 95% CI 0.77 to 9.09; 433 participants; 1 study; moderate-certainty evidence). There is probably no difference in any AE (RR 1.02, 95% CI 0.67 to 1.54; 492 participants; 2 studies; moderate-certainty evidence).

IncobotulinumtoxinA-24 U may be no different to onabotulinumtoxinA-24 U in physician-assessed success rate at week four (RR 1.01, 95% CI 0.96 to 1.05; 381 participants; 1 study; low-certainty evidence) (participant assessment was not measured). One participant reported ptosis with onabotulinumtoxinA, but we are uncertain of the risk of AEs (Peto OR 0.02, 95% CI 0.00 to 1.77; 381 participants; 1 study; very low-certainty evidence).

Compared to placebo, daxibotulinumtoxinA-40 U probably has a higher participant-assessed success rate (RR 21.10, 95% CI 11.31 to 39.34; 683 participants; 2 studies; moderate-certainty evidence) and physician-assessed success rate (RR 23.40, 95% CI 12.56 to 43.61; 683 participants; 2 studies; moderate-certainty evidence) at week four. Major AEs were not observed (716 participants; 2 studies; moderate-certainty evidence). There may be an increase in any AE with daxibotulinumtoxinA compared to placebo (RR 2.23, 95% CI 1.46 to 3.40; 716 participants; 2 studies; moderate-certainty evidence).

Major AEs reported were mainly ptosis; BontA is also known to carry a risk of strabismus or eyelid sensory disorders.

Authors' conclusions

BontA treatment reduces wrinkles within four weeks of treatment, but probably increases risk of ptosis. We found several heterogeneous studies (different types or doses of BontA, number of cycles, and different facial regions) hindering meta-analyses. The certainty of the evidence for effectiveness outcomes was high, low or moderate; for AEs, very low to moderate. Future RCTs should compare the most common BontA (onabotulinumtoxinA, abobotulinumtoxinA, incobotulinumtoxinA, daxibotulinumtoxinA, prabotulinumtoxinA) and evaluate long-term outcomes. There is a lack of evidence about the effects of multiple cycles of BontA, frequency of major AEs, duration of effect, efficacy of recently-approved BontA and comparisons with other treatments.

PLAIN LANGUAGE SUMMARY

How well does botulinum toxin (type A; often called 'Botox') treat wrinkles on the face?

Key messages

Injecting botulinum toxin type A (a Botox-like treatment) reduces wrinkles between the eyebrows, and is relatively safe to use. The effects on wrinkles were seen when measured at four weeks after the injection. Injecting botulinum toxin type A probably increases the risk of eyelid drooping. More studies are needed to assess the longer-term benefits and harms of repeated treatment with botulinum toxin.

Treating facial wrinkles

Continuous movement of muscles in the face can cause the skin to wrinkle as it ages and becomes less elastic. Botulinum toxin type A is a chemical that relaxes muscles; it is produced by a type of bacteria. It is commonly used to smooth out lines and wrinkles by injecting it into the muscles of the face to stop their movement for a short time. Muscle activity usually stops completely within five to 15 days after the injection. The effects on the muscles are temporary and usually last for around four to six months.

What did we want to find out?

We wanted to find out how well botulinum toxin could treat wrinkles on the face, and if it causes any unwanted effects.

What did we do?

We searched for studies that tested the effects of botulinum toxin to treat wrinkles on the face.

What did we find?

We found 65 studies in 14,919 people (mostly women) who went to a day clinic or private office for treatment. The studies lasted from one week to one year; the average length of treatment was 20 weeks. The studies compared one type of botulinum toxin against another type, against a placebo (an injection that did not contain any botulinum toxin), or against an alternative treatment. Several studies were funded by pharmaceutical companies.

The studies tested four types of botulinum toxin that were licensed for use and some other types that were not yet licensed.

All studies assessed the success of treatment by measuring wrinkles and lines when facial muscles were at their most tense. Most studies treated wrinkles that develop between the eyebrows, known as 'glabellar lines'.

What are the main results of our review?

At four weeks after injection, all types of botulinum toxin reduced glabellar lines more than a placebo. This effect was seen whether the wrinkles were assessed by doctors or by the people who had the injections.

Unwanted effects are probably more common with botulinum toxin than with placebo injections. The most commonly reported unwanted effects are drooping eyelids, squinting (when the eyes point in different directions) and numbness of the eyelid.

Two studies compared two different types of botulinum toxin and found no difference between the types for how well they reduced glabellar lines.

What are the limitations of the evidence?

Our confidence in the evidence is moderate to high that botulinum toxin reduces wrinkles between the eyebrows better than a placebo. We are less confident in some of the evidence for other comparisons or studies, because some studies enrolled only a small number of people, and in some studies it was unclear how people were assigned to different treatment groups or if people knew which treatment they received. Further research is likely to increase our confidence in the evidence.

How up to date is this evidence?

The evidence is current up to May 2020.

Summary of findings 1. Summary of Findings Table - OnabotulinumtoxinA 20U compared to placebo in glabellar lines

OnabotulinumtoxinA 20U compared to placebo in glabellar lines

Patient or population: glabellar lines **Setting**: Outpatient **Intervention**: OnabotulinumtoxinA 20U **Comparison**: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with OnabotulinumtoxinA 20U				
Partcipant assessment of success assessed with: Validated tools, considering wrinkles and lines at maximum contraction follow up: 4 weeks	3 per 100	**65 per 100** (29 to 100)	**RR 19.45** (8.60 to 43.99)	575 (4 RCTs)	⊕⊕⊕⊖ MODERATE [a]	
Major adverse events follow up: range 4 weeks to 24 weeks	1 per 100	**2 per 100** (1 to 5)	**OR 3.62** (1.50 to 8.74)	1390 (8 RCTs)	⊕⊕⊕⊖ MODERATE [a]	
Physician assessment of success assessed with: Validate tools, wrinkles and lines at maximum contraction follow up: 4 weeks	4 per 100	**61 per 100** (36 to 100)	**RR 17.10** (10.07 to 29.05)	1339 (7 RCTs)	⊕⊕⊕⊖ MODERATE [a]	
Total adverse events follow up: range 4 weeks to 24 weeks	27 per 100	**31 per 100** (24 to 39)	**RR 1.14** (0.89 to 1.45)	1388 (8 RCTs)	⊕⊕⊖⊖ LOW [a,b]	
Duration of treatment effect assessed with: weeks	The mean duration of treatment effect was **0.4**	MD **18.4 higher** (16.17 higher to 20.63 higher)	-	77 (1 RCT)	⊕⊕⊕⊖ MODERATE [a]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_423103355840383514.

a. Downgraded one level due to serious risk of bias:, unclear risk of bias from blinding of participants, personnel, and outcome assessors.
b. Downgraded one level due to serious imprecision: wide 95% CI, crossing the null.

Summary of findings 2. Summary of Findings Table - AbobotulinumtoxinA 50U compared to placebo for glabellar lines

AbobotulinumtoxinA 50U compared to placebo for glabellar lines

Patient or population: glabellar lines **Setting**: Outpatient **Intervention**: AbobotulinumtoxinA 50U **Comparison**: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with AbobotulinumtoxinA 50U				
Participant assessment of success by analysing scores and scales - 20 weeks (Validated tools, wrinkles and lines at maximum contraction) follow up: 4 weeks	3 per 100	**16 per 100** (5 to 51)	**RR 5.33** (1.67 to 16.99)	300 (1 RCT)	⊕⊕⊕⊕ HIGH	
Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus) follow up: range 4 weeks to 12 weeks	0 per 100	**0 per 100** (0 to 0)	**RR 3.36** (0.88 to 12.87)	1294 (7 RCTs)	⊕⊕⊕⊖ MODERATE [a]	Unable to calculate the risk with the intervention as no major adverse events occurred in the placebo group.
Physician assessment of success by analysing scores and scales - 4 weeks assessed with: Validated tools, wrinkles and lines at maximum contraction follow up: 4 weeks	3 per 100	**53 per 100** (30 to 96)	**RR 15.78** (8.75 to 28.45)	1060 (7 RCTs)	⊕⊕⊕⊖ MODERATE [b]	
Total adverse events follow up: range 4 weeks to 16 weeks	20 per 100	**25 per 100** (21 to 30)	**RR 1.25** (1.05 to 1.49)	1471 (8 RCTs)	⊕⊕⊖⊖ LOW [a,b]	

Duration of treatment effect assessed with: weeks	The mean duration of treatment effect was **99.7** days	MD **17.3 days higher** (15.82 higher to 18.78 higher)	-	100 (1 RCT)	⊕⊕⊕⊖ MODERATE [b]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_423103454361439144.

a. Downgraded one level due to serious imprecision: wide 95% CI, crossing the null.
b. Downgraded one level due to serious risk of bias: unclear risk of bias from blinding of participants, personnel, and assessors.

Summary of findings 3. Summary of Findings Table - IncobotulinumtoxinA 20U compared to placebo for glabellar lines

IncobotulinumtoxinA 20U compared to placebo for glabellar lines

Patient or population: glabellar lines **Setting**: Outpatient **Intervention**: IncobotulinumtoxinA 20U **Comparison**: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with IncobotulinumtoxinA 20U				
Participant assessment of success by analysing scores and scales - 4 weeks	1 per 100	**37 per 100** (7 to 100)	**RR 66.57** (13.50 to 328.28)	547 (2 RCTs)	⊕⊕⊕⊖ MODERATE [a]	
Major adverse events follow up: range 4 weeks to 16 weeks	No major adverse events were observed			547 (2 RCTs)	⊕⊕⊕⊖ MODERATE [a]	

Physician assessment of success by analysing scores and scales assessed with: Validated tools, wrinkles and lines at maximum contraction follow up: 4 weeks	0 per 100	**0 per 100** (0 to 0)	**RR 134.62** (19.05 to 951.45)	547 (2 RCTs)	⊕⊕⊕⊖ MODERATE [a]	Unable to calculate the risk with the intervention as no events occurred in the placebo group.
Total adverse events follow up: range 4 weeks to 16 weeks	29 per 100	**34 per 100** (26 to 45)	**RR 1.17** (0.90 to 1.53)	547 (2 RCTs)	⊕⊕⊖⊖ LOW [a,b]	
Duration of treatment effect - not measured	-	-	-	-	-	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_423103474800544813.

a. Downgraded one level due to serious risk of bias: unclear risk of bias from blinding of participants, personnel, and assessors.
b. Downgraded one level due to serious imprecision: wide 95% CI, crossing the null

Summary of findings 4. Summary of Findings Table - AbobotulinumtoxinA 50U compared to OnabotulinumtoxinA 20U in glabellar lines

AbobotulinumtoxinA 50U compared to OnabotulinumtoxinA 20U in glabellar lines

Patient or population: glabellar lines **Setting**: Outpatient **Intervention**: AbobotulinumtoxinA 50U **Comparison**: OnabotulinumtoxinA 20U

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with OnabotulinumtoxinA 20U	Risk with AbobotulinumtoxinA 50U				

Participant assessment success by analysing scores and scales - 4 weeks assessed with: Validated tools, wrinkles and lines at maximum contraction follow up: 4 weeks	894 per 1000	**894 per 1000** (822 to 965)	**RR 1.00** (0.92 to 1.08)	388 (1 RCT)	⊕⊕⊕⊕ HIGH
Major adverse events - Any major adverse events (eye-lid ptosis, eyelid sensory disorder, s follow up: range 4 weeks to 12 weeks	1 per 100	**2 per 100** (1 to 8)	**OR 2.65** (0.77 to 9.09)	433 (1 RCT)	⊕⊕⊕⊖ MODERATE [a]
Physician assessment of success by analysing scores and scales - 4 weeks (Validated tools, wrinkles and lines at maximum contraction) follow up: 4 weeks	95 per 100	**96 per 100** (90 to 100)	**RR 1.01** (0.95 to 1.06)	388 (1 RCT)	⊕⊕⊕⊕ HIGH
Total adverse events follow up: range 4 weeks to 12 weeks	18 per 100	**19 per 100** (12 to 28)	**RR 1.02** (0.67 to 1.54)	492 (2 RCTs)	⊕⊕⊕⊖ MODERATE [a]
Duration of treatment effect - not measured	-	-	-	-	-

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_423103510517664820.

a. Downgraded one level due to serious imprecision: wide 95% CI, crossing the null.

Summary of findings 5. Summary of Findings Table - IncobotulinumtoxinA 24U compared to OnabotulinumtoxinA 24U in glabellar lines

IncobotulinumtoxinA 24U compared to OnabotulinumtoxinA 24U in glabellar lines
Patient or population: glabellar lines **Setting**: Outpatient **Intervention**: IncobotulinumtoxinA 24U **Comparison**: OnabotulinumtoxinA 24U

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Onabotulinum-toxinA 24U	Risk with Incobotulinum-toxinA 24U				
Participant assessment of success by analysing scores and scales - not measured	-	-	-	-	-	
Major adverse events follow up: range 4 weeks to 12 weeks	1 per 100	**0 per 100** (0 to 2)	**OR 0.02** (0.00 to 1.77)	381 (1 RCT)	⊕⊖⊖⊖ VERY LOW [a,b,c]	Ptosis was reported in one participant in onabotulinum-toxinA group
Physician assessment of success by analysing scores and scales - 4 weeks (Validated tools, wrinkles and lines at maximum contraction) follow up: 4 weeks	96 per 100	**97 per 100** (92 to 100)	**RR 1.01** (0.96 to 1.05)	381 (1 RCT)	⊕⊕⊖⊖ LOW [a,b]	
Total adverse events follow up: range 4 weeks to 12 weeks	1 per 100	**0 per 100** (0 to 2)	**OR 0.02** (0.00 to 1.77)	381 (1 RCT)	⊕⊖⊖⊖ VERY LOW [a,b,c]	
Duration of treatment effect - not measured	-	-	-	-	-	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_423103538603772987.

a. Downgraded one level due to serious risk of bias: unclear risk of bias from randomisation, allocation concealment and blinding.
b. Downgraded one level due to serious imprecision: wide 95% CI, crossing the null.
c. Downgraded one level due to serious imprecision: low number of events.

Summary of findings 6. Summary of Findings Table - DaxibotulinumtoxinA 40U compared to placebo in glabellar lines

DaxibotulinumtoxinA 40U compared to placebo in glabellar lines

Patient or population: glabellar lines **Setting**: Outpatient **Intervention**: DaxibotulinumtoxinA 40U **Comparison**: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with DaxibotulinumtoxinA 40U				
Participant assessment of success by analysing scores and scales - 4 weeks (Validated tools, wrinkles and lines at maximum contraction) follow up: 4 weeks	4 per 100	**79 per 100** (43 to 100)	**RR 21.10** (11.31 to 39.34)	683 (2 RCTs)	⊕⊕⊕⊖ MODERATE [a]	
Major adverse events follow up: range 4 weeks to 24 weeks	No major adverse events were observed.			716 (2 RCTs)	⊕⊕⊕⊖ MODERATE [a]	
Physician assessment of success by analysing scores and scales - 4 weeks (Validated tools, wrinkles and lines at maximum contraction) follow up: 4 weeks	4 per 100	**88 per 100** (47 to 100)	**RR 23.40** (12.56 to 43.61)	683 (2 RCTs)	⊕⊕⊕⊖ MODERATE [a]	
Total adverse events follow up: range 4 weeks to 24 weeks	9 per 100	**21 per 100** (14 to 32)	**RR 2.23** (1.46 to 3.40)	716 (2 RCTs)	⊕⊕⊕⊖ MODERATE [a]	
Duration of treatment effect	The mean duration of treatment effect was **0.4** weeks	MD **22.8 weeks higher** (20.74 higher to 24.8 higher)	-	74 (1 RCT)	⊕⊕⊕⊖ MODERATE [a]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
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See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_423103545427906155.

a. Downgraded one level due to serious risk of bias: unclear allocation concealment.

BACKGROUND

Please note that unfamiliar terms may be listed in the Glossary in Appendix 1.

Description of the condition

Aging is a biological process; however, it is not well accepted by all in western cultures, who desire to retain a youthful appearance and optimal level of beauty, equating it with increased socialisation, power, success, and happiness. Preventing and treating the consequences of aging in the body has become almost a fixation (Garnham 2013).

Facial ageing depends on intrinsic factors, which include genetics (heredity) and ethnicity, and extrinsic factors, such as environmental conditions (e.g. sun exposure, smoking habits, and nutritional status). All of these factors contribute towards the appearance of ageing signs: fat absorption, flaccidity, and wrinkles (Sveikata 2011). The aging process turns the skin thinner, drier, and less elastic, and less able to protect itself from internal and external aggressions. Due to these factors, the continuous muscle movement (facial expression) can lead to wrinkles.One of the first stages of facial aging includes the appearance of dynamic wrinkles. Additionally, the appearance of dynamic wrinkles occurs through increased muscle tone, as shown by electromyographic alterations Le Louarn 2007. Over an individual's lifetime, however, resting muscle tone increases and creases the skin causing fine wrinkles and lines in the skin surface (hyperdynamic wrinkles). If these wrinkles do not receive any treatment, the skin shows a permanent mark (static wrinkles) (Carruthers 2008a). Due to this fact, the dynamic rhytides treatment is more indicated in the clinical practice. Facial wrinkles can be classified in glabellar lines (vertical lines or furrows in the region between the eyebrows, above the nose); forehead lines (vertical or diagonal lines in the forehead region), crow's feet lines (lines or furrows in the periorbicular region, around the eyes).

Several surgical and non-surgical procedures for dynamic wrinkles are available. Amongst all therapies, botulinum toxin type A (BontA) injections are considered the most frequent treatment for this condition. According to the American Society of aesthetic surgery statistics, 4,597,886 injections of BontA were performed in 2016 (ASAPS 2016). The reason for BontA success can be attributed to low cost, no recovery time and temporary effect (Glogau 2012). The BontA average cost for wrinkle treatment is USD 385 per session (ASAPS 2017). This treatment is performed in outpatients, during daily activities. The temporary effect ranges from four to six months.

Description of the intervention

Botulinum toxin has been used since the 1980s; there are eight subtypes available (A, B, C1, C2, D, E, F, and G). Serotypes A and B are commercially available (Berry 2012). Botulinum toxinA is the most used in clinical practice due to its duration effect. Moreover, several brands are available in the market. Although all these toxins are type A, all companies have their particular strains. Due to this fact, each brand has specific biological characteristics: units equivalence (ratio) and dermal diffusion (Glogau 2012).

For this reason, there is a conversion ratio.

- OnabotulinumtoxinA: AbobotulinumtoxinA, ratio = 1 unit (U) : 2.5 U or 3U
- OnabotulinumtoxinA: IncobobotulinintoxinA, ratio = 1 U:1 U
- The other BontA brands (daxibotulintoxinA (DWP450), PraxibotulinumtoxinA, HBTX-A, Prosigne®, CBFC26, MT10109L, Medytox®, Neuronox®) follow the conversion ratio of 1:1

Despite these biological properties differences, the medical community recommend guidelines to treat facial wrinkles.

In 2008 and 2016, an American committee discussed the dose treatment related to onabotulinumtoxinA.

- Glabellar region, the therapeutical dose range from 12 U to 40 U, 2 U to 4 U per injection, distributed in three to seven intramuscular injections points (procerus muscle, corrugator supercilii muscle, orbicularis oculi, muscle depressor supercilii muscle)frontal lines, the therapeutical dose range from 8 U to 25 U distributed in four to eight points of intramuscular injection along the frontal muscle wrinkles with a 2.0 cm above the eyebrows; and crow's feet, the therapeutical dose range from 6 U to 15 U distributed in two to five subcutaneous injections per side (one injection at least 1.5 cm to 2.0 cm from lateral canthus, one injection in the orbital rim next to the eyebrow extremity, and one injection near the zygomatic process in the orbital rim, the other injections along the crow’s feet lines laterally to the previous injections) (Sundaram 2016) (Carruthers 2008a).

In 2010, a European committee addressed the same issues and created an equivalent botulinum toxin type A guideline based on the other brand of BontA, AbobotulinumtoxinA biological properties:

- for the glabellar region, 50U (Speywood units) in five points;
- for frontal lines, 20 U to 60 U in four to six points; and
- for crow's feet, 30 U to 60 U in three points per side (Ascher 2010).

The guidelines shown above studied the most common BontA used in the clinical practice.

Until now, the medical community does not know if these brands behave differently regarding effectiveness, duration of treatment and adverse events.

How the intervention might work

After injection into the muscle, botulinum toxin diffuses to the nerve terminal, where it binds, preventing the release of the neurotransmitter, acetylcholine, from the nerve synapse; thus, preventing its effect on the neuromuscular junction and consequently the muscle does not contract and does not crease the skin (no hyperdynamic wrinkle). Complete lack of muscle activity occurs after approximately five to 15 days (Berry 2012).

It is perceived that there are fewer wrinkles due to the non-contraction of specific facial muscles (Fagien 2003). However, this muscle atrophy due to chemical effect provokes regeneration at the nerve terminal known as 'sprouting'. This process, which lasts for 120 days, will originate in a new terminal at the neuromuscular junction, which will bring back muscle activity (Berry 2012). Because of this, the duration of clinical treatment is in the range of three to six months.

It is important that during the consultation prior to the botulinum toxin procedure, the medical professional establishes the expectations of the person and whether these will be achieved, explains all possible outcomes, safety issues, duration of treatment, and potential adverse effects, and examines the anatomic regions, in rest and contraction, and any pre-existing asymmetry. Otherwise, the botulinum toxin treatment may cause frustration and disappointment.

Moreover, for an optimal result, all medical professionals (dermatologists, plastic surgeons) should have a complete knowledge of functional muscle anatomy (Carruthers 2008a). This injection attenuates wrinkle appearance progressively (within 15 days), but the effect is temporary (four to six months) (Berry 2012; Carruthers 2008a).

Why it is important to do this review

Botulinum toxin has been used to reduce hyperdynamic facial wrinkles for more than 20 years. During this period, several formulations have appeared on the market. Although these neurotoxins are not comparable, the U.S. Food and Drug Administration (FDA), European Medicines Agency (EMA), and other drugs evaluation boards have been attempting to organise and classify them. Currently, there are several botulinum toxin type A products on the market: Botox®/Vistabel®/Vistabex® (Allergan); Dysport®/Disport® (Ipsen); Azzulure® (Galderma); XEOMIN®/Bocouture®/Xeomeen® (Merz Aesthetics); Neuronox®/Siax® (Medytox); Prosigne® (Cristalia); Lantox® (Dermacare), also known as BTXA™ (Lanzhou Institute of Biological Products (LIBP)® - Hong Kong); and Lanzox® (Kalbe - Indonesia) (Brandt 2009; Nettar 2011; Won 2013).

A Cochrane Review that assessed treatments for wrinkles and other skin changes provoked by photoageing included an evaluation of topical treatments (tretinoin, lactic, glycolic acids, moisturiser), and oral and topical polysaccharides and surgical procedures (CO2 laser, YAG laser, dermabrasion), but did not assess botulinum toxin for facial wrinkles (Samuel 2005).

It is important to compare the efficacy of BontA versus different BontA brands, filler (hyaluronic acid, methacrylate, calcium hydroxyapatite, Polyalkylimide, Polylactic acid), and surgery. Also, it is crucial to analyse BontA safety, for example, the major adverse effects are: blepharoptosis (abnormal low-lying upper eyelid margin with the eye in primary gaze) and strabismus (inability of one eye to attain binocular vision with the other because of imbalance of the muscles of the eyeball).

So far, no systematic reviews have been conducted on the effectiveness and safety of botulinum toxin type A in cosmetic procedures. As a consequence of the lack of robust clinical evidence, decisions about the use of different therapies for facial wrinkles are made at the discretion of plastic surgeons or dermatologists working with the person concerned.

The aim of the present systematic review is to determine the effectiveness of botulinum toxin for the treatment of any type of facial wrinkle (dynamic or static).

The methods for this review were published as a protocol '*Botulinum toxin for facial wrinkles*' (Camargo 2014).

OBJECTIVES

To assess the effects of all commercially available botulinum toxin type A products for the treatment of any type of facial wrinkles.

METHODS

Criteria for considering studies for this review

Types of studies

We included, randomised controlled trials (RCTs). Additionally, we also included split-face designs (studies that compared two different treatments, each one applied to one side of the face). We did not include cluster- and cross-over trials. All the studies had to have 50 or more participants.

Types of participants

Individuals of either gender, aged 18 years and above, with a diagnosis of dynamic or static facial wrinkles (glabellar, forehead, or crow's feet).

Types of interventions

All types of botulinum toxin type A in any dose, single or multiple treatments, compared to placebo, other types of botulinum toxin type A, and fillers (hyaluronic acid).

Types of outcome measures

We included studies assessing at least one of the outcomes below.

Primary outcomes

1. Participant assessment of success, measured by validated scores or scales (Bertucci 2020; Carruthers 2003; Honeck 2003; Hund 2006; Rzany 2006). We considered wrinkles and lines at maximum contraction assessed by the following tools.

- Four-point scale (Carruthers 2003)
- Patient Frown Wrinkle Severity (PFWS) scale (Bertucci 2020)
- Facial Line Treatment Satisfaction (FTS) Questionnaire (14-item) (Cox 2003)
- Facial Line Outcomes Questionnaire (FLO-7) (Cox 2003; Fagien 2007b)
- Self perception of age (SPA) (Fagien 2007b; Fagien 2008)
- 5-point Merz Aesthetic Scale (Rzany 2006)

2. Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus).

Secondary outcomes

1. Physician assessment of success, measured by validated scores or scales (Bertucci 2020; Carruthers 2012; Flynn 2012; Kane 2012; Narins 2012; Rzany 2012; Sattler 2012). We considered wrinkles and lines at maximum contraction assessed by the following tools.

- Five-point scale (Flynn 2012)
- Investigator Global AssessmenteFrown Wrinkle Severity (IGA-FWS) (Bertucci 2020)
- Facial Wrinkle Scale (FWS) (Carruthers 2003)
- Brow Positioning Grading Scale (five-point scale) (Carruthers 2008b)

- Forehead Lines Grading Scale (five-point scale) (Carruthers 2008c)
- Crow's Feet Grading Scale (Carruthers 2008d)
- 5-point Merz Aesthetic Scale (Rzany 2006)

2. Any adverse event, measured by the proportion of participants presenting at least one adverse event.

3. Duration of treatment effect

Timing of outcome measurement

We assessed these outcome measures before and after treatment (predominantly focusing on 4, 8, 12, 16 weeks, or more).

Search methods for identification of studies

We aimed to identify all relevant RCTs regardless of language or publication status (published, unpublished, in press, or in progress).

Electronic searches

The Cochrane Skin Information Specialist searched the following databases up to 5 May 2020 using strategies based on the draft strategy for MEDLINE in our published protocol (Camargo 2014):

- the Cochrane Skin Specialised Register using the search strategy listed in Appendix 2;
- the Cochrane Central Register of Controlled Trials (CENTRAL) 2020, Issue 5 in the Cochrane Library using the strategy listed in Appendix 3
- MEDLINE via Ovid (from 1946) using the strategy listed in Appendix 4;
- Embase via Ovid (from 1974) using the strategy listed in Appendix 5; and
- LILACS (Latin American and Caribbean Health Science Information database, from 1982) using the strategy listed in Appendix 6.

Trials registers

We (CPC, RR) searched the following trials registers up to 5 May 2020 using the search terms in Appendix 7:

- the ISRCTN registry (www.isrctn.com);
- ClinicalTrials.gov (www.clinicaltrials.gov);
- the Australian New Zealand Clinical Trials Registry (www.anzctr.org.au);
- the World Health Organization International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/); and
- the EU Clinical Trials Register (www.clinicaltrialsregister.eu).

Searching other resources

References from included studies

We checked the bibliographies of included studies for further references to relevant trials.

Unpublished literature

We contacted specialists in the field, authors of the included trials, and pharmaceutical companies, to request relevant unpublished data.

We handsearched the following plastic and dermatological conference proceedings for further references to relevant RCTs:

- AAD Annual Meeting (2013-2016); and
- Brazilian Congress of Dermatologic Society (2013-2016).

Adverse events

We did not perform a separate search for adverse effects of botulinum toxin. However, we examined data on adverse effects from the included studies we identified.

Data collection and analysis

Selection of studies

Two review authors (CPC and RG) independently assessed and selected studies. We checked the full text of studies for inclusion or exclusion. We recorded reasons for exclusion in the 'Characteristics of excluded studies' tables in the review.

We referred to a third review (CSC) in any case of disagreement.

Data extraction and management

Two review authors (CPC and RG) created, piloted, and managed data extraction forms. They independently extracted data from the full text of the included studies, and a third review author (RR) resolved any discrepancies.

We considered the following data and inserted into the data extraction form:

- publication information (e.g. journal, year, and authors);
- study design, including details of randomisation methods and blinding of treatments;
- methodology, such as inclusion and exclusion criteria and risk of bias (e.g. selection, performance, detection, and attrition);
- population;
- outcome measures of the study (we will indicate where these are our prespecified outcomes for this review);
- dropouts; and
- treatment (e.g. total units, duration, and number of treatments).

Assessment of risk of bias in included studies

Two review authors (CPC and RG) independently applied Cochrane's risk of bias tool (Higgins 2017). We referred to a third review author (RR) in any case of disagreement.

We assessed the following domains to evaluate risk of bias (low, high, or unclear):

(a) random sequence generation;
(b) allocation concealment;
(c) blinding (e.g. blinding of participants, personnel, and outcome assessment);
(d) attrition (i.e. incomplete outcome reporting);
(e) selective reporting bias; and
(f) other risks of bias.

Measures of treatment effect

Considering treatment effects with 95% confidence intervals (CIs), we reported dichotomous outcomes as risk ratios (RR) and

continuous outcomes as standardised mean difference (SMD) when studies used different scales. In rare events (any major adverse event) we reported dichotomous outcomes as Peto odds ratio (OR), since when there is a low number of events, OR is similar to RR.

Score scale	Method	Assessment of outcomes	Type of variable
4-point scale	0 = none 1 = mild 2 = moderate 3 = severe	Mean/median	Ordinal
9-point scale	+4 = complete improvement (100%) 0 = no change -4 = 100% worse	Mean/median	Ordinal
Participant satisfaction	0 to 7		Categorical
FLO	Age perception		Ordinal
FTLS	7-point scale	Mean/median	Ordinal

We considered an 'event' for a dichotomous variable (success) when the patients showed 2-points of improvement in the wrinkles scale.

Unit of analysis issues

We considered the individual participant as the unit of analysis. We also considered each side or region of the face as the unit of analysis for split-face studies, and described these studies narratively.

Dealing with missing data

In case of missing data, we contacted study authors for more information. When the authors did not respond satisfactorily, we did not use the study for quantitative analysis, and we used intention-to-treat (ITT) analysis. We utilised dropouts as ITT analysis.

We considered outcome data complete if the analysis included more than 80% of participants. We applied these criteria to all trials. When data were missing and the study was not included in a meta-analysis, we discussed it in the text of this review.

Assessment of heterogeneity

We used the I^2 statistic to quantify the level of statistical heterogeneity for each outcome. According to the I^2 statistic, we classified heterogeneity as follows: low heterogeneity (0% to 25%), moderate (25% to 75%), or substantial (more than 75%) as suggested in the *Cochrane Handbook for Systematic Review of Interventions* (Higgins 2020).

We performed a random-effect meta-analysis by default, since regardless of statistical heterogeneity, we expected a significant clinical and/or methodological heterogeneity among included RCTs.

Assessment of reporting biases

We contacted study authors to clarify non-reporting of their outcomes. We did not perform a funnel plot because there was less than 10 papers in each analysis.

Data synthesis

We summarised data using the Review Manager 5 software (RevMan). When pooling data was not appropriate or possible (lack of data), we described the results in the main text.

Subgroup analysis and investigation of heterogeneity

We planned the following subgroups analyses:

- age;
- gender;
- ethnic group;
- type of wrinkles: static or dynamic; and
- total doses per area of the face (e.g. glabellar, forehead, periorbicular).

We also planned to undertaken sensitivity analyses by removing studies at high risk of bias.

However, we did not carry out any subgroup analyses due to lack of available data.

Sensitivity analysis

We planned to perform sensitivity analysis considering studies with high risk of bias (allocation) and comparing the results with the overall findings. However, due to the low number of included studies in quantitative synthesis, we deemed this analysis inappropriate.

Summary of findings and assessment of the certainty of the evidence

We created six summary of findings tables for the comparisons below (chosen based on clinical relevance considering type of toxin and face region):

1. OnabotulinumtoxinA 20 units compared to placebo, one cycle of treatment in glabellar lines for facial wrinkles
2. AbobotulinumtoxinA 50 units compared to placebo, one cycle of treatment in glabellar lines for facial wrinkles
3. IncobotulinumtoxinA 20 units compared to placebo, one cycle of treatment in glabellar lines for facial wrinkles
4. AbobotulinumtoxinA 50 units compared to onabotulinumtoxinA 20 units, one cycle of treatment in glabellar lines for facial wrinkles
5. OnabotulinumtoxinA 24 units compared to incobotulinumtoxinA 24 units, one cycle of treatment in glabellar lines for facial wrinkles
6. DaxibotulinumtoxinA 40 units compared to placebo, one cycle of treatment in glabellar lines for facial wrinkles

We included both our primary and secondary outcomes in each table. For participant- and physician-assessment of success we chose the time point closest to four weeks to include in our summary of findings tables. For the major adverse events and treatment duration, we used the longer time point reported. We used the five GRADE criteria (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the certainty of the evidence related with each prespecified primary outcomes. We used methods described in Chapter 14 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2020), and used the platform GRADEpro GDT (GRADEpro GDT). We explained each decisions for down- or upgrading the criteria using footnotes, and added comments where necessary.

RESULTS

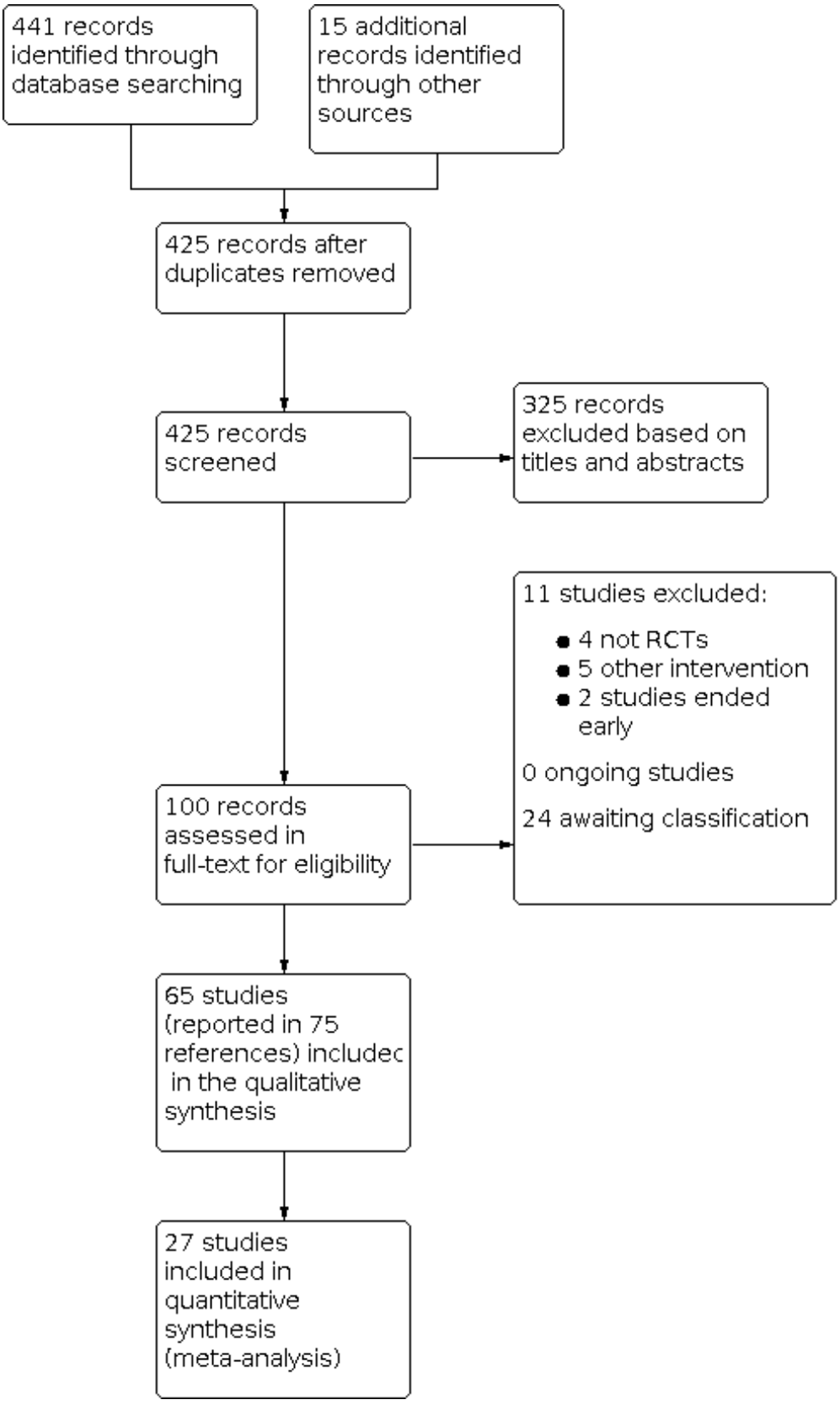
Description of studies

Results of the search

The Electronic searches retrieved 441 records and our handsearches retrieved 15 further records. We had a total of 456 records. After removing duplicates, 425 records were screened. We excluded 325 records based on titles and abstracts. We obtained the full text of the remaining 100 records for further scrutiny against our inclusion criteria. We excluded 11 studies (see Characteristics of excluded studies). Twenty-four studies are awaiting classification (see Characteristics of studies awaiting classification). We included 65 studies reported in 75 references (see Characteristics of included studies). Twenty-seven studies were included in the quantitative synthesis.

For a further description of our screening process, see the study flow diagram Figure 1.

Figure 1. Study flow diagram.



Included studies

We included 65 studies (reported in 75 references), which randomised a total of 14,919 participants. Four were published only as abstracts (Ascher 2018; Firoz 2012; Lee 2013; Solish 2018), and 61 were published as full text (see Characteristics of included studies).

We sent 21 emails to the authors of the following studies asking for additional data (Ascher 2004; Ascher 2005; Ascher 2009; Beer 2006; Beer 2019a; Brandt 2009; Carruthers 2003a; Carruthers 2004; Carruthers 2005a; Cohen 2012; Dayan 2010; Feng 2015; Hexsel 2013; Kane 2009; Kassir 2013; Michaels 2012; Moers-Carpi 2015; Monheit 2007; Rappl 2013; Rzany 2006; Won 2015).

We did not receive any answer from authors of 12 studies (Ascher 2004; Ascher 2005; Ascher 2009; Beer 2006; Beer 2019a; Brandt 2009; Dayan 2010; Feng 2015; Kane 2009; Michaels 2012; Moers-Carpi 2015; Won 2015).

Nine authors answered our emails.

- Four authors answered that data were no longer available because the studies were carried out too long ago (Carruthers 2003a; Carruthers 2004; Carruthers 2005a; Cohen 2012).
- Hexsel 2013 provided a SPSS file, but did not provide any information to clarify our questions.
- Kassir 2013 provided the full paper, but there was no additional information about missing data.
- Monheit 2007 answered the following: “The assessment for primary response was at maximal contraction”
- Rappl 2013 clarified a discrepancy confirming that 21U was the correct dose used.
- Rzany 2006 answered the following: “Concerning the data. This was an IPSEN initiated trial. All analysis was done through IPSEN. I would suggest that you contact IPSEN directly”.

Despite our best efforts, we could not find a validated email for the authors of two studies (Harii 2008; Lee 2013).

Design

Five studies were split-face design (Firoz 2012; Michaels 2012; Kassir 2013; Nettar 2011; Park 2014). The remaining studies were randomised controlled trials (RCTs) with parallel design.

Setting

In total, 51 RCTs were multicentre studies.

- USA (n = 8) (Brandt 2009; Carruthers 2002; Hanke 2013; Kane 2009; Monheit 2019; Beer 2019a; Beer 2019b; Rubin 2009)
- Canada (n = 3) (Carruthers 2017; Rivers 2015; Carruthers 2017)
- Europe, single country (n = 4) (Ascher 2004; Ascher 2005; Ascher 2009; Rzany 2006)
- Europe, two or more countries (n = 5) (Ascher 2018; Ascher 2020; Kerscher 2015; NCT02493946; Satler 2010)
- North America, two or more countries (n = 8) (Bertucci 2020; Carruthers 2004; Carruthers 2010; Carruthers 2013; Carruthers 2003b; Carruthers 2015; Monheit 2007; Solish 2016)
- Transcontinental (n = 8) (Carruthers 2014; Kane 2015; Lowe 2006; Moers-Carpi 2012; Moers-Carpi 2015; De Boulle 2018; Ogilvie 2019; Rzany 2019)
- Asia, single country (n = 11) (Cheon 2019; Feng 2015; Harii 2008; Harii 2017; Kim 2014; Kim 2015; NCT02450526; Won 2013; Won 2015; Wu 2010; Wu 2019)
- South America (n = 1) (Costa 2016)
- No information (n = 3) (Cohen 2012; Dayan 2010; Solish 2018)

Eight RCTs were developed in a single centre: USA (Beer 2006; Michaels 2012; Kassir 2013), Canada (Carruthers 2005a; Carruthers 2005b; Carruthers 2009), Brazil (Hexsel 2013), Austria (Rappl 2013).

Seven studies did not provide any information about setting (Carruthers 2003a; Fagien 2007a; Firoz 2012; Lee 2013; Nettar 2011; Park 2014; Patel 2004).

All patients were outpatients (private office or day clinic).

Study duration

The mean duration of studies was 20.75 weeks ± 11.7 (Nettar 2011) (range 1 to 52 weeks) (Carruthers 2004). The interval between treatments was 24 weeks (six months). Most of the studies analysed the effects from 16 weeks (when the muscle begins to work again) to 24 weeks (the new treatment interval).

Funding

Most of the studies were reported to have received pharmaceutical industry funding.

Participants

The total study population was 14,919 participants. Participants of Carruthers 2015 partially overlapped with participants of Moers-Carpi 2015.

Age

Apart from four studies, which reported age by range (Ascher 2015; Beer 2006; Carruthers A 2003;NCT02493946 Solish 2018), the majority of the studies (58 studies) reported mean age either by treatment group or by total study population. The mean age of study participants ranged from 18 to 65 years in the majority of studies. Two studies did not report the age, gender, or other demographic data (Lee 2013; Patel 2004).

Gender

Seven studies did not provide any information about gender (Fagien 2007a; Feng 2015; Firoz 2012; Lee 2013; Nettar 2011; Patel 2004; Solish 2018). Ten studies included only female participants (Ascher 2018; Beer 2006; Carruthers 2005b; Carruthers 2009; Carruthers 2003a; Carruthers 2010; Cohen 2012; Costa 2016; Kane 2015; Satler 2010). One paper studied only men (Carruthers 2005a).

The majority of the studies included more than 80% female participants (Ascher 2004; Ascher 2005; Ascher 2009; Ascher 2020; Bertucci 2020; Carruthers 2004; Carruthers 2005b; Carruthers 2014; Carruthers 2003b; Carruthers 2015; Carruthers 2017; Cheon 2019; Dayan 2010; De Boulle 2018; Feng 2015; Hanke 2013; Harii 2008; Harii 2017; Hexsel 2013; Kane 2009; Kane 2015; Kassir 2013; Kerscher 2015; Kim 2014; Kim 2015; Lowe 2006; Michaels 2012; Moers-Carpi 2012; Moers-Carpi 2015; Monheit 2007; Monheit 2019;

NCT02450526; NCT02493946; Beer 2019a; Beer 2019b; Ogilvie 2019; Park 2014; Rappl 2013; Rivers 2015; Rubin 2009; Rzany 2006; Rzany 2019; Solish 2016; Won 2013; Won 2015; Wu 2010; Wu 2019).

Facial region

- Glabellar lines (GL): 43 RCTs (Ascher 2004; Ascher 2005; Ascher 2018; Ascher 2020; Beer 2006; Bertucci 2020; Brandt 2009; Carruthers 2004; Carruthers 2005a; Carruthers 2005b; Carruthers 2013; Carruthers 2002; Carruthers 2003b; Carruthers 2017; Costa 2016; Fagien 2007a; Feng 2015; Hanke 2013; Harii 2008; Kane 2009; Kane 2015; Kassir 2013; Kim 2014; Kim 2015; Lee 2013; Lowe 2006; Moers-Carpi 2012; Monheit 2007; Monheit 2019; NCT02450526; NCT02493946; Beer 2019a; Beer 2019b; Patel 2004; Rappl 2013; Rzany 2019; Rubin 2009; Rzany 2006; Satler 2010; Solish 2018; Won 2013; Won 2015; Wu 2010).
- Crow's feet lines: 7 RCTs (Ascher 2009; Carruthers 2014; Cheon 2019; Harii 2017; Nettar 2011; Park 2014; Wu 2019).
- Perioral lines: 2 RCTs (Carruthers 2010; Cohen 2012).
- Forehead line: 2 RCTs (Carruthers 2003a; Solish 2016).
- Forehead lines and crow's feet line: one RCT (Michaels 2012).
- Upper lines (glabellar lines, crow's feet lines, forehead lines): 3 RCTs (Carruthers 2009; Dayan 2010; De Boulle 2018).
- Forehead lines and glabellar lines: 3 RCTs (Firoz 2012; Kerscher 2015; Ogilvie 2019).
- Crow's feet lines and glabellar lines: 3 RCTs (Carruthers 2015; Moers-Carpi 2015; Rivers 2015).
- Full face: one RCT (Hexsel 2013).

Severity of the wrinkles

Most of the papers which treated glabellar lines included moderate-to-severe glabellar lines according to Facial Wrinkle Scale score or Glabellar Lines Severity Scale. The others regions did not present details about severity.

Sample size

The sample size of the studies ranged from 56 to 917 participants (mean = 230.14).

Unit of analysis

Five studies were split-face design (Firoz 2012; Michaels 2012; Kassir 2013; Nettar 2011; Park 2014). In the remaining studies, the unit of analysis was the individual. In meta-analysis we only compared parallel study groups.

Intervention

Types of botulinum toxin type A (BontA)

11 commercial types of BontA (produced from different strains of BontA with unique biological behaviour) were addressed in RCTS:

- Botox®, Vistabel®, Vistabex® (Allergan - onabotulinumtoxinA (Beer 2006; Carruthers 2003a; Carruthers 2004; Carruthers 2005a; Carruthers 2005b; Carruthers 2009; Carruthers 2010; Carruthers 2014; Carruthers 2002; Carruthers 2003b; Carruthers 2015; Carruthers 2017; Cohen 2012; Dayan 2010; De Boulle 2018; Fagien 2007a; Firoz 2012; Harii 2008; Harii 2017; Kane 2009; Kane 2015; Kassir 2013; Lowe 2006; Michaels 2012; Moers-Carpi 2012; Moers-Carpi 2015; Nettar 2011; Ogilvie 2019; Park 2014; Park 2014; Patel 2004; Rappl 2013; Rzany 2019; Rivers 2015; Satler 2010; Solish 2016; Won 2015; Wu 2010; Wu 2019)
- Dysport® (Ipsen); Azzulure® (Galderma - abobotulinumtoxinA (Ascher 2004; Ascher 2005; Ascher 2009; Ascher 2018; Brandt 2009; Hexsel 2013; Kane 2009; Kassir 2013; Lowe 2006; Michaels 2012; Monheit 2007; Monheit 2019; Nettar 2011; Rappl 2013; Rubin 2009; Rzany 2006)
- Xeomeen®, Xeomin®, Bocouture® (Merz Aesthetics - incobotulinumtoxinA (Carruthers 2013; Dayan 2010; Hanke 2013; Kane 2009; Kane 2015; Kerscher 2015; Moers-Carpi 2012; Park 2014; Rappl 2013; Satler 2010)
- HBTX-A (Feng 2015; NCT02493946)
- Neuronox®, Botulift®, Siax®, Medytox® (Medytox, Inc., Cheonwon-gun, Republic of Korea) (Cheon 2019; Lee 2013; Won 2013)
- Liquid BontA (MT10109L) (Kim 2015)
- DaxibotulinumtoxinA (DWP450) (Daewoong Pharmaceutical, Seoul, Korea) (Bertucci 2020; Carruthers 2017; Won 2015)
- Liquid BontA (Ipsen) (Ascher 2018; Ascher 2020; NCT02450526)
- CBFC26 (SNUH) (Kim 2014)
- Prosigne® (Lanzhou Institute of Biological Products) (Costa 2016)
- PrabotulinumtoxinA (Beer 2019a; Beer 2019b; Rzany 2019; Solish 2018)

Number of cycles

- One single cycle of treatment: 54 RCTs (Ascher 2004; Ascher 2009; Ascher 2018; Beer 2006; Beer 2019a; Bertucci 2020; Brandt 2009; Carruthers 2003a; Carruthers 2005a; Carruthers 2005b; Carruthers 2009; Carruthers 2010; Carruthers 2013; Carruthers 2014; Carruthers 2002; Carruthers 2003b; Carruthers 2010; Carruthers 2017; Cheon 2019; Cohen 2012; Costa 2016; Dayan 2010; Fagien 2007a; Feng 2015; Firoz 2012; Hanke 2013; Hexsel 2013; Kane 2009; Kane 2015; Kassir 2013; Kerscher 2015; Kim 2014; Kim 2015; Lee 2013; Lowe 2006; Michaels 2012; Moers-Carpi 2012; Monheit 2007; Monheit 2019; Nettar 2011; NCT02493946; Park 2014; Patel 2004; Rappl 2013; Rivers 2015; Rzany 2006; Rzany 2019; Satler 2010; Solish 2016; Solish 2018 ; Won 2013; Won 2015; Wu 2010; Wu 2019)
- Two cycles of treatment: 3 RCTs (Ascher 2005; Moers-Carpi 2015; Ogilvie 2019)
- Three or more cycles treatments: 8 RCTs (Ascher 2020; Carruthers 2004; Carruthers 2015; De Boulle 2018; Harii 2008; Harii 2017; Rubin 2009; NCT02450526)

Dose of the treatment

The dose ranged according to the facial region and BontA's brand.

Glabellar lines

- OnabotulinumtoxinA, from 8 U to 80 U (Beer 2006; Carruthers 2003a; Carruthers 2004; Carruthers 2005a; Carruthers 2005b; Carruthers 2009; Carruthers 2010; Carruthers 2014; Carruthers 2015; Carruthers 2002; Carruthers 2003b; Carruthers 2017; Cohen 2012; Dayan 2010; De Boulle 2018; Fagien 2007a; Firoz 2012; Harii 2008; Harii 2017; Kane 2009; Kane 2015; Kassir 2013; Lowe 2006; Michaels 2012; Moers-Carpi 2012; Moers-Carpi 2015; Nettar 2011; Ogilvie 2019; Park 2014; Patel 2004; Rappl 2013; Rzany 2019; Rivers 2015; Satler 2010; Solish 2018; Won 2015; Wu 2010)

- AbobotulinumtoxinA, from 20 U to 75 U (Ascher 2004; Ascher 2005; Ascher 2009; Ascher 2018; Brandt 2009; Hexsel 2013; Kane 2009; Kassir 2013; Lowe 2006; Michaels 2012; Monheit 2007; Monheit 2019; Nettar 2011; Rappl 2013; Rubin 2009; Rzany 2006)
- IncobotulinumtoxinA, from 20 U to 24 U (Carruthers 2013; Hanke 2013; Kane 2009; Kane 2015; Kerscher 2015; Moers-Carpi 2012; Rappl 2013; Satler 2010)
- HBTX-A, 20U (Feng 2015; NCT02493946)
- NewBontA [Medytox®], 20 U (Lee 2013)
- NewBontA [Neuronox®], 20 U (Won 2013)
- DaxibotulinumtoxinA (DWP450), 20 U to 60 U (Bertucci 2020; Carruthers 2017; Won 2015)
- MT10109L, 20 U (Kim 2015)
- LiquidBontA 20 U to 75 U (Ascher 2018; Ascher 2020; NCT02450526)
- CBFC26, 20 U (Kim 2014)
- NewBontA [Prosigne®], 20 U (Costa 2016)
- PrabotulinumtoxinA 20U to 60 U (Beer 2019a; Beer 2019b; Rzany 2019; Solish 2018)

Forehead lines

- OnabotulinumtoxinA, 10U to 48 U (Carruthers 2003a; Carruthers 2009; Dayan 2010)
- IncobotulinumtoxinA, 10 U to 20 U (Kerscher 2015)

Crow's feet lines

- OnabotulinumtoxinA 7.5 U to 24 U (Harii 2017; Kassir 2013; Moers-Carpi 2012; Moers-Carpi 2015; Nettar 2011; Park 2014; Rivers 2015; Wu 2019)
- AbobotulinumtoxinA 30 U (Kassir 2013; Nettar 2011)
- IncobotulinumtoxinA 7.5 U to 12 U (Dayan 2010; Kerscher 2015; Park 2014)
- Neuronox® 24U- (Cheon 2019)

Perioral lines

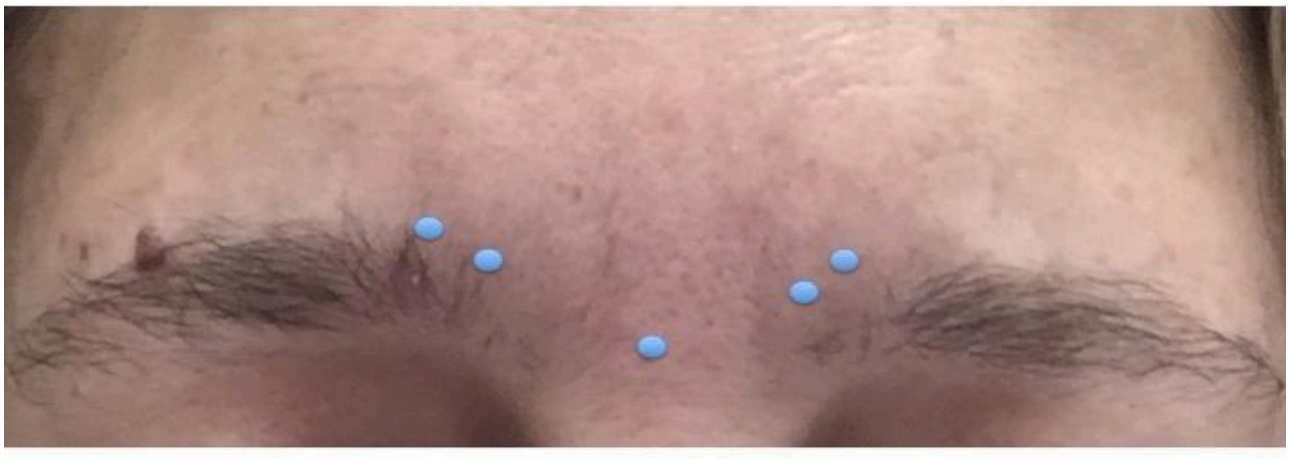
- OnabotulinumtoxinA, from7.5 U to 12 U (Carruthers 2010; Cohen 2012)

Distribution of the injection points

The distribution of all injections points followed the American and European consensus.

- Glabellar lines- three to seven intramuscular injections points (procerus muscle, corrugator supercilii muscle, orbicularis oculi, muscle depressor supercilii muscle) (Figure 2)
- Forehead lines- four to eight points of intramuscular injection along the frontal muscle wrinkles with a 2.0 cm above the eyebrows; and
- Crow's feet- one injection at least 1.5 cm to 2.0 cm from lateral canthus, one injection in the orbital rim next to the eyebrow caudal extremity, and one injection near the zygomatic process in the orbital rim, the other injections along the crow's feet lines laterally to the previous injections per side (Carruthers 2008a; Ascher 2010; Sundaram 2016)
- Perioral lines- four injections, two symmetric injections per lip (lower and upper lip) (Cohen 2012)

Figure 2. Illustration of injection sites in glabellar region. Copyright [2020] [Cristina Pires Camargo]Reproduced with permission



Comparisons

BontA versus placebo, at least one cycle of treatment (36 studies); BontA at different doses, one cycle of treatment (21 studies); BontA versus placebo, at least two cycles of treatment (11 studies); BontA versus facial cream (one study); BontA associated to fillers (2 studies)

The studies tested the effect of different types of BontA in facial wrinkles through the following comparisons.

OnabotulinumtoxinA versus placebo

- OnabotulinumtoxinA versus placebo, glabellar lines, one cycle of treatment**,** both genders (Carruthers 2002; Carruthers 2003b; Carruthers 2017; Fagien 2007a; Rzany 2019; Solish 2018; Wu 2010)
- OnabotulinumtoxinA versus placebo, crow's feet lines, one cycle of treatment, both genders (Carruthers 2014; Wu 2019)
- OnabotulinumtoxinA versus placebo, glabellar lines, and crow's feet lines, one cycle of treatment, both genders (Rivers 2015)
- OnabotulinumtoxinA versus placebo, glabellar lines, forehead lines, and crow's feet lines, one cycle of treatment, both genders (De Boulle 2018)
- OnabotulinumtoxinA versus placebo, glabellar lines, five cycles of treatment (Harii 2017)

OnabotulinumtoxinA, different doses

- OnabotulinumtoxinA, different doses, one cycle of treatment, glabellar lines in men (Carruthers 2005a)
- OnabotulinumtoxinA, different doses, one cycle of treatment, glabellar lines in women (Carruthers 2005b)
- OnabotulinumtoxinA, different doses, one cycle of treatment, upper wrinkles (forehead lines, glabellar lines, crow's feet lines) in women (Carruthers 2009; Dayan 2010)
- OnabotulinumtoxinA, different doses, one cycle of treatment, forehead lines, dose-ranging in women (Carruthers 2003a; Solish 2016)
- OnabotulinumtoxinA, different doses, one cycle of treatment, forehead lines and glabella lines, dose-ranging, both genders (Ogilvie 2019)
- OnabotulinumtoxinA, different doses, one cycle of treatment, perioral lines in women (Cohen 2012)

OnabotulinumtoxinA versus placebo

- OnabotulinumtoxinA versus placebo, glabellar lines, two-three cycles of treatment, both genders (Carruthers 2004)
- OnabotulinumtoxinA versus placebo, glabellar lines and crow's feet lines, two cycles of treatment, both genders (Moers-Carpi 2015; Carruthers 2015)

- OnabotulinumtoxinA versus placebo, glabellar lines, five cycles of treatment, both genders (Harii 2017). We only use double-blind data.

AbobotulinumtoxinA versus placebo

- AbobotulinumtoxinA versus placebo, one cycle of treatment, glabellar lines (Ascher 2005)
- AbobotulinumtoxinA versus placebo, one cycle of treatment, glabellar lines, both gender (Brandt 2009)

AbobotulinumtoxinA, different doses, versus placebo

- AbobotulinumtoxinA versus placebo, different doses, glabellar lines, both genders (Ascher 2004; Monheit 2019; Kane 2009; Monheit 2007; Rzany 2006)
- AbobotulinumtoxinA versus placebo, different doses, crow's feet, both genders (Ascher 2009)
- AbobotulinumtoxinA versus placebo, multiple cycles of treatment, glabellar lines, both genders (Ascher 2020; NCT02450526)
- AbobotulinumtoxinA versus placebo, two cycles of treatment, glabellar lines, both genders (Ascher 2005)
- AbobotulinumtoxinA versus placebo, three cycles of treatment, glabellar lines, both genders (Rubin 2009)

AbobotulinumtoxinA, different doses

- AbobotulinumtoxinA, three different doses in full-face treatment, both genders (Hexsel 2013)

IncobotulinumtoxinA versus placebo

- IncobotulinumtoxinA versus placebo, glabellar lines, both genders (Carruthers 2013; Hanke 2013)
- IncobotulinumtoxinA versus placebo, forehead lines, glabellar lines, and crow's feet lines, both genders (Kerscher 2015)

HBTX-A versus placebo

- HBTX-A versus placebo, glabellar lines, one cycle of treatment, both genders (Feng 2015; NCT02493946)

Neuronox® versus placebo

- Neuronox® versus placebo, crow's feet lines, one cycle of treatment, both genders (Cheon 2019)

Liquid BontA (Ipsen®), different doses, versus placebo

- Liquid BontA (Ipsen®) different doses versus placebo versus abobotulinumtoxinA, glabellar lines, both genders (Ascher 2018)
- Liquid BontA (Ipsen®) versus placebo, glabellar lines, both genders (Ascher 2020)

DaxibotulinumtoxinA versus placebo

- DaxibotulinumtoxinA versus placebo from one cycle to 5 cycles of treatment in crow's feet lines, both genders (Bertucci 2020; Harii 2017; Solish 2018)
- DaxibotulinumtoxinA, dose-ranging, versus onabotulinumtoxinA, one cycle of treatment, both genders (Carruthers 2017)

PrabotulinimtoxinA versus placebo

- PrabotulinimtoxinA versus placebo, one cycle of treatment in glabellar lines, both genders (Beer 2019a; Beer 2019b; Rzany 2019)

BontA versus active control

- OnabotulinumtoxinA versus AbobotulinumtoxinA, one cycle of treatment, glabellar lines and forehead lines, both genders (Firoz 2012)
- OnabotulinumtoxinA versus AbobotulinumtoxinA, one cycle of treatment, glabellar lines, both genders (Kassir 2013; Lowe 2006)
- OnabotulinumtoxinA versus AbobotulinumtoxinA, one cycle of treatment, glabellar lines, crow's feet lines, and forehead lines, both genders (Michaels 2012)
- OnabotulinumtoxinA versus AbobotulinumtoxinA, one cycle of treatment, in crow's feet lines, both genders (Nettar 2011)
- OnabotulinumtoxinA versus IncobotulinumtoxinA, one cycle of treatment, glabellar lines, both genders (Kane 2015; Moers-Carpi 2012; Satler 2010)
- OnabotulinumtoxinA versus IncobotulinumtoxinA, one cycle of treatment, crow's feet lines, both genders (Park 2014)
- OnabotulinumtoxinA versus AbobotulinumtoxinA versus IncobotulinumtoxinA, one cycle of treatment, glabellar lines, both genders (Rappl 2013)
- Neuronox® versus onabotulinumtoxinA, one cycle of treatment, glabellar lines, both genders (Won 2013)
- Liquid BontA (MT10109L) versus onabotulinumtoxinA, one cycle of treatment, glabellar lines, both genders (Kim 2015)
- New BontA (Medytox®) versus onabotulinumtoxinA, one cycle of treatment, glabellar lines, both genders (Lee 2013)
- DaxibotulinumtoxinA versus onabotulinumtoxinA, one cycle of treatment, glabellar lines, both genders (Won 2015)
- CBFC26 versus onabotulinumtoxinA, one cycle of treatment, glabellar lines, both genders (Kim 2014)
- Liquid BontA (Ipsen®) different doses versus AbobotulinumtoxinA, glabellar lines, both genders (Ascher 2018)
- PrabotulinimtoxinA versus placebo, one cycle of treatment in glabellar lines, both genders (Beer 2019a; Beer 2019b; Rzany 2019)
- PrabotulinimtoxinA versus onabotulinumtoxinA, one cycle of treatment in glabellar lines, both genders (Rzany 2019)

BontA associated with creams

- OnabotulinumtoxinA, one cycle of treatment, versus facial cream in glabellar lines in women (Beer 2006)

BontA associated with fillers

- OnabotulinumtoxinA associated with fillers (collagen), one cycle of treatment, versus onabotulinumtoxinA, glabellar lines (Patel 2004)
- OnabotulinumtoxinA associated with collagen, one cycle of treatment, versus collagen, glabellar lines, no information about genders (Patel 2004)
- OnabotulinumtoxinA associated with Hyaluronic acid, one cycle of treatment, versus onabotulinumtoxinA, lips and perioral lines, in women (Carruthers 2010)

- OnabotulinumtoxinA associated with Hyaluronic acid, one cycle of treatment, versus Hyaluronic acid, lips and perioral lines, in women (Carruthers 2010)

Outcomes

Primary outcomes

- Thirty-five studies evaluated participant assessment of success by analysing scores and scales (the responder rate at maximum contraction): Ascher 2020; Ascher 2018; Beer 2019a; Beer 2019b; Brandt 2009; Bertucci 2020; Carruthers 2003a; Carruthers 2005a; Carruthers 2005b; Carruthers 2009; Carruthers 2013; Carruthers 2014; Carruthers 2015; Carruthers 2017; Cheon 2019; De Boulle 2018; Feng 2015; Hanke 2013; Harii 2008; Kane 2009; Kim 2014; Kim 2015; Moers-Carpi 2012; Moers-Carpi 2015; Monheit 2019; NCT02493946; Nettar 2011; Ogilvie 2019; Rzany 2019; Rubin 2009; Solish 2016; Solish 2018; Won 2013; Won 2015; Wu 2019. The most common scales used by studies were Facial Wrinkle Scale and 5-Point Scale.
- Forty-six studies evaluated any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus): Ascher 2020; Ascher 2004; Ascher 2005; Ascher 2009; Ascher 2018; Beer 2006; Beer 2019a; Beer 2019b; Bertucci 2020; Brandt 2009; Carruthers 2003a; Carruthers 2004; Carruthers 2005b; Carruthers 2003b; Carruthers 2002; Carruthers 2010; Carruthers 2013; Carruthers 2015; Carruthers 2017; Cheon 2019; De Boulle 2018; Feng 2015; Hanke 2013; Harii 2008; Harii 2017; Kane 2015; Kassir 2013; Kerscher 2015; Kim 2014; Kim 2015; Moers-Carpi 2015; Monheit 2019; NCT02450526 NCT02493946; Patel 2004; Rivers 2015; Rubin 2009; Rzany 2006; Rzany 2019; Satler 2010; Solish 2016; Solish 2018; Won 2013; Won 2015; Wu 2010; Wu 2019.

Secondary outcomes

- Forty-nine studies evaluated an assessment of the physician assessment of success by analysing scores and scales (responder rate at maximum contraction): Ascher 2020; Ascher 2004; Ascher 2005; Ascher 2009; Ascher 2018; Beer 2019a; Beer 2019b; Bertucci 2020; Carruthers 2003a; Carruthers 2005a; Carruthers 2005b; Carruthers 2009; Carruthers 2010; Carruthers 2013; Carruthers 2014; Carruthers 2003b; Carruthers 2002; Carruthers 2015; Carruthers 2017; Cheon 2019; Cohen 2012; Costa 2016; De Boulle 2018; Hanke 2013; Harii 2008; Harii 2017 Kane 2009; Kane 2015; Kassir 2013; Kerscher 2015; Kim 2014; Kim 2015; Lee 2013; Lowe 2006; Moers-Carpi 2012; Moers-Carpi 2015; Monheit 2019; NCT02450526; NCT02493946;; Rappl 2013; Rivers 2015; Rubin 2009; Rzany 2006; Satler 2010; Solish 2016; Won 2013; Won 2015; Wu 2010; Wu 2019. The most common scale used by studies were Facial Wrinkle Scale and 5-Point Scale.
- Fifty-one studies evaluated the occurrence of any adverse event: Ascher 2020; Ascher 2004; Ascher 2005; Ascher 2009; Ascher 2018; Beer 2006; Beer 2019a; Beer 2019b; Bertucci 2020; Brandt 2009; Carruthers 2003a; Carruthers 2004; Carruthers 2005a; Carruthers 2005b; Carruthers 2009; Carruthers 2010; Carruthers 2013; Carruthers 2002; Carruthers 2003b; Carruthers 2015; Carruthers 2017; Cheon 2019; Cohen 2012; De Boulle 2018; Feng 2015; Hanke 2013; Harii 2008; Harii 2017; Kane 2015; Kerscher 2015; Kim 2014; Kim 2015; Lowe 2006; Moers-Carpi 2012; Moers-Carpi 2015; Monheit 2007; Monheit 2019; NCT02450526; NCT02493946; Rappl 2013; Rivers 2015; Rubin 2009; Rzany 2006; Rzany 2019; Satler 2010; Solish 2016; Solish 2018; Won 2013; Won 2015; Wu 2010; Wu 2019.
- Twenty-one studies evaluated the duration of treatment effect (weeks): Ascher 2005; Bertucci 2020; Brandt 2009; Carruthers 2005a; Carruthers 2009; Carruthers 2010; Carruthers 2014; Carruthers 2017; Cheon 2019; Costa 2016; Feng 2015; Harii 2008; Harii 2017; Kane 2009; Monheit 2019; Beer 2019a; Beer 2019b; Rappl 2013; Rzany 2019; Solish 2016; Wu 2019)
- One RCT (NCT02493946) evaluated only HBTX-A duration in days.

Excluded studies

We excluded 11 studies. Four studies were not randomised clinical trials (Hexsel 2018; Mahmoud 2016; Rzany 2013; 2014-003770-16). Five studies analysed interventions outside the scope of this review (Cartier 2020; NCT02297516; Punga 2016; Wilson 2016; Zhang 2018). Two studies ended when the company involved (Johnson & Johnson) changed their plans to produce the BontA (NCT00752050; NCT00752297) (see Characteristics of excluded studies).

Ongoing studies

No studies were identified as ongoing.

Studies awaiting classification

We identified 24 studies awaiting classification. These studies were listed as completed on the clinical trial register, but no relevant results are available yet. See Characteristics of studies awaiting classification for more details.

Risk of bias in included studies

The risk of bias of each study is detailed in the Characteristics of included studies table. Figure 3 and Figure 4 present the risk of bias summary along with review authors' judgements about each risk of bias item for an individual study. The overall risk of bias of the studies was unclear in all of them as we categorised at least one of the domains as having an unclear risk of bias.

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

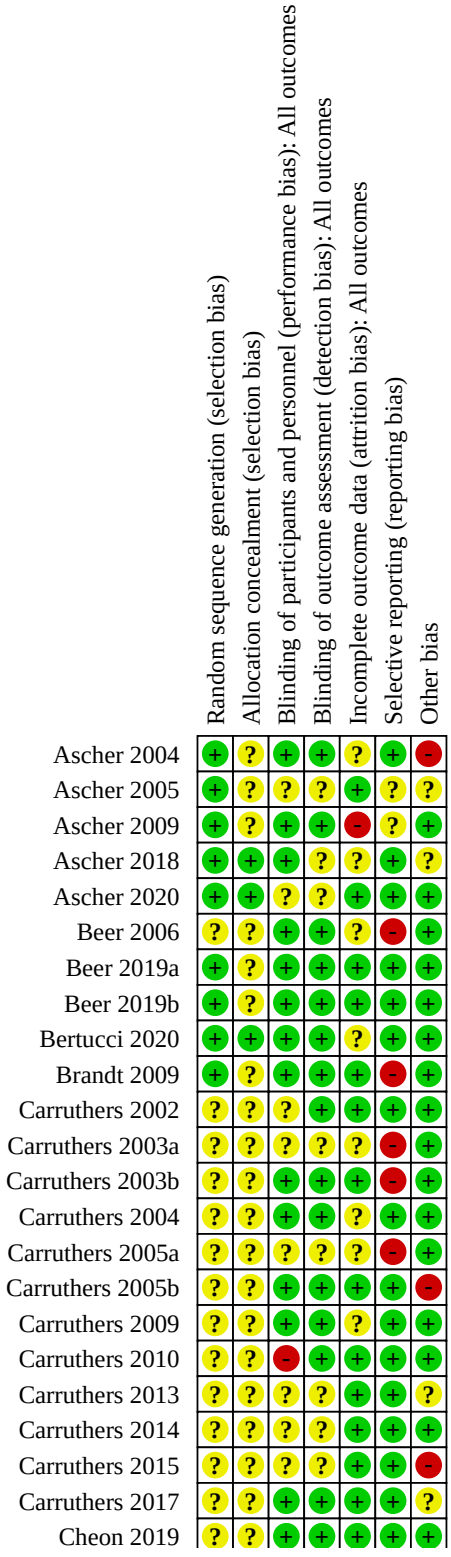


Figure 3. (Continued)

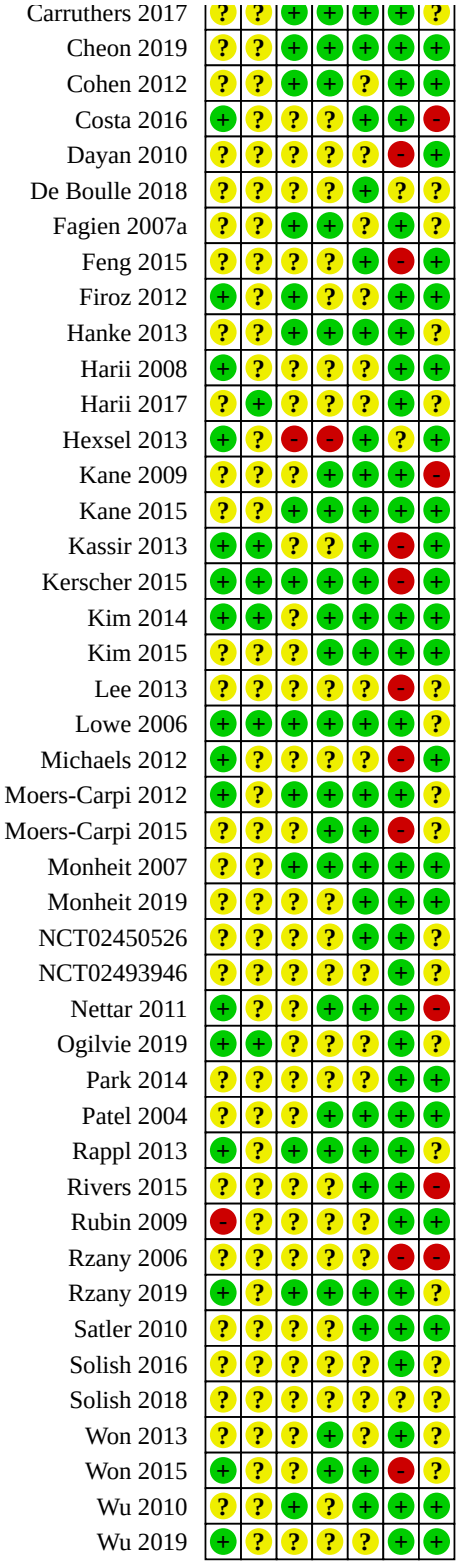
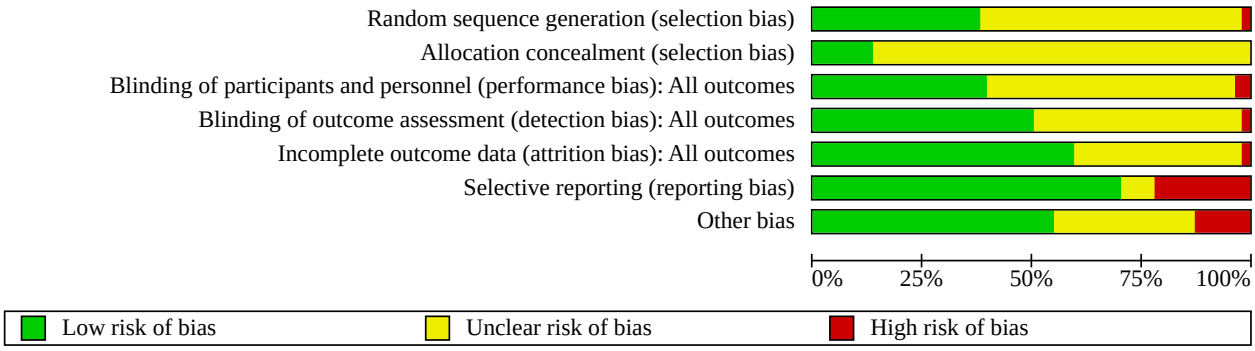


Figure 4. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Random sequence generation

Twenty-five studies described randomisation sequence adequately and were considered as low risk of bias. One study used 'tossing a coin' to generate random sequence (Michaels 2012) and the remaining 24 studies used computer-generated random numbers (Ascher 2004; Ascher 2005; Ascher 2009; Ascher 2018;Ascher 2020 ; Beer 2019a; Beer 2019b; Bertucci 2020; Brandt 2009; Costa 2016; Firoz 2012; Harii 2008; Hexsel 2013; Kassir 2013; Kerscher 2015; Kim 2014; Lowe 2006; Moers-Carpi 2012; Nettar 2011; Ogilvie 2019 ; Rappl 2013; Rzany 2019; Won 2015; Wu 2019).

Thirty-nine studies studies were reported as being randomised, but further description of sequence generation was not reported; hence, we classified these as unclear risk of bias (Beer 2006; Carruthers 2003a; Carruthers 2004; Carruthers 2005a; Carruthers 2005b; Carruthers 2009; Carruthers 2010; Carruthers 2013; Carruthers 2002; Carruthers 2003b; Carruthers 2014; Carruthers 2015; Carruthers 2017; Cheon 2019; Cohen 2012; Dayan 2010; De Boulle 2018; Fagien 2007a; Feng 2015; Hanke 2013; Harii 2017; Kane 2009; Kane 2015; Kim 2015; Lee 2013; Moers-Carpi 2015; Monheit 2007; Monheit 2019;NCT02450526; NCT02493946; Park 2014; Patel 2004; Rivers 2015; Rzany 2006; Satler 2010; Solish 2016; Solish 2018; Won 2013; Wu 2010).

Rubin 2009 added an amendment to a supplementary randomisation for the third cycle (C), but no further information about the method was reported. We considered this study as presenting high risk of bias.

Allocation sequence concealment

Nine studies described allocation concealment and were considered as low risk of bias (Ascher 2018; Ascher 2020; Bertucci 2020; Harii 2017; Kassir 2013; Kerscher 2015; Kim 2014; Lowe 2006; Ogilvie 2019).

Fifty-six studies had reported allocation, but the authors did not show the methods used for maintaining the allocation concealment, and we considered them as presenting unclear risk of bias (Ascher 2004; Ascher 2005; Ascher 2009; Beer 2006; Beer 2019a; Beer 2019b; Brandt 2009; Carruthers 2003a; Carruthers 2004; Carruthers 2005a; Carruthers 2005b; Carruthers 2009; Carruthers 2010; Carruthers 2013; Carruthers 2002; Carruthers 2003b; Carruthers 2014; Carruthers 2015; Carruthers 2017; Cohen 2012; Cheon 2019; Costa 2016; Dayan 2010; De Boulle 2018; Fagien 2007a; Feng 2015; Firoz 2012; Hanke 2013; Harii 2008; Hexsel 2013; Kane 2009; Kane 2015; Kim 2015; Lee 2013; Michaels 2012; Moers-Carpi 2012; Moers-Carpi 2015; Monheit 2007; Monheit 2019; NCT02450526; NCT02493946; Nettar 2011; Park 2014; Patel 2004; Rappl 2013; Rivers 2015; Rubin 2009; Rzany 2006; Rzany 2019; Satler 2010; Solish 2016; Solish 2018; Won 2013; Won 2015; Wu 2010; Wu 2019).

Blinding

Performance bias

Twenty-six studies presented low risk of bias related to performance (Ascher 2004; Ascher 2009; Ascher 2018; Beer 2006; Beer 2019a; Beer 2019b, Bertucci 2020; Brandt 2009; Carruthers 2004; Carruthers 2005b; Carruthers 2009; Carruthers 2003b; Carruthers 2017; Cheon 2019; Cohen 2012; Fagien 2007a; Firoz 2012; Hanke 2013; Kane 2015; Kerscher 2015; Lowe 2006; Moers-Carpi 2012; Monheit 2007; Rappl 2013; Rzany 2019; Wu 2010). In these studies, the authors reported that the person responsible for blinding process was not directly involved in the research.

Thirty-seven studies did not mention the details of how they blinded the participants, and we considered this as an unclear risk of bias (Ascher 2005; Ascher 2020 ; Carruthers 2003a; Carruthers 2005a; Carruthers 2013; Carruthers 2014; Carruthers 2002; Carruthers 2015; Costa 2016; Dayan 2010; De Boulle 2018; Feng 2015; Harii 2008; Harii 2017; Kane 2009; Kassir 2013; Kim 2014; Kim 2015; Lee 2013; Michaels 2012; Moers-Carpi 2015; Monheit 2019; NCT02493946; NCT02450526 ; Nettar 2011; Ogilvie 2019; Park 2014; Patel 2004; Rivers 2015; Rubin 2009; Rzany 2006; Satler 2010; Solish 2016; Solish 2018; Won 2013; Won 2015; Wu 2019).

Two RCTs were considered high risk of bias (Carruthers 2010; Hexsel 2013). Carruthers 2010 was a single-blinded study, and Hexsel 2013 was an open-label trial.

Detection bias

We judged 33 studies as low risk of bias because they provided information about blinding of outcome assessment (Ascher 2004; Ascher 2009; Beer 2006; Beer 2019a; Beer 2019b, Bertucci 2020;

Brandt 2009; Carruthers 2004; Carruthers 2005b; Carruthers 2009; Carruthers 2010; Carruthers 2002; Carruthers 2003b; Carruthers 2017;Cheon 2019; Cohen 2012; Fagien 2007a; Hanke 2013; Kane 2009; Kane 2015; Kerscher 2015; Kim 2014; Kim 2015; Lowe 2006; Moers-Carpi 2012; Moers-Carpi 2015; Monheit 2007; Nettar 2011; Patel 2004; Rappl 2013; Rzany 2019; Won 2013; Won 2015). The authors reported that the person responsible for blinding maintenance was not involved in the research

Thirty-one studies did not describe detection bias, and we considered them as presenting unclear risk of bias (Ascher 2005; Ascher 2018; Ascher 2020; Carruthers 2003a; Carruthers 2005a; Carruthers 2013; Carruthers 2014; Carruthers 2015; Costa 2016; Dayan 2010;De Boulle 2018, Feng 2015; Firoz 2012; Harii 2008; Harii 2017; Kassir 2013; Lee 2013; Michaels 2012; Monheit 2019; NCT02450526 ; NCT02493946; Ogilvie 2019; Park 2014; Rivers 2015; Rubin 2009; Rzany 2006; Satler 2010; Solish 2016; Solish 2018; Wu 2010; Wu 2019).

One study was judged as presenting a high-risk of bias due to open-label design (Hexsel 2013).

Incomplete outcome data

Low risk studies were defined as low dropout rate, comparable drop-out rate between groups, and/or comparable reasons for dropout between groups.

Thirty-nine trials were considered low risk of bias (Ascher 2005; Ascher 2020 ; Beer 2019a; Beer 2019b; Brandt 2009; Carruthers 2005b; Carruthers 2010; Carruthers 2013; Carruthers 2014; Carruthers 2002; Carruthers 2003b; Carruthers 2015; Carruthers 2017; Cheon 2019; Costa 2016; De Boulle 2018; Feng 2015; Hanke 2013; Hexsel 2013; Kane 2009; Kane 2015; Kassir 2013; Kerscher 2015; Kim 2014; Kim 2015; Lowe 2006; Moers-Carpi 2012; Moers-Carpi 2015; Monheit 2007; Monheit 2019; Nettar 2011; NCT02450526; Patel 2004; Rappl 2013; Rivers 2015; Rzany 2019; Satler 2010; Won 2015; Wu 2010). We consider low risk of bias if the authors reported the reasons for dropout.

Twenty-five RCTs were considered unclear risk of bias because they did not provide any reason of dropouts (Ascher 2004; Ascher 2018; Beer 2006; Bertucci 2020; Carruthers 2003a; Carruthers 2004; Carruthers 2005a; Carruthers 2009; Cohen 2012; Dayan 2010; Fagien 2007a; Firoz 2012; Harii 2008; Harii 2017; Lee 2013; Michaels 2012; NCT02493946; Ogilvie 2019; Park 2014; Rubin 2009; Rzany 2006; Solish 2016; Solish 2018; Won 2013; Wu 2019).

One study was consider as a high risk of bias. Ascher 2009 reported protocol violation.

Selective reporting

46 RCTs were considered low risk of bias (Ascher 2004; Ascher 2018; Ascher 2020; Beer 2019a; Beer 2019b; Bertucci 2020; Carruthers 2002; Carruthers 2004; Carruthers 2005b; Carruthers 2009; Carruthers 2010; Carruthers 2013; Carruthers 2014; Carruthers 2015; Carruthers 2017; Cohen 2012; Cheon 2019; Costa 2016; Fagien 2007a; Firoz 2012; Hanke 2013; Harii 2008; Harii 2017; Kane 2009; Kane 2015; Kim 2014; Kim 2015; Lowe 2006; Moers-Carpi 2012; Monheit 2007; Monheit 2019; NCT02450526; NCT02493946; Nettar 2011; Ogilvie 2019; Park 2014; Patel 2004; Rappl 2013; Rivers 2015; Rubin 2009; Rzany 2019; Satler 2010; Solish 2016; Won 2013; Wu 2010; Wu 2019).

We consider low risk of bias if the authors presented all prespecified outcomes.

Five studies were considered as presenting unclear risk of bias (Ascher 2005; Ascher 2009; De Boulle 2018; Hexsel 2013; Solish 2018).

Fourteen RCTs were considered as presenting high risk of bias (Beer 2006; Brandt 2009; Carruthers 2003a; Carruthers 2005a; Carruthers 2003b; Dayan 2010; Feng 2015; Kassir 2013; Kerscher 2015; Lee 2013; Michaels 2012; Moers-Carpi 2015; Rzany 2006; Won 2015). Beer 2006 did not report raw data for patient satisfaction, only P values; Brandt 2009 reported different data in the text compared to the graphic; Carruthers 2003a reported an imbalance in baseline data and missing data; Carruthers 2005a did not report participant satisfaction, only P values; Carruthers 2003b reported better results were seen in the subgroup analysis by age (younger than 50 years old), but no data were shown; Dayan 2010 reported only P values; Feng 2015 did not mention if the investigator assessment was done at rest or at contraction; Kassir 2013 reported inconsistencies in the number of participants included in the study; Kerscher 2015 and Solish 2018 did not report the following outcomes: the response rate at rest by investigator assessment, the proportion of one-point responders based on the investigator's rating of glabellar lines and forehead at rest, and investigator-assessed and participant-assessed outcomes; Lee 2013 reported only the outcomes assessed at week 4; Michaels 2012 only reported P values; Moers-Carpi 2015 reported only P values for investigator-assessed responder rates on crow's feet lines (FWS), participant's global assessment of change in crow's feet lines, patient-reported outcomes; Rzany 2006 did not report the following outcomes: the scores at maximum frown and at rest, by the investigator assessment, at weeks 0, 2, 4, 12, and 16; the subjective assessment of improvement since the first visit by the participant assessment at weeks 2, 4, 12, and 16; Won 2015 did not report patient satisfaction.

Eight studies showed reported clinical trial register numbers (Ascher 2018 (NCT01333397); Carruthers 2014 (NCT01189747); Kane 2015 (NCT02096081); Moers-Carpi 2012 (NCT01271452); Moers-Carpi 2015 (NCT01189760); Rivers 2015 (NCT01777620); Satler 2010 (NCT00777803); Won 2013 (NCT01237977). Of these studies, only Moers-Carpi 2015 had a high risk of bias (Reported Outcomes, no data shown).

Other potential sources of bias

Thirty-six studies were considered low risk of other sources of bias (Ascher 2009; Ascher 2020; Beer 2006; Bertucci 2020; Brandt 2009; Carruthers 2003a; Carruthers 2004; Carruthers 2005a; Carruthers 2009; Carruthers 2010; Carruthers 2014; Carruthers 2002; Carruthers 2003b; Cheon 2019; Cohen 2012; Dayan 2010; Feng 2015; Firoz 2012; Harii 2008; Hexsel 2013; Kane 2015; Kassir 2013; Kerscher 2015; Kim 2014; Kim 2015; Michaels 2012; Monheit 2007;Monheit 2019; Beer 2019a; Beer 2019b; Park 2014; Patel 2004; Rubin 2009; Satler 2010; Wu 2010; Wu 2019).

In 20 studies, at least one of the authors was a sponsor employee, so we consider unclear risk of bias (Ascher 2005; Ascher 2018; Carruthers 2013; Carruthers 2017; De Boulle 2018; Fagien 2007a; Hanke 2013; Harii 2017; Lee 2013; Lowe 2006; Moers-Carpi 2012; Moers-Carpi 2015; NCT02450526 ; Ogilvie 2019; Rappl 2013;Rzany

2019; Solish 2016; Solish 2018, Won 2013; Won 2015). One study was considered as unclear risk of bias because some parts of the text showed discrepancies (Rappl 2013), and another was judged as unclear due to limited information provided about the trial (NCT02493946).

Besides investigators bias, four studies had baseline imbalances that could influence the outcomes, so we consider them as unclear (Ascher 2018; Carruthers 2017; De Boulle 2018; Ogilvie 2019).

Eight studies were considered as high risk of bias (Ascher 2004; Carruthers 2005b; Carruthers 2015; Costa 2016; Kane 2009; Nettar 2011; Rivers 2015; Rzany 2006). Costa 2016 reported protocol violations. In another study rated as high risk of bias, the sponsor was involved in data analysis of the trial (Rzany 2006). Three studies reported at least one of the authors wa ae sponsor stockholder, so we considered this a high risk of bias (Carruthers 2015; Kane 2009; Nettar 2011).

Effects of interventions

See: **Summary of findings 1** Summary of Findings Table - OnabotulinumtoxinA 20U compared to placebo in glabellar lines; **Summary of findings 2** Summary of Findings Table - AbobotulinumtoxinA 50U compared to placebo for glabellar lines; **Summary of findings 3** Summary of Findings Table - IncobotulinumtoxinA 20U compared to placebo for glabellar lines; **Summary of findings 4** Summary of Findings Table - AbobotulinumtoxinA 50U compared to OnabotulinumtoxinA 20U in glabellar lines; **Summary of findings 5** Summary of Findings Table - IncobotulinumtoxinA 24U compared to OnabotulinumtoxinA 24U in glabellar lines; **Summary of findings 6** Summary of Findings Table - DaxibotulinumtoxinA 40U compared to placebo in glabellar lines

COMPARISON 1. OnabotulinumtoxinmtoxinA 10 units versus placebo for glabellar lines, one cycle of treatment

One randomised controlled trial (RCT) (n = 94 participants) assessed this comparison (Harii 2008).

For this reason (one study), we were not able to undertake a meta-analysis, and only a visual representation of the results is shown in the forest plots.

Primary outcomes

Participant assessment of success by analysing scores and scales

The responder rate, by participant assessment, was higher with onabotulinumtoxinA 10 U than placebo; however, because of the wide confidence intervals the results are very uncertain; at week 4 (risk ratio (RR) 40.36, 95% confidence interval (CI) 5.78 to 281.92; participants = 92; studies = 1); week 8 (RR 67.93, 95% CI 4.28 to 1078.29; participants = 91; studies = 1); week 12 (RR 26.29, 95% CI 3.71 to 186.39; participants = 90; studies = 1); and week 16 (RR 35.33, 95% CI 2.18 to 572.97; participants = 90; studies = 1) (Analysis 1.1).

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

This RCT did not report any major adverse events.

Secondary outcomes

Physician assessment of success by analysing scores or scales

The responder rate was higher with onabotulinumtoxinA 10 U than placebo; however, because of the wide confidence intervals the results are very uncertain; at week 4 (RR 83.84, 95% CI 5.31 to 1325.05; participants = 92; studies = 1); at week 8 (RR 32.37, 95% CI 4.60 to 227.65; participants = 91; studies = 1); at week 12 (RR 46.72, 95% CI 2.91 to 749.60; participants = 90; studies = 1); and at week 16 (RR 23.93, 95% CI 1.44 to 396.41; participants = 90; studies = 1) (Analysis 1.2).

Total adverse events

No difference between groups was found (RR 1.14, 95% CI 0.84 to 1.55, participants = 95; studies = 1) (Analysis 1.3).

Duration of treatment effect

This RCT did not assess this outcome.

COMPARISON 2. OnabotulinumtoxinA 20 units versus placebo glabellar lines, one cycle of treatment

Eight RCTs (n = 1390 participants) assessed this comparison (Beer 2006; Carruthers 2003b; Carruthers 2002; Carruthers 2017; Harii 2008; NCT02450526; Rzany 2019; Wu 2010), and the results are included in Summary of findings 1.

Primary outcomes

Participant assessment of success by analysing scores and scales

Four RCTs assessed this outcome (Harii 2008 n = 94; Carruthers 2017 n = 77; NCT02450526 n = 113; Rzany 2019 n = 292).

The responder rate, by participant assessment, was higher with onabotulinumtoxinA 20 U than placebo at week 4 (RR 19.45, 95% CI 8.60 to 43.99; participants = 575; studies = 4; I^2 = 0%; moderate-certainty evidence); at week 8 (RR 28.45, 95% CI 5.92 to 136.74; participants = 204; studies = 2, I^2 = 0%); at week 12 (RR 12.77, 95% CI 2.78 to 58.72; participants = 203; studies = 2, I^2 = 43%); at week 16 (RR 20.71, 95% CI 2.82 to 151.91; participants = 167; studies = 2; I^2 = 0%); at week 24 (RR 4.19, 95% CI 0.21 to 84.41; participants = 77; studies = 1) (Analysis 2.1).

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

Eight studies assessed this outcome (n = 1390) (Beer 2006; Carruthers 2003b; Carruthers 2002; Carruthers 2017; Harii 2008; Rzany 2019; Wu 2010; NCT02450526).

The frequency of adverse events was higher with onabotulinumtoxinA 20 U when compared to placebo (Peto OR 3.62, 95% CI 1.50 to 8.74, participants = 1390; studies = 8; moderate-certainty evidence) (Analysis 2.2).

Secondary outcomes

Physician assessment of success by analysing scores and scales

Seven RCTs reported this outcome (n = 1339) (Carruthers 2003b; Carruthers 2002; Carruthers 2017; Harii 2008; Rzany 2019; Wu 2010; NCT02450526).

The responder rate was higher with onabotulinumtoxinA 20 U when compared to placebo at week 4 (RR 17.10, 95% CI 10.07 to 29.05; participants = 1339; studies = 7; I^2 = 0%; moderate-certainty evidence); at week 8 (RR 21.50, 95% CI 9.68 to 47.75; participants = 1046; studies = 6; I^2 = 15%); at week 12 (RR 10.81, 95% CI 5.79 to 20.16; participants = 1046; studies = 6; I^2 = 10%); at week 16 (RR 15.13, 95% CI 5.98 to 38.27; participants = 933; studies = 5; I^2 = 0%); at week 20 (RR 5.86, 95% CI 0.31 to 109.74; participants = 77; studies = 1); at week 24 (RR 4.19, 95% CI 0.21 to 84.41; participants = 77; studies = 1) (Analysis 2.3).

Total adverse events

Eight RCTs (n = 1388 participants) assessed this comparison (Beer 2006; Carruthers 2003b; Carruthers 2002; Carruthers 2017; Harii 2008; Rzany 2019; Wu 2010; NCT02450526). No difference between groups was found (RR 1.14, 95% CI 0.89 to 1.45; participants = 1388; studies = 8; I^2 = 28%, low-certainty evidence) (Analysis 2.4).

Duration of treatment effect

Only one RCT assessed this outcome (Carruthers 2017); for this reason we were not able to undertake a meta-analysis and only a visual representation of the results is shown in the forest plots. The duration of treatment effect of onabotulinumtoxinA 20 U was higher than in the placebo group (mean difference (MD) 18.40, 95% CI 16.17 to 20.63; participants = 77; studies = 1; low-certainty evidence) (Analysis 2.5).

COMPARISON 3. OnabotulinumtoxinA 20 units versus 10 units for glabellar lines, one cycle of treatment

Two RCTs (n = 131 participants) assessed this comparison (Carruthers 2005b; Harii 2008).

Primary outcomes

Participants assessment of success by analysing scores and scales

There were two studies (Carruthers 2005b; Harii 2008) which assessed this outcome. The meta-analysis showed no clear or substantial difference between these doses at 4 weeks (RR 1.11, 95% CI 0.96 to 1.29; participants = 131; studies = 2; I^2 = 0%); 8 weeks (RR 1.24, 95% CI 1.01 to 1.52; participants = 131; studies = 2; I^2 = 0%); and 16 weeks (RR 1.23, 95% CI 0.75 to 2.01; participants = 131; studies = 2; I^2 = 0%) (Analysis 3.1).

Major adverse events

The meta-analysis showed no clear difference between these doses as the result was imprecise (Peto OR 1.93, 95% CI 0.20 to 18.70; participants = 131; studies = 2) (Analysis 3.2).

Secondary outcomes

Physician assessment of success by analysing scores and scale scores or scales

The meta-analysis showed no clear difference between doses at 4 weeks (RR 1.05, 95% CI 0.91 to 1.20; n = 131; studies = 2; I^2 = 0%); at 8 weeks (RR 1.53, 95% CI 0.76 to 3.10; n = 131; studies = 2; I^2 = 65%); and 16 weeks (RR 1.43, 95% CI 0.76 to 2.69; n = 131; studies = 2; I^2 = 0%) (Analysis 3.3).

Total adverse events

There was no difference in number of events between doses (RR 1.08, 95% CI 0.49 to 2.37; n = 131; studies = 2; I^2 = 0%) (Analysis 3.4).

Duration of treatment effect

Harii 2008 was the only study in this comparison to report this outcome. The mean duration of effect of treatment was 9.4 weeks in the OnabotulinumtoxinA 20U group and 7.9 weeks in the onabotulinumtoxinA 10 U group (no additional data were provided; therefore, we were unable to create a forest plot).

COMPARISION 4. OnabotulinumtoxinA 64 units versus placebo for upper wrinkles, one cycle of treatment.

Only one RCT (n = 469 participants) assessed this comparison (De Boulle 2018). For this reason, we were not able to undertake a meta-analysis, and only a visual representation of the results is shown in the forest plots.

Primary outcomes

Participant assessment of success by analysing scores and scales

The responder rate (participant assessment) was higher in onabotulinumtoxinA 64 U than placebo at week 4 (RR 8.32, 95% CI 4.53 to 15.30; participants = 469; studies = 1); at week 8 (RR 106.50, 95% CI 6.66 to 1702.48; participants = 469; studies = 1); at week 12 (RR 44.50, 95% CI 2.76 to 717.83; participants = 469; studies = 1); at week 16 (RR 26.50, 95% CI 1.63 to 431.99; participants = 469; studies = 1); at week 20 (RR 5.50, 95% CI 0.31 to 98.84; participants = 469; studies = 1); and at week 24 (RR 1.50, 95% CI 0.06 to 36.61; participants = 469; studies = 1) (Analysis 4.1).

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

The major adverse events was similar with onabotulinumtoxinA 64 U and placebo (RR 1.00, 95% CI 0.09 to 10.91; participants = 469; studies = 1). (Analysis 4.2).

Secondary outcomes

Physician assessment of success by analysing scores and scales

The responder rate, by physician assessment was higher in onabotulinumtoxinA 64 U than placebo at week 4 (RR 8.32, 95% CI 4.53 to 15.30; participants = 469; studies = 1); at week 8 (RR 106.50, 95% CI 6.66 to 1702.48; participants = 469; studies = 1), at week 12 (RR 44.50, 95% CI 2.76 to 717.83; participants = 469; studies = 1), at week 16 (RR 26.50, 95% CI 1.63 to 431.99; participants = 469; studies = 1); at week 20 (RR 5.50, 95% CI 0.31 to 98.84; participants = 469; studies = 1); and at week 24 (RR 1.50, 95% CI 0.06 to 36.61; participants = 469; studies = 1) (Analysis 4.3).

Total adverse events

There was higher rate of any adverse event with onabotulinumtoxinA 64 U (RR 1.32, 95% CI 1.03 to 1.71; participants = 469; studies = 1) (Analysis 4.4).

Duration of treatment effect

The RCT did not report this outcome.

COMPARISION 5. OnabotulinumtoxinA 40 units versus placebo for upper wrinkles, one cycle of treatment.

Only one RCT (n = 474 participants) assessed this comparison (De Boulle 2018). For this reason, we were not able to undertake a meta-analysis, and only a visual representation of the results is shown in the forest plots.

Primary outcomes

Participant assessment of success by analysing scores and scales

The responder rate (participant assessment) was higher in onabotulinumtoxinA 40 U than placebo at week 4 (RR 7.41, 95% CI 4.02 to 13.64; participants = 474; studies = 1); at week 8 (RR 86.13, 95% CI 5.38 to 1378.82; participants = 474; studies = 1); at week 12 (RR 39.87, 95% CI 2.47 to 644.08; participants = 474; studies = 1; I^2 = 0%); at week 16 (RR 11.32, 95% CI 0.67 to 190.86; participants = 474; studies = 1); at week 20 (RR 2.26, 95% CI 0.12 to 50.95; participants = 474; studies = 1); and at week 24 (RR 1.48, 95% CI 0.06 to 36.04; participants = 474; studies = 1) (Analysis 5.1).

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

The major adverse events was higher in onabotulinumtoxinA 40 U than placebo (RR 2.45, 95% CI 0.29 to 20.82; participants = 474; studies = 1). (Analysis 5.2).

Secondary outcomes

Physician assessment of success by analysing scores and scales

The responder rate, by physician assessment was higher in onabotulinumtoxinA 40U than placebo at week 4 (RR 7.41, 95% CI 4.02 to 13.64; participants = 474; studies = 1); at week 8 (RR 86.13, 95% CI 5.38 to 1378.82; participants = 474; studies = 1); at week 12 (RR 39.87, 95% CI 2.47 to 644.08; participants = 474; studies = 1); at week 16 (RR 11.32, 95% CI 0.67 to 190.86; participants = 474; studies = 1); at week 20 (RR 2.46, 95% CI 0.12 to 50.95; participants = 474; studies = 1); and at week 24 (RR 1.48, 95% CI 0.06 to 36.04; participants = 474; studies = 1) (Analysis 5.3).

Total adverse event

There was higher in onabotulinumtoxinA 40 U than placebo (RR 1.45, 95% CI 1.13 to 1.86; participants = 474; studies = 1) (Analysis 5.4).

Duration of treatment effect

The RCT did not report this outcome.

COMPARISION 6. OnabotulinumtoxinA 64 units versus onabotulinumtoxinA 40 units for upper wrinkles, one cycle of treatment.

Only one RCT (n = 631participants) assessed this comparison (De Boulle 2018). For this reason, we were not able to undertake a meta-analysis, and only a visual representation of the results is shown in the forest plots.

Primary outcomes

Participant assessment of success by analysing scores and scales

The responder rate (participant assessment) was higher in onabotulinumtoxinA 64 U than OnabotulinumtoxinA 40 U at week 4 (RR 1.12, 95% CI 0.96 to 1.31; participants = 631; studies = 1); at week 8 (RR 1.24, 95% CI 0.98 to 1.57; participants = 631; studies = 1); at week 12 (RR 1.12, 95% CI 0.75 to 1.67; participants = 631; studies = 1); at week 16 (RR 2.40, 95% CI 1.21 to 4.78; participants = 631; studies = 1); at week 20 (RR 2.54, 95% CI 0.50 to 12.99; participants = 631; studies = 1).

However, the responder rate (participant assessment) was similar with onabotulinumtoxinA 64 U and onabotulinumtoxinA 40 U at week 24 (RR 1.02, 95% CI 0.06 to 16.17; participants = 631; studies = 1) (Analysis 6.1).

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

No difference was found (RR 0.41, 95% CI 0.08 to 2.08; participants = 631; studies = 1) (Analysis 6.2).

Secondary outcomes

Physician assessment of success by analysing scores and scales

The responder rate, by physician assessment was higher in onabotulinumtoxinA 64 units than onabotulinumtoxinA 40 units at week 4 (RR 1.12, 95% CI 0.96 to 1.31; participants = 631; studies = 1); at week 8 (RR 1.24, 95% CI 0.98 to 1.57; participants = 631; studies = 1); at week 12 (RR 1.12, 95% CI 0.75 to 1.67; participants = 631; studies = 1); at week 16(RR 2.40, 95% CI 1.21 to 4.78; participants = 631; studies = 1); at week 20 (RR 2.54, 95% CI 0.50 to 12.99; participants = 631; studies = 1).

However, the responder rate (participant assessment) was similar with onabotulinumtoxinA 64 U and OnabotulinumtoxinA 40 U at week 24 (RR 1.02, 95% CI 0.06 to 16.17; participants = 631; studies = 1) (Analysis 6.3).

Total adverse events

No difference between groups was found (RR 0.91, 95% CI 0.77 to 1.08; participants = 631; studies = 1) (Analysis 6.4).

Duration of treatment effect

The RCT did not report this outcome.

COMPARISON 7. OnabotulinumtoxinA 64 units versus 32 units for upper wrinkles, one cycle of treatment

Only one RCT (n = 40 participants) assessed this comparison (Carruthers 2009). For this reason, we were not able to undertake a meta-analysis, and only a visual representation of the results is shown in the forest plots.

Primary outcomes

Participant assessment of success by analysing scores and scales

The responder rate (participant assessment) was higher in onabotulinumtoxinA 64 U than in onabotulinumtoxinA 32 U at week 12 (RR 1.32, 95% CI 1.02 to 1.72; participants = 40; studies = 1) and week 16 (RR 1.73, 95% CI 1.15 to 2.60; participants = 40; studies = 1). However, there was no clear or substantial difference between groups at week 4 (RR 1.17, 95% CI 0.96 to 1.43; participants = 40; studies = 1); at week 8 (RR 1.12, 95% CI 0.91 to 1.38; participants = 40; studies = 1); week 20 (RR 4.00, 95% CI 0.97 to 16.55; participants = 40; studies = 1); and week 24 (RR 1.00, 95% CI 0.16 to 6.42; participants = 40; studies = 1) (Analysis 7.1).

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

This RCT did not report any major event.

Secondary outcomes

Physician assessment of success by analysing scores and scales

The responder rate, by physician assessment, was not different between onabotulinumtoxinA 32 U and onabotulinumtoxinA 64

U at weeks 4 and 8 (RR 1.00, 95% CI 0.91 to 1.10; participants = 40; studies = 1); at week 12 (RR 0.95, 95% CI 0.83 to 1.09; participants = 40; studies = 1). At weeks 16 and week 20 there was no clear difference between groups (RR 0.62, 95% CI 0.33 to 1.15; participants = 40; studies = 1) (RR 0.40, 95% CI 0.09 to 1.83; participants = 40; studies = 1). At week 24, both groups were less than 2/20(10%) (Analysis 7.2).

Total adverse events

No difference between groups was found (RR 0.75, 95% CI 0.49 to 1.14; participants = 40; studies = 1) (Analysis 7.3).

Duration of treatment effect

The RCT assessed this outcome, but did not report the results.

COMPARISON 8. OnabotulinumtoxinA 96 units versus 32 units for upper wrinkles, one cycle of treatment

Only one RCT (n = 40 participants) assessed this outcome (Carruthers 2009). For this reason, we were not able to undertake a meta-analysis, and only a visual representation of the results is shown in the forest plots.

Primary outcomes

Participant assessment of success by analysing scores and scales

The responder rate, by participant assessment, was similar between onabotulinumtoxinA 96U and onabotulinumtoxinA 32 U at weeks 4 and 8 (for both time points: RR 1.17, 95% CI 0.96 to 1.43; participants = 40; studies = 1); and there was no clear difference at week 24 (RR 3.50, 95% CI 0.83 to 14.83; participants = 40; studies = 1); and week 32 (RR 3.50, 95% CI 0.83 to 14.83; participants = 40; studies = 1). The responder rate, by participant assessment, was higher with onabotulinumtoxinA 96 U than onabotulinumtoxinA 32 U at week 12 (RR 1.32, 95% CI 1.02 to 1.72; participants = 40; studies = 1); week 16 (RR 1.64, 95% CI 1.07 to 2.50; participants = 40; studies = 1); week 20 (RR 6.00, 95% CI 1.54 to 23.44; participants = 40; studies = 1); and at week 28 (RR 4.50, 95% CI 1.11 to 18.27; participants = 40; studies = 1) (Analysis 8.1).

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

This RCT did not report any major event.

Secondary outcomes

Physician assessment of success by analysing scores and scales

The responder rate, by physician assessment, was similar between onabotulinumtoxinA 96 U and onabotulinumtoxinA 32 U at weeks 4 and 8 (RR 1.00, 95% CI 0.91 to 1.10; participants = 40; studies = 1) and at week 12 (RR 1.05, 95% CI 0.92 to 1.20; participants = 40; studies = 1). But at week 28 and week 32 we are uncertain which group is favoured due to the wide confidence intervals obtained: (RR 13.00, 95% CI 0.78 to 216.39; participants = 40; studies = 1), (RR 5.00, 95% CI 0.26 to 98.00; participants = 40; studies = 1). The responder rate, by physician assessment, was higher with onabotulinumtoxinA 96u than onabotulinumtoxinA 32 U at week 16 (RR 2.25, 95% CI 1.29 to 3.92; participants = 40; studies = 1); week 20 (RR 7.50, 95% CI 1.97 to 28.61; participants = 40; studies = 1); and week 24 (RR 27.00, 95% CI 1.71 to 425.36; participants = 40; studies = 1) (Analysis 8.2).

Total adverse events

No difference between groups was found (RR 1.25, 95% CI 0.81 to 1.94; participants = 40; studies = 1) (Analysis 8.3).

Duration of treatment effect

This RCT did not assessed this outcome.

COMPARISON 9. OnabotulinumtoxinA 96 units versus 64 units for upper wrinkles, one cycle of treatment.

Only one RCT (n = 40 participants) assessed this comparison (Carruthers 2009). For this reason we were not able to undertake a meta-analysis, and only a visual representation of the results is shown in the forest plots.

Primary outcomes

Participant assessment of success by analysing scores and scales

The responder rate, by participant assessment, was similar between onabotulinumtoxinA 96U and onabotulinumtoxinA 64U, at week 4 (RR 1.00, 95% CI 0.91 to 1.10; participants = 40; studies = 1), at week 8 (RR 1.05, 95% CI 0.92 to 1.20; participants = 40; studies = 1), at week 12 (RR 1.00, 95% CI 0.91 to 1.10; participants = 40; studies = 1), and at week 16 (RR 0.95, 95% CI 0.79 to 1.13; participants = 40; studies = 1). We are less certain of the effect at week 20 (RR 1.50, 95% CI 0.79 to 2.86; participants = 40; studies = 1), and at week 24 (RR 3.50, 95% CI 0.83 to 14.83; participants = 40; studies = 1). The responder rate, by participant assessment, were higher with onabotulinumtoxinA 96U than onabotulinumtoxinA 64U at week 28 and week 32; however, because of the very wide confidence interval the result is very uncertain: at week 28 (RR 19.00, 95% CI 1.18 to 305.88; participants = 40; studies = 1), and at week 32 (RR 17.00, 95% CI 1.05 to 276.03; participants = 40; studies = 1) (Analysis 9.1).

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

This RCT did not report any major event.

Secondary outcomes

Physician assessment of success by analysing scores and scales

The responder rate, by participant assessment, was similar with onabotulinumtoxinA 96U versus onabotulinumtoxinA 64U, at week 4 (RR 0.95, 95% CI 0.83 to 1.09; participants = 40; studies = 1), at week 8 (RR 1.00, 95% CI 0.91 to 1.10; participants = 40; studies = 1), and at week 12 (RR 1.00, 95% CI 0.91 to 1.10; participants = 40; studies = 1). But we are less certain about the effect size at week 16 (RR 1.38, 95% CI 0.97 to 1.97; participants = 40; studies = 1). The responder rate was higher in the 96 U group at week 20 (RR 3.00, 95% CI 1.35 to 6.68; participants = 40; studies = 1), and at week 24 (RR 6.50, 95% CI 1.68 to 25.16; participants = 40; studies = 1). The responder rate, by participant assessment, were also higher with onabotulinumtoxinA 96 units than onabotulinumtoxinA 64 units at week 24 and week 32; however, because of the confidence interval the results are very uncertain: at week 28 (RR 13.00, 95% CI 0.78 to 216.39; participants = 40; studies = 1), and at week 32 (RR 5.00, 95% CI 0.26 to 98.00; participants = 40; studies = 1) (Analysis 9.2).

Any adverse event

No difference between groups was found but the confidence interval was wide (RR 0.94, 95% CI 0.67 to 1.31; participants = 40; studies = 1) (Analysis 9.3).

Duration of treatment effect

This RCT studied this outcome as survival analysis. The authors showed a better duration of treatment effect in onabotulinumtoxinA 96 units group (61.3% of responders at week 24).

COMPARISON 10. OnabotulinumtoxinA 32 units versus 16 units for forehead lines, one cycle of treatment

Only one RCT (n = 39 participants) assessed this comparison (Carruthers 2003a). For this reason, we were not able to undertake a meta-analysis, and only a visual representation of the results is shown in the forest plots.

Primary outcomes

Participant assessment of success by analysing scores and scales

The responder rate, by participant assessment was similar with onabotulinumtoxinA 32U versus onabotulinumtoxinA 16 U at week 8 (RR 1.05, 95% CI 0.36 to 3.07; participants = 39; studies = 1) (Analysis 10.1).

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

Eyelid swelling was similar with onabotulinumtoxinA 32 U and onabotulinumtoxinA 16U (RR 1.05; 95% CI 0.24 to 4.59, n = 39; studies = 1) (Analysis 10.2).

Secondary outcomes

Physician assessment of success by analysing scores and scales

The responder rate, by physician assessment was similar with onabotulinumtoxinA 32U versus onabotulinumtoxinA 16 U at week 8 (RR 0.73; 95% CI 0.41 to 1.29, participants = 39; studies = 1) (Analysis 10.3).

Any adverse event

This RCT did not assess this outcome.

Duration of treatment effect

This RCT did not assess this outcome.

COMPARISON 11. OnabotulinumtoxinA 48 units versus 16 units for forehead lines, one cycle of treatment

Only one RCT (n = 40 participants) assessed this comparison (Carruthers 2003a). For this reason, we were not able to undertake a meta-analysis, and only a visual representation of the results is shown in the forest plots.

Primary outcomes

Participant assessment of success by analysing scores and scales

The responder rate, by participant assessment, was higher with onabotulinumtoxinA 48 U then onabotulinumtoxinA 16 U at week 8, but the results are uncertain due to the confidence interval including 1 (RR 1.60, 95% CI 0.63 to 4.05; participants = 40; studies = 1) (Analysis 17.1).

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

No difference between groups was found, but the confidence interval was wide (RR 2.00; 95% CI 0.58 to 6.91, n = 40; studies = 1) (Analysis 17.2).

Secondary outcomes

Physician assessment of success by analysing scores and scales

The responder rate, by physician's assessment, was similar with onabotulinumtoxinA 48 U and onabotulinumtoxinA 16 U at week 8 (RR 1.00; 95% CI 0.63 to 1.58, n = 40; studies = 1) (Analysis 17.3).

Total adverse events

This RCT did not assess this outcome.

Duration of treatment effect

This RCT did not assess this outcome.

COMPARISON 12. OnabotulinumtoxinA 48 units versus 32 units for forehead lines, one cycle of treatment

Only one RCT (n = 39 participants) assessed this comparison (Carruthers 2003a). For this reason, we were not able to undertake a meta-analysis, and only a visual representation of the results is shown in the forest plots.

Primary outcomes

Participant assessment of success by analysing scores and scales

There was no clear difference for responder rate, by participant assessment, between doses at week 8 (RR 1.52; 95% CI 0.60 to 3.83, n = 39; studies = 1) (Analysis 12.1).

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

No difference between groups was found but the confidence interval was wide (RR 0.47, 95% CI 0.10 to 2.30; participants = 39; studies = 1) (Analysis 12.2)

Secondary outcomes

Physician assessment of success by analysing scores and scales

One RCT assessed this comparison (Carruthers 2003a). The responder rate, by physician assessment, were similar with OnabotulinumtoxinA 48 U versus OnabotulinumtoxinA 32 U at week 8 (RR 1.37; 95% CI 0.77 to 2.43, n = 39; studies = 1) (Analysis 12.3).

Total adverse events

This RCT did not assess this outcome.

Duration of treatment effect

This RCT did not assess this outcome.

COMPARISON 13. OnabotulinumtoxinA 40 units versus placebo for forehead lines and glabellar lines, one cycle of treatment

Only one RCT (n = 116 participants) assessed this comparison (Solish 2016).

For this reason (one study), we were not able to undertake a meta-analysis, and only a visual representation of the results is shown in the forest plots.

Primary outcomes

Participant assessment of success by analysing scores and scales

The responder rate, by participant assessment, was higher with onabotulinumtoxinA 40 U than placebo at week 4 (RR 6.60, 95% CI 3.44 to 12.64; participants = 116; studies = 1); at week 8 (RR 16.91, 95% CI 5.59 to 51.17; participants = 116; studies = 1); at week 12 (RR 4.73, 95% CI 2.27 to 9.84; participants = 116; studies = 1); and at week 20 (RR 6.90, 95% CI 2.17 to 21.96; participants = 116; studies = 1).

Although, the responder rate, by participant assessment, was higher with onabotulinumtoxinA 40 U than placebo, the results are uncertain due to the wide confidence intervals: at week 16 (RR 32.09, 95% CI 4.53 to 227.29; participants = 116; studies = 1), and at week 24 (RR 15.53, 95% CI 2.12 to 113.72; participants = 116; studies = 1) (Analysis 13.1).

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

This RCT did not report any major event.

Secondary outcomes

Physician assessment of success by analysing scores and scales

The responder rate, by physician assessment, was higher with onabotulinumtoxinA 40 U than placebo at week 16 (RR 4.49, 95% CI 2.00 to 10.08; participants = 116; studies = 1).

The responder rate, by physician assessment, was higher with onabotulinumtoxinA 40 U than placebo at week 4 (RR 26.91, 95% CI 6.88 to 105.34; participants = 116; studies = 1); at week 8 (RR 48.65, 95% CI 6.94 to 340.90; participants = 116; studies = 1); at week 12 (RR 10.70, 95% CI 3.46 to 33.04; participants = 116; studies = 1); at week 20 (RR 20.70, 95% CI 2.87 to 149.20; participants = 116; studies = 1); and at week 24 (RR 11.39, 95% CI 1.52 to 85.36; participants = 116; studies = 1) (Analysis 13.2). However, because of the wide confidence intervals the results are very uncertain.

Total adverse events

No difference between groups was found, but the confidence interval was wide (RR 1.38; 95% CI 0.79 to 2.42; participants = 116; studies = 1) (Analysis 13.3).

Duration of treatment effect

The duration of the treatment effect was 16.9 weeks (118.5 days) by physician assessment and 17.8 weeks (125 days) by participant assessment in onabotulinumtoxinA 40U group.

COMPARISON 14. OnabotulinumtoxinA 30 units versus placebo, one cycle of treatment, forehead lines and glabellar lines

Only one RCT (n = 118 participants) assessed this comparison (Solish 2016). For this reason, we were not able to undertake a meta-analysis, and only a visual representation of the results is shown in the forest plots.

Primary outcomes

Participant assessment of success by analysing scores and scales

The responder rate, by participant assessment was higher with onabotulinumtoxinA 30 U group than placebo at week 4 (RR 6.25, 95% CI 3.25 to 12.01; participants = 118; studies = 1); at week 8 (RR 14.00, 95% CI 4.59 to 42.67; participants = 118; studies = 1); at week 12 (RR 4.29, 95% CI 2.05 to 8.98; participants = 118; studies = 1); at week 20 (RR 5.33, 95% CI 1.64 to 17.34; participants = 118; studies = 1); and at week 24 (RR 10.00, 95% CI 1.32 to 75.66; participants = 118; studies = 1) (Analysis 14.1).

Although the responder rate, by participant assessment, was higher with onabotulinumtoxinA 30U group than placebo at week 16, the result is uncertain due to a large confidence interval (RR 22.00, 95% CI 3.06 to 157.95; participants = 118; studies = 1).

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

No difference between groups was found but the confidence interval was wide (RR 5.00, 95% CI 0.25 to 101.97; participants = 118; studies = 1) (Analysis 14.2)

Secondary outcomes

Physician assessment of success by analysing scores and scales

The responder rate, by physician assessment, was higher with onabotulinumtoxinA 30U group than placebo; however, because of the confidence interval the results is very uncertain; at week 4 (RR 24.00, 95% CI 6.11 to 94.23; participants = 118; studies = 1); at week 8 (RR 43.00, 95% CI 6.12 to 302.08; participants = 118; studies = 1); and at week 24 (RR 8.00, 95% CI 1.03 to 61.98; participants = 118; studies = 1) (Analysis 14.3).

The responder rate, by physician assessment, was higher with onabotulinumtoxinA 30 U group than placebo at week 12 (RR 8.67, 95% CI 2.77 to 27.08; participants = 118; studies = 1); and at week 16 (RR 3.33, 95% CI 1.44 to 7.71; participants = 118; studies = 1) (Analysis 14.3).

Total adverse events

No difference between groups was found, but the confidence interval was wide(RR 1.86, 95% CI 0.80 to 4.32; participants = 118; studies = 1) (Analysis 14.4).

Duration of treatment effect

The duration of treatment effect was 16 weeks (113.0 days) by physician assessment and 16.5 weeks (115.5 days) by participant assessment in onabotulinumtoxinA 30u group.

COMPARISON 15. OnabotulinumtoxinA 40 units versus onabotulinumtoxinA 30 units one cycle of treatment, forehead lines and glabellar lines

Only one RCT (n = 116 participants) assessed this comparison (Solish 2016). For this reason, we were not able to undertake a meta-analysis, and only a visual representation of the results is shown in the forest plots.

Primary outcomes

Participant assessment of success by analysing scores and scales

The responder rate, by participant assessment, were similar with onabotulinumtoxinA 40 U versus onabotulinumtoxinA 30U at week 4 (RR 1.06, 95% CI 0.92 to 1.21; participants = 116; studies = 1); at week 8 (RR 1.21, 95% CI 1.00 to 1.47; participants = 116; studies = 1); at week 12 (RR 1.10, 95% CI 0.79 to 1.55; participants = 116; studies = 1); at week 16 (RR 1.46, 95% CI 0.97 to 2.19; participants = 116; studies = 1); at week 20 (RR 1.29, 95% CI 0.75 to 2.24; participants

= 116; studies = 1); and at week 24 (RR 1.55, 95% CI 0.76 to 3.17; participants = 116; studies = 1) (Analysis 15.1).

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

No difference between groups was found, but the confidence interval was wide (RR 0.21, 95% CI 0.01 to 4.22; participants = 116; studies = 1) (Analysis 15.2).

Secondary outcomes

Physician assessment of success by analysing scores and scales

The responder rate, by physician assessment, were similar with onabotulinumtoxinA 40 U versus onabotulinumtoxinA 30 U at week 4 (RR 1.12, 95% CI 0.97 to 1.30; participants = 116; studies = 1); at week 8 (RR 1.13, 95% CI 0.93 to 1.38; participants = 116; studies = 1); at week 12 (RR 1.23, 95% CI 0.85 to 1.79; participants = 116; studies = 1); at week 16 (RR 1.35, 95% CI 0.85 to 2.12; participants = 116; studies = 1); at week 20 (RR 1.38, 95% CI 0.79 to 2.42; participants = 116; studies = 1); and at week 24 (RR 1.42, 95% CI 0.62 to 3.28; participants = 116; studies = 1) (Analysis 15.3).

Total adverse events

No difference between groups was found, but the confidence interval was wide (RR 1.04, 95% CI 0.63 to 1.71; participants = 116; studies = 1) (Analysis 15.4).

Duration of treatment effect

The duration of treatment effect was 118.5 days by investigator assessment and 125 days by participant assessment in OnbotulinumtoxinA 40 U group. The duration of treatment effect was 113.0 days by investigator assessment and 115.5 days by participant assessment in OnabotulinumtoxinA 30 U group.

COMPARISON 16. OnabotulinumtoxinA 40 units versus 20 units one cycle of treatment, glabellar lines

Two RCTs assessed (n = 80 participants) this comparison (Carruthers 2005a; Carruthers 2005b).

Primary outcomes

Participant assessment of success by analysing scores and scales

The meta-analysis showed benefit in favour of onabotulinumtoxinA 40 U group at 4 weeks (RR 1.63, 95% CI 1.13 to 2.35; participants = 80; studies = 2; I^2 = 0%), but not at week 8 (RR 1.52, 95% CI 0.77 to 2.97; participants = 80; studies = 2; I^2 = 44%), or week 16 (RR 2.51, 95% CI 0.88 to 7.16; participants = 80; studies = 2; I^2 = 0%) (Analysis 16.1) (Figure 5).

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

Only Carruthers 2005b assessed this outcome. The rate of eyebrow ptosis was 1/20 (5%) for both doses.

Secondary outcomes

Physician assessment of success by analysing scores and scales

The meta-analysis showed a potential benefit in favour of onabotulinumtoxinA 40 U group at 4 weeks (RR 1.48, 95% CI 0.93 to 2.36; participants = 80; studies = 2; I^2 = 71%); at week 8 (RR 1.35, 95% CI 0.82 to 2.23; participants = 80; studies = 2; I^2 = 21%); and at 16 weeks (RR 1.34, 95% CI 0.51 to 3.53; participants = 80; studies = 2; I^2 = 0%) (Analysis 16.2) (Figure 5), but the difference was small and the result were not very precise.

Total adverse events

No difference between groups was found, but the confidence interval was wide (RR 1.93, 95% CI 0.53 to 7.05; participants = 80; studies = 2; I^2 = 28%) (Analysis 16.3) (Figure 5).

Duration of treatment effect

Only one RCT assessed this outcome (Carruthers 2005b). The mean time of duration of treatment effect for onabotulinumtoxinA 20 U group was 17.6 weeks and 21.7 weeks for onabotulinumtoxinA 40 U group (no standard deviation (SD), P value, or 95% CIs were provided; hence, results were not provided in a forest plot).

COMPARISON 17. OnabotulinumtoxinA 60 units versus 20 units one cycle of treatment, glabellar lines

Only one RCT (n = 40 participants) assessed this comparison (Carruthers 2005a). For this reason, we were not able to undertake a meta-analysis, and only a visual representation of the results is shown in the forest plots.

Primary outcomes

Participant assessment of success by analysing scores and scales

This RCT did not assess this outcome.

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

This RCT did not report any major event.

Secondary outcomes

Physician assessment of success by analysing scores and scales

The responder rate, by participant assessment, were higher with onabotulinumtoxinA 60 U than onabotulinumtoxinA 20 U at week 4 (RR 1.90, 95% CI 1.21 to 2.98; participants = 40; studies = 1), and at week 8 (RR 3.80, 95% CI 1.77 to 8.17; participants = 40; studies = 1). However, there was no clear or substantial difference in responder rate with onabotulinumtoxinA 60 U and onabotulinumtoxinA 20 U at week 12 (RR 2.00, 95% CI 0.72 to 5.59; participants = 40; studies = 1) at week 16 (RR 1.00, 95% CI 0.29 to 3.45; participants = 40; studies = 1); and at week 20 (RR 2.00, 95% CI 0.41 to 9.71; participants = 40; studies = 1) (Analysis 11.1).

Total adverse events

No difference between groups was found, but the confidence interval was wide (RR 1.00, 95% CI 0.07 to 14.90; participants = 40; studies = 1) (Analysis 11.2).

Duration of treatment effect

The duration of treatment effect was 17.6 weeks in onabotulinumtoxinA 20U group, and 22.8 weeks in onabotulinumtoxinA 60 U group.

COMPARISON 18. OnabotulinumtoxinA 80 units versus 2 0units one cycle of treatment, glabellar lines

Only one RCT (n = 40 participants) assessed this comparison (Carruthers 2005a). For this reason, we were not able to undertake a meta-analysis, and only a visual representation of the results is shown in the forest plots.

Primary outcomes

Participant assessment of success by analysing scores and scales

The responder rate, by participant assessment, were higher with onabotulinumtoxinA 80 U than onabotulinumtoxinA 20U at week 4 (RR 3.75, 95% CI 1.51 to 9.34; participants = 40; studies = 1) (Analysis 18.1).

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

This RCT did not report any major event.

Secondary outcomes

Physician assessment of success by analysing scores and scales

The responder rate, by physician assessment, were higher with onabotulinumtoxinA 80 U than onabotulinumtoxinA 20 U at week 4 (RR 1.95, 95% CI 1.27 to 3.01; participants = 40; studies = 1); at week 8 (RR 3.20, 95% CI 1.45 to 7.05; participants = 40; studies = 1); and at week 12 (RR 3.50, 95% CI 1.39 to 8.80; participants = 40; studies = 1). However, the responder rate was similar with onabotulinumtoxinA 80 U and onabotulinumtoxinA 20 U at week 16 (RR 1.00, 95% CI 0.29 to 3.45; participants = 40; studies = 1), and at week 20 (RR 1.00, 95% CI 0.16 to 6.42; participants = 40; studies = 1). At week 24, the result was very uncertain (RR 5.00, 95% CI 0.26 to 98.00; participants = 40; studies = 1) (Analysis 18.2).

Total adverse events

No difference between groups was found, but the confidence interval was wide (RR 4.00, 95% CI 0.49 to 32.72; participants = 40; studies = 1) (Analysis 18.3).

Duration of treatment effect

The duration of treatment effect was 17.6 weeks in onabotulinumtoxinA 20U group and 24.2 weeks in onabotulinumtoxinA 80U.

COMPARISON 19. OnabotulinumtoxinA 80 units versus 60 units one cycle of treatment, glabellar lines

Only one RCT (n = 20 participants) assessed this comparison (Carruthers 2005a). For this reason, we were not able to undertake a meta-analysis, and only a visual representation of the results is shown in the forest plots.

Primary outcomes

Participant assessment of success by analysing scores and scales

This RCT did not assess this outcome.

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

This RCT did not report any major event.

Secondary outcomes

Physician assessment of success by analysing scores and scales

The responder rate, by physician assessment were similar with onabotulinumtoxinA 80U and onabotulinumtoxinA 60 U at week 4 (RR 1.05, 95% CI 0.92 to 1.20; participants = 40; studies = 1); at week 8 (RR 0.84, 95% CI 0.66 to 1.07; participants = 40; studies = 1); at week 12 (RR 1.75, 95% CI 0.95 to 3.22; participants = 40; studies = 1); and at week 16 (RR 1.00, 95% CI 0.29 to 3.45; participants = 40; studies = 1). At week 20 and 24, the effect sizes were less certain: (RR 0.50, 95% CI 0.10 to 2.43; participants = 40; studies = 1) (RR 5.00, 95% CI 0.26 to 98.00; participants = 40; studies = 1) (Analysis 19.1).

Total adverse events

There was no difference between groups, but the confidence interval was wide and included both an increase or a reduction at the risk of total adverse events (RR 2.00, 95% CI 0.41 to 9.71; participants = 40; studies = 1) (Analysis 19.2).

Duration of treatment effect

The duration of treatment effect was 22.8 weeks in onabotulinumtoxinA 60U group, and 24.2 weeks in onabotulinumtoxinA 80 U.

COMPARISON 20. OnabotulinumtoxinA 30 units versus 10 units one cycle of treatment, glabellar lines

One RCT (n = 40 participants) assessed this comparison (Carruthers 2005a).

For this reason (one study), we were not able to undertake a meta-analysis, and only a visual representation of the results is shown in the forest plots.

Primary outcomes

Participant assessment of success by analysing scores and scales

This RCT did not assess this outcome.

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

This RCT did not report any major event.

Secondary outcomes

Physician assessment of success by analysing scores and scales

The responder rate, by physician assessment, were similar with onabotulinumtoxinA 30 U and onabotulinumtoxinA 10 U at week 4 (RR 1.12, 95% CI 0.91 to 1.38; participants = 40; studies = 1), but favoured the 30 U group at week 16, although with some uncertainty (RR 5.00, 95% CI 0.64 to 39.06; participants = 40; studies = 1). The responder rate, by physician assessment, were higher with onabotulinumtoxinA 30 U than onabotulinumtoxinA 10 U at week 8 (RR 2.40, 95% CI 1.04 to 5.55; participants = 40; studies = 1).

Although the responder rate, by physician assessment, were higher with onabotulinumtoxinA 30 U than onabotulinumtoxinA 10 U at week 12, the result is uncertain because of the confidence interval (RR 9.00, 95% CI 1.25 to 64.59; participants = 40; studies = 1) (Analysis 20.1).

Total adverse events

The was no difference between groups (RR 0.25; 95% CI 0.03 to 2.05; participants = 40; studies = 1) (Analysis 20.2).

Duration of treatment effect

This RCT did not assess this outcome.

COMPARISON 21. OnabotulinumtoxinA 40 units versus 10 units one cycle of treatment, glabellar lines

Only one RCT (n = 40 participants) assessed this comparison (Carruthers 2005b). For this reason, we were not able to undertake a meta-analysis, and only a visual representation of the results is shown in the forest plots.

Primary outcomes

Participant assessment of success by analysing scores and scales

There was no clear or substantial difference in responder rate, by participant assessment, between onabotulinumtoxinA 40 U and onabotulinumtoxinA 10 U at week 4 (RR 1.86, 95% CI 0.94 to 3.66; participants = 40; studies = 1); at week 8 (RR 1.00, 95% CI 0.47 to 2.14; participants = 40; studies = 1); at week 12 (RR 1.75, 95% CI 0.61 to 5.05; participants = 40; studies = 1); and at week 16 (RR 1.00, 95% CI 0.16 to 6.42; participants = 40; studies = 1) (Analysis 21.1).

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

This RCT did not report any major event.

Secondary outcomes

Physician assessment of success by analysing scores and scales

The responder rate, by physician assessment, were similar with onabotulinumtoxinA 40 U and onabotulinumtoxinA 10 U at week 4 (RR 1.17, 95% CI 0.96 to 1.43; participants = 40; studies = 1) but the result was more uncertain at week 16 (RR 5.00, 95% CI 0.64 to 39.06; participants = 40; studies = 1). The responder rate, by physician assessment, were higher with onabotulinumtoxinA 40 U than onabotulinumtoxinA 10 U at week 8 (RR 2.80, 95% CI 1.24 to 6.30; participants = 40; studies = 1).

Although the responder rate, by physician assessment, were higher with onabotulinumtoxinA 30u than onabotulinumtoxinA 10u at week 12, the RR is uncertain because of the wide confidence interval (RR 8.00, 95% CI 1.10 to 58.19; participants = 40; studies = 1) (Analysis 21.2).

Total adverse events

No difference between groups was found, but the confidence interval was wide (RR 1.25, 95% CI 0.39 to 3.99; participants = 40; studies = 1) (Analysis 21.3).

Duration of treatment effect

This RCT did not assess this outcome.

COMPARISON 22. OnabotulinumtoxinA 40 units versus 30 units one cycle of treatment, glabellar lines

Only one RCT (n = 40 participants) assessed this comparison (Carruthers 2005b). For this reason, we were not able to undertake a meta-analysis, and only a visual representation of the results is shown in the forest plots.

Primary outcomes

Participant assessment of success by analysing scores and scales

The responder rate, by participant assessment, were similar with onabotulinumtoxinA 40 U and onabotulinumtoxinA 30 U at week 4 (RR 1.30, 95% CI 0.75 to 2.24; participants = 40; studies = 1); at week 8 (RR 1.00, 95% CI 0.47 to 2.14; participants = 40; studies = 1); at week 12 (RR 1.17, 95% CI 0.48 to 2.86; participants = 40; studies = 1); and at week 16 (RR 1.00, 95% CI 0.16 to 6.42; participants = 40; studies = 1) (Analysis 22.1).

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

This RCT did not report any major event.

Secondary outcomes

Physician assessment of success by analysing scores and scales

The responder rate, by physician assessment were similar with onabotulinumtoxinA 40 U and onabotulinumtoxinA 3 0U at week 4 (RR 1.05, 95% CI 0.92 to 1.20; participants = 40; studies = 1;, at week 8 (RR 1.17, 95% CI 0.74 to 1.85; participants = 40; studies = 1); at week 12 (RR 0.89, 95% CI 0.43 to 1.83; participants = 40; studies = 1), and at week 16 (RR 1.00, 95% CI 0.34 to 2.93; participants = 40; studies = 1) (Analysis 22.2).

Total adverse event

No difference between groups was found, but the confidence interval was wide (RR 5.00, 95% CI 0.64 to 39.06; participants = 40; studies = 1) (Analysis 22.3).

Duration of treatment effect

This RCT did not assess this outcome.

COMPARISON 23. OnabotulinumtoxinA 30 units versus 20 units one cycle of treatment, glabellar lines

Only one RCT (n = 40 participants) assessed this comparison (Carruthers 2005b). For this reason (one study), we were not able to undertake a meta-analysis, and only a visual representation of the results is shown in the forest plots.

Primary outcomes

Participant assessment of success by analysing scores and scales

The responder rate, by participant assessment were similar with onabotulinumtoxinA 30 U and onabotulinumtoxinA 2 0U at week 4 (RR 1.11, 95% CI 0.58 to 2.14; participants = 40; studies = 1); at week 8 (RR 1.00, 95% CI 0.47 to 2.14; participants = 40; studies = 1); at week 12 (RR 1.50, 95% CI 0.50 to 4.52; participants = 40; studies = 1); and at week 16 (RR 1.00, 95% CI 0.16 to 6.42; participants = 40; studies = 1) (Analysis 23.1).

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

This RCT did not report any major event.

Secondary outcomes

Physician assessment of success by analysing scores and scales

The responder rate, by physician assessment, were similar with onabotulinumtoxinA 30 U and onabotulinumtoxinA 20 U at week 4 (RR 1.19, 95% CI 0.93 to 1.51; participants = 40; studies = 1); at week 8 (RR 1.00, 95% CI 0.60 to 1.66; participants = 40; studies = 1); at week 12 (RR 1.29, 95% CI 0.60 to 2.77; participants = 40; studies = 1); and at week 16 (RR 1.67, 95% CI 0.46 to 6.06; participants = 40; studies = 1) (Analysis 23.2).

Total adverse events

No difference between groups was found, but the confidence interval was wide (RR 0.25, 95% CI 0.03 to 2.05; participants = 40; studies = 1) (Analysis 23.3).

Duration of treatment effect

This RCT did not assess this outcome.

COMPARISON 24. OnabotulinumtoxinA 60 units versus 40 units one cycle of treatment, glabellar lines

Only one RCT (n = 40 participants) assessed this comparison (Carruthers 2005a). For this reason, we were not able to undertake a meta-analysis, and only a visual representation of the results is shown in the forest plots.

Primary outcomes

Participant assessment of success by analysing scores and scales

This RCT did not assess this outcome.

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

This RCT did not report any major event.

Secondary outcomes

Physician assessment of success by analysing scores and scales

The responder rate, by physician assessment, were similar with onabotulinumtoxinA 60U and onabotulinumtoxinA 40 U at week 4 (RR 1.12, 95% CI 0.91 to 1.38; participants = 40; studies = 1); at week 12 (RR 1.00, 95% CI 0.47 to 2.14; participants = 40; studies = 1);at week 16 (RR 1.00, 95% CI 0.29 to 3.45; participants = 40; studies = 1); and week 20 (RR 1.00, 95% CI 0.29 to 3.45; participants = 40; studies = 1). The responder rate, by physician assessment, was higher with onabotulinumtoxinA 60 U than onabotulinumtoxinA 40 U at week 8 (RR 1.90, 95% CI 1.21 to 2.98; participants = 40; studies = 1) (Analysis 24.1).

Any adverse event

No difference between groups was found, but the confidence interval was wide (RR 0.40, 95% CI 0.09 to 1.83 participants = 40; studies = 1) (Analysis 24.2).

Duration of treatment effect

The duration of treatment effect was 21.7 weeks in onabotulinumtoxinA 40U and 22.8 weeks in onabotulinumtoxinA 60 U.

COMPARISON 25. OnabotulinumtoxinA 80 units versus 40 units one cycle of treatment, glabellar lines

Only one RCT (n = 40 participants) assessed this comparison (Carruthers 2005a). For this reason, we were not able to undertake a meta-analysis, and only a visual representation of the results is shown in the forest plots.

Primary outcomes

Participant assessment of success by analysing scores and scales

This RCT did not assess this outcome.

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

This RCT did not report any major event.

Secondary outcomes

Physician assessment of success by analysing scores and scales

The responder rate, by physician assessment were similar with onabotulinumtoxinA 80 U and onabotulinumtoxinA 40 U at week 4 (RR 1.17, 95% CI 0.96 to 1.43; participants = 40; studies = 1); at week 8 (RR 1.60, 95% CI 0.98 to 2.61; participants = 40; studies = 1), at week 12 (RR 1.75, 95% CI 0.95 to 3.22; participants = 40; studies = 1); and at week 16 (RR 1.00, 95% CI 0.29 to 3.45; participants = 40; studies = 1). At week 20 (RR 0.50, 95% CI 0.10 to 2.43; participants = 40; studies = 1) and at week 24 (RR 5.00, 95% CI 0.26 to 98.00; participants = 40; studies = 1) the effect size is less certain due to wide confidence intervals and/or the inclusion of 1 in the confidence interval (Analysis 25.1).

Total adverse event

No difference between groups was found, but the confidence interval was wide (RR 0.80, 95% CI 0.25 to 2.55; participants = 40; studies = 1) (Analysis 25.2).

Duration of treatment effect

The duration of treatment effect was 21.7 weeks in onabotulinumtoxinA 40 U, and 24.2 weeks in onabotulinumtoxinA 80U.

COMPARISON 26. OnabotulinumtoxinA 80 units versus 60 units one cycle of treatment, glabellar lines

One RCT (n = 40 participants) assessed this comparison (Carruthers 2005a).

For this reason (one study), we were not able to undertake a meta-analysis, and only a visual representation of the results is shown in the forest plots.

Primary outcomes

Participant assessment of success by analysing scores and scales

This RCT did not assess this outcome.

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

This RCT did not report any major event.

Physician assessment of success by analysing scores and scales

The responder rate, by physician assessment, were similar with onabotulinumtoxinA 80 U and onabotulinumtoxinA 60 U at week 4 (RR 1.05, 95% CI 0.92 to 1.20; participants = 40; studies = 1) and at week 16 (RR 1.00, 95% CI 0.29 to 3.45; participants = 40; studies = 1), but was higher in the onabotulinumtoxin 60 U group at week 8 (RR 0.53, 95% CI 0.34 to 0.83; participants = 40; studies = 1). At week 12 it was higher in the onabotulinumtoxinA 80 U group, but the result is less certain due to the confidence interval including 1 (RR 1.75, 95% CI 0.95 to 3.22; participants = 40; studies = 1). At week 20 (RR 0.50, 95% CI 0.10 to 2.43; participants = 40; studies = 1) and at week 24 (RR 5.00, 95% CI 0.26 to 98.00; participants = 40; studies = 1) the effect size is uncertain due to the wide confidence intervals (Analysis 26.1).

Total adverse events

No difference between groups was found, but the confidence interval was wide (RR 2.00, 95% CI 0.41 to 9.71; participants = 40; studies = 1) (Analysis 26.2).

Duration of treatment effect

The duration of treatment effect was 22.8 weeks in onabotulinumA 60 U, and 24.2 weeks in onabotulinumtoxinA 80 U.

COMPARISON 27. OnabotulinumtoxinA 12 units versus 7.5 units one cycle of treatment, perioral lines

Only one RCT (n = 60 participants) assessed this comparison (Cohen 2012). For this reason, we were not able to undertake a meta-analysis, and only a visual representation of the results is shown in the forest plots.

Primary outcomes

Participant assessment of success by analysing scores and scales

This RCT did not assess this outcome.

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

This RCT did not report any major event.

Secondary outcomes

Physician assessment of success by analysing scores and scales

The responder rate, by physician assessment, were similar with onabotulinumtoxinA 12 U and onabotulinumtoxinA 7.5 U at week 4 (RR 1.27, 95% CI 0.96 to 1.69; participants = 60; studies = 1), at week 8 (RR 0.90, 95% CI 0.68 to 1.19; participants = 60; studies = 1), at week 16 (RR 1.32, 95% CI 0.78 to 2.23; participants = 60; studies = 1), and at week 20 (RR 1.23, 95% CI 0.72 to 2.12; participants = 60; studies = 1). The responder rate, by physician assessment, were higher with onabotulinumtoxinA 12U than onabotulinumtoxinA 7.5 U at week 12 (RR 2.14, 95% CI 1.27 to 3.59; participants = 60; studies = 1) (Analysis 27.1).

Total adverse events

Total adverse events were higher with onabotulinumtoxinA 12 U than onabotulinumtoxinA 7.5 U (RR 1.55, 95% CI 1.00 to 2.42 participants = 60; studies = 1) (Analysis 27.2).

Duration of treatment effect

This RCT did not assess this outcome.

COMPARISON 28. OnabotulinumtoxinA 20 units versus placebo three cycles of treatment, glabellar lines

Only one RCT (n = 537 participants) assessed this comparison (Carruthers 2004). For this reason, we were not able to undertake a meta-analysis, and only a visual representation of the results is shown in the forest plots.

Primary outcomes

Participant assessment of success by analysing scores and scales

For the participants who received two or more onabotulinumtoxinA injections, the responder rate were significantly higher after the third cycle of treatment than after the first and second cycle of treatment (P < 0.005). No numeric data were provided.

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

The number of major adverse events in the first cycle was higher in the onabotulinumtoxinA 20 U group compared with placebo, but the result is very imprecise due to the wide confidence intervals (RR 8.84, 95% CI 0.53 to 147.78; participants = 537; studies = 1) (Analysis 28.1).

Secondary outcomes

Physician assessment of success by analysing scores and scales

For the participants who received two or more onabotulinumtoxinA injections the responder rate were higher in the third cycle of treatment than in the first and second cycles at day 30, 60, 90, and 120 days (P < 0.007). No numeric data were provided.

Total adverse events

No difference between groups was found (RR 0.76, 95% CI 0.58 to 0.99; participants = 537; studies = 1) (Analysis 28.2).

The number of adverse events across first, second and third cycle were 106/501 (21.2%) in the first cycle of BontA treatment, 17/362 (4.7%) in the second cycle of treatment, and 5/258 (2%) in the third cycle of treatment. But no numerical data related to placebo group were provided.

Duration of treatment effect

This RCT did not assess this outcome.

COMPARISON 29. OnabotulinumtoxinA 24 units versus placebo, crow's feet lines

Four RCTs (n = 1675 participants) assessed this comparison (Carruthers 2014; Harii 2017; Moers-Carpi 2015; Wu 2019).

Harii 2017 was a two-phase study, so we considered only the first phase (randomised, double-blind).

Primary outcomes

Participant assessment of success by analysing scores and scales

The meta-analysis showed a difference in favour of onabotulinumtoxinA 24;U group at week 4 (RR 12.71, 95% CI 8.67 to 18.63; participants = 1474; studies = 3; I^2 = 0%), week 8 (RR 10.25, 95% CI 7.02 to 14.98; participants = 1474; studies = 3; I^2 = 0%); and week 12 (RR 7.70, 95% CI 4.81 to 12.33; participants = 1474; studies = 3; I^2 = 28%). Only Wu 2019 showed results of onaboltulinuntoxinA versus placebo at week 20 (RR 10.33, 95% CI 3.35 to 31.89; participants = 417; studies = 1) (Analysis 29.1).

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

Two studies (Harii 2017; Wu 2019) assessed this outcome. There was no difference between onabotulinumtoxinA 24 U group and placebo group (Peto OR 1.28, 95% CI 0.12 to 13.10; participants = 665; studies = 2; I^2 = 0%) (Analysis 29.2).

Secondary outcomes

Physician assessment of success by analysing scores and scales

The meta-analysis showed a difference in favour of OnabotulinumtoxinA 24U group at week 4 (RR 12.38, 95% CI 8.93 to

17.16; participants = 1675; studies = 4; I^2 = 0%); at week 8 (RR 10.13, 95% CI 5.34 to 19.23; participants = 1258; studies = 3; I^2 = 63%); at week 12 (RR 9.29, 95% CI 5.95 to 14.50; participants = 1258; studies = 3; I^2 = 0%); and week 16 (RR 5.46, 95% CI 3.19 to 9.32; participants = 1057; studies = 2; I^2 = 0%) (Analysis 29.3).

Total adverse events

Moers-Carpi 2015 showed the number of adverse events per group of intervention not per cycle of treatment. Therefore, only three RCTs (Carruthers 2014; Harii 2017; Wu 2019) were included in the meta-analysis. Total adverse events were similar in both groups (RR 1.17, 95% CI 0.94 to 1.45; participants = 692; studies = 2; I^2 = 0%) (Analysis 29.4).

Duration of treatment effect

Three RCTs assessed this outcome (Carruthers 2014; Harii 2017; Wu 2019), but both studies described the results narratively. The duration of treatment effect for responders (none- mild at maximum smile) was 16.8 weeks (118 days) (physician assessment), and 16.5 (116 days) (participant assessment). The median duration of effect of treatment at day 30, responders with an improvement from baseline of at least 1 grade on the facial wrinkle scale (FWS) - maximum smile, was 17.8 weeks (125 days) (physician assessment) and 20.5 weeks (144 days) (participant assessment) (Carruthers 2014). Harii 2017 showed a duration of treatment effect around 95 days. And Wu 2019 assessed the duration of onabotulinumtoxinA 24 U effect around 150-157 by investigator assessment and 150-157 by participant assessment.

COMPARISON 30. OnabotulinumtoxinA 12 units versus placebo, crow's feet lines

Two RCTs (n = 657 participants) assessed this comparison (Harii 2017, Wu 2019). Harii 2017 was a two-phase study, so we considered only the first phase (randomised, double-blind).

Primary outcome

Participant assessment of success by analysing scores and scales

Neither RCT assessed this outcome.

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

Harii 2017 assessed this outcome and there was no difference between groups was found, but the confidence interval was wide (RR 1.36, 95% CI 0.12 to 14.76; participants = 240; studies = 1) (Analysis 30.1).

Secondary outcomes

Physician assessment of success by analysing scores and scales

Harii 2017 assessed this outcome and the results favoured onabotulinumtoxinA 12 U group at week 4 (RR 6.86, 95% CI 3.45 to 13.62; participants = 196; studies = 1); at week 8 (RR 4.29, 95% CI 2.10 to 8.76; participants = 196; studies = 1); and at week 12 (RR 5.55, 95% CI 1.68 to 18.34; participants = 196; studies = 1) (Analysis 30.2).

Total adverse events

Both studies reported the total adverse events and they were similar across groups (RR 1.33. 95% CI 0.87 to 2.02; participants= 657, studies=2, I^2 = 0%) (Analysis 30.3).

Duration of treatment effect

Harii 2017 described the results narratively. The duration of treatment effect for responders (none- mild at maximum smile) was 85 days in onabotulinumtoxinA 12 U group.

COMPARISON 31. OnabotulinumtoxinA 24 units versus onabotulinumtoxinA 12 units, crow's feet lines

One RCT (n = 294 participants) assessed this comparison (Harii 2017).

Harii 2017 was a two-phase study, we considered only the first phase (randomised, double-blind).

Primary outcomes

Participant assessment of success by analysing scores and scales

This RCT did not assess this outcome.

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

Harii 2017 assessed this outcome and there was no difference between onabotulinumtoxinA 24 U group and onabotulinumtoxinA 12 U group (RR 0.95, 95% CI 0.14 to 6.63; participants = 294; studies = 1) (Analysis 31.1).

Secondary outcomes

Physician assessment of success by analysing scores and scales

The analysis showed a difference in favour of onabotulinumtoxinA 24 U group than onabotulinumtoxinA 12 U group at week 12 (RR 1.90, 95% CI 1.14 to 3.18; participants = 203; studies = 1); but there was a similar response between groups at week 4 (RR 1.21, 95% CI 0.97 to 1.50; participants = 203; studies = 1); and at week 8 (RR 1.36, 95% CI 0.97 to 1.90; participants = 203; studies = 1) (Analysis 31.2).

Total adverse events

In Harii 2017, the total adverse events were similar in both groups (RR 0.86, 95% CI 0.59 to 1.25; participants = 294; studies = 1) (Analysis 31.3).

Duration of treatment effect

Harii 2017 described the results narratively. The duration of treatment effect for responders (none- mild at maximum smile) was 85 days in onabotulinumtoxinA 12 U group and 95 days in onabotulinumtoxinA 24 U group.

COMPARISON 32. OnabotulinumtoxinA 44 units versus placebo one cycle of treatment, glabellar lines and crow's feet lines

Three RCTs (n = 808 participants) assessed this comparison (Carruthers 2015; Moers-Carpi 2015; Rivers 2015).

Primary outcomes

Participant assessment of success by analysing scores and scales

The meta-analysis showed a benefit with onabotulinumtoxinA 44 U at week 4 (RR 16.33, 95% CI 9.27 to 28.76; participants = 808; studies = 2; I^2 = 0%) (Analysis 32.1).

Only one RCT assessed success in the following weeks (Moers-Carpi 2015). The responder rate by participant assessment was higher with onabotulinumtxinA 44 U than placebo at week 8 (RR 8.95, 95%

CI 5.03 to 15.90; participants = 611; studies = 1); at week 12 (RR 5.10, 95% CI 2.80 to 9.28; participants = 611; studies = 1); and at week 16 (RR 2.51, 95% CI 1.31 to 4.81; participants = 611; studies = 1) (Analysis 32.1).

Rivers 2015 did not report this outcome.

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

These RCTs did not report any major event (Moers-Carpi 2015; Rivers 2015). One RCT did not assess this outcome (Carruthers 2015).

Secondary outcomes

Physician assessment of success by analysing scores and scales

Two RCTs (Carruthers 2015; Moers-Carpi 2015) studied this outcome. The meta-analysis showed benefit with onabotulinumtoxinA 44 U at week 4 (RR 11.09, 95% CI 4.12 to 29.83; n = 808; studies = 2; I^2 = 80%); and week 8 (RR 9.94, 95% CI 1.78 to 55.44; n = 808; studies = 2; I^2 = 91%). However, a less certain difference was observed at week 12 due to the wide confidence interval (RR 5.96, 95% CI 0.60 to 58.98; n = 808) (Analysis 32.2).

One study (Rivers 2015), assessed this outcome separately. At week 4, the responders rate (score of none or mild on the glabellar lines (G)L facial wrinkle scale (FWS) compared with the placebo group-FWS) was 50/60 (83.3%) of participants in the onabotulinumtoxinA group, and 1/57(1.8%) in placebo group. The improvement of at least one point was 52/60 (86.7%) in the onabotulinumtoxinA group and 5/57 (8.8%) in placebo group. At week 12, 40/60 (66%) of participants in onabotulinumtoxinA group were responders.

Total adverse events

Carruthers 2015 and Moers-Carpi 2015 reported total adverse events; however, the authors showed the number of adverse events per group of intervention not per cycle of treatment.

For this reason (one study), we were not able to undertake a meta-analysis, and only a visual representation of the results is shown in the forest plot.

One study assessed this outcome (Rivers 2015), total adverse events were similar in both groups (RR 1.16, 95% CI 0.56 to 2.40; participants = 125; studies = 1) (Analysis 32.3).

Duration of treatment effect

These RCTs did not assess this outcome.

COMPARISON 33. OnabotulinumtoxinA 44 units versus placebo two cycles of treatment, glabellar lines and crow's feet lines

Two RCTs (n = 808 participants) assessed this comparison (Carruthers 2015; Moers-Carpi 2015).

Primary outcomes

Participant assessment of success by analysing scores and scales

The meta-analysis showed a benefit with onabotulinumtoxinA 44 U than placebo at week 4 (RR 10.12, 95% CI 6.36 to 16.09; participants = 808; studies = 2; I^2 = 0%) (Analysis 33.1).

One RCT (Moers-Carpi 2015) assessed responder rate at week 8 (RR 8.95, 95% CI 5.03 to 15.90; participants = 611; studies = 1), and at week 12 (RR 4.85, 95% CI 2.66 to 8.84; participants = 611; studies = 1), finding a benefit favouring onabotulinumtoxinA 44 U (Analysis 33.1).

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

Two RCTs assessed this outcome (Moers-Carpi 2015; Carruthers 2015). These RCTs did not report any major event.

Secondary outcomes

Physician assessment of success by analysing scores and scales

The meta-analysis showed a benefit with onabotulinumtoxinA 44 U at week 4 (RR 17.63, 95% CI 9.50 to 32.69; participants = 808; studies = 2; I^2 = 19%), and week 8 (RR 19.86, 95% CI 9.90 to 39.87; participants = 808; studies = 2; I^2 = 0%) (Analysis 33.2).

Total adverse events

The meta-analysis showed no difference between OnabotulinumtoxinA 44 U and placebo (RR 1.13, 95% CI 0.98 to 1.30; n = 808; studies = 2; I^2 = 0%) (Analysis 33.3).

Duration of treatment effect

These RCTs did not assess this outcome.

COMPARISON 34. OnabotulinumtoxinA 24 units versus 12 units five cycles of treatment, crow's feet lines

Only one RCT (n = 300 participants) assessed this comparison (Harii 2017). For this reason, we were not able to undertake a meta-analysis, and only a visual representation of the results is shown in the forest plots.

Primary outcomes

Participant assessment of success by analysing scores and scales

The authors considered only one point of improvement as a cut-off value. For this reason, we did not analyse this outcome.

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

This RCT did not show any major adverse events.

Secondary outcomes

Physician assessment of success by analysing scores and scales

This RCT did not assess this outcome.

Total adverse events

The total adverse events rate was higher with onabotulinumtoxinA 24 U than onabotulinumtoxinA 12 U (RR 1.42, 95% CI 0.41 to 4.93; participants = 294; studies = 1) (Analysis 34.1).

Duration of treatment effect

This RCT did not assess this outcome.

COMPARISON 35. AbobotulinumtoxinA 25 units versus placebo one cycle of treatment, glabellar lines

Only one RCT (n = 45 participants) assessed this comparison (Ascher 2004). For this reason, we were not able to undertake a meta-analysis, and only a visual representation of the results is shown in the forest plots.

Primary outcomes

Participant assessment of success by analysing scores and scales

This RCT did not assess this outcome.

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus

This RCT did not show any major adverse event.

Secondary outcomes

Physician assessment of success by analysing scores and scales

The responders' rates, by physician assessment, were higher with abobotulinumtoxinA 25 U than placebo at week 4 (RR 7.50, 95% CI 1.09 to 51.52; participants = 45; studies = 1); at week 8(RR 17.03, 95% CI 1.09 to 265.91; participants = 45; studies = 1), at week 12 (RR 10.84, 95% CI 0.68 to 173.34; participants = 45; studies = 1); and at week 24 (RR 4.65, 95% CI 0.27 to 81.01; participants = 45; studies = 1) (Analysis 35.1).

Total adverse events

This RCT showed more adverse events in abobotulinumtoxinA 25U than placebo (Peto OR 5.21, 95% CI 0.74 to 36.60; participants = 45; studies = 1) (Analysis 35.2).

Duration of treatment effect

This RCT did not assess this outcome.

COMPARISON 36. AbobotulinumtoxinA 30 units versus placebo one cycle of treatment, glabellar lines

One RCT (n = 99 participants) assessed this comparison (Rzany 2006). For this reason, we were not able to undertake a meta-analysis, and only a visual representation of the results is shown in the forest plot.

Primary outcomes

Participant assessment of success by analysing scores and scales

This RCT did not assess this outcome.

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

This RCT did not report any major event.

Secondary outcomes

Physician assessment of success by analysing scores and scales

The responder's rates, by physician assessment, were higher with abobotulinumtoxinA 30U than placebo at week 4: (RR 4.55, 95% CI 2.32 to 8.93; participants = 109; studies = 1) (Analysis 36.1).

Total adverse events

This RCT did not report any adverse events.

Duration of treatment effect

This RCT did not assess this outcome.

COMPARISON 37. AbobotulinumtoxinA 50 units versus placebo one cycle of treatment, glabellar lines

Nine RCTs (n = 1333 participants) assessed this comparison (Ascher 2004; Ascher 2005; Ascher 2018; Brandt 2009; Kane 2009; Monheit 2007; Monheit 2019; Rzany 2006; NCT02450526), and the results are included in Summary of findings 2.

Primary outcomes

Participant assessment of success by analysing scores and scales

The meta-analysis (Ascher 2018; Brandt 2009; Kane 2009; Monheit 2019; NCT02450526) showed a benefit with abobotulinumtoxinA when compared with placebo at week 4 (RR 21.22, 95% CI 7.43 to 60.56, participants = 915; studies = 5; I^2 = 54%, high-certainty evidence); at week 8 (RR 39.74, 95% CI 14.04 to 112.44; participants = 714, studies = 3; I^2 = 0%); and week 12 (RR 28.71, 95% CI 10.12 to 81.49; participants = 724; studies = 3; I^2 = 0%, low-certainty evidence) (Analysis 37.1).

Only Monheit 2019 assessed the following weeks: 16 week (RR 10.67, 95% CI 3.44 to 33.11; participants = 300; studies = 1); and at 20 weeks (RR 5.33, 95% CI 1.67 to 16.99; participants = 300; studies = 1) (Analysis 37.1).

Ascher 2004; Ascher 2005 did not assess this comparison, and Monheit 2007 and Rzany 2006 did not provide data.

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

A meta-analysis (Ascher 2004; Ascher 2005; Brandt 2009; Rzany 2006; Monheit 2007; Monheit 2019; NCT02450526) showed more adverse events in abobotulinum group when compared to placebo group (RR 3.36, 95% CI 0.88 to 12.87; participants = 1294; studies = 7; I^2 = 0%, moderate-certainty evidence) (Analysis 37.2).

Kane 2009 and Ascher 2018 did not report this outcome.

Secondary outcomes

Physician assessment of success by analysing scores and scales

Ascher 2004; Ascher 2005; Ascher 2018; Brandt 2009; Kane 2009; Monheit 2019; NCT02450526 assessed this comparison. The meta-analysis showed a benefit with abobotulinumtoxinA 50u than placebo at week 4 RR 15.78, 95% CI 8.75 to 28.45; participants = 1060; studies = 7; I^2 = 7%; moderate-certainty evidence); at week 8 (RR 30.84, 95% CI 11.58 to 82.12; participants = 802; studies = 5; I^2 = 2%); at week 12 (RR 17.79, 95% CI 6.70 to 45.28; participants = 900; studies = 6; I^2 = 29%); and at week 16 (RR 29.88, 95% CI 6.01 to 148.52; participants = 371; studies = 2; I^2 = 0%) (Analysis 37.3).

Only Monheit 2019 assessed this outcome at 20 weeks (RR 17.00, 95% CI 2.36 to 122.39; participants = 300; studies = 1) (Analysis 37.3).

At 24 weeks in Ascher 2004, the responder rates were 13.8% in abobotulinumtoxinA group and 0% in placebo group. We did not perform a meta-analysis because only one RCT showed data in this period (Ascher 2004).

Total adverse events

Ascher 2004; Ascher 2005; Ascher 2018; Brandt 2009; Monheit 2007; Rzany 2006; Monheit 2019; NCT02450526 showed data for this analysis. The total adverse events were higher with abobotulinumtoxinA than the placebo group (RR 1.25, 95% CI 1.05 to 1.49; participants = 1471; studies = 7; I^2 = 0%, low-certainty evidence) (Analysis 37.4).

Kane 2009 did not report this outcome.

Duration of treatment effect

Ascher 2005 showed abobotulinumtoxinA reporting a longer duration of effect compared to placebo (MD 17.30, 95% CI 15.82 to 18.78; participants = 100; studies = 1; moderate certainty evidence) (Analysis 37.5).

Brandt 2009 showed median duration of effect of BontA of 12 weeks (85 days).

Kane 2009 showed a duration of effect of 15.3 weeks (107 days) in BontA group.

Monheit 2019 showed median duration of effect of 117 days.

Ascher 2004; Ascher 2018; Monheit 2007; Rzany 2006 and NCT02450526 did not study this outcome.

COMPARISON 38. AbobotulinumtoxinA 50 units versus 25 units one cycle of treatment, glabellar lines

Only one RCT (n = 59 participants) assessed this comparison (Ascher 2004). For this reason, we were not able to undertake a meta-analysis, and only a visual representation of the results is shown in the forest plots.

Primary outcomes

Participant assessment of success by analysing scores and scales

This RCT did not assess this outcome.

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus

This RCT did not show any major adverse events.

Secondary outcomes

Physician assessment of success by analysing scores and scales

The responders' rates, by physician assessment, were higher with abobotulinumtoxinA 50 U than abobotulinumtoxinA 25 U at week 4 (RR 1.52, 95% CI 1.00 to 2.29; participants = 59; studies = 1); at week 12 (RR 1.45, 95% CI 0.77 to 2.72; participants = 59; studies = 1), but there was no difference between abobotulinumtoxinA 50 U and abobotulinumtoxinA 25 U at week 8 (RR 1.03, 95% CI 0.65 to 1.65; participants = 59; studies = 1); and at week 24 (RR 1.03, 95% CI 0.29 to 3.75; participants = 59; studies = 1) (Analysis 38.1).

Total adverse events

No difference between groups was found, but the confidence interval was wide (Peto OR 0.59, 95% CI 0.13 to 2.58; participants = 59; studies = 1) (Analysis 38.2).

Duration of treatment effect

This RCT did not assess this outcome.

COMPARISON 39. AbobotulinumtoxinA 60 units versus placebo one cycle of treatment, glabellar lines

Only one RCT (n = 423 participants) assessed this comparison (Kane 2009). For this reason, we were not able to undertake a meta-analysis, and only a visual representation of the results is shown in the forest plots.

Primary outcomes

Participant assessment of success by analysing scores and scales

The responders' rates, by participant assessment, were higher with abobotulinumtoxinA 60 U than placebo at week 4 (RR 11.48, 95% CI 6.50 to 20.29; participants = 423; studies = 1) (Analysis 39.1).

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

This RCT did not report any major event by units.

Secondary outcomes

Physician assessment of success by analysing scores and scales

The responder's rates, by physician assessment, were higher with abobotulinumtoxinA 60 U than placebo at week 4 (RR 15.98, 95% CI 8.14 to 31.36; participants = 423; studies = 1) (Analysis 39.2).

Total adverse events

This RCT did not report any adverse events by units.

Duration of treatment effect

This RCT did not assess this outcome by units.

COMPARISON 40. AbobotulinumtoxinA 70 units versus placebo one cycle of treatment, glabellar lines

Only one RCT(n = 291 participants) assessed this comparison (Kane 2009). For this reason, we were not able to undertake a meta-analysis, and only a visual representation of the results is shown in the forest plots.

Primary outcomes

Participant assessment of success by analysing scores and scales

The responders' rates, by participant assessment, were higher with abobotulinumtoxinA 70 U than placebo however the confidence interval was very wide showing we are very uncertain with this result; at week 4 (RR 151.39, 95% CI 9.54 to 2402.95; participants = 291; studies = 1) (Analysis 40.1).

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

This RCT did not report any major adverse events by units.

Secondary outcomes

Physician assessment of success by analysing scores and scales

The responders' rates, by physician assessment, were higher with abobotulinumtoxinA 70 U than placebo at week 4; however, the confidence interval is very wide showing uncertainty in the effect size (RR 71.36, 95% CI 10.15 to 501.56; participants = 289; studies = 1) (Analysis 40.2).

Total adverse events

This RCT did not report any adverse events by units.

Duration of treatment effect

This RCT did not assess this outcome by units.

COMPARISON 41. AbobotulinumtoxinA 75 units versus placebo one cycle of treatment, glabellar lines

Only one RCT (n = 45 participants) assessed this comparison (Ascher 2004). For this reason, we were not able to undertake a meta-analysis, and only a visual representation of the results is shown in the forest plots.

Primary outcomes

Participant assessment of success by analysing scores and scales

This RCT did not assess this outcome.

Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus

This RCT did not show any major adverse events.

Secondary outcomes

Physician assessment of success by analysing scores and scales

The responders' rates, by physician assessment, were higher with abobotulinumtoxinA 75 U than placebo at week 4 (RR 11.50, 95% CI 1.71 to 77.18; participants = 45; studies = 1); at week 8 (RR 9.50, 95% CI 1.40 to 64.35; participants = 45; studies = 1); at week 12 (RR 16.00, 95% CI 1.02 to 250.48; participants = 45; studies = 1); and at week 24 (RR 3.61, 95% CI 0.20 to 65.73; participants = 45; studies = 1) (Analysis 41.1).

Total adverse events

This RCT did not show any adverse events.

Duration of treatment effect

This RCT did not assess this outcome.

COMPARISON 42. AbobotulinumtoxinA 75 units versus 25 units one cycle of treatment, glabellar lines

Only one RCT (n = 60 participants) assessed this comparison (Ascher 2004). For this reason, we were not able to undertake a meta-analysis, and only a visual representation of the results is shown in the forest plots.

Primary outcomes

Participant assessment of success by analysing scores and scales

This RCT did not assess this outcome.

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus

This RCT did not show any major adverse event.

Secondary outcomes

Physician assessment of success by analysing scores and scales

The responders' rates, by physician assessment, were higher with AaobotulinumtoxinA 75 U than abobotulinumtoxinA 25 U at week 4 (RR 11.50, 95% CI 2.97 to 44.51; participants = 60; studies = 1).

Although the responders' rates, by physician assessment, were higher with abobotulinumtoxinA 75 U than abobotulinumtoxinA 25 U, the results were very uncertain because of the wide confidence intervals: at week 8 (RR 39.00, 95% CI 2.46 to 617.81; participants = 60; studies = 1); at week 12 (RR 31.00, 95% CI 1.94 to 495.61; participants = 60; studies = 1); and at week 24 (RR 7.00, 95% CI 0.38 to 129.93; participants = 60; studies = 1) (Analysis 42.1).

Total adverse events

This RCT did not assess this outcome.

Duration of treatment effect

This RCT did not assess this outcome.

COMPARISON 43. AbobotulinumtoxinA 75 units versus 50 units one cycle of treatment, glabellar lines

Only one RCT (n = 60 participants) assessed this comparison (Ascher 2004). For this reason, we were not able to undertake a meta-analysis, and only a visual representation of the results is shown in the forest plots.

Primary outcomes

Participant assessment of success by analysing scores and scales

This RCT did not show any major adverse event.

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus

This RCT did not assess this outcome.

Secondary outcomes

Physician assessment of success by analysing scores and scales

The responders' rates, by physician assessment, did not show any difference with abobotulinumtoxinA 75 U or abobotulinumtoxinA 50 U at week 4 (RR 1.01, 95% CI 0.76 to 1.34; participants = 59; studies = 1); at week 8 (RR 1.15, 95% CI 0.75 to 1.76; participants = 59; studies = 1); at week 12 (RR 1.04, 95% CI 0.62 to 1.74; participants = 59; studies = 1); at week 24 (RR 0.72, 95% CI 0.18 to 2.96; participants = 59; studies = 1) (Analysis 43.1).

Total adverse events

This RCT did not show any difference between AbobotulinumtoxinA 75U and AbobotulinumtoxinA 50U (Peto OR 0.12, 95% CI 0.01 to 1.22; participants = 59; studies = 1) (Analysis 43.2).

Duration of treatment effect

This RCT did not assess this outcome.

COMPARISON 44. AbobotulinumtoxinA 80 units versus placebo one cycle of treatment, glabellar lines

Only one RCT (n = 59 participants) assessed this comparison (Kane 2009). For this reason, we were not able to undertake a meta-analysis, and only a visual representation of the results is shown in the forest plots.

Primary outcomes

Participant assessment of success by analysing scores and scales

The responders' rates, by participant assessment, were higher with abobotulinumtoxinA 80 U than placebo at week 4; however, because of the confidence interval the results is very uncertain (RR 40.50, 95% CI 2.58 to 635.35; participants = 59; studies = 1) (Analysis 44.1).

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

This RCT did not report major adverse events by units.

Secondary outcomes

Physician assessment of success by analysing scores and scales

The responders' rates, by physician assessment, were higher with abobotulinumtoxinA 8 0U than placebo at week 4; however, because of the confidence interval the results is very uncertain (RR 32.56, 95% CI 2.06 to 514.19; participants = 59; studies = 1) (Analysis 44.2).

Total adverse events

This RCT did not report any adverse events by units.

Duration of treatment effect

This RCT did not assess this outcome by units.

COMPARISON 45. AbobotulinumtoxinA 15units versus placebo one cycle of treatment, crow's feet lines

Only one RCT(n = 109 participants) assessed this comparison (Ascher 2009). For this reason, we were not able to undertake a meta-analysis, and only a visual representation of the results is shown in the forest plots.

Primary outcomes

Participant assessment of success by analysing scores and scales

This RCT did not assess this outcome.

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

This RCT did not report any major event.

Secondary outcomes

Physician assessment of success by analysing scores and scales

The responders' rates, by physician assessment, were higher with abobotulinumtoxinA 15U versus placebo at week 4 (RR 4.52, 95% CI 1.85 to 11.01; participants = 109; studies = 1) (Analysis 45.1).

Total adverse events

One RCT assessed this outcome (Ascher 2009). Adverse events frequency was 5/42 (13%) in abobotulinumtoxinA 15 U group, but no information was given for the placebo group.

Duration of treatment effect

This RCT did not assess this outcome.

COMPARISON 46. AbobotulinumtoxinA 30 units versus placebo one cycle of treatment, crow's feet lines

Only one RCT (n = 108 participants) assessed this comparison (Ascher 2009). For this reason, we were not able to undertake a meta-analysis, and only a visual representation of the results is shown in the forest plots.

Primary outcomes

Participant assessment of success by analysing scores and scales

This RCT did not assess this outcome.

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

This RCT did not report any major event.

Secondary outcomes

Physician assessment of success by analysing scores and scales

The responders' rates, by physician assessment, were higher with abobotulinumtoxinA 30 U versus placebo week 4 (RR 6.40, 95% CI 2.70 to 15.18; participants = 108; studies = 1) (Analysis 46.1).

Total adverse events

The adverse events frequency was 4/37(11%) in abobotulinumtoxinA 30U group, but no information was given for placebo.

Duration of treatment effect

This RCT did not assess this outcome.

COMPARISON 47. AbobotulinumtoxinA 45units versus placebo one cycle of treatment, crow's feet lines

Only one RCT (n = 108 participants) assessed this comparison (Ascher 2009). For this reason, we were not able to undertake a meta-analysis, and only a visual representation of the results is shown in the forest plots.

Primary outcomes

Participant assessment of success by analysing scores and scales

This RCT did not assess this outcome.

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

One case of eyelid ptosis in AbobotulinumtoxinA 45U was reported.

Secondary outcomes

Physician assessment of success by analysing scores and scales

The responders' rates, by physician assessment, were higher with abobotulinumtoxinA 4 5U versus placebo week 4 (RR 6.20, 95% CI 2.61 to 14.74; participants = 108; studies = 1) (Analysis 47.1).

Total adverse events

The adverse events frequency was 5/40 (13%) in abobotulinumtoxinA 45 U, but no information was given for the placebo group.

Duration of treatment effect

This RCT did not assess this outcome.

COMPARISON 48. AbobotulinumtoxinA 50 units versus placebo three cycles of treatment, glabellar lines

Only one RCT (n = 142 participants) assessed this comparison (Rubin 2009). For this reason, we were not able to undertake a meta-analysis, and only a visual representation of the results is shown in the forest plots.

Primary outcomes

Participant assessment of success by analysing scores and scales

The responders'rates, by participant assessment, were higher with abobotulinumtoxinA 50 U versus placebo week 4 in the third cycle (RR 8.00, 95% CI 3.92 to 16.33; participants = 142; studies = 1) (Analysis 48.1).

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

This RCT did not report any major event.

Secondary outcomes

Physician assessment of success by analysing scores and scales

The responders' rates, by physician assessment, were higher with AbobotulinumtoxinA 50U versus placebo week 4 in the third cycle (RR 20.00, 95% CI 6.58 to 60.80; participants = 142; studies = 1) (Analysis 48.2).

Total adverse events

No difference between groups was found, but the confidence interval was wide at week 4 in the third cycle (RR 1.29; 95% CI 0.81 to 2.05; participants = 142; studies = 1) (Analysis 48.3).

Duration of treatment effect

This RCT did not assess this outcome.

COMPARISON 49. IncobotulinumtoxinA 20 units versus placebo one cycle of treatment, glabellar lines

Two RCTs (n = 547 participants) assessed this comparison (Carruthers 2013; Hanke 2013), and the results are included in Summary of findings 3.

Primary outcomes

Participant assessment of success by analysing scores and scales.

The meta analysis showed a benefit favours incobotulinumtoxinA at week 4 (RR 66.57, 95% CI 13.50 to 328.28; participants = 547; studies = 2; I^2 = 0%); week 8 (RR 7.35, 95% CI 4.79 to 11.29; participants = 547; studies = 2; I^2 = 0%); week 12 (RR 7.29, 95% CI 4.38 to 12.13; participants = 547; studies = 2; I^2 = 0%); and week 16 (RR 4.40, 95% CI 2.61 to 7.41; participants = 547; studies = 2; I^2 = 0%) (moderate-certainty evidence) (Analysis 49.1).

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

These RCTs did not report any major event.

Secondary outcomes

Physician assessment of success by analysing scores and scales

The meta-analysis showed a benefit favouring incobotulinumtoxinA at week 4 (RR 134.62, 95% CI 19.05 to 951.45; participants = 547; studies = 2; I^2 = 0%), but the confidence interval was very wide showing uncertainty (Analysis 49.2). No studies assessed this outcome at other time points (moderate-certainty evidence).

Total adverse events

The meta-analysis did not show any clear difference between intervention groups (RR 1.17, 95% CI 0.90 to 1.53; participants = 547; studies = 2; I^2 = 0%, low-certainty evidence) (Analysis 49.3).

Duration of treatment effect

These RCTs did not assess this outcome.

COMPARISON 50. IncobotulinumtoxinA 54 to 64 units versus placebo one cycles of treatment, glabellar lines, forehead lines, crow's feet lines

Only one RCT (n = 156 participants) assessed this comparison (Kerscher 2015). For this reason, we were not able to undertake a meta-analysis, and only a visual representation of the results is shown in the forest plots.

Primary outcomes

Participant assessment of success by analysing scores and scales

This RCT did not assess this outcome.

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

The major adverse event were higher with incotulinumtoxinA 54 U to 64 U (one unilateral blepharoptosis and the other one bilateral blepharoptosis) and placebo (dry eyes) ,but the RR is uncertain (RR 0.49; 95% CI 0.07 to 3.35; n = 156) (Analysis 50.1).

Secondary outcomes

Physician assessment of success by analysing scores and scales

The responder rate, by physician assessment, was higher with IncobotulinumtoxinA than placebo at week 4 in glabellar lines ((GL) RR 87.81, 95% CI 5.56 to 1386.93; participants = 156; studies = 1); in forehead lines (RR 35.94, 95% CI 5.14 to 251.27; participants = 156; studies = 1); and in crow's feet lines (RR 32.54, 95% CI 4.65 to 227.82; participants = 156; studies = 1) (Analysis 50.2). However, because of the wide confidence intervals the results are very uncertain.

Total adverse events

The frequency of total adverse events were similar with IncobotulinumtoxinA and placebo (RR 1.13, 95% CI 0.84 to 1.51; participants = 156; studies = 1) (Analysis 50.3).

Duration of treatment effect

This RCT did not assess this outcome.

COMPARISON 51. HBTX-A 10units versus placebo one cycle of treatment, glabellar lines

Only one RCT (n = 305 participants) assessed this comparison (Feng 2015). For this reason, we were not able to undertake a meta-analysis, and only a visual representation of the results is shown in the forest plots.

Primary outcomes

Participant assessment of success by analysing scores and scales.

The responder rate, by participant assessment, was higher with HBTX-A 10 U than placebo at week 4 (RR 14.78, 95% CI 6.74 to 32.41; participants = 305; studies = 1; at week 8 (RR 13.78, 95% CI 6.27 to

30.25; participants = 305; studies = 1); and at week 16 (RR 9.44, 95% CI 4.26 to 20.93; participants = 305; studies = 1) (Analysis 51.1).

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

This RCT did not report any major adverse event.

Secondary outcomes

Physician assessment of success by analysing scores and scales

This RCT did not study this outcome.

Total adverse events

One RCT assessed this outcome (Feng 2015), the total adverse events were higher with HBTX-A 10 U than placebo (RR 4.95, 95% CI 2.33 to 10.54; participants = 305; studies = 1) (Analysis 51.2).

Duration of treatment effect

This RCT did not assess this outcome.

COMPARISON 52. HBTX-A 20 units versus placebo one cycle of treatment, glabellar lines

One RCT (n = 305 participants) assessed this comparison (Feng 2015).

For this reason (one study), we were not able to undertake a meta-analysis, and only a visual representation of the results is shown in the forest plots.

Primary outcome

Participant assessment of success by analysing scores and scales.

The responder's rate, by participant assessment, was higher with HBTX-A 20 U than placebo at week 4 (RR 18.33, 95% CI 8.39 to 40.06; participants = 305; studies = 1); at week 8 (RR 17.00, 95% CI 7.77 to 37.19; participants = 305; studies = 1); and at week 16 (RR 15.22, 95% CI 6.95 to 33.36; participants = 305; studies = 1) (Analysis 52.1).

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

This RCT did not report any major adverse event.

Secondary outcomes

Physician assessment of success by analysing scores and scales

This RCT did not assess this outcome.

Total adverse events

The total adverse events were higher with HBTX-A 20 U than placebo (RR 4.67; 95% CI 2.19 to 9.96; participants = 305; studies = 1) (Analysis 52.2).

Duration of treatment effect

This RCT did not assess this outcome.

COMPARISON 53. HBTX-A 50 units versus placebo one cycle of treatment, glabellar lines

One RCT (n = 190 participants) assessed this comparison (NCT02493946).

For this reason (one study), we were not able to undertake a meta-analysis, and only a visual representation of the results is shown in the forest plots.

Primary outcomes

Participant assessment of success by analysing scores and scales

The responder rate, by participant assessment, was higher with HBTX-A 50 U than placebo at week 4 (RR 42.68, 95% CI 6.08 to 299.41; participants = 187; studies = 1); at week 8 (RR 43.28, 95% CI 6.18 to 303.19; participants = 183; studies = 1); and at week 12 (RR 21.67, 95% CI 3.06 to 153.72; participants = 185; studies = 1) (Analysis 53.1).

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

This RCT did not report any major adverse event.

Secondary outcomes

Physician assessment of success by analysing scores and scales

The responder rate, by physician assessment, was higher with HBTX-A 50 U than placebo at week 4 (RR 49.69; 95% CI 7.10 to 347.71, participants = 185, studies = 1); at week 8 (RR 53.52; 95% CI 7.65 to 376.34, participants = 167, studies =1); at week 12 (RR 33.17; 95% CI 4.72 to 233.16, participants = 182, studies = 1 (Analysis 53.2).

Total adverse events

The total adverse event was similar with HBTX-A 50 U and placebo (Peto OR 0.22, 95% CI 0.02 to 2.50; participants = 190, studies = 10) (Analysis 53.3).

Duration of treatment effect

This RCT reported only HBTX-A 50 U mean duration, which was 113 days.

COMPARISON 54. HBTX-A 20 units versus 10 units one cycle of treatment, glabellar lines

One RCT (n = 366 participants) assessed this comparison (Feng 2015).

For this reason (one study), we were not able to undertake a meta-analysis, and only a visual representation of the results is shown in the forest plots.

Primary outcomes

Participant assessment of success by analysing scores and scales.

The responder rate, by participant assessment, was higher with HBTX-A 20 U than HBTX-A 10 U at week 4 (RR 1.24, 95% CI 1.12 to 1.37; participants = 366; studies = 1); at week 8 (RR 1.23, 95% CI 1.10 to 1.39; participants = 366; studies = 1); and at week 16 (RR 1.61, 95% CI 1.35 to 1.92; participants = 366; studies = 1) (Analysis 54.1).

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

This RCT did not report any major adverse event.

Secondary outcomes

Physician assessment of success by analysing scores and scales

This RCT did not assess this outcome.

Total adverse events

The total adverse event was similar with HBTX-A 20 U and HBTX-A 10 U (RR 0.94, 95% CI 0.68 to 1.31; participants = 366; studies = 1) (Analysis 54.2).

Duration of treatment effect

This RCT did not assess this outcome.

COMPARISON 55. AbobotulinumtoxinA 50 units versus OnabotulinumtoxinA 20 units one cycle of treatment, glabellar lines

Two RCTs (n = 479 participants) assessed this comparison (Lowe 2006; NCT02450526). The results are included in Summary of findings 4.

Primary outcomes

Participant assessment of success by analysing scores and scales

Only NCT02450526 assessed this outcome, n = 388.

The responder rate, by participant's assessment, was similar with abobotulinumtoxinA 50 U and onabotulinumtoxinA 20 U at week 4 (RR 1.00, 95% CI 0.92 to 1.08; participants 388, study = 1, high-certainty evidence); at week 8 (RR 0.96, 95% CI 0.88 to 1.05; participants 388, study =1 ; at week 12 (RR 0.94, 95% CI 0.81 to 1.09; participants 388, study = 1).

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

Only one study assessed this outcome (NCT02450526).

The frequency of major adverse events was higher in abobotulinumtoxinA 50 U when compared to onabotulinumtoxinA 20 U (Peto OR 2.65, 95% CI 0.77 to 9.09; participants = 433, study = 1, moderate-certainty evidence) (Analysis 55.2).

Secondary outcomes

Physician assessment of success by analysing scores and scales

The responder rate, by physician's assessment, was similar with abobotulinumtoxinA 50 U and onabotulinumtoxinA 20 U at week 4 (RR 1.01, 95% CI 0.95 to 1.06; participants = 388, studies = 1, high-certainty evidence); at week 8 (RR 0.95, 95% CI 0.89 to 1.02; participants = 449, studies = 2, I^2 = 0% moderate-certainty evidence); at week 12 (RR 0.92, 95% CI 0.60 to 1.40; participants = 488; studies = 2, I^2 = 55%); and at week 16 (RR 0.44, 95% CI 0.13 to 1.55; participants = 59; studies = 1) the RR favours the onabotulinumtoxinA 20 U, but the results are uncertain due to the confidence intervals including 1 (Analysis 55.3).

Total adverse events

The frequency of total adverse events was similar with abobotulinumtoxinA 50 U and onabotulinumtoxinA 20 U (RR 1.02, 95% CI 0.67 to 1.54; participants = 492; studies = 1, moderate-certainty evidence) (Analysis 55.4).

Duration of treatment effect

This RCT did not assess this outcome.

COMPARISON 56. IncobotulinumtoxinA 30 units versus OnabotulinumtoxinA 20 units one cycle of treatment, glabellar lines

Only one RCT (n = 224 participants) assessed this comparison (Moers-Carpi 2012). For this reason, we were not able to undertake a meta-analysis, and only a visual representation of the results is shown in the forest plots.

Primary outcomes

Participant assessment of success by analysing scores and scales

The responder rate, by participant assessment, was similar with IncobotulinumtoxinA 30 U and OnabotulinumtoxinA 20 U at week 4 (RR 0.90, 95% CI 0.78 to 1.04; participants = 224; studies = 1); at week 12 (RR 0.84, 95% CI 0.65 to 1.09; participants = 224; studies = 1); at week 14 (RR 0.93, 95% CI 0.68 to 1.29; participants = 224; studies = 1); and at week 16 (RR 0.94, 95% CI 0.63 to 1.40; participants = 224; studies = 1) (Analysis 56.1).

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

This RCT did not report any major event.

Secondary outcomes

Physician assessment of success by analysing scores and scales

The responder rate, by physician assessment, was similar with IncobotulinumtoxinA 30 U and onabotulinumtoxinA 20 U at week 4 (RR 0.98, 95% CI 0.93 to 1.04; participants = 224; studies = 1); at week 12 (RR 0.90, 95% CI 0.77 to 1.04; participants = 224; studies = 1); at week 14 (RR 0.96, 95% CI 0.79 to 1.16; participants = 224; studies = 1); and at week 16 (RR 0.90, 95% CI 0.70 to 1.16; participants = 224; studies = 1) (Analysis 56.2).

Total adverse events

One RCT assessed this outcome (Moers-Carpi 2012); the total adverse events were higher with incobotulinumtoxinA 30 U compared with onabotulinumtoxinA 20 U, but the result is uncertain due to the low number of events (two events versus one event) (RR 1.96, 95% CI 0.20 to 19.03, participants = 224; studies = 1 (Analysis 56.3).

Duration of treatment effect

This RCT did not assess this outcome.

COMPARISON 57. IncobotulinumtoxinA 24 units versus onabotulinumtoxinA 24 units one cycle of treatment, glabellar lines

Only one RCT (n = 381 participants) assessed this comparison (Satler 2010). For this reason, we were not able to undertake a meta-analysis, and only a visual representation of the results is shown in the forest plots. Results are also shown in Summary of findings 5.

Primary outcomes

Participant assessment of success by analysing scores and scales

This RCT did not assess this outcome.

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

Ptosis was reported in one participant in onabotulinumtoxinA group (OR 0.02 95% CI 0.00 to 1.77; participants = 381; studies = 1, very low-certainty evidence) (Analysis 57.1).

Secondary outcomes

Physician assessment of success by analysing scores and scales

The responder rate, by physician assessment, was similar with incobotulinumtoxinA 24 U and onabotulinumtoxinA 24 U at week 4 (RR 1.01, 95% CI 0.96 to 1.05; participants = 381; studies = 1); and at week 12 (RR 1.02, 95% CI 0.91 to 1.15; participants = 381; studies = 1) (moderate-certainty evidence) (Analysis 57.2).

Total adverse events

There was only one adverse event in the onabotulinumtoxinA 24 U group and zero events in the IncobotulinumtoxinA 24 U group (OR 0.02, 95% CI 0.00 to 1.77; participants = 381; studies = 1) (very low-certainty evidence) (Analysis 57.3).

Duration of treatment effect

This RCT did not assess this outcome.

COMPARISON 58. IncobotulinumtoxinA 20 units versus OnabotulinumtoxinA 20 units one cycle of treatment, glabellar lines

Two RCTs (n = 250 participants) assessed this comparison (Kane 2015; Rappl 2013).

Primary outcomes

Participant assessment of success by analysing scores and scales

These RCTs did not assess this outcome.

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

Rappl 2013 did not report any major adverse event. One RCT studied this outcome (Kane 2015). No difference between groups (Peto OR 0.14, 95% CI 0.01 to 2.26; participants = 250; studies = 1) (Analysis 58.1).

Secondary outcomes

Physician assessment of success by analysing scores and scales

Rappl 2013 did not assess this outcome.

Only one RCT studied this outcome (Kane 2015). The responder rate, by independent observer assessment, was similar with incobotulinumtoxinA 20 U and onabotulinumtoxinA 20 U at week 4 (RR 0.98, 95% CI 0.92 to 1.04; participants = 250; studies = 1); at week 8 (RR 0.97, 95% CI 0.88 to 1.06; participants = 250; studies = 1); at week 12 (RR 0.97, 95% CI 0.85 to 1.12; participants = 250; studies = 1); and at week 16 (RR 0.98, 95% CI 0.80 to 1.20; participants = 250; studies = 1) (Analysis 58.2).

The responder rate, by physician assessment, was similar with incobotulinumtoxinA 20 U and onabotulinumtoxinA 20 U at week 4 (RR 0.97, 95% CI 0.93 to 1.01; participants = 250; studies = 1); at week 8 (RR 0.96, 95% CI 0.90 to 1.03; participants = 250; studies = 1); at week 12 (RR 1.00, 95% CI 0.88 to 1.13; participants = 250; studies = 1); and at week 16 (RR 0.93, 95% CI 0.77 to 1.11; participants = 250; studies = 1) (Analysis 58.3).

Total adverse events

Rappl 2013 did not report total adverse events. One RCT studied this outcome (Kane 2015). The frequency of total adverse events was similar with incobotulinumtoxinA 20 U and onabotulinumtoxinA 20 U (RR 1.05, 95% CI 0.41 to 2.71; participants = 250; studies = 1) (Analysis 58.4).

Duration of treatment effect

One RCT assessed this outcome by gender (Rappl 2013). The duration of treatment effect was 20.8 weeks (146.12 days) for female and 17.3 weeks (121.14 days) for male in incobotulinumtoxinA group.The duration of treatment effect was 20 weeks (140.65 days for female and 16.6 weeks (116.61 days) for male) in onabotulinumtoxinA group. After 180 days, four in the incobotulinumtoxinA group, and two in onabotulinumtoxinA, still showed an effect. All of these participants were botulinum toxin treatment naïve, and all had mild glabellar frown lines at baseline.

Kane 2015 did not study this outcome.

COMPARISON 59. NewBontA [Medytox®] 20 units versus OnabotulinumtoxinA 20 units one cycle of treatment, glabellar lines

Only one RCT (n = 291 participants) assessed this comparison (Lee 2013). For this reason, we were not able to undertake a meta-analysis, and only a visual representation of the results is shown in the forest plots.

Primary outcomes

Participant assessment of success by analysing scores and scales

This RCT did not assess this outcome.

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

This RCT did not report any major event.

Secondary outcomes

Physician assessment of success by analysing scores and scales

The responder rate, by physician assessment, was similar with NewBontA 20U and onabotulinumtoxinA 20 U (RR 0.99, 95% CI 0.94 to 1.05; participants = 291; studies = 1) (Analysis 59.1).

Total adverse events

This RCT did not report any adverse event.

Duration of treatment effect

This RCT did not assess this outcome.

COMPARISON 60. NewBontA [Neuronox®] 20 units versus OnabotulinumtoxinA 20 units one cycle of treatment, glabellar lines

Only one RCT (n = 314 participants) assessed this comparison (Won 2013). For this reason, we were not able to undertake a meta-analysis, and only a visual representation of the results is shown in the forest plots.

Primary outcomes

Participant assessment of success by analysing scores and scales

One RCT assessed this outcome (Won 2013) where the responder rate, by participant assessment, was similar with NewBontA 20 U and onabotulinumtoxinA 20 U at week 4 (RR 0.94, 95% CI 0.87 to 1.02; participants = 314; studies = 1); at week 8 (RR 0.96, 95% CI 0.88 to 1.04; participants = 314; studies = 1); at week 12 (RR 1.02, 95% CI 0.90 to 1.14; participants = 314; studies = 1); and at week 16 (RR 1.07, 95% CI 0.92 to 1.24; participants = 314; studies = 1) (Analysis 60.1).

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

The frequency of eyelid was similar with NewBontA 20U and onabotulinumtoxinA 20 U (RR 0.86, 95% CI 0.30 to 2.51; participants = 313; studies = 1) (Analysis 60.2).

Secondary outcomes

Physician assessment of success by analysing scores and scales

The responder rate, by physician assessment, was similar with NewBontA 20 U and onabotulinumtoxinA 20 U at week 4 (RR 0.99, 95% CI 0.94 to 1.05; participants = 314; studies = 1); at week 8 (RR 1.01, 95% CI 0.92 to 1.10; participants = 314; studies = 1); at week 12 (RR 1.06, 95% CI 0.93 to 1.22; participants = 314; studies = 1); and at week 16 (RR 0.95, 95% CI 0.75 to 1.20; participants = 314; studies = 1) (Analysis 60.3).

Total adverse events

The frequency of adverse events was similar with NewBontA 20 U and onabotulinumtoxinA 20 U (RR 1.21, 95% CI 0.82 to 1.78; participants = 313; studies = 1) (Analysis 60.4).

Duration of treatment effect

This RCT did not assess this outcome.

COMPARISON 61. NewBontA [Neuronox®] 24 units versus OnabotulinumtoxinA 24 units one cycle of treatment, crow's feet lines

Only one RCT (n = 220 participants) assessed this comparison (Cheon 2019). For this reason, we were not able to undertake a meta-analysis, and only a visual representation of the results is shown in the forest plots.

Primary outcomes

Participant assessment of success by analysing scores and scales

One RCT assessed this outcome (Cheon 2019). The responder rate, by participant assessment, was similar with NewBontA 24 U and onabotulinumtoxinA 24 U at week 4 (RR 1.01, 95% CI 0.89 to 1.15; participants = 220; studies = 1); at week 8 (RR 0.93, 95% CI 0.83 to 1.03; participants = 220; studies = 1); at week 12 (RR 1.02, 95% CI 0.90 to 1.16; participants = 220; studies = 1); at week 16 (RR 0.84, 95% CI 0.70 to 1.01; participants = 220; studies = 1) (Analysis 61.1).

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

No difference between groups (Peto OR 7.39, 95% CI 0.15 to 372.38); participants = 220; studies = 1) (Analysis 61.2).

Secondary outcomes

Physician assessment of success by analysing scores and scales

The responder rate, by physician assessment, was similar with NewBontA 24U 24 U and onabotulinumtoxinA 24 U at week 4 (RR 1.00, 95% CI 0.89 to 1.13; participants = 220; studies = 1); at week 8 (RR 0.98, 95% CI 0.86 to 1.11; participants = 220; studies = 1); at week 12 (RR 1.08, 95% CI 0.88 to 1.32; participants = 220; studies = 1); at week 16 (RR 1.14, 95% CI 0.83 to 1.56; participants = 220; studies = 1) (Analysis 61.3).

Total adverse events

The frequency of adverse events was similar with NewBontA 24Us and onabotulinumtoxinA 24 U (RR 0.97, 95% CI 0.65 to 1.45; participants = 220; studies = 1) (Analysis 61.4).

Duration of treatment effect

The median duration of the treatment effect was similar in both groups (112 days after week 4).

COMPARISON 62. Liquid BontA (MT10109L) 20 units versus OnabotulinumtoxinA 20 units one cycle of treatment, glabellar lines

Only one RCT (n = 159 participants) assessed this comparison (Kim 2015). For this reason, we were not able to undertake a meta-analysis, and only a visual representation of the results is shown in the forest plots.

Primary outcomes

Participant assessment of success by analysing scores and scales

The responder rate, by participant assessment, was similar with NewBontA 20 U and onabotulinumtoxinA 20 U at week 4 (RR 0.97, 95% CI 0.88 to 1.07; participants = 159; studies = 1); at week 10 (RR 0.90, 95% CI 0.79 to 1.02; participants = 159; studies = 1); and at week 16 (RR 1.04, 95% CI 0.84 to 1.28; participants = 159; studies = 1) (Analysis 62.1).

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

This RCT did not report any major event.

Secondary outcomes

Physician assessment of success by analysing scores and scales

The responder rate, by physician assessment, was similar with NewBontA 20 U and onabotulinumtoxinA 20 U at week 4 (RR 0.99, 95% CI 0.88 to 1.12; participants = 159; studies = 1). The responder rate was higher with NewBontA 20 U than onabotulinumtoxinA 20 U at week 16 (RR 1.54, 95% CI 1.12 to 2.12; participants = 156; studies = 1) (Analysis 62.2).

Total adverse events

The total adverse events were similar with NewBontA 20U and onabotulinumtoxinA 20 U (RR 1.27, 95% CI 0.69 to 2.32; participants = 156; studies = 1) (Analysis 62.3).

Duration of treatment effect

This RCT did not assess this outcome.

COMPARISON 63. NewBontA [Prosigne®] 20 units versus OnabotulinumtoxinA 20 units one cycle of treatment, glabellar lines

Only one RCT (n = 157 participants) assessed this comparison (Costa 2016). For this reason, we were not able to undertake a meta-analysis, and only a visual representation of the results is shown in the forest plots.

Primary outcomes

Participant assessment of success by analysing scores and scales

This RCT did not assess this outcome.

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

This RCT did not report any major event.

Secondary outcomes

Physician assessment of success by analysing scores and scales

The responder rate by physician assessment was higher in the onabotulinumtoxinA 20 U group at week 12 (RR 0.49, 95% CI 0.21 to 1.19; participants = 157; studies = 1) (Analysis 63.1).

Total adverse events

This RCT did not assess this outcome.

Duration of treatment effect

The duration of treatment effect was 12 weeks (84.5 ± 38.8 days) for NewBontA 20U (Prosigne®), and 12.8 weeks (89.9 ± 41.1 days) for OnabotulinumtoxinA 20 U assessed by three independent observers. The duration of treatment effect by physician assessment was 10.9 weeks: 76.8 ± 46.6 days for NewBontA 20 U (Prosigne®), and 12.5 weeks (88.1 ± 43.6 days) for onabotulinumtoxinA 20 U.

COMPARISON 64. CBFC26 20 units versus OnabotulinumtoxinA 20 units one cycle of treatment, glabellar lines

Only one RCT (n = 249 participants) assessed this comparison (Kim 2014). Hence, we were unable to undertake a meta-analysis and only present results in a forest plot for visual representation.

Primary outcomes

Participant assessment of success by analysing scores and scales

The responder rate by participant assessment was higher with NewBontA 20 U than onabotulinumtoxinA 20 U at week 4 (RR 1.22, 95% CI 1.10 to 1.35; participants = 249; studies = 1); and at week 8 (RR 1.14, 95% CI 1.01 to 1.29; participants = 249; studies = 1). The responder rate was similar with NewBontA 20 U and onabotulinumtoxinA 20 U at week 12 (RR 1.08, 95% CI 0.91 to 1.28; participants = 249; studies = 1); and at week 16 (RR 1.15, 95% CI 0.92 to 1.44; participants = 249; studies = 1) (Analysis 64.1).

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

The major adverse events were higher with NewBontA 20 U than onabotulinumtoxinA 20 U, but the result is uncertain due to the wide confidence interval (RR 2.04, 95% CI 0.52 to 8.01; participants = 271; studies = 1) (Analysis 64.2).

Secondary outcomes

Physician assessment of success by analysing scores and scales

The responder rate by physician assessment was similar with NewBontA 20 U and onabotulinumtoxinA 20 U at week 4 (RR 1.09, 95% CI 0.99 to 1.21; participants = 249; studies = 1); at week 8 (RR 1.09, 95% CI 0.92 to 1.29; participants = 249; studies = 1); at week 12 (RR 1.21, 95% CI 0.96 to 1.51; participants = 249; studies = 1); and at week 16 (RR 1.26, 95% CI 0.94 to 1.68; participants = 249; studies = 1) (Analysis 64.3).

Total adverse events

The total adverse events were similar with NewBontA 20 U andoonabotulinumtoxinA 20 U (RR 0.86, 95% CI 0.60 to 1.24; participants = 249; studies = 1) (Analysis 64.4).

Duration of treatment effect

This RCT did not assess this outcome.

COMPARISON 65. Liquid AbobotulinumtoxinA 20 units versus placebo one cycle of treatment, glabellar lines

Only one RCT (n = 71 participants) assessed this comparison (Ascher 2018). For this reason, we were not able to undertake a meta-analysis, and only a visual representation of the results is shown in the forest plots.

Primary outcomes

Participant assessment of success by analysing scores and scales

The responder rate by participant assessment was similar with liquid abobotulinumtoxinA 20 U and placebo at week 4 (RR 66.81, 95% CI 4.25 to 1050.36, participants = 71; studies = 1); at week 8 (RR 42.14, 95% CI 2.65 to 670.89), participants = 71; studies = 1); at week 12 (RR 44.19, 95% CI 2.78 to 702.51 participants = 71; studies = 1); at week 16 (RR 27.75, 95% CI 1.71 to 449.60, participants = 71; studies = 1) (Analysis 65.1).

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

There was no difference between groups (Peto OR 7.60, 95% CI 0.15 to 383.33, participants = 71; studies = 1) (Analysis 65.2).

Secondary outcomes

Physician assessment of success by analysing scores and scales

The responder rate by physician assessment was similar with liquid abobotulinumtoxinA 20 U and placebo at week 4 (RR 66.81, 95% CI 4.25 to 1050.36; participants = 71; studies = 1); at week 8 (RR 58.58, 95% CI 3.71 to 923.86, participants = 71, studies = 1); at week 12 (RR 40.08, 95% CI 2.51 to 639.27, participants = 71, studies = 1); at week 16 (RR 19.53, 95% CI 1.18 to 323.24, participants = 71, studies = 1) (Analysis 65.3).

Total adverse events

There was no difference between groups (RR 1.23, 95% CI 0.41 to 3.68, participants = 71; studies = 1) (Analysis 65.4).

Duration of treatment effect

This RCT did not assess this outcome.

COMPARISON 66. Liquid AbobotulinumtoxinA 50 units versus placebo one cycle of treatment, glabellar lines

Two RCTs (n = 255 participants) assessed this comparison (Ascher 2018; Ascher 2020).

Primary outcomes

Participant assessment of success by analysing scores and scales

The responder rate by participant's assessment was higher than placebo at week 4 (RR 46.95, 95% CI 9.57 to 230.36, participants = 255, studies = 2); at week 8 (RR 41.87, 95% CI 8.52 to 205.88, participants = 253, studies = 2), at week 12 (RR 24.61, 95% CI 4.97 to 121.91, participants= 253, studies =2); at week 16 (RR 6.54, 95% CI 1.70 to 25.15, participants= 254, studies =2), at week 20 (RR 3.35, 95% CI 1.71 to 6.58, participants= 183, studies =1) (see Analysis 66.1).

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

No difference between groups (Peto OR 4.39, 95% CI 0.07 to 289.31, participants = 256, studies = 2, Analysis 66.2).

Secondary outcomes

Physician assessment of success by analysing scores and scales

The responder rate by physician assessment was higher than placebo at week 4 (RR 16.73, 95% CI 2.84 to 98.58, participants = 255, studies = 2); at week 8 (RR 48.98, 95% CI 9.99 to 240.21, participants = 255, studies = 2); at week 12 (RR 35.93, 95% CI 7.30 to 176.90, participants = 255, studies = 2); at week 16 (RR 21.25, 95% CI 2.95 to 152.88, participants = 255, studies = 2); and at week 20 (RR 25.86, 95% CI 1.60 to 417.34, participants = 184, studies = 1) (see Analysis 66.3).

Total adverse events

There was no difference between the groups (RR 1.11, 95% CI 0.72 to1.71, participants = 255, studies = 2).

Duration of treatment effect

This RCT did not assess this outcome.

COMPARISON 67. Liquid AbobotulinumtoxinA 75 units versus placebo one cycle of treatment, glabellar lines

One RCT (n = 71 participants) assessed this comparison (Ascher 2018).

Primary outcomes

Participant assessment of success by analysing scores and scales

The responder rate by participant's assessment was higher with liquid abobotulinumtoxinA 7 5U than placebo at week 4 (RR 60.64, 95% CI 3.85 to 955.48, participants = 71, studies = 1); at week 8 (RR 62.69, 95% CI 3.98 to 987.11, participants = 71, studies = 1); at week 12 (RR 44.19, 95% CI 2.78 to 702.51, participants = 71, studies = 1); at week 16 (RR 35.97, 95% CI 2.25 to 576.04, participants = 71, studies = 1) (Analysis 67.1).

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

There was no difference between groups (Peto 7.83, 95% CI 0.48 to 127.75, participants = 71, studies = 1) (Analysis 67.2).

Secondary outcomes

Physician assessment of success by analysing scores and scales

The responder rate by physician assessment was higher with liquid abobotulinumtoxinA 20 U and placebo at week (RR 64.75, 95% CI 4.12 to 1018.73; participants = 71; studies = 1); at week 8 (RR 60.64, 95% CI 3.85 to 955.48, participants = 71, studies = 1); at week 12 (RR 56.53 95% CI 3.58 to 892.24, participants = 71, studies = 1); at week 16 (RR 42.14 95% CI2.65 to 670.89, participants = 71, studies = 1) (Analysis 67.3).

Total adverse events

There was no difference between groups (RR 0.82 95% CI 0.24 to 2.81, participants = 71, studies = 1) (Analysis 67.4).

Duration of treatment effect

This RCT did not assess this outcome.

COMPARISON 68. Liquid AbobotulinumtoxinA 20 units versus Liquid AbobotulinumtoxinA 50 units one cycle of treatment, glabellar lines

One RCT (n = 70 participants) assessed this comparison (Ascher 2018).

Primary outcomes

Participant assessment of success by analysing scores and scales

The responder rate by participant's assessment was similar with Liquid Abobotulinumtoxin 20 U and Liquid abobotulinumtoxin 50 U at week 4 (RR 1.07, 95% CI 0.90 to 1.26, participants = 70,studies = 1); at week 8 (RR 1.05, 95% CI 0.69 to 1.60, participant s = 70, studies = 1); at week 12 (RR 1.31, 95% CI 0.84 to 2.06, participants = 70, studies = 1); at week 16 (RR 1.08, 95% CI 0.58 to 2.03, participants = 70, studies = 1) (Analysis 68.1).

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

There was no difference between groups (Peto OR 7.39, 95% CI 0.15 to 372.38, participants = 70, studies = 1) (Analysis 68.2).

Secondary outcomes

Physician assessment of success by analysing scores and scales

The responder rate by participant's assessment was similar with Liquid abobotulinumtoxin 20 U and Liquid abobotulinumtoxin 50 U at week 4 (RR 1.07, 95% CI 0.90 to 1.26; participants = 70; studies = 1); at week 12 (RR 1.19, 95% CI 0.74 to 1.90, participants = 70, studies = 1); at week 16 (RR 0.75, 95% CI 0.36 to 1.55, participants = 70, studies = 1).

The responder rate by participant's assessment was higher with Liquid abobotulinumtoxin 50 U and Liquid abobotulinumtoxin 20 U at week 8 (R 1.47, 95% CI 1.04 to 2.08, participants =70, studies = 1) (Analysis 68.3).

Total adverse events

There was no difference between groups (RR 1.50, 95% CI 0.46 to 4.86, participants = 70, studies = 1) (Analysis 68.4).

Duration of treatment effect

This RCT did not assess this outcome.

COMPARISON 69. Liquid AbobotulinumtoxinA 20 units versus Liquid AbobotulinumtoxinA 75 units one cycle of treatment, glabellar lines

One RCT (n = 70 participants) assessed this comparison (Ascher 2018).

Primary outcomes

Participant assessment of success by analysing scores and scales

The responder rate by participant's assessment was similar with Liquid abobotulinumtoxin 20 U and Liquid abobotulinumtoxin 75 U at week 4 (RR 1.10, 95% CI 0.92 to 1.32, participants = 70, studies = 1); at week 8 (RR 0.67, 95% CI 0.49 to 0.92, participants = 70, studies = 1); at week 12 (RR 0.95, 95% CI 0.66 to 1.38, participants = 70, studies = 1); at week 16 (RR 0.76, 95% CI 0.44 to 1.32, participants = 70, studies = 1) (Analysis 69.1).

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

There was no difference between groups (Peto OR 0.50, 95% CI 0.05 to 5.00, participants = 70, studies = 1) (Analysis 69.2).

Secondary outcomes

Physician assessment of success by analysing scores and scales

The responder rate by physician assessment was similar with Liquid abobotulinumtoxin 20 U and Liquid abobotulinumtoxin 75 U at week 4 (RR 1.03, 95% CI 0.88 to 1.21; participants = 70; studies = 1); at week 8 (RR 0.97, 95% CI 0.77 to 1.21, participants = 70, studies = 1); at week 12 (RR 0.70, 95% CI 0.49 to 1.00, participants = 70, studies = 1); at week 16 (RR 0.55, 95% CI 0.29 to 1.06, participants = 70, studies = 1) (Analysis 69.3).

Total adverse events

There was no difference between groups (RR 2.50, 95% CI 0.87 to 7.22, participants = 70, studies = 1) (Analysis 69.4).

Duration of treatment effect

This RCT did not assess this outcome.

COMPARISON 70. Liquid AbobotulinumtoxinA 50 units versus Liquid AbobotulinumtoxinA 75 units one cycle of treatment, glabellar lines

One RCT (n = 70 participants) assessed this comparison (Ascher 2018).

Primary outcomes

Participant assessment of success by analysing scores and scales

The responder rate by participant's assessment was similar with liquid abobotulinumtoxin 50 U and Liquid abobotulinumtoxin 75 U at week 4 (RR 1.00, 95% CI 0.83 to 1.21 participants = 70, studies = 1; at week 8 (RR 0.63, 0.88 95% CI 0.45 to 0.88, participants = 70, studies = 1); at week 12 (RR 0.76, 95% CI 0.49 to 1.20, participants = 70, studies = 1); at week 16 (RR 0.71, 95% CI 0.40 to 1.25, participants = 70, studies = 1) (Analysis 70.1).

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

There was no difference between groups (Peto 0.13, 95% CI 0.01 to 2.14, participants = 70, studies = 1) (Analysis 70.2).

Secondary outcomes

Physician assessment of success by analysing scores and scales

The responder rate by physician assessment was similar with Liquid abobotulinumtoxin 50 U and Liquid abobotulinumtoxin 75 U at week 4 (RR 0.97, 95% CI 0.81 to 1.16; participants = 70; studies = 1), at week 8 (RR 0.66, 95% CI 0.47 to 0.92, participants = 70, studies = 1); at week 12 (RR 0.59, 95% CI 0.40 to 0.89, participants = 70, studies = 1); at week 16 (RR 0.60, 95% CI 0.35 to 1.03, participants = 70, studies = 1) (Analysis 70.3).

Total adverse events

There was no difference between groups (RR 1.00, 95% CI 0.27 to 3.69, participants = 70, studies = 1) (Analysis 70.4).

Duration of treatment effect

This RCT did not assess this outcome.

COMPARISON 71. Liquid AbobotulinumtoxinA 20 units versus AbobotulinumtoxinA 50 units one cycle of treatment, glabellar lines

One RCT (n = 70 participants) assessed this comparison (Ascher 2018).

Primary outcomes

Participant assessment of success by analysing scores and scales

The responder rate by participant's assessment was similar with Liquid abobotulinumtoxin 20 U and Liquid abobotulinumtoxin 50 U at week 4 (RR 1.10, 95% CI 0.92 to 1.32, participants = 70, studies = 1); at week 8 (RR 0.91, 95% CI 0.62 to 1.33 participants = 70, studies = 1); at week 12 (RR 1.50, 95% CI 0.92 to 2.44, participants = 70, studies = 1); at week 16 (RR 0.93, 95% CI 0.51 to 1.68, participants = 70, studies = 1) (Analysis 71.1).

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

There was no difference between groups (Peto OR 7.39, 95% CI 0.15 to 372.38, participants = 70, studies = 1) (Analysis 71.2).

Secondary outcomes

Physician assessment of success by analysing scores and scales

The responder rate by physician assessment was similar with Liquid abobotulinumtoxin 20 U and Liquid abobotulinumtoxin 50 U at week (RR 1.1, 95% CI 0.96 to 1.46; participants = 70; studies = 1); at week 8 (RR 1.00, 95% CI 0.79 to 1.26, participants = 70, studies = 1); at week 12 (RR 1.00, 95% CI 0.65 to 1.54, participants = 70, studies = 1); at week 16 (RR 0.69, 95% CI 0.34 to 1.41, participants = 70, studies = 1) (Analysis 71.3).

Total adverse events

There was no difference between groups (RR 3.00, 95% CI 0.65 to 13.86), participants = 70, studies = 1) (Analysis 71.4).

Duration of treatment effect

This RCT did not assess this outcome.

COMPARISON 72. Liquid AbobotulinumtoxinA 75 units versus AbobotulinumtoxinA 50 units one cycle of treatment, glabellar lines

One RCT (n = 70 participants) assessed this comparison (Ascher 2018).

Primary outcomes

Participant assessment of success by analysing scores and scales

The responder rate by participant's assessment was similar with Liquid abobotulinumtoxin 75 U and abobotulinumtoxin 50 U at week 4 (RR 1.00, 95% CI 0.81 to 1.24, participants = 70, studies = 1); at week 12 (RR 1.57, 95% CI 0.97 to 2.54, participants = 70, studies = 1); at week 16 (RR 1.70, 95% CI 0.91 to 3.18, participants = 70, studies = 1).

The responder rate by participant's assessment was higher with Liquid abobotulinumtoxin 75 U than abobotulinumtoxin 50 U at week 8 (RR 1.36, 95% CI 1.02 to 1.82, participants = 70, studies = 1) (Analysis 72.1).

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

There was no difference between groups (Peto OR 7.61, 95% CI 0.47 to 124.15, participants = 70, studies = 1) (Analysis 72.2).

Secondary outcomes

Physician assessment of success by analysing scores and scales

The responder rate by physician assessment was similar with Liquid abobotulinumtoxin 75 U and abobotulinumtoxin 50 U at week 4 (RR 1.15, 95% CI 0.93 to 1.43 participants = 70; studies = 1); at week 8 (RR 1.04, 95% CI 0.83 to 1.30, participants = 70, studies = 1); at week 12 (RR 1.42, 95% CI 1.00 to 2.02), participants = 70, studies = 1); at week 16 (RR 1.54, 95% CI 0.92 to 2.58, participants = 70, studies = 1) (Analysis 72.3).

Total adverse events

There was no difference between groups (RR 2.00, 95% CI 0.39 to 10.22, participants = 70, studies = 1) (Analysis 72.4).

Duration of treatment effect

This RCT did not assess this outcome.

Comparison 73. DaxibotulinumtoxinA 60 units versus placebo one cycle of treatment, glabellar lines

One RCT (n = 76 participants) assessed this comparison (Carruthers 2017).

Primary outcomes

Participant assessment of success by analysing scores and scales

The responder rate by participant assessment was higher with daxibotulinumtoxinA 60 U and placebo at week 4 (RR 52.29, 95% CI 3.31 to 825.07; participants = 76; studies = 1); at week 16 (RR 18.00, 95% CI 1.09 to 296.56; participants = 76; studies = 1); and at week 24 (RR 6.00, 95% CI 0.32 to 112.32; participants = 76; studies = 1) (Analysis 73.1).

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

No difference between groups (Peto 7.71, 95% CI 0.43 to 138.48; participants = 76; studies = 1) (Analysis 73.2).

Secondary outcomes

Physician assessment of success by analysing scores and scales

The responder rate by physician assessment was higher with daxibotulinumtoxinA 60 U and placebo at week 4 (RR 69.43, 95% CI 4.42 to 1089.43; participants = 76; studies = 1); at week 8 (RR 55.71, 95% CI 3.54 to 877.94; participants = 76; studies = 1); at week 12 (RR 31.71, 95% CI 1.98 to 507.90; participants = 76; studies = 1); at week 16 (RR 14.57, 95% CI 0.87 to 243.78; participants = 76; studies = 1); at week 20 (RR 14.57, 95% CI 0.87 to 243.78; participants = 76; studies = 1); and at week 24 (RR 4.29, 95% CI 0.21 to 86.39; participants = 76; studies = 1). Although, the effect sizes are uncertain due to the very large confidence interval, which includes 1 at week 16, week 20 and week 24 (Analysis 73.3).

Total adverse events

The total adverse events was higher in daxibotulinumtoxinA 60 U group than in placebo group (RR 2.89, 95% CI 1.23 to 6.75; participants = 107; studies = 1) (Analysis 73.4)

Duration of treatment effect

The duration of effect of daxibotulinumtoxinA 60 U was 22.5 weeks and 0.4 weeks for placebo group (MD 22.10, 95% CI 20.24 to 23.96; participants = 76; studies = 1) (Analysis 73.5).

COMPARISON 74. DaxibotulinumtoxinA 40 units versus placebo one cycle of treatment, glabellar lines

Two RCTs (n = 683 participants) assessed this comparison (Bertucci 2020; Carruthers 2017). Results are also shown in Summary of findings 6.

Primary outcomes

Participant assessment of success by analysing scores and scales

The responder rate by participant assessment was higher with daxibotulinumtoxinA 40 U and placebo at week 4 (RR 21.10, 95% CI 11.31 to 39.34; participants = 683; studies = 2; I^2 = 0%, moderate-certainty evidence); at week 8 (RR 15.75, 95% CI 8.85 to 28.03; participants = 609; studies = 1); at week 12 (RR 24.51, 95% CI 11.12 to 54.05; participants = 609; studies = 1); at week 16 (RR 12.74, 95% CI 6.80 to 23.89; participants = 683; studies = 2; I^2 = 0%); at week 20 (RR 13.60, 95% CI 6.13 to 30.18; participants = 609; studies = 1); and at week 24 (RR 3.09, 95% CI 0.13 to 73.21; participants = 683; studies = 2; I^2 = 0%). (Analysis 74.1)

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

These RCTs did not show any major event.

Secondary outcomes

Physician assessment of success by analysing scores and scales

The responder rate by physician assessment was higher with daxibotulinumtoxinA 40 U and placebo at week 4 (RR 23.40, 95% CI 12.56 to 43.61; participants = 683; studies = 2; I^2 = 0%, moderate-certainty evidence); at week 8 (RR 18.09, 95% CI 10.30 to 31.78;

participants = 683; studies = 2; I^2 = 0%); at week 12 (RR 29.46, 95% CI 13.79 to 62.94; participants = 683; studies = 2; I^2 = 0%); at week 16 (RR 16.84, 95% CI 9.01 to 31.47; participants = 683; studies = 2; I^2 = 0%); at week 20 (RR 18.06, 95% CI 8.42 to 38.76; participants = 683; studies = 2; I^2 = 0%); and at week 24 (RR 15.33, 95% CI 6.06 to 38.78; participants = 683; studies = 2; I^2 = 0%) (Analysis 74.2).

Total adverse events

The risk of any adverse events was higher in daxibotulinumtoxinA group (RR 2.23, 95% CI 1.46 to 3.40; participants = 716; studies = 2; I^2 = 0%, moderate-certainty evidence) (Analysis 74.3).

Duration of treatment effect

One RCT assesses this outcome (Carruthers 2017).The duration of treatment effect was 23.2 weeks for daxibotulinumtoxinA 60 U and 0.4 weeks for placebo group (MD 22.80, 95% CI 20.74 to 24.86; participants = 74; studies = 1) (Analysis 74.4).

Bertucci 2020 pre-specified 24 weeks as duration of treatment effect.

COMPARISON 75. DaxibotulinumtoxinA 20 units versus placebo one cycle of treatment, glabellar lines

One RCT (n = 69 participants) assessed this comparison (Carruthers 2017).

Primary outcomes

Participant assessment of success by analysing scores and scales

The responder rate by participant assessment was higher with daxibotulinumtoxinA 20 U and placebo at week 4 (RR 50.40, 95% CI 3.19 to 797.13; participants = 69; studies = 1); at week 16 (RR 11.31, 95% CI 0.65 to 197.06; participants = 69; studies = 1); at week 24 (RR 3.09, 95% CI 0.13 to 73.21; participants = 69; studies = 1), although the effect size is uncertain due to the very large confidence interval (Analysis 75.1).

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

This RCT did not report any major event.

Secondary outcomes

Physician assessment of success by analysing scores and scales

The responder rate by physician assessment was higher with daxibotulinumtoxinA 20 U and placebo at week 4 (RR 60.69, 95% CI 3.86 to 955.19; participants = 69; studies = 1); at week 8 (RR 33.94, 95% CI 2.12 to 544.26; participants = 69; studies = 1); at week 12 (RR 21.60, 95% CI 1.32 to 354.72; participants = 69; studies = 1); at week 16 (RR 15.43, 95% CI 0.92 to 260.05; participants = 69; studies = 1); at week 20 (RR 9.26, 95% CI 0.52 to 165.65; participants = 83; studies = 1); at week 24 (RR 7.20, 95% CI 0.39 to 134.36; participants = 69; studies = 1), although the effect size is uncertain due to the very large confidence interval (Analysis 75.2).

Total adverse events

The total adverse events was higher in daxibotulinumtoxinA 40 U group than in placebo group (RR 2.17, 95% CI 0.89 to 5.28; participants = 108; studies = 1) (Analysis 75.3).

Duration of treatment effect

The duration of treatment effect of daxibotulinumtoxinA 60 U was 20.8 weeks and 0.4 weeks for placebo group (MD 20.40, 95% CI 18.56 to 22.24; participants = 69; studies = 1) (Analysis 75.4).

COMPARISON 76. DaxibotulinumtoxinA 60 units versus OnabotulimtoxinA 20units one cycle of treatment, glabellar lines

One RCT (n = 83 participants) assessed this comparison (Carruthers 2017).

Primary outcomes

Participant assessment of success by analysing scores and scales

The responder rate by participant assessment was higher with daxibotulinumtoxinA 60 U and onabotulinumtoxinA 20 U at week 4(RR 1.14, 95% CI 0.85 to 1.52; participants = 83; ; studies = 1); and at week 16 (RR 2.05, 95% CI 0.77 to 5.48; participants = 83; studies = 1); but similar at week 24 (RR 2.05, 95% CI 0.77 to 5.48; participants = 83; studies = 1) (Analysis 76.1).

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

No difference between groups (Peto OR 3.62, 95% CI 0.60 to 21.86; participants = 83; studies = 1) (Analysis 76.2).

Secondary outcomes

Physician assessment of success by analysing scores and scales

The responder rate by physician assessment was higher with daxibotulinumtoxinA 60 U and onabotulinumtoxinA 20 U at week 8 (RR 1.49, 95% CI 1.07 to 2.07; participants = 83; studies = 1); but a similar response at week 4 (RR 1.24, 95% CI 1.05 to 1.46); participants = 83; studies = 1); at week 12 (RR 0.97, 95% CI 0.60 to 1.57; participants = 83; studies = 1); at week 16 (RR 2.05, 95% CI 0.67 to 6.28; participants = 83; studies = 1); at week 20 (RR 1.02, 95% CI 0.15 to 6.9; participants = 83; studies = 1); and at week 24 (RR 1.02, 95% CI 0.15 to 6.93; participants = 83; studies = 1) (Analysis 76.3).

Total adverse events

There was no difference between total adverse events between groups (RR 1.15, 95% CI 0.65 to 2.07; participants = 107; studies = 1) (Analysis 76.4).

Duration of treatment effect

There was no difference of duration of treatment between groups (MD 3.70, 95% CI 0.91 to 6.49; participants = 83; studies = 1) (Analysis 76.5).

COMPARISON 77. DaxibotulinumtoxinA 40 units versus OnabotulimtoxinA 20 units one cycle of treatment, glabellar lines

One RCT (n = 250 participants) assessed this comparison (Carruthers 2017).

Primary outcomes

Participant assessment of success by analysing scores and scales

The responder rate by participant assessment was similar between daxibotulinumtoxinA 40 U and onabotulinumtoxinA 20 U at week 4(RR 0.88, 95% CI 0.61 to 1.25; participants = 81; studies = 1); at week

16 (RR 2.15, 95% CI 0.81 to 5.74; participants = 81; studies = 1); and at week 24 (RR 1.08, 95% CI 0.16 to 7.28; participants = 81; studies = 1) (Analysis 77.1).

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

There was no difference between groups (Peto OR 0.15, 95% CI 0.00 to 7.35; participants = 81; studies = 1) (Analysis 77.2).

Secondary outcomes

Physician assessment of success by analysing scores and scales

The responder rate by physician assessment was higher with daxibotulinumtoxinA 40 U and onabotulinumtoxinA 20 U at week 4(RR 1.21, 95% CI 1.01 to 1.44; participants = 81; studies = 1); at week 8 (RR 1.42, 95% CI 1.01 to 2.00; participants = 81; studies = 1); at week 16 (RR 3.77, 95% CI 1.36 to 10.48; participants = 81; studies = 1); but similar at week 12 (RR 0.96, 95% CI 0.59 to 1.57; participants = 81; studies = 1); at week 20 (RR 2.87, 95% CI 0.82 to 10.06; participants = 81; studies = 1); and at week 24 (RR 2.15, 95% CI 0.42 to 11.11; participants = 81; studies = 1) (Analysis 77.3).

Total adverse events

There was no difference between total adverse events between groups (RR 0.95, 95% CI 0.51 to 1.77; participants = 107; studies = 1) (Analysis 77.4).

Duration of treatment effect

The duration of treatment effect was similar in the daxibotulinumtoxinA 40 U group and OnabotulinumtoxinA 20 U group (MD 4.40, 95% CI 1.47 to 7.33; participants = 81; studies = 1) (Analysis 77.5).

COMPARISON 78. DaxibotulinumtoxinA 20 units versus onabotulimtoxinA 20units one cycle of treatment, glabellar lines

One RCT (n = 76 participants) assessed this comparison (Carruthers 2017).

Primary outcomes

Participant assessment of success by analysing scores and scales

The responder rate by participant assessment showed no difference between daxibotulinumtoxinA 20 U and onabotulinumtoxinA 20 U at week 4 (RR 1.10, 95% CI 0.80 to 1.50; participants = 76; studies = 1); at week 16 (RR 1.24, 95% CI 0.39 to 3.92; participants = 76; studies = 1); and at week 24(RR 0.25, 95% CI 0.01 to 4.95; participants = 76; studies = 1) (Analysis 78.1).

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

There was no difference between groups (Peto OR 0.16, 95% CI 0.00 to 8.43; participants = 76; studies = 1) (Analysis 78.2).

Secondary outcomes

Physician assessment of success by analysing scores and scales

The responder rate by physician assessment was similar with daxibotulinumtoxinA 20 U and onabotulinumtoxinA 20 U at week 4 (RR 1.09, 95% CI 0.88 to 1.34; participants = 76; studies = 1); at week 8 (RR 0.90, 95% CI 0.57 to 1.42; participants = 76; studies = 1); at week 12 (RR 1.24, 95% CI 0.58 to 2.62; participants = 76; studies = 1); at week 16 (RR 2.16, 95% CI 0.69 to 6.77; participants = 76; studies = 1); at week 20 (RR 1.65, 95% CI 0.40 to 6.86; participants = 76; studies = 1); and at week 24 (RR 1.85, 95% CI 0.33 to 10.46; participants = 76; studies = 1) (Analysis 78.3).

Total adverse events

There was no difference between daxibotulinumtoxinA 20U and onabotulinumtoxinA 20 U (RR 0.87, 95% CI 0.46 to 1.64; participants = 108; studies = 1) (Analysis 78.4).

Duration of treatment effect

The duration of treatment effect was similar between of daxibotulinumtoxinA 20U and onabotulinumtoxinA 20 U (MD 2.00, 95% CI -0.78 to 4.78; participants = 76; studies = 1) (Analysis 78.5).

COMPARISON 79. PrabotulinumtoxinA 20 units versus placebo one cycle of treatment, glabellar lines

Three RCTs (n = 948 participants) assessed this comparison (Beer 2019a; Beer 2019b; Rzany 2019).

Primary outcomes

Participant assessment of success by analysing scores and scales

The responder rate by participant assessment was higher withdaxibotulinumtoxinA 20 U than placebo at week 4 (RR 18.34, 95% CI 9.68 to 34.76; participants = 930; studies = 3; I^2 = 0%). (Analysis 79.1).

Two RCTs (Beer 2019a; Beer 2019b) showed this outcome at week 8, 12 and 16, but the authors did not separate participant and physician assessment scores.

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

There was no difference between prabotulinumtoxinA 20U and placebo (RR 0.60, 95% CI 0.06 to 5.65; participants = 939; studies = 3; I^2 = 0%) (Analysis 79.2).

Secondary outcomes

Physician assessment of success by analysing scores and scales

The responder rate by physician assessment was similar with prabotulinumtoxinA 20 U and placebo at week 4 (RR 23.96, 95% CI 9.35 to 61.40; participants = 929; studies = 3; I^2 = 26%) (Analysis 79.3).

Two RCTs (Beer 2019a; Beer 2019b) showed this outcome at weeks 8, 12, and 16, but the authors did not separate participant and physician assessment scores.

Total adverse events

There was no difference between prabotulinumtoxinA 20 U and placebo (RR 1.14, 95% CI 0.91 to 1.43; participants = 948; studies = 3; I^2 = 0%) (Analysis 79.4).

Duration of treatment effect

This RCT did not assess this outcome.

COMPARISON 80. PrabotulinumtoxinA 20 units versus OnabotulimtoxinA 20 units one cycle of treatment, glabellar lines

Two RCTs (n = 759 participants) assessed this comparison (Rzany 2019; Won 2015).

Primary outcomes

Participant assessment of success by analysing scores and scales

The responder rate by participant assessment was higher with daxibotulinumtoxinA 20 U than onabotulinumtoxinA 20 U at week 4 (RR 1.04, 95% CI 1.00 to 1.09; participants = 749; studies = 2; I^2 = 0%) (Analysis 80.1).

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

There was no difference between prabotulinumtoxinA 20 U and onabotulinumtoxinA (Peto OR 2.75, 95% CI 0.38 to 19.61; participants = 491; studies = 1) (Analysis 80.2).

Secondary outcomes

Physician assessment of success by analysing scores and scales

The responder rate by physician assessment was similar with prabotulinumtoxinA 20 U and onabotulinumtoxinA at week 4 (RR 1.04, 95% CI 0.94 to 1.14; participants = 483; studies = 1) (Analysis 80.3).

Total adverse events

There was no difference between prabotulinumtoxinA 20U and onabotulinumtoxinA (RR 0.91, 95% CI 0.74 to 1.13; participants = 759; studies = 2; I^2 = 0%) (Analysis 80.4).

Duration of treatment effect

This RCT did not assess this outcome.

COMPARISON 81. OnabotulinumtoxinA 9 units versus hyaluronic acid [JUVEDERM ULTRA ® and/or JUVEDERM ULTRA PLUS®] one cycle of treatment, lips and perioral lines

Only one RCT (n = 60 participants) assessed this comparison (Carruthers 2010). Therefore, we were not able to undertake a meta-analysis, and only a visual representation of the results is shown in the forest plots.

Primary outcomes

Participant assessment of success by analysing scores and scales

This did not assess this outcome.

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

This RCT did not report any major event.

Secondary outcomes

Physician assessment of success by analysing scores and scales

The authors showed a significant difference among the groups (data not shown). No numeric data were provided.

Total adverse events

The total adverse events were higher with onabotulinumtoxinA than hyaluronic acid, but the result is uncertain due to the wide confidence interval (RR 2.00, 95% CI 0.40 to 10.11; participants = 60; studies = 1) (Analysis 81.1).

Duration of treatment effect

The mean duration of treatment effect by physician assessment at maximum contraction of each treatment were: 9.9 weeks (69.3 ± 11.0 days) for onabotulinumtoxinA group; 15.5 weeks (108.9 ± 12 days) 24 g/mL cohesive gel group.

COMPARISON 82. OnabotulinumtoxinA 9 units associated with hyaluronic acid [JUVEDERM ULTRA ® and/or JUVEDERM ULTRA PLUS®] versus onabotulinumtoxinA 9 units one cycle of treatment, lips and perioral lines

Only one RCT (n = 60 participants) assessed this comparison (Carruthers 2010). Hence, we were not able to undertake a meta-analysis, and only a visual representation of the results is shown in the forest plots.

Primary outcomes

Participant assessment of success by analysing scores and scales

This RCT did not assess this outcome.

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

This RCT did not report any major event.

Secondary outcomes

Physician assessment of success by analysing scores and scales

The authors showed a significant difference among the groups (data not shown). No numerical data were provided.

Total adverse events

The frequency of adverse events was similar with onabotulinumtoxinA and onabotulinumtoxinA associated with filler (RR 0.75, 95% CI 0.18 to 3.07; participants = 60; studies = 1) (Analysis 82.1).

Duration of treatment effect

The mean duration of treatment effect by investigator assessment at maximum contraction were 15.2 weeks (106.6 ± 10.6 days) in the BontA plus 24-mg/mL cohesive gel and 9.9 weeks (69.3 ± 11.0 days) for onabotulinumtoxinA.

COMPARISON 83. Hyaluronic acid versus OnabotulinumtoxinA 9 units associated with hyaluronic acid [JUVEDERM ULTRA ® and/or JUVEDERM ULTRA PLUS®] one cycle of treatment, lips and perioral lines

Only one RCT (n = 60 participants) assessed this comparison (Carruthers 2010). For this reason, we were not able to undertake a meta-analysis, and only a visual representation of the results is shown in the forest plots.

Primary outcomes

Participant assessment of success by analysing scores and scales

This RCT did not assess this outcome.

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

This RCT did not report any major event.

Secondary outcomes

Physician assessment of success by analysing scores and scales

The authors showed a significant difference among the groups. No numeric data were provided.

Total adverse events

no difference between groups (RR 0.67; 95% CI 0.12 to 3.71, participants = 60; studies = 1) (Analysis 83.1).

Duration of treatment effect

The mean duration of treatment effect by investigator assessment at maximum contraction were 15.2 (106.6 ± 10.6 days) in the onabotulinumtoxinA plus 24-mg/mL cohesive gel group, and 15.5 weeks (108.9 ± 12 days) in 24-mg/mL cohesive gel.

COMPARISON 84. IncobotulinumtoxinA 21 units versus AbobotulinumtoxinA 63 units, one cycle of treatment, glabellar lines

Only one RCT (n = 120 participants) assessed this comparison (Rappl 2013).

Primary outcomes

Participant assessment of success by analysing scores and scales

This RCT did not assess this outcome.

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

No serious adverse events were reported.

Secondary outcomes

Physician assessment of success by analysing scores and scales

The authors showed a significant difference among the groups. No numerical data were provided.

Total adverse events

Two participants reported mild bruising, which resolved within 2 to 3 days (the authors did not provide this results by intervention group) (very low-certainty evidence).

Duration of treatment

For females, the mean duration of treatment effect was 146.12 days for incobotulinumtoxinA versus 139.69 days for abobotulinumtoxinA. For males, these results were 121.14 and 115.81, respectively (no SD or P value were provided).

COMPARISON 85. AbobotulinumtoxinA 50 units versus OnabotulinumtoxinA 18 units one cycle of treatment, glabellar and crow's feet lines

One RCT (n = 85 participants) assessed this comparison (Kassir 2013). This was a split-face study design, so the results are described narratively.

Primary outcomes

Participant assessment of success by analysing scores and scales

This RCT did not assess this outcome.

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

One participant in the abobotulinumtoxinA group reported ptosis.

Secondary outcomes

Physician assessment of success by analysing scores and scales

The responder rate for glabellar lines, by physician assessment, was similar with abobotulinumtoxinA 30 U compared to onabotulinumtoxinA 8 U from week 4 to week 16.

The responder rate for crow's feet lines, by physician assessment, was similar with AbobotulinumtoxinA 30U and onabotulinumtoxinA 10 U from week 4 to week 16.

Total adverse events

This RCT did not assess this outcome.

Duration of treatment

This RCT did not assess this outcome.

COMPARISON 86. AbobotulinumtoxinA 30 units versus OnabotulinumtoxinA 10 units one cycle of treatment, crow's feet lines

One RCT (n = 90 participants) assessed this comparison (Nettar 2011).

Primary outcomes

Participant assessment of success by analysing scores and scales

The score (Merz scale) rate by participant assessment was higher with abobotulinumtoxinA treatment (2.34) than onabotulinumtoxinA (2.13), P = 0.03 at week 4.

Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

No major adverse events were reported.

Secondary outcomes

Physician assessment of success by analysing scores and scales

The score (Merz scale) rate by participant assessment was higher with abobotulinumtoxinA treatment (2.60) than onabotulinumtoxinA (2.33), P = 0.01 at week 4.

Total adverse events

One patient from onabotulinumtoxinA group showed a bruise.

Duration of treatment effect

This RCT did not assess this outcome.

COMPARISONS WITHOUT USABLE DATA

We were unable to collect usable data on the following comparisons, because the studies did not collect or report relevant data:

- AbobotulinumtoxinA different doses comparison (full face treatment): one RCT (n = 90, Hexsel 2013). The doses compared were too similar and did not allow any validate comparisons (no clinical relevance). Moreover, there was dose overlap among the dose range (Hexsel 2013).
- OnabotulinumtoxinA versus facial cream (Strivectin®) one cycle of treatment (glabellar lines): one RCT (n = 32, Beer 2006).
- OnabotulinumtoxinA versus facial cream (Wrinklerelax™) one cycle of treatment (glabellar lines): one RCT (n = 31, Beer 2006).
- OnabotulinumtoxinA versus facial cream (Hydroderm™) one cycle of treatment (glabellar lines): one RCT (n = 31, Beer 2006).
- OnabotulinumtoxinA 25 units versus abobotulinumtoxinA 62.5 units one cycle of treatment (glabellar lines, crow's feet, and forehead lines (split-face)): One RCT (n = 53, Michaels 2012).
- OnabotulinumtoxinA 20 units versus abobotulinumtoxinA 50 units one cycle of treatment (crow's feet lines): one RCT (n = 90, Nettar 2011).
- OnabotulinumtoxinA 7.5 units versus incobotulinumtoxinA 7.5 units one cycle of treatment (crow's feet lines): one RCT (n = 56, Park 2014).
- AbobotulinumtoxinA 63 units versus onabotulinumtoxinA 32 units one cycle of treatment (glabellar lines): one RCT (n = 119, Rappl 2013).
- OnabotulinumtoxinA 25 units versus onabotulinumtoxinA 25 units associated to collagen one cycle of treatment (glabellar lines): One RCT (n = 45, Patel 2004).
- OnabotulinumtoxinA 25 units versus collagen one cycle of treatment (glabellar lines): one RCT (n = 42, Patel 2004).
- OnabotulinumtoxinA 25 units associated with collagen versus collagen one cycle of treatment (glabellar lines): one RCT (n = 45, Patel 2004).
- OnabotulinumtoxinA units not shown versus abobotulinumtoxin units not shown one cycle of treatment of glabellar lines and frontal lines, split-face study: one study (Firoz 2012).
- OnabotulinumtoxinA 25 units versus abobotulinumtoxin 62.5 units one cycle of treatment of glabellar lines, periorbital lines and frontal lines (Michaels 2012).

DISCUSSION

Summary of main results

We included 65 randomised controlled trials (RCTs), involving 14,919 randomised participants. Here we summarise the results for the main comparisons that assessed the treatment of the facial region glabellar lines.

Summary of findings 1: based on moderate-certainty evidence, onabotulinumtoxinA-20 units (U) probably has a higher success rate than placebo when measured at four weeks by participants or physicians. OnabotulinumtoxinA-20 U probably increased the risk of major adverse events compared to placebo (moderate-certainty evidence), but there may be no difference between groups in any adverse events (low-certainty evidence). Adverse events were collected over the duration of these studies, which ranged from four weeks to 24 weeks.

Summary of findings 2: abobotulinumtoxinA-50 U showed a higher success rate than placebo at week four by participant assessment (high-certainty evidence), and abobotulinumtoxinA-50 U probably has a higher success rate by physician assessment (moderate-certainty evidence). Compared to placebo, abobotulinumtoxinA-50 U probably increases the occurrence of major adverse effects(moderate-certainty evidence; collected in studies of four to 12 weeks duration) and may increase the occurrence of any adverse events (low-certainty evidence; collected in studies of four to 16 weeks duration).

Summary of findings 3: there is probably a higher success rate with incobotulinumtoxinA-20 U than placebo at week four by both participant assessment (moderate-certainty evidence) and physician assessment (moderate-certainty evidence). Major adverse events were not observed (moderate-certainty evidence), and there may be no difference between groups in any adverse events (low-certainty evidence; collected in studies of four to 16 weeks duration).

Summary of findings 4: there is no difference in the participant-assessed or physician-assessed success rate between abobotulinumtoxinA-50 U and onabotulinumtoxinA-20 U at four weeks (high-certainty evidence). AbobotulinumtoxinA-50 U probably increases the occurrence of major adverse events compared to onabotulinumtoxinA-20 U (moderate-certainty evidence), but there is probably no difference in any adverse events (moderate-certainty evidence; collected in studies of four to 12 weeks duration).

Summary of findings 5: there may be no difference in the success rate between incobotulinumtoxinA-24 U and onabotulinumtoxinA-24 U at four weeks (by physician assessment; low-certainty evidence). Participant assessment was not measured. Ptosis was reported in one participant in the onabotulinumtoxinA group, but the certainty of this evidence is very low, so we are uncertain of the risk of adverse events (collected in studies of four to 12 weeks duration).

Summary of findings 6: daxibotulinumtoxinA 40 U probably has a higher success rate than placebo when assessed at four weeks by either participants or physicians (moderate-certainty evidence). Major adverse events were not observed. There may be an increase in any adverse events with daxibotulinumtoxinA than with placebo (moderate-certainty evidence; collected in studies of four to 24 weeks duration).

Adverse events: ptosis was the main major adverse event. Botulinum toxin type A (BontA) are associated with a risk of strabismus or eyelid sensory disorders.

Overall completeness and applicability of evidence

Analysing the data, some ethnicities (Middle East, Latin America) and males are underrepresented. More than 80% of the total number of study participants were female. Ethnicity and anatomic characteristics such as skin width, oily skin, the skeletal structure can potentially impact on outcomes for BontA treatment. In general, men have stronger muscles than women, and this fact could interfere in the relationship between the units of BontA needed to treat and duration of effect.

Our review aimed to assess treatment of any type of facial wrinkle, but almost two-thirdsof studies assessed treatment of the glabella region (43/65 studies). The other types of wrinkles assessed in this review: crow's feet lines: seven RCTs; forehead lines: two RCTs; forehead lines and crow's feet lines: one RCT; upper

lines (glabellar lines, crow's feet lines, and forehead lines): three RCTs; forehead lines and glabellar lines: three RCTs; crow's feet lines and glabellar lines: three RCTs; full face: one RCT; perioral area: two RCTs.

Most of the studies that treated glabellar lines included moderate-to-severe glabellar lines according to Facial Wrinkle Scale score (FWS)or Glabellar Lines Severity Scale (GLSS). The studies that assessed others regions did not show details about wrinkle severity. In clinical practice, physicians treat mild-to-moderate glabellar lines.

The main commercial BontA treatments were addressed in the included studies. These included onabotulinumtoxinA, abobotulinumtoxinA, incobotulinumtoxinA, HBTX-A, NewBontA (Medytox®, Neuronox®, Prosigne®), liquid BontA (MT101109L), daxibotulinumtoxinA (DWP450), praxibotulinumtoxinA, liquid BontA (Ipsen), and CBFC26. However, these treatments were not assessed by equal numbers of studies. Half of the studies assessed onabotulinumtoxinA, with 71% of the rest of the studies assessing abobotulinumtoxinA or incobotulinumtoxinA. Some types of BontA (e.g. liquid BontA (MT101109L)) were only assessed by single studies, or two studies (HBTXA).

The mean study duration was 20.75 weeks ± 11.7 (range: 1 to 52 weeks).

There was huge variation in doses, number of cycles, and duration of follow-up. These factors precluded data pooling and compromised the robustness of evidence. We assessed the following comparisons: BontA versus placebo, at least one cycle of treatment (36 studies); BontA at different doses, one cycle of treatment (21 studies); BontA versus placebo, at least two cycles of treatment (11 studies); BontA versus facial cream (one study); BontA associated to fillers (two studies). Eighty-three per cent of the studies assessed a single cycle of treatment, and as BontA has a temporary effect on wrinkles, the single cycle does not reflect the need for repeated treatments. Some studies administered much higher doses than those recommended by two different consensus groups (Carruthers 2008a; Sundaram 2016).

The most common comparator was placebo (36 studies). An active control was used in 19 studies. There were eight dose-ranging studies of onabotulinumtoxinA, and a small number of studies compared against fillers. Direct comparisons of different BontA treatments were lacking. OnabotulinumtoxinA and abobotulinumtoxinA were the most common BontA comparators (seven studies each), followed by incobotulinumtoxinA (five studies). OnabotulinumtoxinA was compared with abobotulinumtoxinA (five studies), onabotulinumtoxinA was compared with incobotulinumtoxinA (four studies), and the following were compared in single studies against onabotulinumtoxinA: liquid BontA (MT101109L), New BontA (Medytox®), and Neuronox.

Duration of treatment was the least-reported outcome of interest (21 studies). Physician assessment of success was more often reported (49 studies) than participant assessment of success (35 studies). Seventy-one per cent of studies assessed major adverse events, and 78% evaluated the occurrence of any adverse events. However, long-term adverse effects were not measured.

Unfortunately, there was disparity in the definition of outcome tools, inhibiting pooling.

Most of the studies had pharmaceutical support with no description about the role of the research development, planning, conduct, statistical analysis and reporting.

Quality of the evidence

As presented in the summary of findings tables, the certainty of the body of evidence obtained for each outcome was usually rated as very low, low or moderate certainty. Only three effect sizes were rated as high certainty. Most outcomes were downgraded for study limitations. Such limitations included an unclear/high risk of bias of selection bias from random sequence generation and allocation concealment, and unclear/high risk of performance or detection bias from blinding of participants, study personnel and outcome assessors. Many outcomes were also downgraded for imprecision as the estimates had wide confidence intervals which crossed the null effect.

Moreover, the studies were poorly reported, and patient double count was difficult to detect. Design study complexity was another obstacle to data collection.

Potential biases in the review process

This review followed strictly all the recommendations of the *Cochrane Handbook* (Higgins 2020) on searching, study selection, data collection, and data analysis to avoid bias.

Strengths of this review include a wide and recently updated literature search. The limitations of this review include no assessment of publication bias through funnel plot analysis because there were less than 10 studies included in each meta-analysis.

We changed some items from protocol to the review as a tentative measure to decrease potential bias: minimal number of participants for included studies from 20 to 50; we assessed the responder rates only during 'muscle contraction', rather than 'at rest', as: for clinical practice this last approach was less relevant, and at label, BontA was indicated for hyperdynamic facial wrinkles; and we did meta-analysis only in parallel group studies; we did not include split face studies in this analysis.

The 24 studies in 'Studies awaiting classification' may alter the conclusions of the review once assessed.

Agreements and disagreements with other studies or reviews

In general, all systematic reviews (SRs) showed similar results.

- The majority of the studies injected onabotulinumtoxinA, followed by abbobotulinumtoxinA and incobotulinumtoxinA.
- The most frequent facial region was glabellar lines, crow's feet lines and forehead lines.
- The frequency of adverse effects is similar between BontA and placebo, except for the occurrence of blepharoptosis. Blepharoptosis is higher in the BontA groups than the placebo groups.

Ghadia and colleagues (Ghadia 2009) analysed 11 articles (1063 participants). The primary endpoint was the efficacy of BontA in facial wrinkles, and the secondary endpoint was safety. This systematic review studied the effect of treatment of onabotulinumtoxinA and abobotulinumtoxinA. The age ranged from 31 to 59 years, whereas in our systematic review, age range was broader (18 to 65 years). Regarding efficacy, we found similar results to Ghadia and colleagues: BontA in facial wrinkles was more effective than the placebo group, but because of a high level of heterogeneity this conclusion was uncertain. In Ghadia 2009, the overall quality of evidence was considered good (Jadad scale). In our systematic review, we largely showed a range from very low- to moderate-certainty evidence according to GRADE pro GDT (GRADEpro GDT).

Cavallini and colleagues studied 35 articles, 8787 participants (Cavallini 2014). In this systematic review, the authors only considered onabotulinumtoxinA, abobotulinumtoxinA, and incobotulinumtoxinA, and analysed only safety outcomes(Cavallini 2014). Because of limited search on the most common BontA brands, this review also limited their results (Cavallini 2014).

Jia and colleagues reported another systematic review of adverse events. The authors limited their search strategy to articles in the English language, some BontA (onabotulinumtoxinA, abobotulinumtoxinA, incobotulinumtoxinA, and HBTX-A), and some regions (glabellar and crow's feet lines). This systematic review studied 34 articles, 42,405 participants (Jia 2016). The meta-analysis was different, because they used a fixed-effect analysis, whereas our systematic review used random-effects analysis, In general, both systematic reviews agreed that BontA was safe for glabellar and crow's feet lines (Jia 2016).

AUTHORS' CONCLUSIONS

Implications for practice

This systematic review found that BontA is effective for reducing facial wrinkles within four weeks of treatment, but carries a risk of ptosis. There was a lack of long-term data, and data on adverse effects were limited. The formulations of BontA tested appeared to be similarly effective in short-term assessment. Longer-term effects of treatment are unclear, and this applies to both efficacy and adverse effects.

Analysing the data, some ethnicities (Middle East, Latin America) and gender (male) are underrepresented. Depending on the ethnicity, anatomic characteristics such as skin width, oiliness of the skin, and the skeletal structure, can interfere in the BontA treatment.

In general, males have stronger muscles than females; this fact could interfere in the relationship between the units of BontA needed to treat and duration of effect. Most of the studies analysed moderate-to-severe glabellar lines, but in clinical practice, physicians treat mild-to-moderate glabellar lines.

Regarding major adverse events, only ptosis was reported in the trials; however, BontA is known to carry a risk of strabismus and eyelid sensory disorders. The trials reported ptosis in less than 5% of BontA-treated participants, and no episodes of ptosis were reported in placebo-treated trial participants.

Implications for research

In recent years, new BontA formulations have become available. However, despite all the safety and clinical indications, some crucial questions remain that future BontA research should aim to address.

Therefore, according to the PICOT acronym, further research could focus on the following.

- Population: different ethnicities should be assessed.
- Intervention: studies should assess multiples cycles of treatment and seek to find the most effective dilution. There should be a standard conversion ratio among all available BontA brands.
- Comparator: it would help to compare all available BontA brands regarding the duration of treatment effect (time between wrinkles treatment session) with assessment of different facial regions (glabella, canthal lines, frontal lines), liquid BontA versus lyophylised BontA, what is the most effective treatment association (hyaluronic acid, peeling, laser, radiofrequency, surgery), and what are the consequences of therapy of several facial regions in the same session.
- Outcome: helpful outcomes to measure in future studies include duration of treatment in multiples sessions, the time between BontA dilution and clinical application, the effectiveness and safety of multiple cycles of treatment, and the longer-term effectiveness of multiple cycles of treatment.

Future studies should also aim to improve study methodology. The main issue identified in the existing literature was failure to describe adequate methods of randomisation or allocation concealment. There is a need for better powered studies and more homogeneity of study design. There is a need for new studies that answer clinical questions such as the duration of the effect of BontA, one cycle versus multiple cycles, as well as active comparator studies, so we can more confidently compare different BontA treatment options.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ascher 2004

Study characteristics	
Methods	**Study design**- multicentre, randomised, double-blind, parallel-design in glabellar lines **Study date**- start date March and June 2002" no information about end date **Study centre**- outpatients from three centres
Participants	**Randomised** 119 participants with mean age of 48. 6 ±7.9 years in BontA 25 U group; 50.9 ± 7.5 years in BontA 50 U group; 48.8 ± 7.7 years in BontA75u group; 48.3 ± 6.4 years in placebo group; 49. 3 ±7.5 years total population. Gender: 114/119 (95.8%) female and 5/119 (4.2%) male in total population, 33/34 (97.1%) female and 1/34 (2.9%) male in BontA 25 U group; 32/34 (94.1%) female and 2/34 (5.9%) male in BontA 50 U group; 32/34 (94.1%) female and 2/34 (5.9%) male in BontA75 U group; 17/17 (100% female) and 0/17 (0%) male in placebo group **Inclusion criteria** • Males and females aged 18-70 years with moderate to severe (grade 2 and 3) glabellar lines during maximum frown and at rest **Exclusion criteria** • Previous face procedure (dermabrasion, fillers) in the face or any prior botulinum toxin treatment in the last 12 months • Ptosis or facial nerve palsy that can confound efficacy and safety. Previous insertion of non-absorbable material or surgical removal of the corrugator, procerus or supercilii, or a combination of these • Participants taking medication, with facial conditions affecting neuromuscular function • Women with pregnancy test positive **Severity of disease**- moderate to severe glabellar lines at rest **Ethnicity**- no information
Interventions	**Duration of study**- 24 weeks **Intervention** • AbobotulinumtoxinA (25 U) (N = 34), AbobotulinumtoxinA 50 U(N = 34) • AbobotulinumtoxinA (75 U) in glabella, 0.05 mL/site, 5 points (N = 34) **Comparator** • Placebo in glabella (0.05 mL per injection, 5 injections) (N = 17)
Outcomes	**Primary outcome** • Percentage of responders defined as patients with grade 0 or 1 glabellar line (standardised severity scale of 0 = none to 3 = severe) at rest 1 month after treatment, glabellar lines at rest and maximum frown by the investigator (4-point) **Secondaries outcomes** • Criteria from day 14 to month 6 allowed us to assess the time course and duration of action of the treatment. • Adverse events

Ascher 2004 *(Continued)*

Notes	"Supported by Beaufour Ipsen Pharma SAS. Disclosure: Dr Zakine is an employee of Beaufour Ipsen Pharma"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "This multicenter, randomised, double-blind study compared..." page 224 "Patients were randomly assigned to receive BTX-A, according to a computer-generated randomisation schedule" page 225 Comment: we considered low risk of bias
Allocation concealment (selection bias)	Unclear risk	No information available to allow a judgement Comment: we consider this unclear risk of bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "To maintain the study blind, treatments were reconstituted and syringes for injection prepared by a third party not involved with the patient treatment or assessment" page 225 Comment: we considered this low risk of bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind... study" To maintain the study blind, treatments were reconstituted and syringes for injection prepared by a third party not involved with the patient treatment or assessment" page 224/225 Comment: we considered this low risk of bias
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote:"two patients withdrew before the first month" page 227 Comment: we considered a unclear risk of bias because the authors did not explain the reason of drop outs
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported. Comment: we considered this low risk of bias
Other bias	High risk	Quote: "the two series of glabellar severity scores were not fully superimposable: taking the objective double-blind, digital photographic baseline results as a reference, it appears that clinical scoring overestimated the occurrence of medium scores (scores of 2) by including patients with a mild score (score of 1). Conversely, severe scores were slightly underestimated by the investigators." page 227 Comment: to clarify this information an e-mail was sent on 23 May 2015, we did not receive any answer.

Ascher 2005

Study characteristics

Methods	**Study design** -multicentre, parallel-design. First phase randomised, double-blind, month to month evaluation until 6 months. Second phase, open-label, pragmatic study, month to month evaluation between month 3 and month 6 in glabellar lines **Study date**- no information

Ascher 2005 *(Continued)*

	Study setting- outpatients from five centres
Participants	**Randomised** 100 participants, mean age of 50.4 ± 7.7 years in BontA group, 49.1 ±8.6 years in placebo group, 49.8 ± 8.2 years total population. Gender: 94/100 (94%) female and 6/100 (6.0%) male total population; 48/50 (96%) female and 2/50 (4.0%) male in BontA group; 46/50 (92%) female and 4/50 (8.0%) male in placebo group **Inclusion criteria** • Male and female aged 18-70 years with moderate to severe (grade 2 and 3) glabellar lines during maximum frown and at rest **Exclusion criteria** • Previous treatment with BoNT-A (regardless of the time since former treatment); facial conditions that could confound safety or efficacy results (such as eyelid and/or eyebrow ptosis) or facial palsy • Treatment with fillers, skin abrasions, or photo rejuvenation in the glabellar area in the last 12 months; or treatment with drugs interfering with neuromuscular function (e.g. aminoglycosides) • A previous insertion of non-absorbable material or surgical removal of the corrugators, procerus, depressor supercilii or a combination of these also excluded the patient from participation. • Pregnancy and breast-feeding were other exclusion criteria **Severity of disease**- moderate to severe glabellar rhytides at rest **Ethnicity**- no information
Interventions	**Duration**- two phases (12 weeks and 24 weeks) **Intervention** • AbobotulinumtoxinA (50 U) in glabella (N = 50) **Comparator** • Placebo in glabella (0.05mL/per site, 5 sites (N = 50)
Outcomes	**Primary outcome** • The time measured in months separating the randomised first injection and the open-label second injection consensually decided between the investigator and the patient. The mutual decision for the time of the second injection could be taken no earlier than Month 3 and no later than Month 6 after the first injection **Secondary outcomes** • Clinical evaluation of the severity of the glabellar lines by the investigator, as determined by the standardised clinical score and the patient's subjective assessment according to a 4-point scoring scale (1 = completely satisfied, 2 = satisfied, 3 = somewhat satisfied, 4 = not satisfied). • For the double-blind phase, the efficacy criteria were the percentage of responders at rest and maximum frown as deter- mined by the investigator at each monthly visit between Month 3 and Month 6 (depending on the second injection date), and on the day of the second injection. A patient was considered as a responder if his/her standardised clinical glabellar score was 0 or 1 after treatment • For the open-label phase, the secondary efficacy criteria were the percentage of responders at rest and maximum frown as determined by the investigator at Month 1 and Month 3 after the second injection. During both phases, each patient provided his/her own monthly assessment of the treatment efficacy from Month 1 after the first injection to Month 3 after the second injection • Adverse events
Notes	"This study was funded by Beaufour Ipsen SAS, Paris, France. Dr. Zakine is an employee of Beaufour Ipsen SAS. Drs. Ascher, Kestemont, Baspeyras, Niforos, Malet, and Santini received payment for conducting the study."

Ascher 2005 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A multicenter, randomised, placebo-controlled study" page 366 "Patients were randomly assigned to receive 50 U BoNT-A or placebo according to a computer-generated randomisation schedule prepared prior to the start of the study" page 367 Comment: we consider this low risk of bias
Allocation concealment (selection bias)	Unclear risk	No information available to allow a judgement Comment: we consider this unclear risk of bias
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "The first phase was conducted according to a double-blind...The second injection, which started the second phase of the study, was pragmatically" page 366 Comment: we consider this unclear risk of bias (first phase), because the authors did not mention the method used for blinding the participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "The first phase was conducted according to a double-blind...The second injection, which started the second phase of the study, was pragmatically" page 366 Comment: we consider this unclear risk of bias (first phase), because the authors did not mention how they blinded the outcome assessor
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "One patient of BontA group did not receive the second injection.The patient was "completely satisfied" from Month 1 to Month 6 and then refused the second injection. Also, 2 patients in each group withdrew from the study after the second injection, none of them for AEs. Protocol deviation was responsible for the withdrawal of 2 patients, and a professional problem and an administrative reason for the other 2 cases" page 370 Comment: we consider this low risk of bias (first phase) due to number of withdraw was low and there was a balance between groups regarding this number and the reasons of withdraws
Selective reporting (reporting bias)	Unclear risk	The percentages of responders (i.e. patients with clinical scores of 0 or 1) at rest and at maximum frown - only P value was provided (page 372) Comment: we consider this unclear risk of bias. An e-mail was sent for the authors on 23 May 2015. No reply until the date
Other bias	Unclear risk	Quote: "Dr. Zakine is an employee of Beaufour Ipsen SAS." page 375 Comment: We considered this unclear risk of bias

Ascher 2009

Study characteristics

Methods	**Study design**- multicentre, randomised, double-blind, parallel-design, dose-ranging in crow's feet lines

Ascher 2009 *(Continued)*

	Study date- no information **Study setting**- outpatients from nine centres
Participants	**Randomised**- 220 participants, with mean age of 47.6 ± 7.6 years in BontA 15 U group; 47.8 ± 9.5 years in BontA 30 U group; 48.3 ± 10 years in BontA 45 U group; 47.6± 8.2 years in placebo group. Gender: 48/55 (87%) female, 7/55(13%) male in BontA 15 U group; 48/54 (89%) female, 6/54 (11%) male in BontA 30 U group; 46/55 (84%) female, 9/55 (16%) male in BontA 45 U group; 50/53 (93%) female, 4/54 (7%) male in placebo group **Inclusion criteria** • Male and female aged 18-65 years with moderate to severe (grade 2 and 3) crow's feet during maximum smile and mild to severe (grade 1,2,3) crow's feet at rest (both sides of the face) **Exclusion criteria** • Any prior surgery affecting the area around the eye or any prior botulinum toxin treatment • Participants taking medication, with facial skin conditions affecting neuro-muscular function, or with psychiatric illnesses that in the investigator's opinion could affect the safety, conduct, or outcome of the study were also excluded • Women of child-bearing potential were required to have a negative pregnancy test before study entry **Severity of disease**- "moderate to severe crow's feet at maximum smile" **Ethnicity**- BontA(15u) 54/55 (98%) Caucasian; 1/55 (2%) non-Caucasian; BontA (30u) 54/54 (100%) Caucasian; BontA (45u) 55/55 (100%) Caucasian; placebo 54/54 (100%) Caucasian
Interventions	**Duration of study**- 16 weeks **Interventions** • AbobotulinumtoxinA (15 U) (N = 55), • AbobotulinumtoxinA (30 U) (N = 54) • AbobotulinumtoxinA (45 U) crow's feet, 0.05 mL/injection per site, 3 point (N = 55) **Comparator** • Placebo, crow's feet, 0.05 mL/injection per site, 3 point (N = 54)
Outcomes	**Primary outcome** • Percentage of responders at maximum smile at Week 4, as assessed by blinded independent panel review of the standardised photographs **Secondary outcomes** • Assessments at maximum smile, response was defined as an improvement in severity of crow's feet from moderate or severe (Grade 2 or 3) at baseline to none or mild (Grade 0 or 1) on both sides. Clinicians and the independent panel assessors assessed the severity of the subject's crow's feet at rest and at maximum smile using the following 4-point. • Participants' own assessment of satisfaction with the overall appearance of their crow's feet was made using a 4-point rating scale • Adverse events
Notes	"*Ipsen, Ltd. provided the Dysport and the funding for this study.*"

Risk of bias

Bias	Authors' judgement	Support for judgement

Ascher 2009 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "a multicenter, randomised, double-blind" page 1479 "Subjects were randomly assigned to one of four treatment arms (BoNT-A 15, 30, or 45 U per eye or placebo) according to a computer-generated" page 1479 Comment: we consider this low risk of bias
Allocation concealment (selection bias)	Unclear risk	No information available to allow a judgement Comment: we consider this unclear risk of bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "An independent reconstitutor reconstituted the study medication (active treatment or placebo) to maintain the study blind" page 1479 Comment: we consider this low risk of bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: ″assessment by an independent panel of four expert clinicians blinded to treatment group and study time point." page 1480 Comment: we consider this low risk of bias
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "200 patients completed the study. "Because of a high incidence of protocol violations at one centre, efficacy data for all subjects from that site were excluded, resulting in an ITT population of 193 subjects. The mITT (maximum smile) population consisted of 162 subjects; 31 were excluded because severity ratings were missing or were rated none or mild at baseline by the independent panel. The mITT (rest) population consisted of 188 subjects; five subjects were excluded because severity ratings were missing or were rated none at baseline by the independent panel" page 1481 Coment: we consider a high risk of bias, protocol violation
Selective reporting (reporting bias)	Unclear risk	Subject evaluation, only graphic no data showed Comment: we consider this unclear risk of bias, because the authors did not show data. We sent an e-mail to authors on 23 May 2015. No reply until the date
Other bias	Low risk	We considered this study at low risk of other bias

Ascher 2018

Study characteristics	
Methods	**Study design**- multicentre, randomised, phase II, double-blind, parallel-design, placebo-controlled in glabellar lines **Study date**- start in March 2011 ; end in DecembeR 2011 **Study centre**- outpatients eight centres
Participants	**Randomised** 176 female participants with mean age of 47.0 ± 6.6 years in AbobotulinumtoxinA 50 group; 47.9 ± 6.0 years in Liquid AbobotulinumtoxinA 75 U group; 48.1± 6.9 years in Liquid AbobotulinumtoxinA 50 U group; 46.7 ± 8.4 years in Liquid AbobotulinumtoxinA 20 U group; 46.8 ± 6.4 years in placebo group.100% female. **Inclusion criteria** • Aged 30 to 60 years (inclusive)

Ascher 2018 *(Continued)*

- Moderate to severe GL at maximum frown at BL (Day 1, pre-treatment), as assessed by the investigator's and participants' assessment using a validated 4-point photographic scale
- All participants were required to be naïve to previous treatment with any serotype of botulinum toxin (BoNT)
- Non-childbearing potential or if female of childbearing potential must return a negative outcome from a pregnancy test

Exclusion criteria

- Any prior treatment with fillers (eg, collagen-type implants), skin abrasions or photo rejuvenation within 12 months of enrolment or any previous injections with silicone in the upper face
- Participants who had any planned facial cosmetic surgery during the study period or had a history of ablative skin resurfacing of the area to be treated during the study

Severity of disease- 17/35 (48.6%) severe and 18/35 (51.4%) moderate in AbobotulinumtoxinA 50 group; 15/35 (42.8%) severe and 20/35(57.1%) moderate in Liquid AbobotulinumtoxinA 75 U group; 15/35 (42.8%) severe and 20/35(57.1%) moderate in Liquid AbobotulinumtoxinA 50 U group; 14/36(38.9%) severe and 22/36(61.1%) moderate in Liquid AbobotulinumtoxinA 20 U group; 14/35 (60%) severe and 14/35 (61.1%0 moderate in placebo group).

Ethnicity- 5/176 (2.8%) Hispanic/Latina, 171/176 (97.2%) not Hispanic/Latina

Interventions

Duration of study- 26 weeks

Interventions

- Liquid botulinum toxin A, five injections (0.05 mL per injection; total injection volume of 0.25 mL) glabellar lines 20 U (N = 36)
- Liquid botulinum toxin A, five injections (0.05 mL per injection; total injection volume of 0.25 mL) glabellar lines50 U (N = 35)
- Liquid botulinum toxin A, five injections (0.05 mL per injection; total injection volume of 0.25 mL) glabellar lines75 U (N = 35)

Comparators

- Placebo, five injections (0.05 mL per injection; total injection volume of 0.25 mL) glabellar lines (N = 35)
- AbobotulinumtoxinA, five injections (0.05 mL per injection; total injection volume of 0.25 mL) glabellar lines 50 U (N = 35)

Outcomes

Primary outcomes

- Proportion of responders in the Investigator's Live Assessment (ILA) of GL at maximum frown at Day 29, defined as a participant with severity grade of moderate [2] or severe [3] at maximum frown at BL improving to a severity grade of none [0] or mild [1]
- Proportion of responders in the Subject's Self-Assessment (SSA) of GL at maximum frown at Day 29, as defined for the ILA

Secondary outcomes

- Proportion of responders at maximum frown at all other post-treatment visits (Days 8, 15, 57, 85, and 113) as assessed by the ILA and SSA
- Proportion of participants assessed as responders at maximum frown at Day 29 who remain responders on Day 113
- Proportion of participants with a reduction of two or more grades in the severity of GL at maximum frown at all post-treatment visits, as measured by the ILA and SSA
- Adverse events

Notes

Philippe Picaut was Ipsen employee

Risk of bias

Ascher 2018 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Computer-generated randomization lists were cre- ated by a sponsor statistician independent from the study using a validated in-house system developed with SAS software (SAS Institute, Inc., Cary, NC). The randomization schedule is generated using the SAS procedure PLAN "...page2 Comment: we consider this low risk of bias
Allocation concealment (selection bias)	Low risk	No information available to allow a judgement Comment: we consider this unclear risk of bi
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No information available to allow a judgement Comment: we consider this unclear risk of bias
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information available to allow a judgement Comment: we consider this unclear risk of bias
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information available to allow a judgement Comment: we consider this unclear risk of bias
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported. Comment: we considered this a low risk of bias
Other bias	Unclear risk	Group liquid formulation 20u showed an imbalance (fewer participants with severe GL at maximum frown). Comment: we consider this unclear risk of bias

Ascher 2020

Study characteristics	
Methods	Randomised, double-blind (first cycle), placebo-controlled and open-label Phase (2-5 cycles) multicentre study, phase III trial
Participants	185 participants **Inclusion criteria** • Provision of written informed consent prior to any study-related procedures • Male or female participants between 18 and 65 years of age • Have moderate or severe (Grade 2 or 3) vertical glabellar lines at maximum frown at Baseline (Day 1), as assessed by the ILA using a validated 4- point photographic scale • Have moderate or severe (Grade 2 or 3) vertical glabellar lines at maximum frown at Baseline (Day 1), as assessed by the SSA using a validated 4-point categorical scale • Are dissatisfied or very dissatisfied (Grade 2 or 3) with their glabellar lines at Baseline (Day 1), as assessed by the participant's level of satisfaction • Have a negative pregnancy test (for females of childbearing potential only). No childbearing potential is defined as post-menopausal for at least 1 year, surgical sterilisation at least 3 months before entering the study, or hysterectomy

Ascher 2020 *(Continued)*

- Have both the time and the ability to complete the study and comply with study instructions

Exclusion Criteria

- Previous treatment with any serotype of BTX
- Any prior treatment with permanent fillers in the upper face including the glabellar lines area
- Any prior treatment with any dermal fillers in the upper face including the glabellar lines area within the past 3 years and/or skin abrasions/resurfacing (whatever the interventional technic used) within the past 5 years, or photo rejuvenation or skin/vascular laser intervention within the past 12 months
- Any planned facial cosmetic surgery during the study
- A history of eyelid blepharoplasty or brow lifts within the past 5 years
- An inability to substantially reduce glabellar lines by physically spreading them apart or lack of capacity to frown
- An active infection or other skin problems in the upper face including the glabellar lines area (e.g. acute acne lesions or ulcers)
- Use of concomitant therapy, which in the investigator's opinion, would interfere with the evaluation of the safety or efficacy of the investigational medicinal product (IMP), including medications affecting bleeding disorders (antiplatelet agents and/or anticoagulants given for treatment or prevention of cardio/cerebrovascular diseases)
- Pregnant women, nursing mothers, or women who are planning a pregnancy during the study, or believe they may be pregnant at the start of the study. Throughout the course of the study, women of childbearing potential must use a reliable form of contraception (e.g. oral contraceptives for more than 12 consecutive weeks, or spermicide and condoms)
- Treatment with an experimental drug or use of any experimental device within 30 days prior to the start of the study and during the conduct of the study.
- Known allergy or hypersensitivity to any component of BTX-A-HAC NG
- Clinically-diagnosed significant anxiety disorder, or any other significant psychiatric disorder (e.g. depression) that might interfere with the participant's participation in the study
- Use of medications that affect neuromuscular transmission, such as curare-like non depolarising agents, lincosamides, polymyxins, anticholinesterases and aminoglycoside antibiotics, within the past 30 days
- A history of facial nerve palsy
- Marked facial asymmetry, ptosis, excessive dermatochalasis, deep dermal scarring, or thick sebaceous skin
- The presence of any other condition (e.g. neuromuscular disorder or other disorder that could interfere with neuromuscular function), laboratory finding or circumstance that, in the judgement of the investigator, might increase the risk to the subject or decrease the chance of obtaining satisfactory data to achieve the objectives of the study

Interventions	**Intervention** Clostridium Botulinum Toxin Type A (BTX A HAC NG), total treatment volume 0.25 mL will be divided into 5 injections (0.05 mL per injections) injected in 5 pre-defined sites across the glabellar region. A total of 50 U of BTX-A-HAC NG will be injected/cycle. **Comparator** Placebo volume 0.25 mL will be divided into 5 injections (0.05 mL per injections) injected in 5 pre-defined sites across the glabellar region. Administered in Cycle 1 of the double-blind phase only.
Outcomes	**Primary outcome** • The proportion of responders at Day 29 Cycle 1 as measured by Investigator Live Assessment (ILA) of glabellar lines at maximum frown. [Time Frame: Day 29 of Cycle 1] **Secondary outcomes**

Ascher 2020 *(Continued)*

- The proportion of responders at each post-treatment visit (except Day 29 Cycle 1) as measured by the ILA at maximum frown. [Time Frame: Days 8, 57 and 85 and then every 28 days until retreatment or up to a maximum of 15 months from treatment (end of study), Cycle 1]
- The proportion of responders on Day 29 Cycle 1 who remain responders on Days 57, 85 as measured by the ILA at maximum frown. [Time Frame: Days 57 and 85 and then every 28 days until retreatment or up to a maximum of 15 months from treatment (end of study), Cycle 1]
- The proportion of responders at each post-treatment visit to the study centre as measured by the ILA at rest. [Time Frame: Days 8, 29, 57 and 85 and then every 28 days until retreatment or up to a maximum of 15 months from treatment (end of study), Cycle 1]
- The proportion of responders at each post-treatment visit to the study centre as measured by the Subject's Self-Assessment (SSA) at maximum frown. [Time Frame: Days 8, 29, 57 and 85 and then every 28 days until retreatment or up to a maximum of 15 months from treatment (end of study), Cycle 1]
- The proportion of responders at each post-treatment visit to the study centre as measured by the participant's level of satisfaction with the appearance of their glabellar lines. [Time Frame: Days 8, 29, 57 and 85 and then every 28 days until retreatment or up to a maximum of 15 months from treatment (end of study), Cycle 1]
- The time to onset of treatment response based on the participant's diary card. [Time Frame: Day 1 to 7, Cycle 1]
- Mean change from Baseline to all post-treatment visits in the Face-Q. [Time Frame: Days 1, 8, 29, 57 and 85 and then every 28 days until retreatment or up to a maximum of 15 months from treatment (end of study), Cycle 1]
- The proportion of responders at each post-treatment visit to the study centre as measured by the ILA at maximum frown. [Time Frame: Days 8, 29, 57 and 85 and then every 28 days until retreatment or up to a maximum of 15 months from treatment (end of study), Cycle 1]
- The proportion of responders at each post-treatment visit to the study centre as measured by the ILA at rest. [Time Frame: Days 8, 29, 57 and 85 and then every 28 days until retreatment or up to a maximum of 15 months from treatment (end of study), Cycle 1]
- The proportion of responders at each post-treatment visit to the study centre as measured by the SSA at maximum frown. [Time Frame: Days 8, 29, 57 and 85 and then every 28 days until retreatment or up to a maximum of 15 months from treatment (end of study), Cycle 1]
- The proportion of responders at each post-treatment visit to the study centre as measured by the participant's level of satisfaction with the appearance of their glabellar lines. [Time Frame: Days 8, 29, 57 and 85 and then every 28 days until retreatment or up to a maximum of 15 months from treatment (end of study), Cycle 1]
- Time between two consecutive injections. [Time Frame: Day 1 Cycle 2 to 5]
- Mean change from Baseline to all post-treatment visits in the Face-Q. [Time Frame: Day 29 in Cycle 1 and Day 85 in Cycles 2 to 5]

Notes	Sponsor Ipsen Other study ID Y-52-52120-214 We sent an email on April,28 2019. “The Ipsen company answered:These trials have not been published unfortunately.” on June, 27, 2019.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer-generated randomization lists that were created by "...page95 Comment: we considered it low risk of bias
Allocation concealment (selection bias)	Low risk	Quote: "computer-generated randomization lists that were created by "...page95 Comment: we considered it low risk of bias

Ascher 2020 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: No information Comment: we considered it unclear risk of bias
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: No information Comment: we considered it unclear risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote:Patient disposition is shown in Figure 1...page 95 and 97 Comment: we considered it low risk of bias
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported Comment: we considered this low risk of bias
Other bias	Low risk	no other risk of bias was identified

Beer 2006

Study characteristics	
Methods	**Study design**- single-centre, randomised, investigator-blinded, placebo controlled, parallel-design. Two phases in glabellar lines **Study date**- no information **Study setting**- outpatients from one centre (USA)
Participants	**Randomised** 77 women, age range from 31.5 to 67.5years (age range, by treatment group, from 46.8 to 55.8 years). Gender 100% female **Inclusion criteria** • Females aged 18-65 years with moderate to severe (grade 2 and 3) glabellar lines during maximum frown **Exclusion criteria** • Pregnancy • Disorders that could interfere with neuromuscular function • Previous eyebrow surgery, and use of retinoids, hydroxy acids, or products containing vitamins A, C, and E **Severity of disease**- moderate-to-severe glabellar lines at maximum frown **Ethnicity**- 86% to 100% white
Interventions	**Duration of study**- 12 weeks (phase 1) and 4 weeks (phase 2) **Intervention** • OnabotulinumtoxinA (20U) in glabellar lines (N = 16) **Comparator**- Facial creams in glabellar lines • Strivectin® (N = 16) • Hydroderm® (N = 15)

Beer 2006 *(Continued)*

- Wrinklerelax® (N = 15)
- Placebo-0.1 mL/site, 5 points (N = 15)

Outcomes	**Primary outcome** • Investigator's evaluation of the severity of glabellar lines at maximum contraction and at rest on the FWS **Secondary outcomes** • Participants' global assessment of change in the appearance of glabellar lines; each of the four glabellar-specific, subject- reported, self-perception ratings; and satisfaction with treatment • Adverse events
Notes	"This study was supported by an unrestricted educational grant from Allergan, Inc."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Subjects randomised to receive either botulinum toxin type A or placebo injection" page 186 Comment: we considered this unclear risk of bias because the authors did not explain how they randomised the participants
Allocation concealment (selection bias)	Unclear risk	No information available to allow a judgment. Comment: we consider this unclear risk of bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "In order to maintain the blind, the injection syringes for botulinum toxin type A treatment and for placebo injection were prepared by a qualified staff member rather than the principal investigator. In addition, injections were given by another physician who had not prepared the syringes and who was not involved in the clinical evaluation of the subjects." page 186 Comment: we consider this low risk of bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "In order to maintain the blind, the injection syringes for botulinum toxin type A treatment and for placebo injection were prepared by a qualified staff member rather than the principal investigator. In addition, injections were given by another physician who had not prepared the syringes and who was not involved in the clinical evaluation of the subjects." page 186 Comment: we considered this low risk of bias to OnabotulinumtoxinA versus placebo, but a high risk of bias for the other groups (creams)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "More than 80% of the subjects in each treatment group completed the study as planned and no differences between groups in subject disposition were observed" page 188 Comment: we considered this unclear risk of bias because the percentage of drop outs were almost 20% and we are not sure in which extension this fact could affect the results
Selective reporting (reporting bias)	High risk	For patient satisfaction, only P value was provided and no numeric data was showed. Comment: we considered a high risk of bias. We sent an e-mail on 21 November 2015. No reply until the date

Beer 2006 *(Continued)*

Other bias	Low risk	We considered this study at low risk of other bias

Beer 2019a

Study characteristics	
Methods	**Study design**- multicentre, randomised (3:1) , phase II, double-blind, parallel-design, placebo-controlled, single-dose in glabellar lines (EV-001) **Study date**- start in March 2015 ; end in September 2015 **Study centre** outpatient, 10 centres (USA)
Participants	**Randomised** 330 participants, with a mean age of 50.2 ±11.76 years in PrabotulinumtoxinA group and 50.4 ±11.95 years in placebo group. Gender: 220/246 (92.3%) female in PrabotulinumtoxinA group, 79/84 (94%) female in placebo group. Previous botulinum toxin treatment: 103/246 (41.9%) in PrabotulinumtoxinA group and 31/84(36.9%) in placebo group **Inclusion criteria** • At least 18 years of age • Who had moderate to severe glabellar lines at maximum frown, as independently agreed by investigator and subject assessment using the same validated 4-Point photo numeric- Glabellar Line Scale • Women of childbearing potential had to have a negative pregnancy test result and be willing to use an acceptable form of contraceptive **Exclusion criteria** • Previous treatment with botulinum toxin in any body region within the last 6 months • Any planned treatment during the study period • Previous treatment with any facial aesthetic procedure in the glabellar area within the last12 months • Previous insertion of permanent material in the glabellar area • Any surgery in the glabellar area or any other planned facial aesthetic procedure during the study • Marked facial asymmetry; • Ptosis of eyelid and/or eyebrow, or history of eyelid and/or eyebrow ptosis **Severity of the disease**- by investigator assessment moderate 78/246 (31.7%) and severe 168/246(68.3%) in PrabotulinumtoxinA group, and moderate 28/84 (33.3%) and severe 56/84 (66.7%) in placebo group ; by participant assessment moderate 56/246 (22.8%) and severe 190/84(77.2%) in PrabotulinumtoxinA group, and moderate 18/84 (21.4%) and severe 66/84 (78.6%) in placebo group. **Ethnicity**- 205/246 (83.3%) white, 18/246 (7.3%) African-American, 2/246 (0.8%) Asian, 21/246 (8.5%) other in PrabotulinumtoxinA group; 63/84 (75%) white, 7/84 (8.3%) African-American, 4/84 (4.8%) Asian, 10/84(11.9%) other in placebo group.
Interventions	**Duration of study**- 20weeks **Intervention** PrabotulinumtoxinA (20 U) (N = 246), 0.1 mL injected into each of 5 sites) of either(administered as 4 U/0.1 mL) **Comparator** Placebo (N = 84), 0.1 mL injected into each of 5 sites)

Beer 2019a *(Continued)*

Outcomes	**Primary endpoint** • Percentage of participants With a ≥2 Point improvement in Glabellar Line Scale (GLS) as independently assessed by investigator and participant [Time Frame: Day 30] **Secondary outcome** • Proportion of participants, as independently agreed by both investigator- and participant-assessment, with a>=2-point improvement on the GLS at maximum frown from Day 0 on each of Days 90, 120, and 150 • Participant's self-assessment of change in severity of glabellar lines at Day 30 • Participants assessed their level of overall satisfaction, and GAIS scale on the 5-point Subject Satisfaction Scale • Adverse events
Notes	"As sponsor of the EV-001 and EV-002 studies, Evolus, Inc., of Newport Beach, CA, was involved in the design of these studies and provided funding, study materials, equipment, and medications to all investigational sites. Evolus also provided funding to contract organizations involved in data collection, analysis, and reporting of the results. R. L. Avelar is the Head of R&D and Chief Medical Officer for Evolus, Inc., and receives compensation in salary, stock, and stock options. Before and during the time of these studies and manuscript preparation, J. E. Gross was the Chief Scientific Officer at Evolus, Inc.; he will receive royalty and milestone payments should the product be approved. Anneke Jonker of Medical Writing Associates, West Vancouver, BC, Canada, provided technical assistance with manuscript preparation and submission; she holds stock in Evolus, Inc." This study was a phase III trial identical to NCT02334436. Both studies had the same reference than the NCT02334436

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Random numbers had been generated using SAS PROC PLAN (SAS Institute, Inc., Cary NC); a block randomization scheme with no stratification was used, with each block containing assignments for 3 prabotulinumtoxinA subjects and 1 placebo subject"... page 1382-3 Comment: we considered this low risk of bias
Allocation concealment (selection bias)	Unclear risk	No information Comment: we considered this unclear risk of bias because the authors did not explain the methods used to maintain the allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote:"At each study site, designated protocoltrained study personnel selected a study vial, which contained either 100 U of prabotulinumtoxinA or placebo according to the randomization schedule, reconstituted the vial with 2.5 mL of 0.9% sterile saline, filled the injection syringe, and provided it to the investigator in a blinded manner."...page 1383 Comment: we considered this low risk of bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote:"At each study site, designated protocoltrained study personnel selected a study vial, which contained either 100 U of prabotulinumtoxinA or placebo according to the randomization schedule, reconstituted the vial with 2.5 mL of 0.9% sterile saline, filled the injection syringe, and provided it to the investigator in a blinded manner."...page 1383 Comment: we considered this low risk of bias

Beer 2019a *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: " figur2 3...page 1385 Comment: we considered this low risk of bias
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported Comment: we considered this low risk of bias
Other bias	Low risk	We considered this study at low risk of other bias

Beer 2019b

Study characteristics	
Methods	**Study design**- multicentre, randomised (3:1), phase II, double-blind, parallel-design, placebo controlled, single-dose in glabellar lines (EV-002) **Study date**- start in March 2015 ; end in September 2015 **Study centre** outpatient, 10 centres (USA)
Participants	**Randomised** 324 participants, with a mean age of 51.5 ± 11.54 years in PrabotulinumtoxinA group and 50.4 ± 10.14 years in placebo group. Gender: 219/246 (89%) female in PrabotulinumtoxinA group, 72/78 (92.3%) female in placebo group. Previous botulinum toxin treatment: 91/246 (37%) in PrabotulinumtoxinA group and 26/78(33.3%) in placebo group **Inclusion criteria** • At least 18 years of age • Who had moderate to severe glabellar lines at maximum frown, as independently agreed by investigator and participant assessment using the same validated 4-point photo numeric- Glabellar Line Scale • Women of childbearing potential had to have a negative pregnancy test result and be willing to use an acceptable form of contraceptive **Exclusion criteria** • Previous treatment with botulinum toxin in any region of the body within the last 6 months • Any planned treatment during the study period • Previous treatment with any facial aesthetic procedure in the glabellar area within the last 12 months • Previous insertion of permanent material in the glabellar area • Any surgery in the glabellar area or any other planned facial aesthetic procedure during the study • Marked facial asymmetry • Ptosis of eyelid and/or eyebrow, or history of eyelid and/or eyebrow ptosis **Severity of the disease**- by investigator assessment moderate 42/246 (17.1%) and severe 204/246(82.9%) in PrabotulinumtoxinA group, and moderate 12/78 (15.4%) and severe 66/78 (84.6%) in placebo group ; by participant assessment moderate 46/246 (18.7%) and severe 200/84(81.3%) in PrabotulinumtoxinA group, and moderate 13/78 (16.7%) and severe 65/78 (83.3%) in placebo group. **Ethnicity**- 215/246 (87.4%) white, 19/246 (7.7%) African-American, 5/246 (2%) Asian, 7/246 (2.8%) other in PrabotulinumtoxinA group; 69/78 (88.5%) white, 6/78 (7.7%) African-American, 2/78 (2.6%) Asian, 1/78(1.3%) other in placebo group
Interventions	**Duration of study**- 20 weeks **Intervention**

Beer 2019b *(Continued)*

	PrabotulinumtoxinA (20 U) (N = 246), 0.1 mL injected into each of 5 sites of either(administered as 4 U/0.1 mL) **Comparator** Placebo (N=78), 0.1 mL injected into each of 5 sites
Outcomes	**Primary endpoint** • Percentage of participants With a ≥2 Point Improvement in Glabellar Line Scale (GLS) as Independently Assessed by Investigator and participant [Time Frame: Day 30] **Secondary outcome** • Proportion of participants, as independently agreed by both investigator and participant assessment, with a>=2-point improvement on the GLS at maximum frown from Day 0 on each of Days 90, 120, and 150 • Participant's self-assessment of change in severity of glabellar lines at Day 30 • Participants assessed their level of overall satisfaction, and GAIS scale on the 5-point Subject Satisfaction Scale • Adverse events
Notes	"As sponsor of the EV-001 and EV-002 studies, Evolus, Inc., of Newport Beach, CA, was involved in the design of these studies and provided funding, study materials, equipment, and medications to all investigational sites. Evolus also provided funding to contract organizations involved in data collection, analysis, and reporting of the results. R. L. Avelar is the Head of R&D and Chief Medical Officer for Evolus, Inc., and receives compensation in salary, stock, and stock options. Before and during the time of these studies and manuscript preparation, J. E. Gross was the Chief Scientific Officer at Evolus, Inc.; he will receive royalty and milestone payments should the product be approved. Anneke Jonker of Medical Writing Associates, West Vancouver, BC, Canada, provided technical assistance with manuscript preparation and submission; she holds stock in Evolus, Inc." This study was a phase III trial identical to NCT02334423. Both studies had the same reference than the NCT02334423

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Random numbers had been generated using SAS PROC PLAN (SAS Institute, Inc., Cary NC); a block randomization scheme with no stratification was used, with each block containing assignments for 3 prabotulinumtoxinA subjects and 1 placebo subject"... page 1382-3 Comment: we considered this low risk of bias
Allocation concealment (selection bias)	Unclear risk	No information Comment: we considered this unclear risk of bias because the authors did not explain the methods used to maintain the allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote:"At each study site, designated protocoltrained study personnel selected a study vial, which contained either 100 U of prabotulinumtoxinA or placebo according to the randomization schedule, reconstituted the vial with 2.5 mL of 0.9% sterile saline, filled the injection syringe, and provided it to the investigator in a blinded manner."...page 1383 Comment: we considered this low risk of bias
Blinding of outcome assessment (detection bias)	Low risk	Quote:"At each study site, designated protocoltrained study personnel selected a study vial, which contained either 100 U of prabotulinumtoxinA or place-

Beer 2019b *(Continued)*

All outcomes		bo according to the randomization schedule, reconstituted the vial with 2.5 mL of 0.9% sterile saline, filled the injection syringe, and provided it to the investigator in a blinded manner."...page 1383 Comment: we considered this low risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: " figur2 3...page 1385 Comment: we considered this low risk of bias
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported Comment: we considered this low risk of bias
Other bias	Low risk	We considered this study at low risk of other bias

Bertucci 2020

Study characteristics	
Methods	**Study design**- multicentre, randomised, double-blinded, placebo-controlled, parallel-design. Phase III in glabellar lines (SAKURA 1 and SAKURA 2). NCT03014622 and NCT03014635 **Study date**-started December 5, 2016, and ended on 14 November 2017 **Study setting**- outpatients, 30 centres (24 in the USA and 6 in Canada
Participants	**Randomised** 609 participants with age range 50.2 ± 10.56 years in DaxibotulinumtoxinA group, and 49.8 ±10.58 years in placebo group. Gender 335/405(88.1%) females in DaxibotulinumtoxinA group, and 175/204 (85.8%) in placebo group. Prior treatment- 213/405(52.6%) in DaxibotulinumtoxinA group and 105/204(51.5%) in placebo group. **Inclusion criteria** • Provide written informed consent including authorisation to release health information • Moderate (2) or severe (3) glabellar lines during maximum frown based on the Investigator Global Assessment Frown Wrinkle Severity (IGA-FWS) scale • Moderate (2) or severe (3) glabellar lines during maximum frown based on the Patient Frown Wrinkle Severity (PFWS) scale • Willing and able to follow all trial procedures, attend all scheduled visits, and successfully complete the trial **Exclusion criteria** • Any neurological condition that may place the participant at increased risk with exposure to botulinum toxin type A, including peripheral motor neuropathic diseases such as amyotrophic lateral sclerosis and motor neuropathy, and neuromuscular junctional disorders such as Lambert-Eaton syndrome and myasthenia gravis • Active skin disease, infections or inflammation at the injection sites • Plan to receive botulinum toxin type A anywhere in the face through the duration of the study • History of allergy or sensitivity to any botulinum toxin preparations or to any component of the test article • Current enrolment in an investigational drug or device trial or participation in such a trial within the last 30 days prior to screening through end of trial **Severity of the disease**- moderate 252/405(62.2%) in DaxibotulinumtoxinA group, and 133/204(65.2%) in placebo group.

Bertucci 2020 *(Continued)*

	Ethinicity- caucasian 353/405 (87.2%),19/405(4.7%) African American, 18/405 (4.4%) Asian, 15/405 (3.7%) other in DaxibotulinumtoxinA group; Caucasian 173/204 (87.4.8%),11/204(5.4%) African American, 7/204 (3.4%) Asian, 13/204 (6.4%) other in
Interventions	**Duration:** 36 weeks **Intervention** DaxibotulinumtoxinA 40 U, (N = 405), two 0.1-mL injections into each corrugator muscle and one 0.1-mL injection into the procerus muscle. Intramuscular injection in glabella region **Comparator** Placebo (N = 204), two 0.1-mL injections into each corrugator muscle and one 0.1-mL injection into the procerus muscle.lintramuscular injection in glabella region.
Outcomes	**Primary outcomes** • Proportion of participants who achieve the following status concurrently at Week 4: A score of 0 or 1 (i.e. none or mild wrinkles in severity) on both IGA-FWS and PFWS assessments; At leas tone-point improvement from baseline on both IGA-FWS and PFWS assessments [Time Frame: Week 4] **Secondary outcomes** • Proportion of participants who achieve a score of ≥ 1 on the investigator's assessment of GAIS [Time Frame: From Week 2 to Week 24] • Proportion of participants who achieve a score of ≥ 1 on the participant's self-assessment of GAIS [Time Frame: From Week 2 to Week 24] • Duration of the treatment • Adverse events
Notes	"We thank Revance Therapeutics, Inc, for sponsoring the studies and funding the development of the manuscript."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote:"An independent statistician produced a computer-generated randomization code (using SAS PROC PLAN [SAS Institute, Inc, Cary, NC])...page 840 Comment: we considered this low risk of bias
Allocation concealment (selection bias)	Low risk	Quote:" Study treatments were provided in sequentially numbered clinical trial kits containing single use 50-U vials,"... page 840
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote:"All vials looked identical to each other before and after reconstitution"...page 840 Comment: we considered this low risk of bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote:"All vials looked identical to each other before and after reconstitution"...page 840 Comment: we considered this low risk of bias
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote:"Discontinuations were attributable predominantly to withdrawal of consent and loss to follow-up, with none being due to adverse events (Supplemental Fig 1)...page 841

Bertucci 2020 *(Continued)*

		Comment: we considered this low risk of bias
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported Comment: we consider low risk of bias
Other bias	Low risk	Pharmaceutical sponsored

Brandt 2009

Study characteristics	
Methods	**Study design**- multicentre, randomised, double-blind, placebo-controlled, parallel-design, phase III trial in glabellar lines **Study date**- start (18 Nov 2005), end (28 July 2006) **Study setting**- outpatients from three centres
Participants	**Randomised**- 158 participants, with mean age of 43.1 ± 10.3 years in BontA group; 42.7 ± 9.1 years in placebo group; 42.9 ±9.9 years total population. Gender: 90/105 (86%) female, 15/105 (14%) male in BontA group; 45/53 (85%) female, 8/53 (15%) male in placebo group; 135/158 (85%) female, 23/158 (15%) male total population **Inclusion criteria** • Patients aged 18 and older provided written informed consent. Eligible participants had moderate to severe glabellar lines according to an independent investigator and patient self-assessment at baseline, and female subjects of child-bearing potential had to have a negative pregnancy test and adequate contraceptive use **Exclusion criteria** • Previous treatment with botulinum toxin type A, facial plastic surgery procedures such as tissue augmentation or brow lifts, dermal resurfacing, or any procedure or concurrent therapy considered by the investigator to interfere with the evaluation of the study medication • Patients were also excluded because of pregnancy • Active infection in the glabellar area • Chronic drug or alcohol abuse • Clinically-diagnosed anxiety or depression • Current facial palsy or neuromuscular junction disorders, or any other condition or circumstance that might pose a risk to the patient or interfere with the ability to acquire satisfactory clinical data **Severity of disease**- moderate to severe glabellar lines **Ethnicity**- BontA 52/105 (50%) white, 50/105 (48%) Hispanic, 2/105 (2%) African American, 1/105 (1%) Asian; placebo 25/53 (47%) Caucasian, 25/53 (47%) Hispanic, 2/53 (4%) Asian, 1/53 (2%) other; Total population 77/158 (49%) Caucasian, 75/158 (47%) Hispanic, 2/158 (1%) African American, 3/158 (2%) Asian, 1/158 (1%) other
Interventions	**Duration of study**- 24 weeks **Intervention** • AbobotulinumtoxinA(50 U) in glabellar lines, 0.05 mL per site/ 5 points (N = 105) **Comparator**

Brandt 2009 *(Continued)*

	• Placebo in glabellar lines, 0.05 mL per site/ 5 points (N = 53)
Outcomes	**Primary outcome** • Response at maximum frown at Day 30, evaluated according to the investigator and subject individually and as a composite response **Secondary outcomes** • Response (at maximum frown and at rest) at Days 14, 30, 60, 90, 120, 150, and 180, with participants also using a 9-point dynamic scale for global assessment of the change in the appearance of glabellar lines at those time points • Onset and duration of treatment • Subgroup analysis by gender and age. • Adverse events (treatment-emergent adverse events)
Notes	"Medicis Aesthetics, Inc. provided funding and the material Dysport for this study. Dr. Baumann is a consultant and advisory board member for the both Medicis and Allergan."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Subjects were randomised using a unique randomisation code generated by a Beaufour Ipsen Industrie SAS randomisation manager (SAS Institute, Inc., Cary, NC)." page 1895 Comment: we considered this low risk of bias
Allocation concealment (selection bias)	Unclear risk	No information available to allow a judgment Comment: we considered this unclear risk of bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Treatment vials (BoNT-A or placebo) were not identifiable apart from a unique sequential number, and the investigator (or trained designee) prepared the individual's study dose for injection" page 1895 Comment: we considered this low risk of bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Investigators did not evaluate subjects for safety at Day 14 or until after the efficacy assessment at Day 30 to maintain blinding, and the blind was not broken during the study," page 1895 Comment: we considered this low risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Of the 158 subjects enrolled, 143 (91%) completed the 180-day study: 92% in the active group and 87%in the placebo group" page 1896-7 Comment: we considered this low risk of bias
Selective reporting (reporting bias)	High risk	Quote: "the co-primary endpoint- investigator assessment: 89.5%, vs 7.5% placebo", but in the graphic figure 2,placebo = 3.9% page 1897 Data was different from table to the graphic about placebo Comment: we considered this high risk of bias. We sent an e-mail to Dr Brandt on 27 October 2015. Dr Brandt passed away. Another two messages by e-mail were sent to Dr Baumann on 14 November 2015 and on 21 November 2015. No reply until the date.

Brandt 2009 *(Continued)*

Other bias	Low risk	We considered this study at low risk of other bias

Carruthers 2002

Study characteristics	
Methods	**Study design**- multicentre, double-blind, randomised, placebo-controlled parallel design study in glabellar lines **Study date**- no information **Study setting**- outpatients of 14 centres
Participants	**Randomised**- 264 participants, with a mean age of 44.7 ± 11 years in BontA group; 44.3 ± 11.3 years in placebo group. Gender: 173/203 (85.2%) female, 30/203 (14.8%) male in BontA group; female 47/61 (77%), 14/61 (23%) male in placebo group **Inclusion criteria** • Patients had to be between 18 and 75 years of age with glabellar lines of at least moderate severity at maximum frown (graded on a 4-point scale, ranging from 0 = none to 3 = severe). There was no requirement for a minimum severity rating for glabellar lines at rest. Patients may have had prior BTX-A treatment for glabellar lines, provided that they met this severity requirement. Patients also had to be in medically stable condition, able to complete the entire study, and able to comply with study instruction. **Exclusion criteria** • Any disorder (e.g. myasthenia gravis or Eaton-Lambert syndrome) or use of any agent (e.g. aminoglycoside antibiotics) that might interfere with neuromuscular function • Any other condition or situation that might put the patient at significant risk, confound the study results (e.g. significant pre-existing brow or eyelid ptosis), or interfere with the patient's participation in the study • Allergy or sensitivity to either study treatment • Had participated in another clinical study within 30 days of the study start date • Patients planning other facial cosmetic procedures during the study period • Pregnancy, lactating, or planning a pregnancy. **Severity of disease**- moderate to severe glabellar lines at maximum frown **Ethnicity**- 174/203 (85.7%) white, Hispanic 16/203 (7.9%), black 7/203 (3.4%), Asian 3/203 (1.5%), other 3/203(1.5%) in BontA; 49/61 (80.3%) white, Hispanic 6/61 (9.8%), black 1/61 (6.6%), Asian 4/61 (6.6%), other 1/61(1.6%) in placebo
Interventions	**Duration of study**- 4 weeks **Intervention** • OnabotulinumtoxinA 20 U, 0.1mL/site, 5 points in glabellar lines (N = 203) **Comparator** • Placebo 0.5mL, 0.1mL/site, 5 points in glabellar lines (N = 61)
Outcomes	**Primary outcome** • Physician's assessment: physicians graded glabellar line severity during every visit, both at maximum frown and at rest on a scale of 0 to 3.

Carruthers 2002 *(Continued)*

Secondary outcomes

- Patients' assessment: patients graded the change in appearance of glabellar lines at every post-injection visit by responding to the question, “How would you rate the change in the appearance of your glabellar lines compared with immediately before your injection?” The patients scored the change on a 9-point scale.
- Adverse events.

Notes	"Funding sources: Allergan, Inc. Disclosure: Drs Carruthers and Lowe are paid consultants of Allergan"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "At each study centre, randomisation to treatment was stratified by age group (≤50 years and ≥ 51 years). Within each age group, patients were randomly assigned in blocks of 8, with a ratio of 3:1 (BTX-A/placebo)." page 842 Comment: we considered this unclear risk of bias because the authors did not explain how they randomised the participants
Allocation concealment (selection bias)	Unclear risk	Quote: "At each study centre, randomisation to treatment was stratified by age group (≤50 years and ≥ 51 years). Within each age group, patients were randomly assigned in blocks of 8, with a ratio of 3:1 (BTX-A/placebo)." page 842 Comment: we considered this unclear risk of bias because the authors did not explain the methods used for maintaining the allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Randomization block size was not divulged to the physician investigators to help maintain blinding. In addition, two investigators co-evaluated each patient on day 0, one of whom was to do the day 7 assessment, while the other was to do the day 30 assessment. This prevented the evaluation on day 30 from being influenced by the patient’s appearance on day 7." page 842 Comment: we considered this unclear risk of bias due to the visual aspect of BontA and placebo was not described.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Randomization block size was not divulged to the physician investigators to help maintain blinding. In addition, two investigators co-evaluated each patient on day 0, one of whom was to do the day 7 assessment, while the other was to do the day 30 assessment. This prevented the evaluation on day 30 from being influenced by the patient’s appearance on day 7." page 842 Comment: we considered this low risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "two patients (both in the BTX-A group) did not complete the study. One moved out of state, and the other was unable to keep to scheduled appointments for personal reasons. A third patient was randomly assigned (placebo group) but declined treatment because of the visit schedule requirements." page 841 Comment: we considered this low risk of bias
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported Comment: we considered this low risk of bias
Other bias	Low risk	We considered this study at low risk of other bias

Carruthers 2003a

Study characteristics	
Methods	**Study design**- randomised, double-blind, dose-ranging, parallel-design in forehead lines in female **Study date**- no information **Study setting**- no information
Participants	**Randomised**- 59 women, with age between 18-50 years old. Gender 100% female **Inclusion criteria** • Women 18 to 50 years of age, with moderate to severe horizontal forehead rhytides at maximum brow elevation **Exclusion criteria** • Significant brow ptosis, had previously received treatment with botulinum toxin type A • They were taking any agent (e.g. aminoglycoside antibiotics) or had any disorder (e.g. myasthenia gravis, Eaton-Lambert syndrome) that might interfere with neuromuscular function • Previous cosmetic surgery or visible scars in the treatment area • Profound atrophy or weakness in the target muscles • Known allergy or sensitivity to the study medication **Severity of disease**- moderate to severe horizontal forehead rhytides at maximum brow elevation **Ethnicity**- no information
Interventions	**Duration of study**- 48 weeks **Intervention/Comparator** • OnabotulinumtoxinA (16 U), 0.08 mL/ site, 8 points in forehead region, procerus muscles (two injection sites), frontalis muscle (four injection sites), and the lateral orbicularis oculi muscles (two injection sites (N = 20) • OnabotulinumtoxinA (32 U), 0.08 mL/ site, 8 points in forehead region, procerus muscles (two injection sites), frontalis muscle (four injection sites), and the lateral orbicularis oculi muscles (two injection sites (N = 19) • OnabotulinumtoxinA (48 U), 0.08 mL/ site, 8 points in forehead region, procerus muscles (two injection sites), frontalis muscle (four injection sites), and the lateral orbicularis oculi muscles (two injection sites (N = 20)
Outcomes	**Primary outcome** • Patients were assessed at injection (baseline) and at weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48 after injection at maximum frown and at rest **Secondary outcomes** • Relapse rate-contraction and repose between 2-4 weeks of outcome • Adverse events
Notes	"Drs. Carruthers are consultants to Allergan, and supplies for this study were provided by Allergan."

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Carruthers 2003a *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomised to receive 16, 32, or 48 U of" page 462 Comment: we considered this unclear risk of bias because the authors did not detailed how they randomised the participants
Allocation concealment (selection bias)	Unclear risk	No information available to allow a judgment Comment: we considered this unclear risk of bias
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "A Prospective, Double-Blind, Randomized" page 461 Comment: we considered this unclear risk of bias because the authors did not explain how they blinded the participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "A Prospective, Double-Blind, Randomized" page 461 Comment: we considered this unclear risk of bias because the authors did not explain how they blinded the outcome assessor
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Only two patients were lost to follow-up and did not complete treatment" page 461 Comment: we considered this unclear risk of bias because the authors did not mention the reasons for lost to follow up or which group these patients came from
Selective reporting (reporting bias)	High risk	Quote: "No difference between the groups (observer evaluation), although by self-assessment, patients in the 32-U botulinum toxin type A group had a significantly higher FWS at contraction than either the 16- or 48-U botulinum toxin type A treatment groups" page 461 -There was missing data, and figure seven showed a divergent data from text. page 461 Comment: we considered high risk of bias because group imbalance and missing data, we sent an e-mail on June 24 2015, answered on June 25 2015 "The study was done almost 10 years ago. The data will be buried in our basement. Getting out the raw data would be very labor intensive. Alastair."
Other bias	Low risk	We considered this study at low risk of other bias

Carruthers 2003b

Study characteristics	
Methods	**Study design**- multicentre, double-blind, randomised, placebo-controlled, parallel-design, in glabellar lines **Study date**- start (April 1999), end (November 1999) **Study setting**- outpatients
Participants	**Randomised**- 273 participants, with a mean age of 47.7 ± 11.4 years in BontA group, 46.4 ± 12 years in placebo group. Gender: 161/202(79.7%) female, 41/202 (20.3%) male in BontA group; 59/71(83.1%) female, 12/71(16.9%) male in placebo group **Inclusion criteria**

Carruthers 2003b *(Continued)*

- Patients were required to be 18 to 75 years of age with glabellar lines of at least moderate severity at maximal frown (on a scale of none, mild, moderate, or severe). Patients could have undergone prior botulinum toxin treatment for glabellar lines, provided that they met this severity requirement. There was no minimal severity requirement for the resting appearance of glabellar lines. Patients were also required to be able to complete the study and to comply with study instructions.

Exclusion criteria

- Any disorder (e.g. myasthenia gravis or Eaton-Lambert syndrome) or were taking any agent (e.g. aminoglycoside antibiotics) that might interfere with neuro- muscular function
- Uncontrolled systemic disease, or if any other condition or situation existed that might have put the patient at significant risk, confounded the study results (e.g. significant pre-existing brow or eyelid ptosis), or interfered with the patient's participation in the study
- Allergy or sensitivity to botulinum toxin
- Had participated in another clinical study within 30 days of the study start date
- Patients planning other facial cosmetic procedures during the study period
- Pregnancy, breast-feeding, or planning to become pregnant during the study period

Severity of disease- glabellar lines of at least moderate severity at maximal frown

Ethnicity- 167/202 (82.7%) Caucasian, 14/202 (6.9%) black, 6/202 (3%) Asian, 14/202 (6.9%) Hispanic, 1/202 (0.5%) other in BontA; 60/71 (84.5%) Caucasian, 6/71 (8.5%) black, 0 (0%) Asian, 5/71 (7%) Hispanic, 0 (0%) other in placebo

Interventions	**Duration of study**- 4 weeks **Intervention** • OnabotulinumtoxinA (20 U), 0.5mL, 0.1mL/site, 5 points, two in each corrugator muscle and one in the procerus muscle (N =202) **Comparator** • Placebo = 0.5mL, 0.1mL/site, 5 points, two in each corrugator muscle and one in the procerus muscle (N=71)
Outcomes	**Primary outcome** • Physicians' assessment- Glabellar Line Severity Score- maximum frown by investigator day 7, 30 and 120,responder rate-(percentages of patients with follow-up severity scores of none or mild at maximal frown) and at rest **Secondary outcomes** • Subgroup analysis by age moderate -severe lines,response,mean severity scores • Patient global assessment scale • Participant's assessment responder rate • Adverse events
Notes	"This study was sponsored by Allergan, Inc. (Irvine, Calif.). Dr. Carruthers owns stock in Allergan, Inc. Dr. Lowe has received research grants and consultant payments from and owns stock in Allergan, Inc."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomly assigned to receive either botulinum toxin or placebo, in a 3:1 ratio, by using a block-of-eight design," page 1090

Carruthers 2003b *(Continued)*

		Comment: we considered this unclear risk of bias because the authors did not explain how they randomised the participants
Allocation concealment (selection bias)	Unclear risk	Quote: "Patients were randomly assigned to receive either botulinum toxin or placebo, in a 3:1 ratio, by using a block-of-eight design" page 1090 Comment: we considered this unclear risk of bias because the authors did not explain the methods used for maintaining the allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "vials of Botox and placebo had identical investigational labels, which prevented identification of the contents." page 1090 Comment: we considered this low risk of bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "vials of Botox and placebo had identical investigational labels, which prevented identification of the contents." page 1090 Comment: we considered this low risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Four subjects (two in the botulinum toxin group and two in the placebo group) were lost to follow-up monitoring during the study (Table I). One additional patient was enrolled but not treated. The remaining 268 patients completed the study" page 1092 Comment: we considered this low risk of bias
Selective reporting (reporting bias)	High risk	Subgroup analysis, better results in subpopulation younger than 50 years old. No data showed Comment: we considered this high risk of bias
Other bias	Low risk	We considered this study at low risk of other bias

Carruthers 2004

Study characteristics	
Methods	**Study design**- multicentre, randomised, placebo- controlled, parallel -design in glabellar lines. Phase one- randomised clinical trial, double-blind, duration 4 months two arms (BontA versus placebo), and phase two- open-label, duration 8 months **Study date**- start (Feb 1999), end (June 2000) **Study setting**- outpatients from 30 centres
Participants	**Randomised**- 537 participants, with a mean age of 46.2 years in BontA group; 45.5 years in placebo group; and 46 years total population. Gender 334/405 (82.5%) female, 71/405 (17.5%) male in BontA group; 106/132 (80.3%) female, 26/132 (19.7%) in placebo group; 440/537 (81.9%) female, 97/537 (18.1%) total population **Inclusion criteria** • Patients aged 18 to 75 years with moderate to severe glabellar frown lines at maximum frown (severity score of 2 or 3 on the facial wrinkle scale [FWS]), as assessed by the investigator, were eligible for inclusion in the study. The FWS rates the severity of glabellar frown at rest as 0 (none), 1 (mild), 2 (moderate), or 3 (severe) **Exclusion criteria**

Carruthers 2004 *(Continued)*

- Patients were not eligible if they have any disorder (such as myasthenia gravis, Eaton-Lambert Syndrome) or agent (such as aminoglycoside) that might interfere with neuromuscular function, or any condition that might put the patient at risk or confound outcome(such as significant pre-existing brow or eyelid ptosis), or interfere with patient's participation in the study
- Also excluded were individuals who had glabellar lines that were so severe that they could not be lessened by spreading them apart with the fingers
- Allergy or sensitivity to any study component
- Participated in another clinical trial within 30 days of the study start date
- Patients planning other facial cosmetic procedures during the study period
- Pregnancy, breastfeeding, or planning a pregnancy during the study
- Facial surgery recently

Severity of the disease- moderate to severe glabellar frown lines at maximum frown

Ethnicity- BontA: 341/405 (84.2%) Caucasian, 21/405 (5.2%) black, 9/405 (2.2%) Asian, 30/405 (7.4%) Hispanic, 4/405 (1%) other; placebo: 109/132 (82.6%) Caucasian, 28/132 (5.3%) black, 4/132 (3%) Asian, 11/132 (8.3%) Hispanic,1/132 (0.8%) other; total 450/537 (83.8%) Caucasian, 28/537(5.2%) black, 13/537(2.4%) Asian, 41/537 (7.6%) Hispanic, 5/537 (0.9%) other

Interventions	**Duration of study**- Phase one- 16 weeks, phase two 32 weeks **Intervention** • OnabobulinumtoxinA (20 U), 0,1mL/site, 5 points glabellar lines (N = 405) **Comparator** • Placebo, 0.5m, 0,1mL/site, 5 points in glabellar lines (N = 132)
Outcomes	**Primary outcome** • Physician's assessment of glabellar lines (FWS) at maximum frown, and at rest **Secondary outcome** • Patient self assessment response rate in contraction and repose, subgroup analysis (moderate/severe), antibody • Adverse events
Notes	The first phase of this study was previous published as Carruthers 2002; Carruthers 2003b so this first phase was not reconsidered double count of patients

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "4-month, randomised, double-blind" page2 Comment: we considered this unclear risk of bias because the authors did not show how they randomised the participants (phase 1). Phase 2 was open-label
Allocation concealment (selection bias)	Unclear risk	No information available to allow a judgment Comment: we considered this an unclear risk of bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "vials of botulinum toxin patients and placebo were identical,identified only by patient number and study number, and required identical dilution and injection procedure" page 3-4

Carruthers 2004 *(Continued)*

		Comment: we considered this low risk of bias (Phase 1). Phase 2 was open-label.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "vials of botulinum toxin patients and placebo were identical,identified only by patient number and study number, and required identical dilution and injection procedures.To help maintain blinding randomisation block size was not divulged to the physician investigator" page2 Comment: we considered this low risk of bias (Phase 1). Phase 2 was open-label
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	At phase 1, there were 4 withdraws at BontA group due to the following reasons: lost of follow-up (2), personal reasons (1) and other (1). For placebo group, the chart showed 4 withdraws but in table 2, there were 5 patients (inconsistence) due to the following reasons: lost of follow-up (1), personal reasons (2), other (2). Comment:we considered an unclear risk of bias. Despite a low number of withdraw and a balance between interventions group regarding number and reason of withdraw, we are not sure about in which extension the inconsistence stated below could affect the results An e-mail sent on 24 June 2015, answer on 25 June 2015 "The study was done almost 10 years ago. The data will be buried in our basement. Getting out the raw data would be very labor intensive. Alastair."
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported. Comment: we considered this a low risk of bias
Other bias	Low risk	We considered this study at low risk of other bias

Carruthers 2005a

Study characteristics	
Methods	**Study design**- single-centre, double-blind, randomised, parallel-design, dose-ranging in glabellar lines in men **Study date**- no information **Study setting**- outpatients, one centre (Canada)
Participants	**Randomised** 80 men, with a mean age of 44.2 ± 14.6 years in BontA 20u group; 38.6 ± 8.2 years in BontA 40u group; 44.0 ± 12.8 years in BontA 60u group; 39.6 ± 13.2 years in BontA 80u group. Gender 100% male **Inclusion criteria** • Males between 18 and 65 years of age with moderate to severe (grade 2 and 3- FWS) glabellar at maximum contraction **Exclusion criteria** • Use of any agent (e.g. aminoglycoside antibiotics) that could interfere with neuromuscular transmission or any condition(e.g. Eaton-Lambert syndrome, myasthenia gravis., excessive weakness, or atrophy of target muscles that could amplify the effects of treatment with botulinum toxin type A. • Allergy or sensitivity to any component of the study medication

Carruthers 2005a *(Continued)*

	• Prior cosmetic procedures, soft tissue augmentation, or visible scars on the treatment area; or had received treatment with botulinum toxin within 1 year of baseline evaluation **Severity of disease**- moderate to severe glabellar lines at maximum frown **Ethnicity**- BontA 20 U- 100% white; 40 U- 18/20 white, 2/20 other; 60 U- 19/20 white and 1/20 other; 80 U 16/20 white, 1/20 Hispanic and 3/20 other
Interventions	**Duration of study**- 52 weeks I**ntervention/Comparator** • OnabotulinumtoxinA (20 U), in seven points 20% of total dose in procerus muscle, 15% in each corrugator muscle, 50% over orbicularis muscle (15% each two in the medial canthus and 10% into each above mid pupillary line) (N = 20) • OnabotulinumtoxinA (4 0U, in seven points 20% of total dose in procerus muscle, 15% in each corrugator muscle, 50% over orbicularis muscle (15% each two in the medial canthus and 10% into each above mid pupillary line) (N = 20) • OnabotulinumtoxinA (60 U), in seven points 20% of total dose in procerus muscle, 15% in each corrugator muscle, 50% over orbicularis muscle (15% each two in the medial canthus and 10% into each above mid pupillary line) (N = 20) • OnabotulinumtoxinA (80 U), in seven points 20% of total dose in procerus muscle, 15% in each corrugator muscle, 50% over orbicularis muscle (15% each two in the medial canthus and 10% into each above mid pupillary line) (N = 20)
Outcomes	**Primary outcome** • Observer assessment, severity of wrinkles at maximum frown (FWS) compared to baseline **Secondary outcomes** • Maximum treatment effect(observer assessment) • Response rate (peak between 2weeks to 4 weeks) by investigator • Duration of effect • Relapse time by investigator • Responders rate(any improvement). Self assessment (scale 0 to 6) • Global assessment • Adverse events
Notes	Drs Carruthers are consultants of Allergan

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "prospective, double-blind, randomised" page 1297 "participants were randomly assigned into one of four possible treatment groups using a block-of-eight design" page 1298 Comment: we considered this unclear risk of bias because the authors did not explain how they randomised the participants
Allocation concealment (selection bias)	Unclear risk	No information available to allow a judgment Comment: we considered this unclear risk of bias
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "to maintain blind, vials were prepared by a registered nurse who took no further part in the study" page 1298

Carruthers 2005a *(Continued)*

		Comment: we considered this unclear risk of bias due to the visual aspect of intervention and placebo was not detailed
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "to maintain blind, vials were prepared by a registered nurse who took no further part in the study" page 1298 Comment: we considered this unclear risk of bias due to the visual aspect of intervention and placebo was not detailed.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Two participants withdrew consent, and one discontinued without providing information" page 1299 Comment: we considered this unclear risk of bias, because the authors did not mention the reason of drop out neither which group these patients came from
Selective reporting (reporting bias)	High risk	Patient self assessment no data, only P value. Comment: e-mail sent on 24 June 2015, answer on 25 June 2015 "The study was done almost 10 years ago. The data will be buried in our basement. Getting out the raw data would be very labor intensive. Alastair."
Other bias	Low risk	We considered this study at low risk of other bias

Carruthers 2005b

Study characteristics	
Methods	**Study design**- single centre, double-blind, randomised, dose-ranging trial followed by a 1-year open-label extension period. **Study date**- no information **Study setting**- outpatients from a private clinic, one centre (Canada)
Participants	**Randomised** 80 women, with a mean age of 49 ± 8.9 years in BontA 10u group; 49.9 ± 9.3 years in BontA 20u group; 46.2 ± 9.1 years in BontA 30u group; and 45.3 ± 8.2years in BontA 40u group. Gender 100% female **Inclusion criteria** • Female, any race, aged 18-65 years, with at least moderate (score ≥ 2) glabellar rhytides at maximum frown, as evaluated by a trained observer (graded on a 4- point Facial Wrinkle Scale ranging from 0 = none to 3 = severe). Participants also had to be mentally competent and understand the study requirements **Exclusion criteria** • Use of any agent (e.g. aminoglycoside antibiotics) that might interfere with neuromuscular transmission or any condition (e.g. Eaton-Lambert syndrome, myasthenia gravis, excessive weakness, or atrophy of tar-get muscles) that could amplify the effects of botulinum toxin type A treatment • Allergy or sensitivity to any component of the study medication • Prior cosmetic procedures, soft tissue augmentation, or visible scars on the treatment area; had received botulinum toxin type A treatment within 1 year of baseline evaluation • Pregnancy, planning a pregnancy, or nursing. U group, 7/20 (35%) BontA 30 U, 3/20 (15%) BontA 40 U. Severe at maximum frown: 15/20 (75%) BontA10 U, 20/20 (100%) BontA 20 U, 19/20 (95%) BontA 30 U, 15/20 (75%) BontA 40 U.

Carruthers 2005b *(Continued)*

	Reported by self-evaluation questionnaire: severe at rest: 3/20(15%) BontA 10 U, 3/20 (16%) BontA 20 U, 9/20 (45%) BontA 30 U, 4/20 (20%) BontA 40 U maximum frown 13/20 (65%) BontA 10 U, 15/20 (79%) BontA 20 U, 19/20 (95%) BontA 30 U, 14/20 (70%) BontA 40 U. **Ethnicity**- BontA 10 U, 20U, 30 U- 95% Caucasian, 40 U- 100% Caucasian.
Interventions	**Duration of study**- phase one- one year, phase two- one year **Comparator/Comparator**- (phase one) • OnabotulinumtoxinA (10 U), 0.4 mL in all groups (procerus, 0.08 mL; corrugator and medial orbicularis, 0.06 mL each on both sides; and mid pupillary orbicularis, 0.04 mL on each side (N = 20) • OnabotulinumtoxinA (20 U), 0.4 mL in all groups (procerus, 0.08 mL; corrugator and medial orbicularis, 0.06 mL each on both sides; and mid pupillary orbicularis, 0.04 mL on each side (N = 20), • OnabotulinumtoxinA (30 U), 0.4 mL in all groups (procerus, 0.08 mL; corrugator and medial orbicularis, 0.06 mL each on both sides; and mid pupillary orbicularis, 0.04 mL on each side (N = 20) • OnabotulinumtoxinA (40 U), 0.4 mL in all groups (procerus, 0.08 mL; corrugator and medial orbicularis, 0.06 mL each on both sides; and mid pupillary orbicularis, 0.04 mL on each side (N = 20) **Phase two** • OnabotulinumtoxinA (30 U),0.4 mL in all groups (procerus, 0.08 mL; corrugator and medial orbicularis, 0.06 mL each on both sides; and mid pupillary orbicularis, 0.04 mL on each side (N = 40)
Outcomes	**Primary outcome** • Observer's assessment of the severity of wrinkles at both maximum frown and repose compared with baseline. Wrinkle severity was measured using a 4-point Facial Wrinkle Scale. Responder rate at maximum frown and repose was defined as the percentage of participants with a rating on the wrinkle scale of none or mild. Relapse was defined as a return to baseline for two consecutive visits (assessed at maximum frown and repose) and a return to baseline ability to frown by comparison with pretreatment photo- graphs **Secondary outcomes** • Participant's self-assessments of wrinkle severity at both maximum frown and repose (using the Facial Wrinkle Scale) in double-blind phase • Adverse events
Notes	"This study was funded by a grant from Allergan, INC. Alastair Carruthers and Jean Carruthers are Allergan consultants."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "This study was a 1-year, double-blind, randomised, dose- ranging trial" page 414 Comment: we considered this a unclear risk of bias because the authors did not explain how they randomised the participants
Allocation concealment (selection bias)	Unclear risk	Quote: "For the double-blind trial, subjects were randomised into one of four possible treatment groups." page 415 Comment: we considered an unclear risk of bias, the authors did not mentioned methods to maintain allocation concealment

Carruthers 2005b *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "One physician (S.S.) prepared all doses in identical syringes marked only with the subject number. This physician did not see the subjects or administer any of the injections" page 415 Comment: we considered this low risk of bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "One physician (S.S.) prepared all doses in identical syringes marked only with the subject number. This physician did not see the subjects or administer any of the injections" page 415 Comment: we considered this a low risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "80 subjects participated, 74 completed the study. Four patients withdrew the consent, and two were lost to follow-up." page 416 Comment: we considered this a low risk of bias
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported. Comment: we considered this a low risk of bias
Other bias	High risk	Quote: "Group 40u and 30u of BontA were younger than the others. A post hoc pair-wise comparison of trained observer assessments, however, demonstrated that baseline Facial Wrinkle Scale scores at maximum frown were significantly higher in the 20 U group than in both the 10 and 40 U groups (P = 0.047)." page 416 Quote: "percentage of subjects rated as severe in the 20 U group at baseline was significantly higher (by 25%) than both the 10 and 40 U groups " page 421 Comment: we considered this a high risk of bias

Carruthers 2009

Study characteristics	
Methods	**Study design**- single-centre, randomised, double-blind, dose-ranging, parallel-design in upper facial wrinkles **Study date**- no information **Study setting**- outpatients from one centre (Canada)
Participants	**Randomised**- 60 women, with a mean age of 42.6 ±8.3 years in BontA 32 U group, 42.5 ± 9.0 years in BontA 64 U group, and 39.5 ± 8.8 years in BontA 96u group. Gender 100% female **Inclusion criteria** • Female patients of any race, between 18 and 65 years of age, were eligible for the trial. Those of childbearing potential had to have a negative urine pregnancy test result at the baseline visit and practice a reliable method of contraception throughout the study. Patients were required to have upper facial rhytids that met the following specifications on a 4- point facial wrinkle scale (FWS) (0 = none; 1 = mild; 2 = moderate; and 3 = severe as determined at maximum attempted muscle contraction by a trained observer): moderate or severe glabellar lines; mild, moderate, or severe forehead lines; and bilaterally symmetric moderate or severe crow's feet **Exclusion criteria** • Breast-feeding was not allowed during the study

Carruthers 2009 *(Continued)*

	• Any disorder, condition, or situation that would impair their ability to comply with the study or that could potentially confound results as previously described • Therapy with botulinum toxin of any serotype within 120 days preceding the baseline visit precluded participation **Severity of disease**- upper rhydites, glabella, crow's feet **Ethnicity**- BontA20 U group 19/20 white, 1/20 Asian; BontA 64 U group 19/20 white, 1/20 Asian; BontA 96 U group 19/20 white, 1/20 other
Interventions	**Duration of study**- 52 weeks I**ntervention/Comparator** • OnabotulinumtoxinA (32 U),5 injections in the glabellar, 5 injections in the forehead, and 3 injections in each lateral canthal area for crow's feet (N = 20) • OnabotulinumtoxinA (64 U), 5 injections in the glabellar, 5 injections in the forehead, and 3 injections in each lateral canthal area for crow's feet (N = 20) • OnabotulinumtoxinA (96 U), 5 injections in the glabellar, 5 injections in the forehead, and 3 injections in each lateral canthal area for crow's feet (N = 20)
Outcomes	**Primary outcome** • Facial Line Outcome (FLO-11) **Secondary outcome** • Self -Perception of Age(SPA)
Notes	"Supported by a grant from Allergan Inc, Irvine, California. Disclosure: Drs Carruthers and Carruthers are consultants and investigators for and receive honoraria from Allergan Inc, which sponsored the study and the preparation of the article. They are also consultants and investigators for Merz GmbH and Solstice Neurosciences Inc."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "a single-center, prospective, double- blind, randomised, dose-comparisons" page 973 Comment: we considered this unclear risk of bias because the authors did not show how they randomised the participants
Allocation concealment (selection bias)	Unclear risk	Quote: "female patients randomly assigned to one of 3 treatment groups of 20 patients per group: 32, 64, and 96 U" page 973 Comment: we considered this an unclear risk of bias because the authors did not describe the methods used to maintain the allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "All injection volumes were 0.06 mL. To maintain the study blind, vials were not prepared by the same person who performed the injections." page 973 Comment: we considered this as low risk of bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All injection volumes were 0.06 mL. To maintain the study blind, vials were not prepared by the same person who performed the injections." page 973 Comment: we considered this as low risk of bias

Carruthers 2009 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Discontinued before 52 weeks: group 32u = 0, 64u = 2/20 (10%), 96u = 2/20 (10%)" table 1, page 974 Comment: we considered this as unclear risk of bias, because the authors did not mention the reason of drop outs.
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported. Comment: we considered this a low risk of bias
Other bias	Low risk	We considered this study at low risk of other bias

Carruthers 2010

Study characteristics	
Methods	**Study design**- multicentre, single-blind, randomised, parallel-design **Study date**- no information **Study setting**- outpatients from three centres
Participants	**Randomised**- 90 women, with mean age of 48.4 ± 5.5 years, median 49.9 years in 24-mg/mLCohesive Gel group; 48.6 ± 4.4 years, median 49.1 years in BontA 20 U group; 47.3 ± 5.3 years, median 48 years in BontA Plus 24-mg/mL Cohesive gel group; 48.1 ± 5.1 years, median 49.1 years total population. Gender 100% female **Inclusion criteria** • Nonpregnant, non lactating, non-smoking female volunteers aged 35 to 55. Participants of childbearing potential were required to practice reliable birth control during the study. Suitability for lower facial rejuvenation was based on mild to moderate lip fullness at rest, mild to moderate oral commissures at rest, and mild to moderate perioral lines at maximal attempted contraction. Participants had to be able to provide written informed consent **Exclusion criteria** • Treatment of any serotype during the preceding 12 months, nor could they have undergone any other cosmetic procedures in the lower face, including dermal fillers, laser treatment, and dermabrasion. Any condition that could affect evaluation (e.g. scars, tattoos, piercings) precluded participation. • Active inflammation, infection, cancerous or precancerous lesions, or unhealed wounds of the perioral • Participants with deep nasolabial folds or etched-in perioral lines were ineligible • Participants with severe malocclusion, dento-facial or maxillofacial deformities, or significant asymmetries of the perioral area or lower face • Profound atrophy or excessive weakness of muscles in target areas of injection • History of facial nerve palsy; and any medical condition that could increase risk of exposure to botulinum toxin, such as diagnosed myasthenia gravis, Eaton-Lambert syndrome, amyotrophic lateral sclerosis, or any other disease that could interfere with neuromuscular function • Participants could not be using aminoglycoside antibiotics, curare-like agents, or agents that could interfere with neuromuscular function • Participants with allergy or sensitivity to any study medication or its components • Participants could not have been exposed to an investigational drug study within 30 days of the baseline visit • Participants with evidence of alcohol or drug abuse; medical or psychiatric problems that could interfere with adherence or interpretation of results; or with a history of poor cooperation, non- compliance with medical treatment, or unreliability were disqualified

Carruthers 2010 *(Continued)*

	Severity of disease- investigator's assessment scale: perioral (upper lip at maximum contraction): 2.43 ± 0.6 total population, 2.63 ± 0.49 24-mg/mL Cohesive gel, 2.43 ±0.63 BontA, 2.23 ± 0.63 (BontA Plus 24-mg/mL Cohesive gel. Lip fulness: 1.52 ± 0.5 total population, 1.53 ± 0.51 24-mg/mL Cohesive gel, 1.53 ± 0.51 BontA, 1.50 ± 0.51 (BontA Plus 24-mg/mL Cohesive gel. Oral commissure: 1.90 ± 0.3 total population, 1.90 ± 0.31 24-mg/mL Cohesive gel, 1.90 ± 0.31 BontA, 1.90 ± 0.3 (BontA Plus 24-mg/mL Cohesive gel). Assessing investigator's assessment: perioral 1.53±0.64 total population, 1.50 ± 0.57 24-mg/mL Cohesive gel, 1.60 ±0.77 BontA, 1.50 ± 0.57 (BontA Plus 24-mg/mL Cohesive gel. Lip fullness: 1.63±0.57 total population, 1.63 ± 0.61 24-mg/mL Cohesive gel, 1.67 ±0.55 BontA, 1.60 ± 0.56 (BontA Plus 24-mg/mL Cohesive gel. Oral commissure: 1.86±0.57 total population, 1.83 ± 0.53 24-mg/mL Cohesive gel, 1.93 ±0.58 BontA, 1.80 ± 0.61 (BontA Plus 24-mg/mL Cohesive gel **Ethnicity**- 29/30 (96.7%) Caucasian, 1/30 (3.3%) Hispanic, 0% Asian, 0% other in 24-mg/mL Cohesive Gel group; 25/30 (83.3%) Caucasian, 2/30 (6.7%) Hispanic, 2/30 (6.7%) Asian, 1/30 (3.3%) in other BontA; 28/30 (93.3%) Caucasian, 1/30 (3.3%) Hispanic,1/30 (3.3%) Asian, 0% other in BontA Plus 24-mg/mL Cohesive gel
Interventions	**Duration of study**- 26 weeks **Intervention/Comparator** • Hyaluronic acid Cohesive gel 24mg/mL 0.8mL/serynge [JUVEDERM ULTRA ® and/or JUVEDERM ULTRA PLUS®] (N = 30) • OnabotulinumtoxinA (20 U) - 3U perioral +6U mento (N = 30), • OnabotulinumtoxinA (20 U) and hyaluronic acid 24-mg/mL Cohesive gel [JUVEDERM ULTRA ® and/or JUVEDERM ULTRA PLUS®] (N = 30)
Outcomes	**Primary outcome** • Perioral rhytides at maximum contraction **Secondary outcomes** • Duration • Adverse events
Notes	"The authors received research grant support from Allergan, Inc. for this study and for manuscript preparation."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "multicenter (3 site), prospective, single-blind, randomised, parallel-group study comprising three treatment groups" page 2123 Comment: we considered this unclear risk of bias because the authors did not show how they randomised the participants
Allocation concealment (selection bias)	Unclear risk	Quote: "Subjects were randomly assigned to one of the three treatment groups on a 1:1:1 basis." page 2123 Comment: we considered unclear risk, because the authors did not explain the methods used to maintain the allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "maintain the single blind, a treating investigator performed injections" page2123 Comment: we considered this high risk of bias

Carruthers 2010 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "maintain the single blind, a treating investigator performed injections, and an assessing investigator who was masked to the treatment that the subject received conducted effectiveness evaluations." page 2123 Comment: we considered this low risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Ninety subjects were enrolled and had at least one postbaseline visit. Seventeen (18.9%) discontinued before week 24. Significantly more subjects (n = 9) in the onabotulinumtoxinA-alone group discontinued than those in the combination group (n = 1). A total of two subjects withdrew because of an AE, 11 were lost to follow-up, and four withdrew consent." page2126 Comment: we considered this low risk of bias
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported Comment: we considered this low risk of bias
Other bias	Low risk	We considered this study at low risk of other bias

Carruthers 2013

Study characteristics	
Methods	**Study design**- multicentre, randomised, double-blind, placebo-controlled, parallel design, phase III study in glabellar lines **Study date**- no information **Study setting**- outpatients from eight centres
Participants	**Randomised**- 276 participants, with a mean age of 46.6 ± 9.87 years, median 46 years in BontA group; 46.4 ± 10.56 years, median 48 years in placebo group. Gender: 162/184 (88%) female, 22/184 (12.0%) male in BontA group; 76/92 (82.6%) female, 16/92 (17.4%) male in placebo group **Inclusion criteria** • Patients aged 18 and older with moderate to severe glabellar frown lines at maximum frown (severity score of 2 or 3 on the facial wrinkle scale [FWS]), as assessed by the investigator, were eligible for inclusion in the study. The FWS rates the severity of glabellar frown lines as 0 (none), 1 (mild), 2 (moderate), or 3 (severe). Patients were required to be in a stable medical condition, as determined during the screening period according to medical history, physical examination, vital signs, and assessment of concomitant medications and procedures within the 30 days before screening. Final medical suitability for randomisation was determined at the injection visit (Visit 1, Day 0) **Exclusion criteria** • Treatment with botulinum toxin of any serotype in the glabellar area within the past 8 months • Any previous insertion of permanent material in the glabellar area • Previous treatment with any facial aesthetic procedure (e.g. biodegradable fillers) in the past 12 months **Severity of disease**- moderate to severe glabellar frown lines at maximum frown (FWS) **Ethnicity**- 163/184 (88.6%) Caucasian, 3/184 (1.6%) black, 10/184 (5.4%) Asia, 7/184 (3.8%) Hispanic, 1/184 (0.5%) other in BontA group ; 83/92 (90.2%) Caucasian, 3/92 (3.3%) black, 1/92 (1.1%) Asian, 3/92 (3.3%) Hispanic, 2/92 (2.2%) other in placebo group
Interventions	**Duration of study**- 28 weeks

Carruthers 2013 *(Continued)*

	Intervention • IncobotulinumtoxinA (20 U), 0.01mL/site, 5 points, one injection in the procerus muscle, one injection on each side in the central part of the corrugator muscle approximately 1 cm above the bony orbital rim on an imaginary line drawn vertically from the caruncle, one injection on each side in the middle part of the corrugator muscle at least 1.5 cm above the bony orbital rim on an imaginary line drawn vertically from the centre of the pupil (N = 184) **Comparator** • Placebo = 0.5mL, 0.01mL/site, 5 points, one injection in the procerus muscle, one injection on each side in the central part of the corrugator muscle approximately 1 cm above the bony orbital rim on an imaginary line drawn vertically from the caruncle, one injection on each side in the middle part of the corrugator muscle at least 1.5 cm above the bony orbital rim on an imaginary line drawn vertically from the centre of the pupil (N = 92)
Outcomes	**Primary outcome** • Measured at Visit 3 (Day 30) using a composite endpoint comprising investigator and patient evaluations. Composite endpoint treatment success (CETS) was defined as at least a 2-point improvement at maximum frown on the 4-point FWS from baseline as assessed by the investigator and an improvement from baseline of at least two points at maximum frown according to the patient assessment (CETS) was defined as at least a 2-point improvement at maximum frown on the 4-point FWS from baselines assessed by the investigator and an improvement from baseline of at least two points at maximum frown according to the patient assessment **Secondary outcomes** • Percentage of responders at maximum frown and at rest at Day 30 according to investigator • Adverse events
Notes	"This study was funded by Merz Pharmaceuticals GmbH. Editorial assistance was provided by Ogilvy 4D, Oxford, UK. Alastair Carruthers, Jean Carruthers, William P. Coleman III, Lisa Donofrio, Timothy Flynn, Michael Gold, Moritz Heinz, Derek Jones, David McDaniel, Thomas Rohrer, Nowell Solish, and Robert Weiss are paid investigators in this Phase III trial. Andrea Schlo€be and Moritz Heinz are employees of Merz Pharmaceuticals GmbH, and Laura Harrington is an employee of Ogilvy 4D."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were randomised 2:1 to receive 20 U of incobotulinumtoxinA or placebo" page 552 Comment: we considered this unclear risk of bias because the authors did not show how they randomised the participants
Allocation concealment (selection bias)	Unclear risk	no information Comment: we considered this unclear risk of bias because the authors did not presented the methods used to maintain the allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double-blind, placebo-controlled," page 552 Comment: we considered this unclear risk of bias because the authors did not explain how they blinded the participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double-blind, placebo-controlled," page 552 Comment: we considered this unclear risk of bias because the authors did not explain how they blinded the participants

Carruthers 2013 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Nine patients discontinued the study; three from the incobotulinum-toxinA group withdrew consent (with one case of an adverse event), and three were lost to follow-up, and three in the placebo group withdrew consent.One hundred seventy-eight completed the study in the incobotulinumtoxinA group and 89 in the placebo group." page 554 Comment: we considered this low risk of bias
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported Comment: we considered this low risk of bias
Other bias	Unclear risk	Pharmaceutical support and some authors were Allergan employees. Comment: we considered unclear risk of bias

Carruthers 2014

Study characteristics	
Methods	**Study design**- multicentre, randomised, double-blind, placebo-controlled parallel design study, in crow's feet lines **Study date**- no information **Study setting**- outpatients of 23 centres
Participants	**Randomised** 445 participants, with a mean age of 46.7 years in BontA group; 46.2 years in placebo group; and 46.4 years total population. Gender: female 86.9%, in BontA group; female 85.7% in placebo group; female 86.3% total population **Inclusion criteria** • Male or female at least 18 years of age, bilaterally symmetrical moderate-to-severe crow's feet lines at maximum smile on the FWS as rated by both investigator and participant on day 1 (before study), sufficient visual acuity without the use of eyeglasses (contact lens use acceptable), to accurately assess their facial wrinkles, female participants of childbearing potential must have had a negative urine pregnancy test at day 1 prior to study treatment; must be using a reliable means of contraception **Exclusion criteria** • Concurrent or previous botulinum toxin treatment of any serotype • Facial treatments or procedures within particular time points prior to study that could interfere with treatments in this study or with interpretation of results • Prior upper or midfacial surgery or permanent aesthetic procedures/treatments • Marked facial asymmetry, dermatochalasis, deep dermal scarring, excessively thick sebaceous skin, or the inability to substantially lessen lateral canthal rhytides even by physically spreading them apart, as determined by the investigator • Presence of any clinically relevant abnormal finding as observed from the neurologic assessment • Any eyebrow or eyelid ptosis at baseline as determined by the investigator • History of facial nerve palsy • Pregnancy, nursing, or planning a pregnancy • Any uncontrolled systemic disease • Current enrolment in an investigational drug or device study or participation in such a study within 30 days of entry into this study • Permanent make-up that would interfere with the assessment of facial wrinkles

Carruthers 2014 *(Continued)*

	• Subject had a condition or was in a situation that in the investigator's opinion may have put the participant at significant risk, confounded the study results, or interfered significantly with the participant's participation in the study Severity of disease- moderate-to-severe CFL (maximum smile) **Ethnicity**- white 88.7%, black 3.2%, Asian 1.8%, Hispanic 5.4,other 0.9% in BontA group; white 88.8%, black 3.1%, Asian 2.2 %, Hispanic 4.9%, other 0.9% in placebo group; white 88.8%, black 3.1%, Asian 2.0%, Hispanic 5.2%, other 0.9% in total population
Interventions	**Duration of study**- 20 weeks **Intervention** • OnabotulinumtoxinA (24 U), 0.6 mL, 3 points in crow's feet lines (CFL) (N = 222) **Comparator** • Placebo = 0.6 mL, 3 points in crow's feet lines (N = 223)
Outcomes	**Primary outcome**- • FWS-rated severity of CFL at maximum smile as assessed by both investigators and subjects both investigators and subjects at day 30 after treatment **Secondary outcome**- • Responder rates for these 2 endpoints were defined as the proportion of subjects with an improvement from baseline in CFL severity of at least 1 grade at maximum smile and at least 1 grade at rest • Duration of the treatment, patient-reported outcomes (PRO) • Self-Perception of Age (SPA). • Adverse events
Notes	"Dr Carruthers is a consultant and investigator for Allergan, Inc., Merz Pharmaceuticals, Merz Aesthetics USA, and Solstice Neurosciences"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Eligible subjects were randomised in a 1:1 ratio"...page 1182 Comment: we considered this unclear risk of bias because the authors did not show how they randomised the participants
Allocation concealment (selection bias)	Unclear risk	Quote: "Eligible subjects were randomised in a 1:1 ratio."page 1182 Comment: we considered this unclear risk of bias due to the authors did not clarify the methods used to maintain the allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Reconstitution and preparation of syringes were undertaken by individuals with no study responsibilities involving interactions with subjects" page 1182 Comment:we considered this unclear risk of bias due to the visual aspect of BontA and placebo was not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Reconstitution and preparation of syringes were undertaken by individuals with no study responsibilities involving interactions with subjects" page 1182

Carruthers 2014 *(Continued)*

		Comment:we considered this unclear risk of bias due to the visual aspect of BontA and placebo was not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Botox, 210/222 (94.5%) completed the study, 12 withdrew (lost of follow up = 8, personal reasons = 2, protocol violation = 1, not treated = 1). Placebo group 205/223 (91.9%), 10 withdrew (lost of follow up = 12, personal reasons = 4, protocol violation = 1, not treated = 1)" page 1185 (figure 2) Comment: we considered low risk of bias
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported Comment: we considered low risk of bias
Other bias	Low risk	We considered this study at low risk of other bias

Carruthers 2015

Study characteristics	
Methods	**Study design**- multicentre, double-blind, randomised, parallel-design, placebo-controlled extension study of participants who completed the 7- month phase 3 study (Study 191622-099; www. clinicaltrials.gov identifier: NCT01224015) in crow's feet and/or glabellar lines **Study date**- no information **Study setting**- outpatients
Participants	**Randomised**- 684 participants, with a mean age of 49.7 ± 9.48 years in BontA 44 U/44U group; 49.4 ± 9.35 years in BontA 24 U/24 U group; 49.4 ± 9.23 in Placebo/BontA 0/44 U group; 49.1 ± 9.32 in Placebo/placebo group; 49.4 ± 9.36 years total population. Gender: 226/260 (86.9%) female, 34/260 (13.1%) male BontA 44 U/44 group; 203/227 (89.4%) female, 24/227 (11.9%) male in BontA 24 U/24 U group; 89/101 (88.1%) female, 12/101 (11.9%) male in Placebo/BontA 0/44 U group; 80/96 (83.3%) female, 16/96 (16.7%) male in Placebo/placebo group; 598/684 (87.4%) female, 86/684 (12.6%) male total population **Inclusion criteria** • Male or female at least 18 years of age, bilaterally symmetrical moderate-to-severe crow's feet lines at maximum smile on the FWS as rated by both investigator and participant on day 1 (before study), sufficient visual acuity without the use of eyeglasses (contact lens use acceptable), to accurately assess their facial wrinkles, female participants of childbearing potential must have had a negative urine pregnancy test at day 1 prior to study treatment; must be using a reliable means of contraception **Exclusion criteria** • Concurrent or previous botulinum toxin treatment of any serotype • Specified facial treatments or procedures within particular time points prior to study that could interfere with treatments in this study or with interpretation of results • Prior upper or midfacial surgery or permanent aesthetic procedures/treatments • Marked facial asymmetry, dermatochalasis, deep dermal scarring, excessively thick sebaceous skin, or the inability to substantially lessen lateral canthal rhytides even by physically spreading them apart, as determined by the investigator • Presence of any clinically relevant abnormal finding as observed from the neurologic assessment • Any eyebrow or eyelid ptosis at baseline as determined by the investigator • History of facial nerve palsy • Pregnancy, nursing, or planning a pregnancy • Any uncontrolled systemic disease

Carruthers 2015 *(Continued)*

	• Current enrolment in an investigational drug or device study or participation in such a study within 30 days of entry into this study **Severity of disease**- moderate-to-severe bilaterally symmetrical CFL at maximum smile and moderate-to-severe GL at maximum frown **Ethnicity**- white 232/260 (89.2%), non-white 28/260 (10.8%) in Botox 44/44 U, white 200/227 (88.1%), non-white 27/227 (11.9%) in BontA 24/24 U group; white 89/101 (88.1%, non-white 12/101 (11.9%) in placebo group; BontA44 U group; white 84/96 (87.5%), non-white 12/96 (12.5%) in placebo/placebo group; white 605/684 (88.5%), non-white 79/684 (11.5%) in total population
Interventions	**Duration of study**- 20 weeks **Intervention/ Comparator** • OnabotulinumtoxinA crow's feet (24 U), glabella (20U) (N = 260) • OnabotulinumtoxinA (24 U) Crow's feet lines, Glabellar lines (zero U) (N = 227) • Placebo to onabotulinumtoxinA (44 U, 24u crow's feet lines, 20u glabellar lines)(N = 101) • Placebo crow's feet lines and Glabellar lines (N = 96) Total (N = 684) • Placebo crow's feet (0.6 mL), glabella (0.5 mL)
Outcomes	**Primary outcome** • Proportion of participants achieving a grade of none or mild at maximum smile on Day 30 of treatment cycle 3 based on investigator's Facial Wrinkle Scale (FWS) ratings **Secondary outcomes** • Proportion of participants achieving none or mild at other time points (maximum smile), the proportion achieving an improvement from baseline of at least 1 grade in CFL severity at maximum smile, and the proportion achieving an improvement from baseline of at least 1 grade in CFL severity at rest, among participants who were rated at least mild at baseline • Participant-rated end points included the proportion of participants achieving a grade of none or mild in CFL severity at maximum smile • The proportion achieving an improvement from baseline of at least 1 grade in CFL severity at maximum smile, and the proportion achieving an improvement from baseline of at least 1 grade in CFL severity at rest, among participants who rated themselves at least mild at baseline • Participant's Global Assessment of Change in Crow's Feet, Lines (SGA-CFL), the validated Facial Line Outcomes Questionnaire (FLO-11) psychological impact (Items 2, 5, and 8), and Self-Perception of Age (SPA) and the Subject Satisfaction of Appearance • Adverse events
Notes	"J. Carruthers and A. Rivkin are consultants and investigators for Allergan, Inc. L. Donofrio is an investigator for Allergan, Inc. V. Bertucci is a speaker, consultant, and investigator for Allergan, Inc. X. Lei is an employee of Allergan, Inc., and receives compensation in salary, as well as stock or stock options (or both). C. Somogyi and F. C. Beddingfield were employees of Allergan, Inc. at the time of this study and received compensation in salary, as well as stock or stock options (or both). The other authors have indicated no significant interest with commercial supporters." This RCT was a continuation of previous RCT published (Moers-Carpi 2015), so we will consider only the patients that received placebo (Moers-Carpi 2015) and were re randomised for BotoxR 44u and placebo in this study to avoid double count of participants.

Risk of bias

Bias	Authors' judgement	Support for judgement

Carruthers 2015 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Quote: "Randomization took place on Day 1 of this study, corresponding to the last day of Study 191622-099. Subjects who had received onabotulinumtoxinA in Study 191622-099 continued to receive the same dose (44 U for CFL + GL, 24 U for CFL alone) in this study. Subjects who had received placebo in Study 191622- 099 were re randomised in a double-blind fashion to either 44 U onabotulinumtoxinA (CFL + GL) or to placebo in a 1:1 ratio" page 703 Comment: we considered this unclear risk of bias because the authors did not explain how they randomised the participants
Allocation concealment (selection bias)	Unclear risk	Quote: "Randomization took place on Day 1 of this study, corresponding to the last day of Study 191622-099. Subjects who had received onabotulinumtoxinA in Study 191622-099 continued to receive the same dose (44 U for CFL + GL, 24 U for CFL alone) in this study. Subjects who had received placebo in Study 191622- 099 were re-randomized in a double-blind fashion to either 44 U onabotulinumtoxinA (CFL + GL) or to placebo in a 1:1 ratio" page 703 Comments: we considered this unclear risk of bias because the authors did not explain the methods used for maintaining the allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "To maintain the blind, all medications were reconstituted and prepared by individuals who had no interactions with subjects." page 104 (from Moers-Carpi 2015) Comment: we considered this unclear risk of bias due to the visual aspect of BontA and placebo was not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "To maintain the blind, all medications were reconstituted and prepared by individuals who had no interactions with subjects." (from Moers-Carpi 2015) Comment: we considered this unclear risk of bias due to the author did not provide information about blinding of outcome assessor
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Of 684 subjects enrolled, 641 (93.7%) completed this study A total of 667 subjects (97.5%) received the third treatment. Most subjects who received a third dose (80.2%; 535/667) received their dose at Day 1 visit of Study 191622-104. A total of 414 subjects (60.5%) received 2 treatments (treatment cycles 3 and 4): 149 onabotulinumtoxinA 24 U/24 U, 123 onabotulinumtoxinA 44 U/44 U, 69 placebo/ onabotulinumtoxinA 44 U, and 73 placebo/placebo. In this study, 253 subjects (37.0%) received only 1 treatment (treatment cycle 3): 74 onabotulinumtoxinA 24 U/24 U, 126 onabotulinumtoxinA 44 U/44 U, 31 placebo/onabotulinumtoxinA 44 U, and 22 placebo/placebo. Seventeen subjects failed to meet re-treatment criteria after they received treatment 2 in Study 191622-099 and therefore did not receive any treatment in this study: 4 onabotulinumtoxinA 24 U/ 24 U, 11 onabotulinumtoxinA 44 U/44 U, 1 placebo/ onabotulinumtoxinA 44 U, and 1 placebo/placebo" page 705 Comment: we considered this low risk of bias
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported Comment: we considered this low risk of bias
Other bias	High risk	Comment: we considered a high risk of bias because C. Somogyi and F. C. Beddingfield were employees of Allergan and conducted this trial

Carruthers 2017

Study characteristics	
Methods	**Study design**- multicentre, double-blind, randomised, parallel-design,dose--ranging, placebo-controlled (www. clinicaltrials.gov identifier: NCT0020303002) in glabellar lines **Study date**- start December 2014; end December 2015 **Study setting-** outpatients, 9 private practice settings
Participants	**Randomised-** 268 participants with a mean age of 50 years in OnabotulinumtoxinA 20U group; 47 years in DaxibotulinumtoxinA 60 U groups; 50 years in DaxibotulinumtoxinA 40 U groups; 49 years in DaxibotulinumtoxinA 20U groups and 50 years in placebo group. Gender: 38/42(90%) female and 4/42(10%) male onabotulinumtoxinA 20U group; 37/41(76%) female and 4/41(24%) male in DaxibotulinumtoxinA 60 U groups; 36/39(92%) female and 3/39(8%) male in DaxibotulinumtoxinA 40 U groups; 36/39(91%) female and 3/34(9%) male in DaxibotulinumtoxinA 20 U groups and 31/35(89%) female and 4/35(11%) male in placebo group. **Inclusion criteria** • Moderate or severe glabellar lines during maximum frown according to both the Investigator Global Assessment—Facial Wrinkle Severity (IGA-FWS) scale and the Patient Facial Wrinkle Severity (PFWS) scale • Both genders, 30 to 65 years of age • To be willing to refrain from treatment with facial fillers, lasers, and products that could affect skin remodelling or cause an active dermal response in the treatment area **Exclusion criteria** • They were not allowed to have a history of a topical steroid on the treatment area • Any immunosuppressants, in the previous 30 days • A prescription retinoid in the treatment area during the previous 3 months • Botulinum toxin Type A in the face in the previous 6 months • Chemical peels of at least medium depth during the previous 9 months • They were also not allowed to have undergone any procedure that may affect the glabellar region during the previous 12 months **Severity of disease-** IGA-FWSrating at maximum frown 28/42(67%) moderate and 14/42 (33%) severe in OnabotulinumtoxinA 2 0U group; 24/41(59%) moderate and 14/41 (41%) severe in DaxibotulinumtoxinA 60U groups; 27/39(69%) moderate and 12/39 (31%) severe in DaxibotulinumtoxinA 40 U groups; 22/34(65%) moderate and 12/34 (35%) severe in DaxibotulinumtoxinA 20 U groups and 24/35(69%) moderate and 11/35 (31%) severe in placebo group **Ethinicity-**Caucasian 38/42 (90%) in OnabotulimtoxinA 20 U group; Caucasian 38/41 (93%) in DaxibotulinumtoxinA 60 U groups; Caucasian 37/39(95%) in DaxibotulinumtoxinA 40 U groups; Caucasian 31/34 (91%) in DaxibotulinumtoxinA 20 U groups and 31/35 (89%) in placebo group.
Interventions	**Duration of study**- 36 weeks **Intervention/ Comparator** • OnabotulinumtoxinA glabellar lines(20 U); five 0.1 mL injections, 2 in each corrugator muscle and one in the procerus muscle (N = 42) • DaxibotulinumtoxinA glabellar lines (20 U); five 0.1 mL injections, 2 in each corrugator muscle and one in the procerus muscle (N = 34) • DaxibotulinumtoxinA glabellar lines (40 U); five 0.1 mL injections, 2 in each corrugator muscle and one in the procerus muscle (N = 39) • DaxibotulinumtoxinA glabellar lines (60 U); five 0.1 mL injections, 2 in each corrugator muscle and one in the procerus muscle (N = 41

Carruthers 2017 *(Continued)*

	• Placebo glabellar lines; five 0.1 mL injections, 2 in each corrugator muscle and one in the procerus muscle (N=35)
Outcomes	**Primary outcomes** • Proportion of responders at Week 24 (a responder being a participant with at least a 1-point improvement from baseline in glabellar severity at maximum frown according to the IGA-FWS scale) • Proportion of responders every 4 weeks and if the score at maximum frown had not yet returned to baseline at Week 24, evaluations were continued every 4 weeks until this had occurred (up to Week 36) **Secondary outcomes** • The median duration of response (time since injection for at least a 1-point improvement in IGA-FWS score to revert to baseline levels) was another primary out- come measure. • Participant assessment using IGA-FWS score • Investigators and participants evaluated the global improvement in aesthetics at each post baseline visit using the • Global Aesthetic Improvement Scale (GAIS) • Adverse events
Notes	"Supported by Revance Therapeutics, Inc. J.D. Carruthers is a consultant and researcher for Revance, Allergan, Merz, and Alphaeon. N. Solish received a grant from Revance for participating in this study and is a consultant to Revance, Allergan, and Galderma. S. Humphrey has received research grants from Revance Therapeutics. V. Bertucci is a consultant to, and receives payment for lectures, including service on speaker bureaux, from Allergan, Galderma, and Merz. He is also an investigator for Allergan, Galderma, Alphaeon, Merz, and Revance. A. Swift received an investigator fee from Revance Therapeutics, Inc. A. Metelitsa has been a consultant for Galderma and Merz. R.G. Rubio is an employee of, and holder of stock/stock options in, Revance Therapeutics, Inc. J. Waugh was an employee of, and held stock/stock options in, Revance Therapeutics, Inc. J. Quiring is an employee of QST Consultations, Ltd., which has received fees from Revance Therapeutics, Inc. for performing statistical analyses. G. Shears is an employee of Write on Target Ltd., which has received fees from Revance Therapeutics, Inc. for medical writing services. A. Carruthers is a consultant and researcher for Revance, Allergan, Merz, and Alphaeon. The remaining authors have indicated no significant interest with commercial supporters. DaxibotulinumtoxinA is an investigational agent."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "An independent statistician provided a randomization scheme of treatment assignments for each study site and subjects eligible for randomization were given the next available subject number"...page1322 Comment: we considered this unclear risk of bias because the authors did not explain how they randomised
Allocation concealment (selection bias)	Unclear risk	Quote:"An independent statistician provided a randomization scheme of treatment assignments for each study site and subjects eligible for randomization were given the next available subject number"...page1322 Comment: we considered this unclear risk of bias because the authors did not explain how they randomised
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote:"assigned product was reconstituted by an unblinded preparer and the masked product was provided to the investigator in a syringe. The subjects, investigators, and other site staff remained blinded to the treatment assignments."...page 1323 Comment: we considered this low risk of bias

Carruthers 2017 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote:"assigned product was reconstituted by an unblinded preparer and the masked product was provided to the investigator in a syringe. The subjects, investigators, and other site staff remained blinded to the treatment assignments."...page 1323 Comment: we considered this low risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Overall, 98% of subjects completed the study (3 discontinued from the placebo group and 2 from the 20U daxibotulinumtoxinA group due to subject withdrawals or loss to follow-up). Per protocol analyses required the exclusion of 77 subjects, most of these (57/77) being attributable to the Week 24 visit being more than 5 days off schedule (Table 2)."...page 1324 Comment: we considered this low risk of bias
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported Comment: we considered this low risk of bias
Other bias	Unclear risk	Comment: we considered a unclear risk of bias because J. Waugh was an employee of, and held stock/stock options in, Revance Therapeutics, Inc. J. Quiring is an employee of QST Consultations, Ltd. and G. Shears is an employee of Write on Target Ltd., which has received fees from Revance Therapeutics, Inc. for medical writing services.

Cheon 2019

Study characteristics	
Methods	**Study design**- multicentre, double-blind, randomised, active-drug controlled, phase I/III study designed to determine the non-inferiority of Neuronox® compared to Onabotulinumtoxin A in the treatment of moderate to severe lateral canthal lines. NCT03317574 **Study date**- no information **Study setting-** outpatients, 5 centres (South Korea)
Participants	**Randomised** 220 participants with a mean age of 47.14 ±7.87yearsinn Nuronox® group and 49.03± 8.28 years in onabotulinumtoxinA group. Gender 88/110 (80%) female and 22/110 (20) males in Neuronox® group, and 92/110 (83.64%) female and 18/110(16.36%) male in onabotulinumtoxinA group. Previous BontA treatment 14/110(12.73%) in Neuronox® group and 17/110 (15.45%) in Onabotulinumtoxin A group. **Inclusion criteria** • Males or females • Aged 20 to 65 years • With moderate to severe LCL at maximum smile as assessed by the investigator using an LCL severity scale **Exclusion criteria** • Neuromuscular disorders, • Specified facial surgery or permanent aesthetic treatments within the past 6 months to a year that would affect the assessment of LCL, • Deep LCL

Cheon 2019 *(Continued)*

	• Difficult to lessen even by physical methods, • BoNT-A treatment in the past 3 months or plans to receive BoNT-A treatment during study participation, • Hypersensitivity to any components of the investigational product, or infection at the injection site. **Severity of the disease**- moderate 29/110(26%), severe 81/110 (74%) in Neuronox® group; moderate 35/110 (32%), severe 75/110 (68%) in onabotulinumtoxinA group.
Interventions	**Duration of study**- 16 weeks **Intervention** Neuronox® 24u (N=110)- 4 U (0.1 mL), 3 sites each side **Comparator** OnabotulinumtoxinA 24 U (N=110)- 4 U (0.1 mL), 3 sites each side
Outcomes	**Primary outcome** • Responder rate at a maximum smile as assessed by the investigators at Week 4 **Secondary outcomes** • Responder rate at maximum smile at Weeks 8, 12, and 16 as assessed by the investigators independently • Responder rate at rest at Weeks 4, 8, 12, and 16 as assessed by the investigators independently • Responder rate at rest and at maximum smile at Weeks 4, 8, 12, and 16 as assessed by the participant • Proportion of participants with more than 1-grade point and 2-grade point improvements from baseline on the LCL severity scale at maximum smile and at rest as assessed by the investigators at Weeks 4, 8, 12, and 16 • Proportion of participants with Grade+2 (moderate improvement) or more on the subjective global assessment (9-point grading scale; from +4, complete improvement, to -4, very marked worsening) at Weeks 4, 8, 12, and 16 • Proportion of participants with Grade 6 (satisfied) or above on the subject satisfaction assessment (7-point grading scale; from 7, very satisfied, to 1, very dissatisfied) at Weeks 4, 8, 12, and 16. • Duration of the treatment • Adverse events
Notes	"This study was sponsored by Medytox Inc., Korea. W.S. Lee is an employee of Medytox Inc."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote:"Dynamic Allocation was used to randomize eligible subjects"...page no number Comment: we considered this an unclear risk of bias because the authors did not explain how thy randomise the participants
Allocation concealment (selection bias)	Unclear risk	Quote:"Dynamic Allocation was used to randomize eligible subjects"...page no number Comment: we considered this an unclear risk of bias because the authors did not explain how thy randomise the participants
Blinding of participants and personnel (performance bias)	Low risk	Quote: "The pharmacist or designee responsible for the reconstitution was kept unblinded, and performed the dilution and

Cheon 2019 *(Continued)*

All outcomes		preparation of the syringe in a separate room. All other individuals, including investigators and subjects were kept blinded throughout the study."... page no information. Comment: we considered this low risk of bias.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The pharmacist or designee responsible for the reconstitution was kept unblinded, and performed the dilution and preparation of the syringe in a separate room. All other individuals, including investigators and subjects were kept blinded throughout the study."... page no information. Comment: we considered this low risk of bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote:" due to major protocol deviation by seven subjects (two from Neuronox® and five from ONA (Figure 2)."...pgae no information Comment; we considered this a low risk of bias
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported Comment: we considered this low risk of bias
Other bias	Low risk	Quote:"This study was sponsored by Medytox Inc., Korea. W.S. Lee is an employee of Medytox Inc."..page no information Comment: we considered this a low risk of bias

Cohen 2012

Study characteristics	
Methods	**Study design**- multicentre, randomised, double-blind, parallel-design, in perioral lines **Study date**- no information **Study setting**- no information
Participants	**Randomised**- 60 women, with a mean age of 41. 9 ± 8 years total population; 40.8 ± 7.1 years in BontA 7.5 U group; 43.2 ± 8.7 years in BontA 12 U group. Gender 100% female **Inclusion criteria** • Women of any race aged 25 to 60 with a perioral line (POL) score of 2 or 3 (moderate or severe) at maximal attempted muscle contraction based on a 4-point scale that considered the upper and lower lips **Exclusion criteria** • Participants were excluded if they had undergone prior cosmetic surgery or exhibited facial scars that may have affected evaluation of response or the quality of photography • Asymmetric line severity between the upper and lower lips; imprinted etched-in lines at rest in the perioral area; the presence of facial hair affecting the evaluation of response or quality of photography; • Injection of nonpermanent lip filler into the perioral area in the 18 months preceding visit 1 • Previous botulinum toxin therapy in the mid or lower face within the 12 months preceding visit 1 • Previous permanent procedure or treatment in the lower face • Any medical condition or use of concurrent medication that might increase their risk of exposure to botulinum toxin medical or psychiatric problems that severe enough to interfere with the study results

Cohen 2012 *(Continued)*

	• Allergy or sensitivity to any component of the study medication **Severity of disease**- POL score of 2 or 3 (moderate or severe) at maximal attempted muscle contraction based on a 4-point scale that considered the upper and lower lips **Ethnicity**- 54/60 (90%) Caucasian, 3/60 (5%) black, 3/60 (5%) Hispanic total population; 30/31 (96.8%) Caucasian, 1/31 (3.2%) black, 0% Hispanic in BontA 7.5u group; 24/29 (82.8%) Caucasian, 2/29 (6.9%) black, 3/29 (10.3%), Hispanic in BontA 12u group
Interventions	**Duration of study**- 20 weeks. **Intervention** • OnabotulinumtoxinA (7.5 U), 2 sites per lip:5 U upper lip; 2.5 U lower lip (N = 31) **Comparator** • OnabotulinumtoxinA (12 U), 2 sites per lip: 8 U upper lip; 4 U lower lip (N = 29)
Outcomes	**Primary outcome** • Investigator-assessed POL severity scale at maximal contraction, reduction of at least 1 point in perioral lines **Secondary outcomes** • Investigator satisfaction, baseline of at least 1 grade in CFL severity at rest, among subjects who rated themselves at least mild at baseline • Adverse events.
Notes	The authors received research grant support from Allergan Inc. for this study and for manuscript preparation. Dr Cohen and two other authors are consultants and investigators for Allergan Inc. This study finished in 2016 - results added to clinical trial register May 28, 2019.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "this study was a multicenter, randomised... parallel-design, in which subjects were randomised in a 1:1 ratio" page 1498. Comment: we considered this unclear risk of bias because the authors did not show how they randomised the participants
Allocation concealment (selection bias)	Unclear risk	No information Comment: we considered this unclear risk of bias because the authors did not show the methods used for maintaining the allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "this study was...double-blind.Onabotulinumtoxin A was reconstituted in preserved saline. The volume of reconstituted toxin in each syringe was 0.30mL to maintain the blind." page 1498 Comment: we considered this low risk of bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "this study was...double-blind..Onabotulinumtoxin A was reconstituted in preserved saline. The volume of reconstituted toxin in each syringe was 0.30mL to maintain the blind." page 1498

Cohen 2012 *(Continued)*

		Comment: we considered this low risk of bias
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Fifty-one subjects (85%) completed the study, of whom 26 and 25 subjects were from the 12.0-U and 7.5-U arms, respectively." page 1499 Comment: we consider unclear risk of bias, the authors did not mention the reason of drop outs An e-mail was sent to the authors on 21 November 2015. Answer on 22 November 2015: "I'm not sure I actually remember this. And the study was done so long ago, that I'm not sure we have these records on site any longer. You might want to inquire with Allergan, as they have the documents. I would imagine several patients were simply lost to follow up between the 3 sites"
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported Comment: we considered this low risk of bias
Other bias	Low risk	We considered this study at low risk of other bias

Costa 2016

Study characteristics	
Methods	**Study design**- multicentre, double-blind, randomised, parallel-design in glabellar lines **Study date**- started 2012, ended 2014 **Study setting**- outpatients three centres
Participants	**Randomised**- 157 female participants with mean age of 43.9 years in BontA1 (Prosigne®) group and 43.7 years in OnabotulinumtoxinA group **Inclusion criteria** • Healthy females, age between 35 and 50 years, photo type from I to IV, BontA naive with moderate to severe glabellar lines at maximum contraction and mild to moderate glabellar lines at rest according 4-point scale **Exclusion criteria** • Bleeding disorders or previous use of any medication that can interfere in coagulation process • Previous use of any type of botulinum toxin • Antibiotics, cyclosporine, or any substance that interfere in neuromuscular function • Local infection • Allergy or sensitivity to any component of the study medication • Prior upper or midfacial surgery or permanent aesthetic procedures/treatments • Current enrolment in an investigational drug or device study or participation in such a study within 30 days of entry into this study **Severity of disease**- moderate to severe glabellar lines at maximum contraction and mild to moderate glabellar lines at rest **Ethnicity**- no information
Interventions	**Duration of study**- 12 weeks **Intervention**

Costa 2016 *(Continued)*

	• BontA [Prosigne®] (20 U), 4U per site, five sites (N = 85) **Comparator** • OnabotulinumtoxinA (20 U), 4U per site, five sites (N = 72)
Outcomes	**Primary outcome** • One point improvement in 4-point scale at maximum contraction at day 15 by investigator and photographic assessment evaluated by three independent investigator. **Secondary outcomes** • Duration of the treatment by photographic assessment evaluated by three independent investigators; at least one-point improvement at rest at 120 days; pain tolerability by visual analogic scale during BontA injection • Adverse events
Notes	Pharmaceutical support

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Realizou-se a aleatorização em blocos de quatro, utilizando-se o Random Allocation Software 1.0 para alocar os pacientes nos grupos" page 35 Comment: we consider low risk of bias (translation of quote: the authors wrote they use a software to randomise the patients)
Allocation concealment (selection bias)	Unclear risk	Quote: "Realizou-se a aleatorização em blocos de quatro, utilizando-se o Random Allocation Software 1.0 para alocar os pacientes nos grupos." page 35 Comment: we considered unclear risk of bias because the authors did not explain how the methods used for maintaining the allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Um investigador reconstituiu os frascos da Toxina 1 e da Toxina 2, aspirou 20 unidades de cada produto com seringa BD com capacidade para 1ml, agulha curta, e entregou para o segundo investigador que injetou a toxina já diluída sem saber qual produto havia na seringa."... page 35 (translation- one of the investigator reconstituted toxin 1 and toxin 2, he used 20u for each toxin, seringe BD, 1mL, short needle, and delivered to the second blinded investigator that injected the diluted toxin)Comment: we considered unclear risk of bias due to the authors did not reported methods for blinding visual aspect of interventions
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Três avaliadores independentes analisaram todas as fotografias realizadas durante o estudo e classificaram a gravidade das rugas glabelares".. page 35 (translation- Three independents investigators evaluated all the study pictures and they classified all of them) Comment: we consider unclear risk of bias due to the due to the authors did not reported methods for blinding visual aspect of interventions
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Houve seis perdas de seguimento na visita 2 (V2) (uma da Toxina 1, e cinco da Toxina 2), pela dificuldade de as pacientes seguirem as datas de retorno do protocolo. Da visita V2 (15 dias) até a V6 (120 dias), 16 sujeitos de pesquisa perderam o seguimento por faltar às visitas, mesmo após inúmeras tentativas de contato pelo centro do estudo (também por dificuldade de seguir o calendário do estudo). Completaram o estudo 119 pacientes (63

Costa 2016 *(Continued)*

		e 56 nos braços Toxina 1 e Toxina 2, respectivamente."... page 36 (translation- There was six drop outs in visit 2 (one in toxin 1 group and five in toxin 2 group), because the patients lost their follow-up visit. From visit 2(15 days) to visit 6 (120 days), 16 patients did not show up, even though several previous contact. 119 subjects (63 and 56 in toxin1 and toxin 2 groups, respectively) completed the study Comment: we consider low risk of bias
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported Comment: we consider low risk of bias
Other bias	High risk	High number of protocol violation (17 in BontA (Prosigne®) group and 4 in OnabotulinumtoxinA group). Comment: we consider this high risk of bias

Dayan 2010

Study characteristics	
Methods	**Study design**- multicentre, double-blind, randomised, placebo-controlled, parallel-design in glabellar lines, forehead lines, and crow's feet lines **Study date**- no information **Study setting**- outpatients
Participants	**Randomised** 100 participants, with a mean age of 48.3 ± 9.3 years (range 25-73). Gender 96% female, 4% male **Inclusion criteria** • Women and men aged 18 and older and of all races were included in enrolment **Exclusion criteria** • Any conditions that contra-indicated the use of onabotulinumtoxinA or had been treated with any procedure that might affect the action of outcome of onabotulinumtoxinA • Any previous treatment with BoNTA or had undergone ablative resurfacing treatments within 6 months **Severity of disease**- glabellar lines, forehead and crow's feet lines **Ethnicity**- no information
Interventions	**Duration of study**- 12 weeks **Intervention** • OnabotulinumtoxinA (30.3 U) ± 1.9 (N = 50) **Comparator** • Placebo 1.0-1.2mL (N =50)
Outcomes	**Primary outcome** • Quality of Life Enjoyment and Satisfaction QuestionnaireFShort Form (Q-LES-Q-SF)

Dayan 2010 *(Continued)*

	Secondary outcome • Heatherton and Polivy State Self-Esteem (HPSS) Scale6 were used to measure QOL and self-esteem, respectively, differences between previous BonTA experience and Naive
Notes	"The authors have indicated no significant interest with commercial supporters."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "double-blind, randomised, placebo-controlled" page 2089 Comment: we consider unclear risk of bias because the authors did not explain how they randomised the participants
Allocation concealment (selection bias)	Unclear risk	No information Comment: we considered unclear risk of bias because the authors did not explain how the methods used for maintaining the allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "An unblinded nurse prepared the injections, keeping the physician and participant blinded to treatment for the duration of the 3-month survey." page 2089 Comment: we considered unclear risk of bias due to the authors did not reported methods for blinding participants, including visual aspect of interventions
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "An unblinded nurse prepared the injections, keeping the physician and participant blinded to treatment for the duration of the 3-month survey." page 2089 Comment: we considered unclear risk of bias due to the authors did not reported methods for blinding assessors, including visual aspect of interventions
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Follow-up data at the time of the telephone call were available for 97% of the entire cohort (BoNTA, 96%; placebo, 98%) and for 80% of the entire cohort at 3 months (BoNTA, 74%; placebo, 86%)." page 2090 Comment: we considered unclear risk of bias because the authors did not explain drop-out reason
Selective reporting (reporting bias)	High risk	Only P value was shown. Comment: we considered this high risk of bias, we sent an e-mail on 22 November 2015. We received no answer.
Other bias	Low risk	We considered this study at low risk of other bias

De Boulle 2018

Study characteristics

Methods	**Study design**- multicentre, double-blind, randomised, multicentre, placebo-controlled, parallel-design in upper facial lines, forehead lines, and crow's feet lines. Period 1 (Days 1–180) comprised a double-blind, placebo-controlled, single-treatment parallel-group study design comparing onabotulinumtoxinA and placebo. Period 2 (Days 180–360), participants could receive up to 2 additional open-label

De Boulle 2018 *(Continued)*

	treatments (Cycles 2 and 3, >= 84 days apart) with onabotulinumtoxinA 64 U, administered using the same 16-point pattern **Study date**- started October 2014 and finished April 2016 **Study setting**- outpatient 24 sites (10 in the USA, 14 in Europe)
Participants	Randomised 787 participants. Age ranging: Onabot40 U group-47.6 years old (range 21-75), Onabot 64 U group-45.5 years old (range 21-76), placebo group- 48.1 (range 22-73). Gender: Onabot40 U group 87.4% female, Onabot64 U group 90.7% female, placebo group 88.7% female. **Inclusion criteria** • Moderate to severe FHL at maximum eyebrow elevation based on investigator and subject assessments using the Facial Wrinkle Scale with Photo numeric Guide (FWS; 0 = none, 3 = severe) **Exclusion criteria** • Eyelid ptosis or excessive forehead and eyebrow skin laxity;eyelid folds that reached the pupil or touched the upper lash line; use of the frontalis muscle to move the upper eyelid • Periocular and eyebrow asymmetry • Marked dermatochalasis • Deep dermal scarring • Excessively thick sebaceous skin • Inability to substantially lessen facial lines, even by physically spreading them apart • Women of childbearing potential had a negative urine pregnancy test on Day 1 pretreatment **Severity of disease (according investigator rating of FHL severity eyebrow elevation in baseline):** Onabot40U group 54.1% (moderate), 45.9%(severe); Onabot64U group 51.8% (moderate), 48.2%(severe); placebo group 51.9% moderate, 48.1% severe **Ethnicity**- 90.3% Caucasian in Onabot40U group; 91.1% Caucasian in Onabot64U group; 92.9% Caucasian in placebo group
Interventions	**Duration of study:** Period 1 (Days 1–180). Period 2 (Days 180–360) **Intervention** • OnabotulinumtoxinA 64 U(FHL 20 U, GL 20 U, and CFL 24 U), • OnabotulinumtoxinA 40 U(FHL 20 U,GL20 U, placebo [saline] in CFL **Comparator** • Placebo (FHL, GL, and CFL). were administered as 0.1 mL injections distributed over 16 sites: 5 in FHL, 5 in GL, and 3 in CFLon each side **Ratio:** period 1 (2:2:1 Onabot44 U:Onabot64 U: placebo) Period 2 no information
Outcomes	**Primary outcomes** • FDA-proportion of participants (ITT population) who achieved at least a 2-grade improvement from baseline on both investigator and subject FWS ratings of FHL severity at maximum eyebrow elevation on Day 30 of the double-blind period • European agency -the proportion of participants (mTT) population achieving an investigator-assisted and a participant-assisted FWS rating of none/mild for FHL severity at maximum eyebrow elevation at Day 30 o the double-blind period **Secondary outcomes**

De Boulle 2018 *(Continued)*

- Investigator FWS rating of none/mild for FHL severity at maximum eyebrow elevation at Day 30,
- At least a 1-grade improvement from baseline in investigatorFWSrating of FHLseverity at rest at Day 30,
- At least a 3-point improvement from baseline on FLO-11 Item 4 (looking older than actual age)
- Adverse events

Notes	"This study was sponsored by Allergan plc. Writing and editorial assistance was provided by K.E. Larsen and J. Street of PelotonAdvantage, Parsippany, NJ, and was funded by Allergan plc Dublin, Ireland. K. De Boulle has served as a consultant on an advisory board and speakers' bureau, and has received honoraria from Allergan plc. W.P. Werschler has served on an advisory board, as a speaker, and as a consultant and/or received research funding from Allergan plc.M.H. Gold serves as a consultant and has received research funding from Allergan plc. S. Bruce has served on an advisory board and on a speakers' bureau, has received research grants, and serves as an investigator trainer forAllergan plc. G. Sattler has received a research grant for participation in this study. P. Ogilvie received research grants from Allergan plc and serves as a consultant, advisory board member, and trainer for Allergan plc. D. Vitarella was an employee of Allergan plc at the time of this study. J. Street and K.E. Larsen serve as medical writers forPeloton Advantage, which received funding for editorial services from Allergan plc. E. Lee, X. Lei, C. Mao, and I.Yushmanova are employees of Allergan plc and may own stock or options in the company."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "On Day 1, after randomization (2:2:1), subjects"...page 1438 Comment: we considered unclear risk of bias because the authors did not mention how they randomise the participants
Allocation concealment (selection bias)	Unclear risk	Quote:"On Day 1, after randomization (2:2:1), subjects"...page 1438 Comment: we considered unclear risk of bias because the authors did not mention how they randomise the participants
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote:"Period 1 (Days 1–180) comprised a double-blind, placebo-controlled"...page 1438 Comment: we considered unclear risk of bias because the authors did not mention how they blind the participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote:"Period 1 (Days 1–180) comprised a double-blind, placebo-controlled"...page 1438 Commet: we considered unclear risk of bias because the authors did not mention how they keep the participants blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: Figure 2 ...page1440 Coment: we considered low risk of bias
Selective reporting (reporting bias)	Unclear risk	All prespecified outcomes were reported Comment: e consider a low risk of bias
Other bias	Unclear risk	Quote:"E. Lee, X. Lei, C. Mao, and I.Yushmanova are employees of Allergan plc and may own stock or options in the company"....page1437 Comment: we consider unclear risk of bias because professional aspects of some authors

Fagien 2007a

Study characteristics	
Methods	**Study design**- double-blind, randomised, placebo-controlled, parallel-design, in glabellar lines **Study date**- no information **Study setting**- no information
Participants	**Randomised**- 70 participants, with mean age of 44 years (30-54 years). Gender- no information **Inclusion criteria** • Moderate or severe glabellar lines (on a scale of none, mild, moderate, or severe) at maximum attempted contraction. Patients were also required to be between 30 and 55 years of age and, if of childbearing potential, to have a negative urine pregnancy test at the screening and baseline visits and to use a reliable method of contraception throughout the study **Exclusion criteria** • Previous cosmetic surgery or an intention to undergo a non- study facial cosmetic procedure during the study period • Marked facial asymmetry, dermatochalasis, deep dermal scarring, or excessively thick sebaceous skin • Myasthenia gravis, Eaton–Lambert syndrome, amyotrophic lateral sclerosis, or any other disease that might interfere with neuromuscular function • Use of an aminoglycoside antibiotic, curare-like agent, or other agent that might interfere with neuromuscular function • Profound atrophy/excessive weakness of muscles in the target area of injection • History of facial nerve palsy or bleeding disorders • Dermabrasion, laser resurfacing, soft tissue augmentation or therapy with any botulinum toxin serotype in the preceding 12 months • Pregnancy, breastfeeding, or an intention to become pregnant during the study **Severity of disease**- moderate to severe glabellar lines at contraction **Ethnicity**- 97% Caucasian
Interventions	**Duration of study**- 12 weeks **Intervention** • OnabotulinumtoxinA (20 U) in glabellar lines, 5 sites, 4 U/site (N = 35) **Comparator** • Placebo 0.4mL in glabella lines, 5 sites, 0.08mL/site (N = 35)
Outcomes	**Primary outcome** • Investigator assessments of efficacy were FWS the evaluation of glabellar line severity at rest and at maximum attempted contraction using the Facial Wrinkle Scale **Secondary outcomes** • Patients assessment: FLO Questionnaire, rated their global assessment of the change in their frown lines, and reported their self-perception of age • Adverse event

Fagien 2007a *(Continued)*

Notes	"This research was funded by Allergan, Inc. All authors received compensation for their work in the study. Jonathan Kowalski is a paid employee/researcher for Allergan. Drs. Kowalski, Cox, and Finn are stockholders in Allergan."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "A Double-Blind, Randomized, Placebo-Controlled Study" page S3 " The patients were assigned to one of the treatments groups (in a 1:1 ratio) in accordance with a randomisation schedule generated by the independent clinical research organization." page S3 Comment: we considered this unclear risk of bias because the authors did not explain how they randomised the participants
Allocation concealment (selection bias)	Unclear risk	Quote: "The patients were assigned to one of the treatments groups (in a 1:1 ratio) in accordance with a randomisation schedule generated by the independent clinical research organization." page S3 Comment: we considered this unclear risk of bias because the authors did not explain the methods used for maintaining the allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "To maintain the study blinding, the syringes for treatment were prepared with botulinum toxin type A or placebo by an assistant and the injector was unaware of which treatment was in each syringe." page S4 Comment: we considered low risk of bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "To maintain the study blinding, the syringes for treatment were prepared with botulinum toxin type A or placebo by an assistant and the injector was unaware of which treatment was in each syringe." page S4 Comment: we consider low risk of bias
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "A total of 70 patients were enrolled, of whom 65 (93%) completed" page S5 Comment: we considered unclear risk of bias because the authors did not explain the drop-out reason
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported Comment: we considered low risk of bias
Other bias	Unclear risk	One of the authors (V) was Allergan employee. Pharmaceutical support Comment: we considered this a unclear risk of bias because one of the authors was Allergan employee

Feng 2015

Study characteristics

Methods	**Study design**- multicentre, randomised, dose-ranging placebo-controlled, parallel-design in glabellar lines

Feng 2015 *(Continued)*

	Study date- start (25 November 2009), end (27 November 2010) **Study setting**- outpatients from seven centres
Participants	**Randomised**- 448 participants, with mean age of 44.34 years in placebo group; 44.2 years in low-dose BontA (10 u) group; 42.79 years in high-dose BontA (20 u). Gender: male 17/122 (13.93%), female 105 /122 (86.07%) in placebo group; male 29/183 (15.85%), female 154/183 (84.15%) in BontA low-dose group; male 27/183(14.75%), female 156/183 (85.25%) in BontA hig- dose group **Inclusion criteria** • Moderate-or-severe glabellar lines; and age: 18 to 65 years **Exclusion criteria** • Previous BontA treatment • Systemic neuromuscular junction disorder • Known allergy to BontA or excipients • Disease at an injection site or any conditions interfering with study assessments • Cosmetic surgical procedures scheduled during the study period • And any significant comorbidity precluding BontA treatment **Severity of disease**- Participants with moderate-to-severe glabellar lines **Ethnicity**- no information
Interventions	**Duration of study**- 16 weeks **Intervention** • BontA(HBTX-A) (10 U) (N = 183), BontA- 20 U (N =183) **Comparator** • Placebo-0.5 mL (N =122)
Outcomes	**Primary outcome** • Clinical glabellar line severity score at maximum contraction on day 30 **Secondary outcomes** • Improvement in graded severity of glabellar lines during relaxation; overall assessment of glabellar line severity reduction; participant satisfaction • Adverse events.
Notes	“The authors have indicated no significant interest with commercial supporters.”

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "double-blind trial and randomly divided into" page S56 Comment: we consider unclear risk of bias because the authors did not explain how they randomised the participants
Allocation concealment (selection bias)	Unclear risk	Quote: "Participants were assigned to low-dose (10 units, n = 183), high-dose (20 units, n = 183), or saline" page S57

Feng 2015 *(Continued)*

		Commen: we consider unclear risk of bias because the authors did not explain the methods used for maintaining the allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Participants who met the inclusion and exclusion criteria were enrolled in a double-blind, placebo-controlled" page S57 Comment: we consider unclear risk of bias because the authors did not explain how they blinded the participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Participants who met the inclusion and exclusion criteria were enrolled ina double-blind, placebo-controlled" page S57 Comment: we consider unclear risk of bias because the authors did not explain how they blinded the outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Four participants were lost to follow-up (one in the placebo group, 2 in the low dose, and 1 in the high-dose group), and excluded from primary end point data. Another 13 participants statistically 'out of the time window' were excluded from analysis, including 5 participants in the placebo group, 5 in the low-dose group, and 3 in the high- dose groups, respectively. One participant in the high-dose group receiving combined therapy was not included in the per protocol set (PPS). The final PPS consisted of 449 (92.01%) participants, including 111, 167, and 171 in the placebo, low-dose and high-dose arms, respectively." page S58 Comment: we consider low risk of bias
Selective reporting (reporting bias)	High risk	The authors did not mention if the investigator assessment was done at rest or at contraction Comment: we consider this high risk of bias, we sent an e-mail on 21 November 2015. We received no answer
Other bias	Low risk	We considered this study at low risk of other bias

Firoz 2012

Study characteristics	
Methods	**Study design**- randomised, double-blind, split-face design, active controlled, parallel 2-arm, onabotulinumtoxinA versus AbobotulinumtoxinA in glabellar and forehead lines (Poster) **Study date**- no information **Study setting**- no information
Participants	**Randomised** 74 participants, with mean age of 50 years (32-65 years). Gender- no information **Inclusion criteria**- no information **Exclusion criteria**- no information **Severity of disease**- moderate to severe glabellar lines and raising forehead- split face **Ethnicity**- 43.2% Caucasian, 2.8% black, 51.4% Hispanic, 1.4% Asian and 1.4% other
Interventions	**Duration of study**- 24 weeks **Intervention**

Firoz 2012 *(Continued)*

	• OnabotulinumtoxinA (no U specified) 0.4mL; 0.1 mL into the procerus and each corrugator, 0.05 mL/site, four injections in frontalis (N =70) **Comparator** • AbobotulinumtoxinA (no U specified) 0. 4mL; 0.1 mL into the procerus and each corrugator, 0.05mL/site, four injections in frontalis (N =70) **Ratio**- no information
Outcomes	**Primary outcome** • Onset of action **Secondary outcomes** • Duration of action • Patient satisfaction • Pain during injection
Notes	"Commercial support: None identified"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Using a random number generator, patients received" page AB210 Comment: We considered low risk of bias
Allocation concealment (selection bias)	Unclear risk	No information Comment: we considered unclear risk of bias due to the authors did not provide the methods used for maintain the allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "patients received identical volumes and injection patterns of one product in the right corrugator and frontalis, and the other product in the left." (page AB21) Comment: We considered low risk of bias since the authors adopted proper actions to assure blinding of personnel and patients.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information about outcome assessors blinding Comment: we considered unclear risk of bias
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information about losses Comment: we considered unclear risk of bias
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported Comment: we considered low risk of bias
Other bias	Low risk	We considered this study at low risk of other bias

Hanke 2013

Study characteristics	
Methods	**Study design**- multicentre, randomised, double-blind, placebo-controlled, parallel -design, phase III in glabellar lines **Study date**- no information **Study setting**- outpatients from eight centres
Participants	**Randomised**- 271 participants, with mean age of 46.9 ± 9.3 years (median = 46.5 years) BontA group; 45.7 ± 11.4 years (median 46 years) placebo group. Gender: 170/182 (93.4%) female, 12/182 (6.6%) male in BontA group; placebo- 84/89 (94.4%) female, 5/89 (5.%) male in placebo group **Inclusion criteria** • Men and women age 18 and older with moderate (severity score 2) to severe (severity score 3) glabellar frown lines at maximum frown on the Facial Wrinkle Scale (FWS),18 as assessed according to an investigator's rating at screening. An additional inclusion criterion was a stable medical condition **Exclusion criteria** • Previous treatment with botulinum toxin of any serotype in the glabellar area within the last 8 months • Previous insertion of permanent material in the glabellar area, previous treatment with any facial aesthetic procedure (e.g. chemical peeling, injection with biodegradable fillers, photo rejuvenation) in the glabellar area within the last 12 months, • Any planned treatment with botulinum toxin of any serotype in any body region or any other planned facial aesthetic procedure during the study period • Marked facial asymmetry or ptosis of the eyelid or eyebrow **Severity of disease**- moderate to severe glabellar frown lines at maximum frown (FWS) **Ethnicity**- 119/182 (65.4%) Caucasian, 8/182 (4.4%) black, 51/182 (28%) Hispanic, 2/182 (1.1%) Asian, and 2/182 (1.0%) other in BontA group; 58/89 (65.2%) Caucasian, 3/89 (3.4%) black, 28/89 (31.5%) Hispanic, 0% Asian, and 0% other in placebo group
Interventions	**Duration of study**- 16 weeks **Intervention** • IncobotulinumtoxinA (20 U) (N = 182) **Comparator** • Placebo- 0.5mL 0.1 mL per site (N = 89)
Outcomes	**Primary outcome** • Composite endpoint treatment success (CETS) comprising the following efficacy variables: responders with at least a 2-point improvement compared with baseline at maximum frown at Day 30 according to the investigator assessment on the FWS, and responders with at least a 2-point improvement compared with baseline at maximum frown at Day 30 according to the participant's assessment on a 4-point scale **Secondary outcomes** • Proportion of responders at maximum frown and at rest on Day 30 according to investigator rating on FWS (responder was defined as a participant with a rating of none (0) or mild (1) and the proportion of responders at maximum frown and at rest on Day 30 according to participant assessment on the 4-point scale (responder was defined as a participant with at least a 1-point improvement from baseline) • Onset of treatment

Hanke 2013 *(Continued)*

- Adverse events

Notes	"This study was supported by Merz Pharmaceuticals GmbH. The sponsor was involved in the design and conduct of the study; in the collection, analysis, and interpretation of data; and in the preparation, review, and approval of this manuscript. C. William Hanke, Rhoda S. Narins, Fredric S. Brandt, Joel L. Cohen, Lisa M. Donofrio, Jeanine Downie, David H. McDaniel, Mark Nestor, Joel Schlessinger, Amy Taub, and Robert Weiss are paid consultants and researchers for Merz. Moritz Heinz and Andrea Schlo€ be are employees of Merz Pharmaceuticals GmbH."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "At Visit 1 (Day 0), subjects were randomised 2:1 to receive a total dose of 20 U of incobotulinumtoxinA" page 893 Comment: we considered unclear risk of bias because the authors did not mention how they randomised the participants
Allocation concealment (selection bias)	Unclear risk	Quote: "At Visit 1 (Day 0), subjects were randomised 2:1 to receive a total dose of 20 U of incobotulinumtoxinA" page 893 Comment: we considered unclear risk of bias because the authors did not mention due to the authors did not provide the methods used for maintain the allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The study investigators, centre staff, and subjects were blinded to the assigned medication" page 893 Comment: we considered low risk of bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The study investigators, centre staff, and subjects were blinded to the assigned medication" page 893 Comment: we considered low risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Three subjects (1.1%) discontinued the study prematurely; one (0.5%) in the incobotulinumtoxinA group withdrew consent, and two (2.2%) in the placebo group were lost to follow-up. Twenty-one subjects were major protocol deviators and were not included in the PPS; 6.6% (n = 12) and 10.1% (n = 9) in the incobotulinumtoxinA and placebo groups, respectively." page 894 Comment: we considered low risk of bias
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported Comment: we considered low risk of bias
Other bias	Unclear risk	Quote: "This study was supported by Merz Pharmaceuticals GmbH. The sponsor was involved in the design and conduct of the study; in the collection, analysis, and interpretation of data; and in the preparation, review, and approval of this manuscript." Comment: we considered this a unclear risk of bias

Harii 2008

Study characteristics

Harii 2008 *(Continued)*

Methods	**Study design**- multicentre, double-blind, randomised, placebo-controlled, two- dose, parallel design in glabellar lines in Japanese participants **Study date**- no information **Study setting**- outpatients
Participants	**Randomised** 142 participants, with mean age of 45.7± 9.1 years. Gender: 90% female, 10% male **Inclusion criteria** • BoNTA-näıve patients aged 20–64 years with glabellar lines of at least moderate severity at maximal contraction **Exclusion criteria** • Any condition (such as myasthenia gravis, Lambert-Eaton syndrome, amyotrophic lateral sclerosis, or systemic neuromuscular junction disorder) that could influence the effect of treatment (e.g. deterioration in atonia) • Pregnancy • History of hypersensitivity to any component of the treatment product • Any condition that could impair the safety of the participant (e.g. severe heart, kidney, liver, or respiratory disease); • Infection or skin disease at the injection site(s) • Use of a peripheral muscle relaxant within 2 weeks of the start of the study; • History of surgery at the treatment site(s) • Previous aesthetic procedures within 6 months of the beginning of the study **Severity of disease**-Quote: "All subjects had either moderate (50.7%) or severe (49.3%) glabellar lines at maximal contraction." **Ethnicity**- 100% Japanese
Interventions	**Duration of study**- 16 weeks **Intervention** • OnabotulinumtoxinA (10 U), 2 U (0.1 mL) per site, two injections in each corrugator supercilii muscle and one injection in the procerus muscle for a total of five injection sites (N = 45), • OnabotulinumtoxinA (20 U), 4 U (0.1 mL) per site, two injections in each corrugator supercilii muscle and one injection in the procerus muscle for a total of five injection sites (N = 46), **Comparator** • Placebo = 0.5 mL, 0.1 mL per site, two injections in each corrugator supercilii muscle and one injection in the procerus muscle for a total of five injection sites (N = 49)
Outcomes	**Primary outcome** • Physician-rated line severity 4 weeks after treatment at maximal contraction **Secondary outcomes** • Physician-assessed line severity at maximal contraction at all other posttreatment visits, line severity at rest at all visits • Participant-assessed improvement ratings at each visit • Patient satisfaction ratings at weeks 4 and 16 and for the entire study period (rated at week 16) • Adverse events
Notes	"This study was funded by Allergan, Inc., Irvine, California."

Harii 2008 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Using the random-number-generation function of SAS (Statistical Institute, Inc., Cary, NC), subjects were allocated to one of three treatment groups: 10-U BoNTA, 20-U " page 725 Comment: we considered this low risk
Allocation concealment (selection bias)	Unclear risk	Quote: "Using the random-number-generation function of SAS (Statistical Institute, Inc., Cary, NC), subjects were allocated to one of three treatment groups: 10-U BoNTA, 20-U" page 725 Comment: we considered unclear risk of bias due to the authors did not provide the methods used for maintain the allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Vials used for treatment administration were coded to maintain the blind." page 725 Comment: we considered unclear risk of bias due to no information about visual aspect of interventions was provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Vials used for treatment administration were coded to maintain the blind" page 725 Comment: we considered unclear risk of bias due to no information about visual aspect of interventions was provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Six subjects in the full analysis data set discontinued: two in the 20-U group discontinued before treatment, two in the 10-U group moved away, one in the 20-U group retracted consent, and one in the placebo group became pregnant." page 726 At the beginning the authors mentioned 140 participants, but they treated 139 participants and there was no explanation about the missing one. Comment: We considered unclear risk of bias because data discrepancy. We sent an e-mail on 23 November 2015, but the electronic address was wrong and we could not find a valid e-mail.
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported Comment: we considered low risk of bias
Other bias	Low risk	We considered this study at low risk of other bias

Harii 2017

Study characteristics

Methods	**Study design**- multicentre, phase III. First period (6 months) was a double-blind, randomised, placebo-controlled, two- dose, parallel design in crow's feet lines in Japanese participants. Second period was an open-label study (7 months) **Study date**- no information **Study setting**- outpatients

Harii 2017 *(Continued)*

Participants	**Randomised** 300 participants, with mean age of 50.2± 6.05 years in OnabotulinumtoxinA 24U (first period)/OnabotulinumtoxinA 24U (second period) group; 50.6 ± 6.11 years in OnabotulinumtoxinA 12 U (first period)/OnabotulinumtoxinA 12 U (second period) group; 49.3 ± 7.24 years in Placebo(first period)/OnabotulinumtoxinA 24 U (second period); 48.3 ± 8.10 years in placebo(first period)/OnabotulinumtoxinA 12 U (second period); 49.7 ± 6.64 years in total populatio. Gender: 84/104(80.8%) female and 20/104(9.2%) male in OnabotulinumtoxinA 24 U (first period)/OnabotulinumtoxinA 24 U (second period) group; 70/99(70.7%) female and 29/99(29.3%) male in OnabotulinumtoxinA 12 U (first period)/OnabotulinumtoxinA 12 U (second period) group; 36/48(75%) female and 12/48(25%) male in placebo(first period)/OnabotulinumtoxinA 24 U (second period); 34/49(69.4%) female and 15/39(29.6%) male in Placebo(first period)/OnabotulinumtoxinA 12 U (second period); 224/300(74.7%) female and 76/300 (25.33%) in total population. **Inclusion criteria** • Japanese males and nonpregnant females aged 20–64 years • Bilaterally symmetrical moderate to severe CFL at maximum smile, as measured by the investigator using the FWS-A **Exclusion criteria** • Previous cosmetic treatments or surgical procedures at the treatment sites • Eyebrow or eyelid ptosis and eyelid hooding or other skin laxity likely to interfere with onabotulinumtoxinA treatment or CFL assessments. **Severity of disease**- according to investigator assessment using FWS-A at maximum smile: 51/104(49%) moderate and 53/104(51%) severe in OnabotulinumtoxinA 24 U (first period)/OnabotulinumtoxinA 24 U (second period) group; 49/99(49.5%) moderate and 50/99(50.5%) in OnabotulinumtoxinA 12 U (first period)/OnabotulinumtoxinA 12 U (second period) group; 23/48(47.9%) moderate and 25/48(52.1%) severe in Placebo(first period)/OnabotulinumtoxinA 24U (second period); 24/49(49%) moderate and 25/49(51%) severe in Placebo(first period)/OnabotulinumtoxinA 12 U (second period); 147/300(49%) moderate and 153/300(51%) severe in total population. **Ethnicity**- 100% Japanese
Interventions	**Duration of study**- first period 24 weeks and second period 35 weeks **Interventions** • OnabotulinumtoxinA 24 U (first period)/OnabotulinumtoxinA 24 U (second period); crow's feet lines; 6 intramuscular injections in the lateral aspect of the orbicularis oculi (3 injections per side; 0.1 mL per injection site); (N = 104) • OnabotulinumtoxinA 12 U (first period)/OnabotulinumtoxinA 12 U (second period); crow's feet lines; 6 intramuscular injections in the lateral aspect of the orbicularis oculi (3 injections per side; 0.1 mL per injection site); (N = 99) **Comparator** • Placebo(first period)/OnabotulinumtoxinA 24 U (second period); crow's feet lines; 6 intramuscular injections in the lateral aspect of the orbicularis oculi (3 injections per side; 0.1 mL per injection site); (N = 48) • Placebo(first period)/OnabotulinumtoxinA 12 U (second period); crow's feet lines; 6 intramuscular injections in the lateral aspect of the orbicularis oculi (3 injections per side; 0.1 mL per injection site); (N = 49)
Outcomes	**Primary outcome** • Proportion of investigator-assessed responders at day 30 after initial treatment, with responders defined as participants achieving CFL severity of none or mild severity at maximum smile on the FWS-A **Secondary outcomes**

Harii 2017 *(Continued)*

- Investigator-assessed FWS-A included the following: the proportion of participants achieving at least a 1-grade improvement in CFL severity at maximum smile and at rest (responders) at day 30
- Duration of effect, defined as the median time until loss of efficacy (from responder to nonresponder in treatment period 1 for day 30 responders), using the following FWS-A responder definitions: CFL severity of none or mild at maximum smile, at least a 1-grade improvement in CFL severity at maximum smile, and C1-grade improvement in CFL severity at rest
- Responder analyses at time points other than day 30 of treatment period 1.
- Participants achieving global assessment of change in CFL (SGA- CFL) was evaluated on a 7-point scale ranging from 1 (very much improved) to 7 (very much worse). On the self- perception of age (SPA), subjects reported if they perceived themselves as looking their current age, older than their current age, or younger than their current age.
- Participants' perception of the effect of their facial lines on their appearance was assessed using specific items from the 11-item Facial Line Outcomes (FLO-11) Questionnaire including the psychological impact items 2 (''look older''), 5 (''look less attractive''), and 8 (''look tired''). Responses were based on a scale wherein 0 indicates ''not at all'' and 10 indicates ''very much''; responders were subjects achieving at least a 2-point improvement for items 2 and 5 and at least a 3-point improvement for item 8
- Subject Assessment of Satisfaction with Appearance was based on a 5-point scale (1 = very unsatisfied; 5 = very satisfied), and responders were defined as participants who rated their satisfaction as improved (ie, from neutral or worse at baseline to very satisfied or satisfied after treatment).
- Satisfaction with treatment was assessed by the Facial Line Satisfaction Questionnaire (FLSQ) overall satisfaction item. Responses were based on a 5-point Likert scale ranging from -2 (very dissatisfied) to +2 (very satisfied)
- Participants' perception of onset of effect was assessed by asking subjects at weeks 1 and 2 if they noticed an improvement in CFL appearance; those who answered yes were asked when (in number of days) the improvement was first noticed.
- Adverse events

Notes	"This study was sponsored by Allergan plc, Dublin, Ire- land. Writing and editorial assistance was provided to the authors by Emily H. Seidman, MSc, of Peloton Advantage, Parsippany, NJ, and was funded by Allergan plc." Elisabeth Lee was Alergan employee.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote:"Subjects were assigned a randomization number (not disclosed to the study center),"...page 1187 Comment: we considered unclear risk of bias because the authors did not explain how they randomised the participants
Allocation concealment (selection bias)	Low risk	Quote:"An interactive voice or web response system designed by Allergan Data Management provided a specific kit number for each subject, and the study center administered treatment. ,"...page 1188 Comment: we considered low risk of bias
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: no information Comment: we considered an unclear risk of bias, because the authors did not explain how and who prepared the medication. We sent an e-mail on November 12, 2017
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: no information Comment: we considered an unclear risk of bias, because the authors did not explain how and who prepared the medication. We sent an e-mail on November 12, 2017

Harii 2017 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote:" The majority of subjects completed the study (89.3%)"...page1189 Coment: we considered an unclear risk of bias, because the author did not explain the drop outs. We sent an e-mail on November 12, 2017
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported Comment: we considered low risk of bias
Other bias	Unclear risk	Comment: we considered unclear risk of bias because one of the authors (Elisabeth Lee) was Allergan employee

Hexsel 2013

Study characteristics	
Methods	**Study design**- single-centre, randomised, open-label study of full face, parallel- design, phase IV **Study date**- start October 2009, end December 2010 **Study setting**- outpatients from one private clinic (Brazil)
Participants	**Randomised**- 90 participants, with mean age of 48.3 ± 7.2 years (30-60 years). Gender: 82/90 (96.5%) female, 8/90 (3.5%) male. Other demographic data: 62.4% nonsmokers, 60% BontA naive, non fillers-63.5% **Inclusion criteria** • Patients were 30-60 years, BontA naive or had not received BontA treatment in the previous six months, not do any cosmetic or surgical facial procedure during study period. The presence of at least two indications for BontA treatment on each third of the face (upper, middle, lower) **Exclusion criteria** • Pregnancy • Presence of scars or other cosmetic or dermatological conditions that could interfere with the outcome • Neuromuscular disease **Severity of disease**- wrinkles in full face **Ethnicity**- 79/90 (92.9%) Caucasian
Interventions	**Duration of study**- 16 weeks **Intervention/Comparator**- AbobotulinumtoxinA group 1 (166 U ± 4), group 2 (194 U ± 12), and group 3 (214 U ± 11)
Outcomes	**Primary outcome** • Investigator rating on FWS (responder was defined as a participant with a rating of none (0) or mild (1) and the proportion of responders at maximum frown and at rest on Day 30 according to participant assessment on the 4-point scale) **Secondary outcome** • Adverse events

Hexsel 2013 *(Continued)*

Notes	"Dr Hexsel has conducted clinical trials for Ipsen, Allergan, Galderma, and Medicis. The other authors have no relevant conflicts of interest to declare. Scientific grant was received from Galderma Inc., France"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomisation list was generated by a statistician and subjects were sequentially allocated into 3 groups" page 1356 Comment: we considered this low risk of bias
Allocation concealment (selection bias)	Unclear risk	Quote: "The randomisation list was generated by a statistician and subjects were sequentially allocated into 3 in a 1:1:1 proportion″ page 1356 Comment: we consider this unclear risk of bias, because the authors did not explain the methods used for maintain the allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "open-label study" page 1356 Comment: we considered this high risk of bias
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "open-label study" page 1356 Comment: we considered this high risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "85 completed the study: 5 discontinued due to loss of follow-up" page 1357 Comment: we considered this low risk of bias
Selective reporting (reporting bias)	Unclear risk	Only P value was showed. Comment: we considered this unclear risk of bias. We e-mailed the author on 6 March 2015. Answer on 10 March 10 2015: the authors sent a SPSS file
Other bias	Low risk	We considered this study at low risk of other bias

Kane 2009

Study characteristics

Methods	**Study design**- multicentre, randomised, double-blind, placebo-controlled study, parallel-design, phase III **Study date**- no information **Study setting**- outpatients from 27 centres
Participants	**Randomised**- 816 participants, with mean age of 49.2 ± 10.31 years in placebo group, 48.7 ± 10.33 years in AbobotulinumtoxinA group. Gender: 238/272 (88%) female, 34/272 (13%) male in placebo group; 481/544 (88%) female, 63/544 (12%) male in BontA group. Patients stratified by race/ethnicity. Severity of disease- moderate to severe glabellar lines

Kane 2009 *(Continued)*

	Other demographic data- Fitzpatrick skin type: Placebo- 1 (extremely fair, always burns, never tans) 7/272 (3%), 2 (white, always burns, sometimes tans) 91/272 (33%), 3 (white, sometimes burns, always tans) 79/271 (29%), 4 (olive brown, rarely burns, always tans) 47/272 (17%), 5 (brown, never burns) 30/272 (11%), 6 (heavily pigmented or black, never burns) 18/272 (7%). Dysport- 1 (extremely fair, always burns, never tans) 19/544 (3%), 2 (white, always burns, sometimes tans) 161/544(30%), 3 (white, sometimes burns, always tans) 185/544 (34%), 4 (olive brown, rarely burns, always tans) 86/544 (67%), 5 (brown, never burns) 53/544 (10%), 6 (heavily pigmented or black, never burns) 140/544 (7%). BontA naive 221/272 (81%) in placebo group; 51/272 (10%) not naive in placebo group. BontA naive in AbobotulinumtoxinA group 437/544 (80%) BontA naive; 107/544(20%) not BontA naive **Inclusion criteria** • Patients aged 18 years or older with moderate to severe glabellar lines **Exclusion criteria** • Previous treatment with Dysport® within 150 days of entry and were prohibited from treatment to areas other than the glabellar area during the study • Were unable to substantially reduce glabellar lines by manually spreading them • Previous facial plastic surgery procedures such as tissue augmentation or brow lifts, or any procedure or concurrent therapy that the investigator considered would interfere with the evaluation of Dysport® • Any active infection in the glabellar area • Chronic drug or alcohol abuse • Clinically diagnosed anxiety or depression • Current facial palsy or neuromuscular junction disorders, or any other condition or circumstance that might pose a risk to the patient or interfere with the ability to acquire satisfactory clinical data **Severity of disease**- patients with grade 2 or 3, corresponding to moderate to severe wrinkles at maximum contraction **Ethnicity**- 191/271 (70%) Caucasian, 54/272 (20%) African American, 19/271 (7%) Hispanic, 2/272 (<1%) Asian, 2/272(<1%) Native American, 3/272 (<1%) other in placebo group; 364/544 (67%) Caucasian, 106/544 (19%) African American, 57/544 (10%) Hispanic, 8/544 (1%) Asian, 1/544 (<1%) Native American, 8/544 (1%) other in BontA group
Interventions	**Duration of study**- 20 weeks **Intervention** • AbobotulinumtoxinA, women received 50 U, 60 U, or 70 U and men received 60 U, 70 U, 80 U, 5-point of injection. "Procerus: This injection was located at a point inferior to a line joining the eyebrows and superior to the root of the nose. Corrugator: These two injections were administered bilaterally directly above the inner canthus and above the bony orbital rim. Lateral corrugator/orbicularis: These two injections were the most crucial because of the possibility of producing eyelid ptosis. The injection site was directly above the pupil and approximately 1 cm above the bony orbital rim, bilaterally" (N = 544) **Comparator**- • Placebo, women 0.4 mL to 0.6 mL, men 0.5 mL to 0.7mL, 5 points of injection. Quote: "Procerus: This injection was located at a point inferior to a line joining the eyebrows and superior to the root of the nose. Corrugator: These two injections were administered bilaterally directly above the inner canthus and above the bony orbital rim. Lateral corrugator/orbicularis: These two injections were the most crucial because of the possibility of producing eyelid ptosis. The injection site was directly above the pupil and approximately 1 cm above the bony orbital rim, bilaterally" (N = 272)
Outcomes	**Primary outcome**- • Evaluator and patient self-assessment at maximum frown using the Glabellar Line Severity Score. **Secondary outcome**-

Kane 2009 *(Continued)*

- Onset of the treatment
- Duration of treatment effect
- Subgroup analysis by ethnicity, gender, BontA naivety
- Adverse events.

Notes	"Medicis Aesthetics, Inc. (Scottsdale, Ariz.) provided Dysport and study funding to the authors. Michael A. C. Kane is a consultant, speaker, stockholder, and investigator for Medicis; a consultant, speaker, and stockholder for Allergan; a consultant and stockholder for Mentor; a consultant and speaker for QMed; and a consultant, investigator, and stock option holder for Revan"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomised in a 2:1 ratio to one treatment of variably dosed" page 1620 Comment: we considered unclear risk of bias because the authors did not explain how they randomised the participants
Allocation concealment (selection bias)	Unclear risk	Quote: "Patients were randomised in a 2:1 ratio to one treatment of variably dosed" page 1620 Comment: we considered unclear risk of bias because the authors did not explain the methods used for maintain the allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Double-Blind, Placebo-Controlled" page 1620 Comment: we considered unclear risk of bias because the authors did not explain how they blinded the participants
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Double-Blind, Placebo-Controlled" page 1620. "Duration of Response Assessed by Blinded Evaluator at Maximum Frown"page 1623 Comment: we considered low risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Patient disposition can be seen in Table 3. No patient discontinued because of an adverse event or lack of product efficacy". Placebo completed 265/272 (97%). Withdraw reasons: lost of follow-up 1/272(<1%), patient decision 6/272 (2%), patient not compliant study requirements 0%. Dysport completed 534/544 (98%). Withdraw reasons: lost of follow-up 7/544 (1%), patient decision 2/544 (<1%), patient not compliant study requirement 1/544 (<1%) page 1622 Comment: we considered this low risk of bias
Selective reporting (reporting bias)	Low risk	Duration of Response Assessed by Blinded Evaluator at Maximum Frown (table 4). In the second row: No. (%) of patients who became non responders during the study observation period, the authors reported 30/272 = 97%, but the correct percentage was 30/272 = 11% Comment: we considered this low risk of bias. We sent an e-mail on 1st November 2015. No answer to date
Other bias	High risk	One of the authors was stockholder of pharmaceutical company Comment: we considered this high risk of bias

Kane 2015

Study characteristics	
Methods	**Study design**- multicentre, randomised, double-blind, parallel-design in glabellar lines **Study date**- start February 2014, end no information **Study setting**- outpatients from ten centres
Participants	**Randomised**- 250 females participants, with mean age of 39.3 ± 7.4 years in incobotulinumtoxinA group, 39.4 ± 7.8 years in onabotulinumtoxinA group, 39.3 ± 7.6 years total population **Inclusion criteria** • Female participants, aged 18 to 50 years, with moderate-to-severe GFL at maximum frown (severity score of 2 or 3 on the 4-point FWS **Exclusion criteria** • FWS score of severe (3) at rest • Any previous treatment with BontA (any serotype) in the upper third of the face within the 6 months before injection • Previous treatment with biodegradable or permanent fillers in the glabellar area • Any surgery or scar in the glabellar area • History of facial nerve palsy • Any severe or uncontrolled systemic disease or medical condition • Known hypersensitivity to incobotulinumtoxinA or onabotulinumtoxinA or any of their excipients • Pregnancy, nursing, or planning to become pregnant during the study **Severity of disease**- moderate-to-severe glabellar lines at maximum frown **Ethnicity**- IncobotulinumtoxinA 23/122 (18.9%) Hispanic, 99/122 (81.1%) non-Hispanic. Onabptulinumtoxin A 35/128 (27.3%) Hispanic, 93/128 (72.7%) non-Hispanic, total population 58/250(23.2%) Hispanic, 192/250(76.8%) non-Hispanic. **Race**- IncobotulinumtoxinA 104/122 (85.2%) white, 14/122 (11.5%) black or African American, 4/122 (3.3%) Asian, 0/122 (0%) American Indian or Alaska native, 0/122(0%) other; OnabotulinumtoxinA 107/128 (83.6%) white, 13/128 (10.2%) black or African American, 4/128 (3.1%) Asian, 1/128 (0.8%) American Indian or Alaska native,3/128 (2.3%) other; total population 211/250 (84.4%) white, 27/250(10.8%) black or African American, 8/250 (3.2%) Asian, 1/250 (0.4%) American Indian or Alaska native,3/250 (1.2%) other
Interventions	**Duration of study**- 16 weeks **Intervention** • IncobotulinumtoxinA**(**20 U) in glabellar lines, 0.1 mL (4 U) to 5 injection points in the procerus muscle, each side of the medial (inner) part of the corrugator muscle, and each side of the middle part of the corrugator muscle (N = 122) **Comparator** • OnabotulinumtoxinA**(**20 U) in glabellar lines, 0.1 mL (4 U) to 5 injection points in the procerus muscle, each side of the medial (inner) part of the corrugator muscle, and each side of the middle part of the corrugator muscle (N = 128)
Outcomes	• **Primary outcome** Responder rate to treatment, defined as a ≥1-point improvement from base- line on the FWS at maximum frown

Kane 2015 *(Continued)*

Secondary outcomes

- Response, as rated by the independent panel at 2, 3, and 4 months after injection (60, 90, and 120 days 6 7 days at each time point)
- Clinical response as rated by the treating physician at 1, 2, 3, and 4 months after injection
- Overall patient- reported treatment satisfaction at 1, 2, 3, and 4 months after injection, assessed using the categories: "extremely satisfied", "satisfied", "slightly satisfied", "slightly dissatisfied", "dissatisfied", and "extremely dissatisfied"(subject assessment)
- Patient-reported date of onset and peak effect
- Adverse events

Notes	"The study was sponsored by Merz North America, Inc. All authors except E. Finn have been consultants and/or investigators for Merz North America, Inc. E. Finn (on behalf of Complete Medical Communications, which provided editorial support funded by Merz North provides services to the biopharmaceutical industry) America, Inc."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "An independent biostatistician created the randomization schedule to obtain a balanced 1:1 randomization. As a result, blocks of appropriate" page 1311 Comment: we considered this unclear risk of bias because the authors did not detail how they randomised the participants
Allocation concealment (selection bias)	Unclear risk	No information available to allow a judgment Comment: we considered this unclear risk of bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "IncobotulinumtoxinA and onabotulinumtoxinA were reconstituted out of view of the treating physician and the subject by designated unblinded site personnel. Site personnel were monitored to ensure that exactly the same reconstitution volume was added to each vial." page 1312 Comment: we considered this low risk of bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Both an independent masked panel of physicians and the treating physician who was also masked evaluated subject photographs in a blinded fashion" page 1312 Commet: we consider low risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: figure 2 Comment: we consider low risk of bias
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported Comment: we consider low risk of bias
Other bias	Low risk	We considered this study at low risk of other bias

Kassir 2013

Study characteristics	
Methods	**Study design**- single-centre, randomised, triple-blind, active-controlled, split-face in glabellar lines and crow's feet lines **Study date**- no information **Study setting**- outpatients, one- centre (USA)
Participants	**Randomised**- 85 participants, with mean age of 47 years. Gender: 87 women, 6 men **Inclusion criteria** • Patients were 30-60 years, BontA naive or had not received BontA treatment in the previous six months, not do any cosmetic or surgical facial procedure during study period. The presence of at least two indications for BontA treatment on each third of the face (upper, middle, lower) **Exclusion criteria** • Pregnancy • Treatment with ABO or ONA in the preceding 9 months • Surgery around the eye, facial scars that would interfere with assessment of wrinkles • Thick sebaceous skin, dermatochalasis • Neuromuscular disorders such as myasthenia gravis or multiple sclerosis • Use of aminoglycoside or curare-like agents • History of facial nerve palsy • Psychiatric illnesses that would interfere with subject assessment of wrinkles **Severity of disease**- moderate to severe wrinkles in either the glabellar or crow's feet area, or both **Ethnicity**- most of the patients were Caucasian
Interventions	**Duration of study**- 20 weeks **Intervention** • AbobotulinumtoxinA (20 U) in glabella and 30 U in crow's feet (N = 85) **Comparator** • OnabotulinumtoxinA (8 U) in glabella and 10 U in crow's feet (N = 85) **Ratio**- glabella 2.5:1 (AbobotulinumtoxinA: OnabotulinumtoxinA) crow's feet 3:1 (AbobotulinumtoxinA: OnabotulinumtoxinA)
Outcomes	**Primary outcome** • Onset **Secondary outcomes** • Duration • Responders rate by investigator • Patient satisfaction • Adverse events
Notes	"Dr Ramtin Kassir is a national trainer for Medicis. Dr Aparanjita Kolluru and Dr Martin Kassir declare no conflicts of interest."

Kassir 2013 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomised into one of two groups using a computer-generated randomisation list" page 181 Comment: we considered low risk of bias
Allocation concealment (selection bias)	Low risk	Quote: "A medical assistant kept the randomisation list and was the only person who knew which side" page 181 Comment: we considered low risk of bias
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "A medical assistant kept the randomisation list and was the only person who knew which side" page 181 Comment: we considered unclear risk of bias due to the authors did not reported methods for blinding participants, including visual aspect of interventions
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "A medical assistant kept the randomisation list and was the only person who knew which side" page 181 Comment: we considered unclear risk of bias due to the authors did not reported methods for blinding participants, including visual aspect of interventions
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "No patients discontinued visits due to adverse effects from the treatment." page183 Comment: we considered this low risk of bias
Selective reporting (reporting bias)	High risk	The number of participants did not match Quote: "A total of 85 patients with moderate to severe wrinkle" page 179 Quote: "Ninety-three patients were treated with ABO and ONA over a period of 2 months (87 women and 6 men)" page 183 Patient satisfaction was not showed. Comment: We considered high risk of bias. We sent an e-mail on June, 21 2015 and November 23 2015. He sent the full paper but no additional information was provided about the missing data
Other bias	Low risk	We considered this study at low risk of other bias

Kerscher 2015

Study characteristics

Methods	**Study design**- multicentre, randomised, double-blind, parallel-design in forehead lines, glabellar lines, and crow's feet lines **Study date**- start July 2012, end October 2013

Kerscher 2015 *(Continued)*

	Study setting- outpatients from ten centres
Participants	**Randomised** 156 participants, with a mean age of 47.4 ± 10.1 years in IncobotulinumtoxinA group, and 47.5 ± 8.4 years in placebo group. Gender: 94/105 (89.5%) females and 11/105 (10.5%) males in the incobotulinumtoxinA group, and 41/51 (80.4%) females and 10/51 (19.6%) males in the placebo group. **Inclusion criteria** • Male or female aged 18 years or older; evaluated as having significant psychologic strain according to the FLQA-k questionnaire; glabellar lines, forehead lines and symmetrical crow's feet lines of moderate-to-severe intensity at maximum frown (assessed by 5-point scale); stable medical condition; use an effective method of birth control (for fertile women) **Exclusion criteria** • Previous administration of botulinum toxin of any type in the forehead, glabellar, and/or periorbital area within the last 6 months • Any previous facial cosmetic procedure (e.g. dermal filling, chemical peeling, photo rejuvenation) in the forehead, glabellar, and/or periorbital areas within the last 8 months • Any previous insertion of permanent material in the forehead, glabellar, and/or periorbital area (regardless of the time between previous treatment and this study) • Any facial cosmetic procedure planned for within the study period • Presence of very severe lines (GFL, HFL, and/or LPL) at maximum contraction, as assessed by the investigator using the MAS inability to substantially lessen UFL by physically spreading them apart • Any previous surgery/existing scars in the treatment areas • Marked facial asymmetry • Pregnancy or lactation • Known hypersensitivity to the study medication **Severity of disease**- glabellar lines: moderate 32/105(30.5%), severe 73/105 (69.5%) in IncobotulinumtoxinA group; 13/51 (25.5%), severe 38/51 (74.5%) in placebo group. Forehead lines: moderate 18/105 (17.1%), severe 87/105 (82.9%) in IncobotulinumtoxinA group; 13/51 (25.5%), severe 38/51 (74.5%) in placebo group. Crow's feet lines: moderate 28/105 (26.7%), severe 76/105 (72.4%) in IncobotulinumtoxinA group; 14/51 (27.5%), severe 37/51 (72.5%) in placebo group **Ethnicity**- no information
Interventions	**Duration of study**- 16 weeks **Intervention** • IncobotulinumtoxinA, total dose (54 to 64 U) (1.35 mL to 1.6 mL, depending on the dose applied to the forehead area), split between the 3 aesthetic treatment areas: GFL (20 U, i.e. 0.5 mL in equal aliquots administered across 5 injection points), HFL (10–20 U, i.e. 0.25 mL to 0.5 mL across 5 horizontally oriented points), and LPL (12 U, i.e. 0.3 mL in equal aliquots administered across 3 on each side of the face [24 U, 0.6 mL in total]); for injection points and dosage points (N = 105) **Comparator** • Placebo volume =1.35mL to 1.6 mL, depending on the dose applied to the forehead area), split between the 3 aesthetic treatment areas: GFL (0.5 mL in equal aliquots administered across 5 injection points), HFL (0.25 ml to 0.5 mL across 5 horizontally oriented points), and LPL (0.3 mL in equal aliquots administered across 3 on each side of the face [0.6 mL in total]); for injection points and dosage points (N = 51)
Outcomes	**Primary outcome** • Rate of response as calculated by the proportion of investigator-assessed scores of "none" (0) or "mild" (1) on the 5-point MAS at maximum contraction on Day 30 for each individually treated area (GFL, HFL, and LPL) and also the investigator-assessed combined MAS sum score of #3 at maximum contraction on Day 30 for the 3 treated areas combined (GFL, HFL plus LPL)

Kerscher 2015 *(Continued)*

Secondary outcomes

- Investigator-assessed response of "none" or "mild" on the MAS at maximum contraction on Days 8, 60, 90, and 120, individually for each treated area (GFL, HFL, and LPL) and simultaneously for GFL, HFL plus LPL (i.e. a sum score)
- Participant-assessed response of "none" or "mild" on the MAS at maximum contraction on Days 8, 30, 60, 90, and 120 for GFL, HFL, and LPL individually
- Investigator- and participant-assessed response of "none" or "mild" on the MAS at rest on Days 8, 30, 60, 90, and 120 for GFL, HFL, and LPL individually
- Investigator- and participant-assessed MAS response of at least 1-point improvement from baseline at rest and maximum contraction on Days 8, 30, 60, 90, and 120 for GFL, HFL, and LPL individually
- Investigator- and participant-assessed responses on Day 30 for the overall appearance of the upper face according to the clinician's and participant's Global Impression of Change Scale (GICS)
- Onset of treatment effect after each injection for GFL, HFL, and LPL, individually
- Adverse events

Notes	Pharmaceutical support

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "using the computerized randomisation program RANCODE (Version 3.6; IDV Datenanalyse und Versuchsplanung, Gauting, Germany). Randomization in blocks of appropriate size and the blockwise distribution" page 1150 Comment: we consider low risk of bias
Allocation concealment (selection bias)	Low risk	Quote: "The randomisation schedule was sealed and locked in the total quality management depart- ment of the study sponsor and was not accessible before database close." page 1150 Comment: we consider low risk of bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Placebo vials had the same appearance as the test product vials to ensure that the identity of the individual study materials remained unknown to the investigator, medical staff, and all subjects. All other individuals involved in the study also remained blinded, with the exception of one individual who was responsible for reporting adverse events (AEs) to the relevant authorities" page 1150 Comment: we consider low risk of bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All other individuals involved in the study also remained blinded, with the exception of one individual who was responsible for reporting adverse events (AEs) to the relevant authorities" page 1150 Comment: we consider low risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "In total, 240 subjects were screened and 156 randomised as detailed in Figure 3" page 1152 Comment: we consider low risk of bias
Selective reporting (reporting bias)	High risk	The response rate by participant assessment, the response rate at rest by investigator assessment, the proportion of 1-point responders based on the investigator's rating of GFL and HFL at rest, investigator-assessed and subject-assessed ratings only P value

Kerscher 2015 *(Continued)*

		Comment: we consider this high risk of bias. We sent an e-mail to the authors (22 May 2016), no answer to date
Other bias	Low risk	We considered this study at low risk of other bias

Kim 2014

Study characteristics	
Methods	**Study design**- multicentre, randomised, double-blind, parallel-design in glabellar lines **Study date**- start July 2011, end December 2012 **Study setting**- outpatients from six centres
Participants	**Randomised**- 271 participants with mean age of 48 ± 9.8 years in NTC group; 49 ± 9.4 years in onbotulinumtoxinA group; total population 48.5 ± 9.6 years. Gender: 113/134 (84.3%) female and 21/134 (15.7%) male in NTC group; 111/134 (82.8%) female and 23/134 (17.2%) male in OnabotulinumtoxinA group; total population 224/268 (83.6%) female and 38/268 (14.2%) male. Previous botulinum toxin treatment 20/134 (14.9%) in NTC group, 18/134 (13.4%) onabotulinumtoxinA group; total population 38/268 (14.2%) **Inclusion criteria** • Participants aged 18–65, with moderate-to-severe glabellar lines [severity score of 2 or 3 on the Facial Wrinkle Scale (FWS)] at maximum frown, were included (supplementary information for FWS) **Exclusion criteria** • Previous facial plastic surgery or other procedures that may have affected glabellar lines within 6 months • Any skin diseases or scars in the glabellar area • Marked facial palsy or ptosis, • Neuromuscular junction disorders • Previous injection of botulinum toxin within 3 months (type A) or 4 months (type B), administration of muscle relaxants within 4 weeks • Scheduled facial cosmetic procedure during the study period • Wrinkles that could not be physically flattened • History of hypersensitivity to botulinum toxins or additional ingredient • Pregnancy or breast- feeding status • Any other medical condition that could be risky for patients injected with botulinum toxins **Severity of disease**- moderate-to-severe glabellar lines **Ethnicity**- no information
Interventions	**Duration of study**- 16 weeks **Intervention** • CBFC26 (20 U), 0.5 mL, which was divided into five separate injections of 0.1 mL (4 U) into the procerus muscle and medial and middle parts of both corrugator muscles (N = 134) **Comparator** • OnabotulinumtoxinA (20 U), 0.5 mL, which was divided into five separate injections of 0.1 mL (4 U) into the procerus muscle and medial and middle parts of both corrugator muscles (N = 134)

Kim 2014 *(Continued)*

	Ratio- 1:1
Outcomes	**Primary outcome** • Physician assessment response rate at maximum frown 4 weeks after injection **Secondary outcomes** • Physician assessment response rates of the FAS and PPS were higher in the CBFC26 group than those in the onabotulinumtoxin A group both at maximum frown and at rest at weeks 8, 12 and 16 • Response rates of photographic assessments and the participants' improvement assessments • Adverse events
Notes	Pharmaceutical support (This study was supported by SNUH research fund (H 1106-010-364).)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A blocked random allocation sequence was created by computer-generated random numbers," page 1762 Comment: we consider low risk of bias
Allocation concealment (selection bias)	Low risk	Quote: "allocation to the either one of the two was performed by a third party. All dermatologists, managing nurses and patients were unaware of group assignments. Randomization codes were secured until all data entry was complete." page 1762 Comment: we consider low risk of bias
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information available to allow a judgment Comment: we consider this unclear risk of bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All dermatologists, managing nurses and patients were unaware of group assignments. Randomization codes were secured until all data entry was complete." page1762 Comment: we consider low risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "In summary, 262 subjects (n = 130, NTC; n = 132, onabotulinumtoxin A) completed the study (Fig. 2)" page 1763 Comment: we consider low risk of bias
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported Comment: we considered this low risk of bias
Other bias	Low risk	We considered this study at low risk of other bias

Kim 2015

Study characteristics

Methods	**Study design**- multicentre, randomised, double-blind, active–controlled, parallel-design, phase III trial

Kim 2015 *(Continued)*

	Study date- no information **Study setting**- outpatients from three centres
Participants	**Randomised**- 168 participants, with a mean age of 48.94 ± 9.13 years in M10109L group; 49.86 ± 9.13 years in BontA group years. Gender: 59/78 (75.64%) female, 19/78 (24.36%) male in M10109L group; 66/81 (81.48%) female, 15/81 (18.52%) male in BontA group **Inclusion criteria** • Male and female volunteers aged 20 to 65 years with glabellar lines **Exclusion criteria** • Any medical condition (e.g. myasthenia gravis, Lambert-Eaton syndrome, or amyotrophic lateral sclerosis) that could have put the patient at risk for use of botulinum toxin • Prior use of medications that could have affected the neuromuscular junction (e.g. muscle relaxants, spectinomycin hydrochloride, aminoglycosides, polypeptide antibiotics, anticholinergics, or benzodiazepines) • Any allergies or hypersensitivity to the drugs or their components • Previous treatment with botulinum toxin within 6 months • Other procedures that could have affected glabellar or forehead lines within 6 months • Any history of glabellar treatment (including the forehead) such as face lifting and/or permanent implants, or scars that could affect the treatment results • Patients whose glabellar lines could not be satisfactorily improved even with manual stretching • Any dermatologic disorders or infection at potential injection sites • History of facial nerve paralysis or ptosis • Pregnancy or lactating women **Severity of disease**- moderate to severe (severity score 2 to 3) glabellar frown lines according to the Facial Wrinkle Scale **Ethnicity**- 100% Korean
Interventions	**Duration of study**- 16 weeks **Intervention** • BontA M10109L (20 U), 0.1 ml (4 U) in the procerus muscle, 0.1 ml (4 U) in each medial corrugator supercilii muscle, and 0.1 ml (4 U) in the middle of each corrugator supercilii muscle (N = 78) **Comparator** • OnabotulinumtoxinA (20 U), 0.1 ml (4 U) in the procerus muscle, 0.1 ml (4U) in each medial corrugator supercilii muscle, and 0.1 ml (4 units) in the middle of each corrugator supercilii muscle (N = 81) **Ratio**- 1:1 (MT10109L:OnabotulinumtoxinA)
Outcomes	**Primary outcome** • Percentage of responders at maximum frown at week 4 based on the investigators' live assessment **Secondary outcomes** • Percentage of responders at maximum frown at week 16 • Percentage of responders of glabellar lines at rest based on investigators' live assessment at weeks 4 and 16 • Percentage of responders at maximum frown and at rest based on photographic assessment at week 4 • Adverse events

Kim 2015 *(Continued)*

Notes	"This study was supported by Medytox, Inc., Republic of Korea, and the province of Chungcheong-buk-do, Republic of Korea. Medytox, Inc., is the manufacturer of MT10109L."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "All eligible subjects were randomised into two groups at a 1:1 ratio" page 733 Comment: we considered this unclear risk of bias because the authors did not explain how they allocated the participants
Allocation concealment (selection bias)	Unclear risk	Quote: "All eligible subjects were randomised into two groups at a 1:1 ratio" page 733 Comment: we considered this unclear risk of bias because the authors did not explain the methods used for maintain the allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "in a double-blind manner." page 733 Coment: we consider this unclear risk of bias because the authors did not explain how they blinded the participants
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Three blinded raters assessed the photographs at maximum frown" page 733 Comment: we considered this low risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Of 168 subjects who were enrolled, 159 completed the study and therefore constituted the per-protocol set, of which 78 subjects were in the MT10109L group and 81 subjects were in the Botox group." page 735 Comment: we considered this low risk of bias
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported Comment: we considered this low risk of bias
Other bias	Low risk	We considered this study at low risk of other bias

Lee 2013

Study characteristics

Methods	**Study design**- double-blinded, randomised, active-controlled, parallel-design, phase III study in glabellar lines (Poster) **Study date**- no information **Study setting**- no information
Participants	**Randomised** 314 participants. Age- no information. Gender - no information **Inclusion criteria**- no information **Exclusion criteria**- no information

Lee 2013 *(Continued)*

	Severity of disease- moderate to severe glabellar lines at maximal contraction **Ethnicity**- no information
Interventions	**Duration of study**- 16 weeks **Intervention** • New BontA (20 U) [Medytox®] (N = 157) **Comparator** • OnabotulinumtoxinA (20 U) (N = 157) **Ratio**- 1:1 (New BontA[Medytox®]: OnabotulinumtoxinA)
Outcomes	**Primary outcome** • Responder rate by the investigator's live assessment at maximum frown at week 4 **Secondary outcomes** • Responder rates by investigator's live assessment with frowning and at rest at weeks 8, 12 and 16, with additional photographic assessment by a panel of blinded raters four weeks after the injections • Subjective satisfaction • Adverse events
Notes	WS Lee worked in the Medical Department of Medytox Inc., Ochang, South Korea

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "patients was randomised at a 1:1 ratio to receive 20U of toxin" page 116 Comment: we considered unclear risk of bias because the authors did not explain how they randomised the participants
Allocation concealment (selection bias)	Unclear risk	Quote: "patients was randomised at a 1:1 ratio to receive 20U of toxin" page 116 Comment: we considered unclear risk of bias because the authors did not explain the methods used for maintain the allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double-blinded" page 116 Comment: we considered this unclear risk of bias because the authors did not explain how they blinded the participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double-blinded" page 116 Comment: we considered this unclear risk of bias because the authors did not explain how they blinded the outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information about losses Comment: we considered unclear risk of bias
Selective reporting (reporting bias)	High risk	Incomplete data. The authors reported only the outcomes assessed at week 4 Comment: we considered this high risk of bias

Lee 2013 *(Continued)*

		We e-mailed authors on June 21, 2018, but the electronic address was wrong and we could not find a valid e-mail.
Other bias	Unclear risk	The author worked for Medy-tox Comment: we considered this a unclear risk of bias

Lowe 2006

Study characteristics	
Methods	**Study design**- single centre, double-blind, randomised study, active-controlled, parallel-design **Study date**- start (March 2003), end (March 2005) **Study setting**- outpatients from one private clinic
Participants	**Randomised** 62 participants, with mean age of 41 years (range 27-60 years) total population; 44 ± 7.3 years in BontA1 group; 39 ± 6.6 years in BontA2 group. Gender- 90% female, 10% male **Inclusion criteria** • Moderate or severe glabellar lines at maximum contraction (graded by the investigator using a scale of none, mild, moderate, or severe) and were 18 to 55 years of age. Female patients of childbearing potential were required to have a negative urine pregnancy test result **Exclusion criteria** • Any of the following reasons: facial cosmetic procedure planned during the study • Visible scars or prior cosmetic procedures that could interfere with the evaluation of response • Marked facial asymmetry, ptosis, excessive dermatochalasis, deep dermal scarring, thick sebaceous skin, or an inability to substantially lessen glabellar lines even by physically spreading them apart • Myasthenia gravis, Eaton-Lambert syndrome, amyotrophic lateral sclerosis, or any other disease that might interfere with neuro- muscular function; use of an aminoglycoside antibiotic, curare-like agent, or other agent that might interfere with neuromuscular function • Profound atrophy or excessive weakness of the muscles in the target injection areas • History of facial nerve palsy • Systemic infection or an infection at the injection site • Recent evidence of alcohol or drug abuse • Participation in an investigational drug study in the preceding 30 days • Treatment with any botulinum toxin serotype in the preceding 12 months **Severity of disease**- moderate or severe glabellar lines at maximum contraction. BontA group comprised 15 of 31 patients (48%) with moderate glabellar lines and 16 patients (52%) with severe glabellar lines. In the BontA2 group, 17 of 31 patients (55%) had moderate glabellar lines and 14 (45%) had severe glabellar lines at baseline. **Ethnicity**- 97% Caucasian
Interventions	**Duration of study**- 16 weeks **Intervention** • OnabotulinumtoxinA (20 U), 0.1mL/site, 5 points, one in the procerus muscle and two in each corrugator muscle (N = 31) **Comparator**

Lowe 2006 *(Continued)*

	• AbobotulinumtoxinA (50 U), 0.1mL/site, 5 points, one in the procerus muscle and two in each corrugator muscle (N = 31) **Ratio**- 1:2.5 (OnabotulinumtoxinA: AbobotulinumtoxinA)
Outcomes	**Primary outcome** • Incidence of at least 1-grade improvement in the severity of the glabellar lines evaluated by the investigator from photographs taken at week 16 **Secondary outcomes** • Incidence of patients whose glabellar line severity was graded as none or mild at maximum contraction • Incidence of relapse (return of glabellar line severity to baseline levels for two consecutive visits) • Patient satisfaction (7-point) • Adverse events
Notes	"Drs P. Lowe and R. Patnaik have received research grants from Allergan, Inc. Dr N. Lowe owns stock in Allergan, Inc, and has received research grants, consulting payments, and educational grants from Allergan, Inc. He has also received research grants and consulting payments from Medicis. Gill Shears, PhD (of Gill Shears, Inc), provided assistance with the writing of the manuscript."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "a computer-generated randomisation code, in block sizes of 6, that determined treatment assignments for each individual. "Randomization cards" were prepared" page 976 Comment: we considered this low risk of bias
Allocation concealment (selection bias)	Low risk	Quote: "randomisation number and contained the treatment assignment. These were kept in a secure location and neither the investigator nor the patients had access to them or their contents. The treatment assigned to each patient was determined at the baseline visit by a pharmacist who opened the card with the lowest available randomisation number in order to discover the treatment assignment and then prepared the appropriate syringe" page 976 Comment: we considered this low risk of bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The investigator and the patients were masked as to which product was being used—the syringes were identical in appearance and the volume to be injected was the same regardless of the product" page 976 Comment: we considered this low risk of bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The investigator and the patients were masked as to which product was being used—the syringes were identical in appearance and the volume to be injected was the same regardless of the product." page 976 Comment: we considered this low risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "A total of 62 patients were enrolled, of whom 59 (95%) completed the study (Fig 1). No patient discontinued because of lack of efficacy or adverse effects and one each discontinued for personal reasons, withdrawal of consent, and need for surgery." page 977 Comment: we considered this low risk of bias

Lowe 2006 *(Continued)*

Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported. Comment: we considered this low risk of bias
Other bias	Unclear risk	Dr N. Lowe owns stock in Allergan, Inc. Comment: we considered this unclear risk of bias

Michaels 2012

Study characteristics	
Methods	**Study design**- single centre, randomised, double- blind, active -controlled, split-face design in glabellar lines, forehead lines, and crow's feet lines **Study date**- no information **Study setting**- outpatients from one private clinic (USA)
Participants	**Randomised**- 53 participants, with mean of age of 50 years (range 34-65 years). Gender: 52 female, one male. Other demographic data: eight were smokers, and 26 had undergone treatment with BoNT-ONA in the past **Inclusion criteria** • Both men and women between the ages of 20 and 90 with glabellar and/or periorbital wrinkles (crow's feet) **Exclusion criteria** • Pregnancy or plans to become pregnant • Known cardiovascular or neuromuscular disorders, dysphasia • History of recent facial infections, allergies to milk proteins or albumin, or current aminoglycoside therapy • Patients who had undergone BontA-ONA or BontA-ABO treatments within the previous six months • Patients on any blood-thinning medications were excluded to minimise injection site bleeding complications **Severity of disease**- glabella, crow's feet, forehead lines. **Ethnicity**- no information
Interventions	**Duration of study**- 20 weeks **Intervention** • OnabotulinumtoxinA (2 5U) in one side (N = 53) **Comparator** • AbobotulinumtoxinA (62.5 U) in the other side.(N = 53) **Ratio**- 1:2.5 (OnabotulinumtoxinAOna:AbobotulinumtoxinA)
Outcomes	**Primary outcome** • Fitzpatrick Wrinkle Scale, eyebrow height

Michaels 2012 *(Continued)*

	Secondary outcomes • Percentage of patients with continued aesthetic effect • Adverse events
Notes	"The authors declared no potential conflicts of interest with respect to the research, authorship, and publication of this article."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A coin toss was used to randomly assign the side of the face to receive BoNT-ONA as follows: “heads” meant that BoNT-ONA was injected on the right side, whereas “tails” meant that BoNT-ONA was injected on the left" page 98 Comment: we considered this low risk of bias
Allocation concealment (selection bias)	Unclear risk	Quote: "A coin toss was used to randomly assign the side of the face to receive BoNT-ONA as follows: “heads” meant that BoNT-ONA was injected on the right side, whereas “tails” meant that BoNT-ONA was injected on the left" page 98 Comment: we considered this unclear risk of bias due to the authors did not reported methods of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Patients were blinded to the laterality of treatments" page 97 Comment: we considered this unclear risk of bias because the authors did not explain how they blinded the participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double-blinded" page 97 Comment: we considered this unclear risk of bias because the authors did not explain how they blinded the investigators
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information about losses Comment: we considered this unclear risk of bias
Selective reporting (reporting bias)	High risk	Only P value, no data were showed Comment: we considered this a high risk of bias. We sent an e-mail to authors on 23 November 2015. No answer to date
Other bias	Low risk	We considered this study at low risk of other bias

Moers-Carpi 2012

Study characteristics

Methods	**Study design**- multicentre, double-blind, randomised, active controlled, parallel- design in glabellar lines, one cycle **Study date**- start November 2010, end April 2011 **Study setting**- outpatients from seven centres

Moers-Carpi 2012 *(Continued)*

Participants	**Randomised**- 224 participants, with mean age of 45.0 ±10.8 years in OnabotulinumtoxinA group; 45.4 ± 9.8 years in IncobotulinumtoxinA group. Gender: 102/112 (91.1%) female, 10/112 (8.9%) male in OnabotulinumtoxinA group; 98/112 (87.5%) female, 14/112 (12.5%) male in IncobotulinumtoxinA group **Inclusion criteria** • Adults aged 18–65 years old with moderate to severe glabellar lines at full contraction as assessed by the injector using the Facial Wrinkle Scale (FWS) with Photo numeric Guide **Exclusion criteria** • Participants who were unable to substantially lessen glabellar line severity even by physically spreading them apart, or who exhibited glabellar lines of FWS grade III (severe) at rest • Participants who had received aesthetic treatment with botulinum toxin within the last six months or planned such treatment in any bodily region • Any previous surgery within the glabellar region, who had received any previous treatments with fillers or the insertion of permanent material in the glabellar area, or had undergone previous treatment with any facial aesthetic procedure in the glabellar area within the last six months • Any allergy to any of the medication ingredients were ineligible, as were those with any disorder affecting muscular function, infection at the proposed injection site • Marked facial asymmetry or ptosis of eyelid or eyebrow • History of facial nerve palsy • History of bleeding disorders • Use of aminoglycoside antibiotics or other agents that might interfere with neuromuscular function • Psychiatric problems or other conditions that the injector believed could interfere with the study results • Females of childbearing potential must have provided a negative urine pregnancy test **Severity of disease**- Moderate glabellar lines 47.3% BontA1 group and 45.5% BontA2 group; Severe glabellar lines 52.7% BontA1 group and 54.5% BontA2 group **Ethnicity**- 110/112 (98.2%) white, 2/112 (1.8%) other in BontA1 group; 109/112(97.3%) white, 3 (2.7%) other in BontA2 group
Interventions	**Duration of study**- 14.9 weeks **Intervention** • IncobotulinumtoxinA (30 U), 0.5mL, 0.1mL/site, one injection in the procerus muscle, one injection on each side in the central part of the corrugator muscle approximately 1 cm above the bony orbital rim on an imaginary line drawn vertically from the caruncle, one injection on each side was given in the middle part of the corrugator muscle at least 1 cm above the bony orbital rim on an imaginary line drawn vertically from the midpupillary line (N = 112) **Comparator** • OnabotulinumtoxinA (20 U), 0.5mL, 0.1mL/site, one injection in the procerus muscle, one injection on each side in the central part of the corrugator muscle approximately 1 cm above the bony orbital rim on an imaginary line drawn vertically from the caruncle, one injection on each side was given in the middle part of the corrugator muscle at least 1 cm above the bony orbital rim on an imaginary line drawn vertically from the mid pupillary line (N = 112) **Ratio**- Quote: "higher dose of incobotulinumtoxinA would produce results comparable to the established 20 units of onabotulinumtoxinA in the treatment of glabellar lines. An incobotulinumtoxinA dose of 30 units was selected for comparison based on the product's label, the disparity in biological activity testing"
Outcomes	**Primary outcome** • Blinded injector's evaluation of treatment response on day 28, where treatment response was defined as an improvement from baseline of 1 point or more on the FWS at maximum contraction

Moers-Carpi 2012 *(Continued)*

	Secondary outcomes • Injector's assessment of glabellar lines severity on days 84, 98, and 112, and the subject's assessment of glabellar lines severity at all postinjection time points using the FWS • Adverse events
Notes	"This study was sponsored by Allergan, Inc. Dr. Moers-Carpi has acted as a lecturer for Allergan. Dr. Phillip-Dormston has acted as a lecturer, consultant and has received educational grants from Allergan, Ipsen and Merz. Dr. Hoffman has acted as a consultant for Allergan. Prof Dirschka has acted as a consultant for Allergan. Drs. Fulford- Smith and Tan are employed by Allergan, Marlow, UK and Mary Ann Chapman, PhD, is a paid writer/ consultant to Allergan. Dr. Rütter, Dr. Feller-Heppt and Dr. Hilton report no conflicts of interest."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Subjects were assigned to a treatment group based on a computer generated paper randomisation list at each centre" page 297 Comment: we considered this low risk of bias
Allocation concealment (selection bias)	Unclear risk	Comment: we considered unclear risk of bias because the authors did not explain the methods used for maintain the allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "In preparation for injection, clinic staff member(s) with no other study responsibilities reconstituted vials containing,..The injectors, who were blinded to study treatment..The products were diluted to different concentrations so that they could be injected in equal volumes (0.5 mL) in order to maintain study blinding" page 297 Comment: we considered this low risk of bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "In preparation for injection, clinic staff member(s) with no other study responsibilities reconstituted vials containing ,...The injectors, who were blinded to study treatment...The products were diluted to different concentrations so that they could be injected in equal volumes (0.5 mL) in order to maintain study blinding," page 297 Commment: we considered this low risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Of the 224 subjects in the intent to treat analysis set, 16 subjects violated protocol criteria: 4 randomisation failures, 6 unauthorised concomitant therapy, 5 missing primary endpoint data or visit outside of allowable window on day 28, and 1 study site staff" page 299 Comment: we considered this low risk of bias
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported Comment: we considered this low risk of bias
Other bias	Unclear risk	Drs. Fulford-Smith and Tan are employed by Allergan Quote: "Limitations+Possible limitations with this study include the following. The study incorporated a 1-point change on the FWS as the primary endpoint, whereas placebo-controlled trials have generally used ratings of none or mild on the FWS as the primary outcome measure"

Moers-Carpi 2012 *(Continued)*

	Comment: we considered this unclear risk of bias because two authors were Allergan employees

Moers-Carpi 2015

Study characteristics	
Methods	**Study design**- multicentre, randomised, double-blind, placebo-controlled, parallel-design, Phase III study with 2 treatment cycles in crow's feet lines and/or glabellar lines **Study date**- no information **Study setting**- outpatients from 34 centres
Participants	**Randomised** 917 participants, with mean age of 50 ±9.7 years in OnabotulinumtoxinA 44 U group; 49.6 ± 9.5 years in OnabotulinumtoxinA 24 U group; 49 ± 9.3 years in placebo group; 49.5±9.5 years total population. Gender: female = 87.5% in OnabotulinumtoxinA 44 U group; female = 89.2% in OnabotulinumtoxinA 24 U group; female = 86.9% in placebo group; female = 87.6% total population **Inclusion criteria** • Male or female at least 18 years of age, bilaterally symmetrical moderate-to-severe crow's feet lines at maximum smile on the Facial Wrinkle Scale as rated by both investigator and participant on day 1 (before study), sufficient visual acuity without the use of eyeglasses (contact lens use acceptable), to accurately assess their facial wrinkles, female participants of childbearing potential must have had a negative urine pregnancy test at day 1 prior to study treatment; must be using a reliable means of contraception **Exclusion criteria** • Concurrent or previous botulinum toxin treatment of any serotype • Specified facial treatments or procedures within particular time points prior to study that could interfere with treatments in this study or with interpretation of results • Prior upper or midfacial surgery or permanent aesthetic procedures/treatments • Marked facial asymmetry, dermatochalasis, deep dermal scarring, excessively thick sebaceous skin, or the inability to substantially lessen lateral canthal rhytides even by physically spreading them apart, as determined by the investigator • Presence of any clinically relevant abnormal finding as observed from the neurologic assessment • Any eyebrow or eyelid ptosis at baseline as determined by the investigator • History of facial nerve palsy • Females who were pregnant, nursing, or planning a pregnancy • Any uncontrolled systemic disease • Current enrolment in an investigational drug or device study or participation in such a study within 30 days of entry into this study **Severity of disease**- Moderate wrinkles (investigator rating crow's feet lines at maximum smile) 35.7% in OnabotulinumtoxinA44 U group, 37.6% in OnabotulinumtoxinA 24 U group, 36.9% in placebo group, 36.8% total population Severe (investigator rating crow's feet lines at maximum smile) 64.3% in OnabotulinumtoxinA 44 U group, 62.4% in BontA 24 U group, 63.1% in placebo group, 63.2% total population Moderate participant assessment (maximum smile at baseline)) 36.1% in OnabotulinumtoxinA 44 U group, 36.9% in OnabotulinumtoxinA24 U group, 36.6% in placebo group, 36.5% total population. Severe (participant assessment (maximum smile at baseline)) 63.9% in OnabotulinumtoxinA 44 U, 63.1% in OnabotulinumtoxinA 24 U, 63.4% in placebo group, 63.5% total population

Moers-Carpi 2015 *(Continued)*

	Ethnicity - 88.25% white in OnabotulinumtoxinA 44 U group; 88.2% white in OnabotulinumtoxinA24 U group; 86.6% white in placebo group; 87.7% white in total population
Interventions	**Duration of study**- 28 weeks (7 months), two treatment cycles **Intervention** • OnabotulinumtoxinA (44 U)- 24U to crow's feet lines and 20 U in glabellar lines, glabella and crow's feet, 0.01 mL/site, 3 points in each side of crow's feet lines and 5 points in glabellar lines (N = 305) • OnabotulinumtoxinA (24 U)- 24 U to crow's feet lines and 0U in glabellar lines, glabella and crow's feet, 0.01mL/site, 3 points in each side of crow's feet lines and 5 points in glabellar lines crow's feet, (N = 306) **Comparator** • Placebo zero U to crow's feet lines and 0 U in glabellar lines, glabella and crow's feet, 0.01mL/site, 3 points in each side of crow's feet lines and 5 points in glabellar lines glabella and crow's feet (no information) (N = 306)
Outcomes	**Primary outcome** • Investigator and subject assessments of CFL severity at maxi- mum smile using the FWS (CFL-FWS) • Responder rates for the co-primary end points were the proportion of subjects achieving a Grade of 0 (none) or 1 (mild) on the FWS, as assessed independently by investigators and participants **Secondary outcomes** • Proportion of participants achieving at least a 1-grade improvement in the CFL-FWS during maximum smile and at rest, as assessed by the investigator • Assessment of facial lines by patient-reported outcomes (PROs) included the Subject's Global Assessment of Change in CFL (SGA-CFL), 3 of 11 items comprising the Facial Line Outcomes (FLO-11) questionnaire (Item 2: "look older", Item 5: "look less attractive", and Item 8: "look tired"), the Self- Perception of Age (SPA), and the Subject Assessment of Satisfaction of Appearance • FLO-11 and SPA are validated instruments • Assessments of CFL, investigators assessed several other end points, including GL severity during maximum frown and at rest (GL- FWS) • Responder rates were the proportion of participants with an improvement from baseline of at least 1 grade on the GL-FWS • Adverse events
Notes	"M. Moers-Carpi, J. Carruthers, S. Fagien, M. Lupo, H. Delmar, and D. Jones are consultants and/or investigators for Allergan, Inc. C. Somogyi, E. Lee, X. Lei, S. MacKinnon, and F. C. Beddingfield are employees of Allergan, Inc., and receive compensation in salary, as well as stock or stock options (or both), at the time the study was conducted. The remaining authors have indicated no significant interest with commercial supporters."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Eligible subjects were randomised 1:1:1 to 1 of 3 groups on Day 1" page 104 Comment: we considered this unclear risk of bias because the authors did not explain how they randomised the patients
Allocation concealment (selection bias)	Unclear risk	Quote: "Eligible subjects were randomised 1:1:1 to 1 of 3 groups on Day 1" page 104 Comment: we considered this unclear risk of bias because the authors did not explain the methods used to maintain the allocation concealment

Moers-Carpi 2015 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "To maintain the blind, all medications were reconstituted and prepared by individuals who had no interactions with subjects." page 104 Comment: we considered this unclear risk of bias due to, for instance, the visual aspect of interventions were not described; and it is not possible to know if the participants were aware about the allocation.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "To maintain the blind, all medications were reconstituted and prepared by individuals who had no interactions with subjects." page 104 Comment: we considered this low risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Of 684 subjects enrolled, 641 (93.7%) completed this study A total of 667 subjects (97.5%) received the third treatment. Most subjects who received a third dose (80.2%; 535/667) received their dose at Day 1 visit of Study 191622-104. A total of 414 subjects (60.5%) received 2 treatments (treatment cycles 3 and 4): 149 onabotulinumtoxinA 24 U/24 U, 123 onabotulinumtoxinA 44 U/44 U, 69 placebo/ onabotulinumtoxinA 44 U, and 73 placebo/placebo. In this study, 253 subjects (37.0%) received only 1 treatment (treatment cycle 3): 74 onabotulinumtoxinA 24 U/24 U, 126 onabotulinumtoxinA 44 U/44 U, 31 placebo/onabotulinumtoxinA 44 U, and 22 placebo/placebo. Seventeen subjects failed to meet retreatment criteria after they received treatment 2 in Study 191622-099 and therefore did not receive any treatment in this study: 4 onabotulinumtoxinA 24 U/ 24 U, 11 onabotulinumtoxinA 44 U/44 U, 1 placebo/ onabotulinumtoxinA 44 U, and 1 placebo/placebo" page 106 (figure 2) Comment: we considered this low risk of bias
Selective reporting (reporting bias)	High risk	Investigator-Assessed Responder Rates on Crow's Feet Lines–Facial Wrinkle Scale, Subject's Global Assessment of Change in Crow's Feet Lines, Patient-Reported Outcomes, no data shown Comment: we considered this high risk of bias We sent an e-mail on 23 October 2015. No answer to date
Other bias	Unclear risk	C. Somogyi, E. Lee, X. Lei, S. MacKinnon, and F. C. Beddingfield are employees of Allergan, Inc Comment: we considered this unclear risk of bias because some authors were Allergan employees

Monheit 2007

Study characteristics	
Methods	**Study design**- multicentre, randomised, double-blind,dose-ranging, placebo-controlled, parallel design in glabellar lines **Study date**- no information **Study setting**- outpatients
Participants	**Randomised**- 373 participants, with a mean age of 41.5 ± 9.7 years in AbobotulinumtoxinA 20 U group; 41.9 ±10.1 years in AbobotulinumtoxinA 50 U group; 42.1 ±10.3 years in AbobotulinumtoxinA 75 U group; 42.5 ± 9.9 years in placebo group; 42.0 ±10.0 total population. Gender: 79/91 (86.8%) female, 12/91 (13.2%) male in AbobotulinumtoxinA 20 U group; 72/93 (77.4%) female, 21/93 (22.6%) male in AbobotulinumtoxinA 50 U group; 78/95 (82.1%) female, 17/95 (17.9%) male in AbobotulinumtoxinA 75

Monheit 2007 *(Continued)*

	U group; 84/94 (89.4%) female, 10/94(10.6%) male in placebo group; 313/373 (83.9%) female, 60/373 (16.1%) male in total population. Subgroup ≤ 50 years 77/91 (84.6%), > 50 years 14/91 (15.4%) AbobotulinumtoxinA 20 U group; ≤ 50 years 74/93 (79.6%), > 50 years 19/93 (20.4%) in AbobotulinumtoxinA 50 U group; ≤ 50 years 43/95 (77.9%), > 50 years 21/95 (22.1%) in AbobotulinumtoxinA 75 U group; placebo ≤ 50 years 73/94 (77.7%), > 50 years 21/94 (22.3%); ≤ 50 years 298/373 (80%), > 50 years 75/373 (20%) total population **Inclusion criteria** • Moderate or severe vertical glabellar lines at maximum frown **Exclusion criteria**- no information **Severity of disease**- investigator's assessment (glabellar lines at maximum frown), moderate 43/91 (47.3%) in AbobotulinumtoxinA20 U group, 35/93 (37.6%) in AbobotulinumtoxinA 50 U group, 48/95 (50.5%) in AbobotulinumtoxinA 75 U group, 42/94 (44.7%) in placebo group. Severe 48/91 (52.7%) in AbobotulinumtoxinA 2 Uu group, 58/93 (62.4%) in AbobotulinumtoxinA50 U group, 47/95 (49.5%) in AbobotulinumtoxinA 75 U group, 52/94 (55.3%) in placebo group. Investigators' assessment (glabellar lines at rest), none 5/91 (5.5%) in AbobotulinumtoxinA 20 U group, 4/93 (4.3%) in AbobotulinumtoxinA 50 U group, 5/95 (5.3%) in AbobotulinumtoxinA 75 U group, 3/94 (3.2%) in placebo group. Mild 35/91 (38.5%) in AbobotulinumtoxinA 20 U group, 42/93 (45.2%) in AbobotulinumtoxinA 50 U group, 40/95 (42.1%) in AbobotulinumtoxinA 75 U group, 42/94 (44.7%) in placebo group. Moderate 47/91 (51.6%) in AbobotulinumtoxinA 20 U group, 41/93 (44.1%) in AbobotulinumtoxinA 50u group, 46/95 (48.4%) in AbobotulinumtoxinA 75u group, 44/94 (46.8%) in placebo group. Severe 4/91 (4.4%) in AbobotulinumtoxinA 20u group, 6/93 (6.5%) in AbobotulinumtoxinA 50 U group, 4/95 (4.2%) in AbobotulinumtoxinA 75 U group, 5/94 (5.3%) in placebo group **Ethnicity**- 70/91 (76.9%) white, 21/91 (25.5%) non-Caucasian in AbobotulinumtoxinA 20 U group; 64/93 (68.8%) Caucasian, 29/93 (31.2%) non-Caucasian in AbobotulinumtoxinA 50 U group; 74/95 (77.9%) Caucasian, 21/95 (22.1%) non-Caucasian in AbobotulinumtoxinA 75 U group; 70/94 (74.5%) Caucasian, 24/94 (25.5%) non-Caucasian in placebo group; 278/373 (74.5%) Caucasian, 95/373 (25.5%) non-Caucasian total population
Interventions	**Duration of study**- 16 weeks **Intervention** • AbobotulinumtoxinA (20 U) (N = 91), 0.05mL/site, 5 points in procerus muscle corrugator muscle and orbicularis muscle • AbobotulinumtoxinA (50 U) (N = 93), 0.05mL/site, 5 points in procerus muscle corrugator muscle and orbicularis muscle, • AbobotulinumtoxinA (75 U) (N = 95), 0.05mL/site, 5 points in procerus muscle corrugator muscle and orbicularis muscle **Comparator** • Placebo, (N = 94) 0.005mL/site, 5 points in procerus muscle corrugator muscle and orbicularis muscle
Outcomes	**Primary outcome** • Investigators' live assessment of glabellar lines at maximum frown at Day 30 and the participant's self-assessment of change in severity of glabellar lines at Day 30 **Secondary outcomes** • Investigator's assessment at Days 60, 90, and 120 • Participant's self-assessment of change in severity of glabellar lines at Day 30 • Neutralising antibody • Adverse events

Monheit 2007 *(Continued)*

Notes	"This study was a Phase II FDA investigation and was supported by funds from Ipsen Biopharm Limited and Inamed Corporation. Each of the authors was a paid investigator for the study by the sponsoring companies"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "A Randomized, Double-Blind" page S52 Comment: we considered this unclear risk of bias because the authors did not explain how they randomised the participants
Allocation concealment (selection bias)	Unclear risk	No information Comment: we considered this unclear risk of bias because the authors did not explain the methods used to maintain the allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Both participants and investigators were blinded to the treatment" page S52 Comment: we considered this low risk os bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Both participants and investigators were blinded to the treatment" page S52 Comment: we considered this low risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "The demographic data relating to the ITT population are shown " page S55. "No deaths were reported and no adverse event led to withdrawal of a participant from the study." page S57 Comment: we considered this low risk of bias
Selective reporting (reporting bias)	Low risk	The authors showed participant assessment, but they did not specify if the outcome was at maximum frown or at rest Comment: we considered this low risk of bias We sent an e-mail on November 1st, 2015. The author answered on 1st November 2015: "The assessment for primary response was at maximal contraction"
Other bias	Low risk	We considered this study at low risk of other bias

Monheit 2019

Study characteristics

Methods	**Study design**- multicentre, randomised (2:1), double-blind,dose-ranging, placebo-controlled, parallel design in glabellar lines **Study date**- no information **Study setting**- outpatients, 5 centres (USA)
Participants	**Randomised**- 300 participants, with a mean age of 44.7 (21-71) years in AbobotulinumtoxinA group; 43.2 (24 to 66) years in placebo group. Gender- 28/200(14%) male and 172/200(86%) female in AbobotulinumtoxinA group, 12/100 (12%)male and 88/100(88%) male in placebo group.

Monheit 2019 *(Continued)*

	Inclusion criteria • 18 years and older • who were treatment-naïve for botulinum toxin, • with moderate to severe glabellar lines at maximum frown. **Exclusion criteria** • pregnancy, • glabellar area infections, • presence of neuromuscular junctional disorders, • history of facial palsy, or use of medication affecting neuromuscular transmission • allergy of any druf component **Ethnicity**- Caucasian 149/200(75%), Native American 1/200(0.5%), Hispanic 37/200(19%), Asian 5/200(3%), 4/200(2%) other in Abobotulinumtoxin group.Caucasian 76/100(76%), Native American 0, Hispanic 18/100(18%), Asian 0, 1/100(1%) other in placebo group.
Interventions	**Duration of study**- 20 weeks **Intervention** AbobotulinumtoxinA (50 U) (N = 200),,0.05mL/site, 5 points in procerus muscle corrugator muscle and orbicularis muscle, **Comparator** • Placebo, (N =100) 0.005mL/site, 5 points in procerus muscle corrugator muscle and orbicularis muscle
Outcomes	**Primary outcome** • Proportion of treatment responders at Day 30 by investigator and participant assessment **Secondary outcomes** • Onset of treatment effect • Duration of the treatment effect • Participant satisfaction was assessed at each follow-up visit using a 9-point global assessment scale to evaluate self-perceived change in appearance of glabellar lines after treatment (days 14, 30. 60, 90, 120, 150 days) by investigator and participant assessment • One-Grade Improvement in Glabellar Line Severity • Subgroup analysis at day 30 • Adverse events
Notes	Quote: "Medicis Pharmaceutical corp., funded the study and provided the study products. G.D. Monheit, R. Rand, C. Maas, and L. Baumann serve as consultants for Galderma and Ipsen. R. Down of Zenith Healthcare Communications Ltd., provided medical writing assistance, funded by Galderma. The authors have indicated no significant interest with commercial supporters."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote:"prospective, single-dose, multicenter, randomized, parallel-group, placebo-controlled, double-blind "...page 61 Comment: we consider unclear risk of bias because the authors did not explain how they randomise the participants

Monheit 2019 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Quote:"prospective, single-dose, multicenter, randomized, parallel-group, placebo-controlled, double-blind "...page 61 Comment: we consider unclear risk of bias because the authors did not explain how they randomise the participants
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote:"prospective, single-dose, multicenter, randomized, parallel-group, placebo-controlled, double-blind "...page 61 Comment: we consider unclear risk of bias because the authors did not explain how they blind the participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote:"prospective, single-dose, multicenter, randomized, parallel-group, placebo-controlled, double-blind "...page 61 Comment: we consider unclear risk of bias because the authors did not explain how they blind the participants
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote- the authors did not mention any drop out during the study Comment: we consiider a low risk of bias
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported Comment: we considered this low risk of bias
Other bias	Low risk	We considered this study at low risk of other bias

NCT02450526

Study characteristics	
Methods	**Study design**- randomised, first phase double-blind, second phase open-label, multicentre, active andpPlacebo-controlled study. Phase III **Study date**- start December 2009, end August 2010 **Study setting**
Participants	520 participants, with a mean age raging from 18-65 years. Gender: 86.8% (282/325) femal,13.2%, (9/325) male in Abobotulinumtoxin 50 U group, 86.4% (57/66) female, 13.6%, (9/66) male in Abobotulin placebo group, 87.9% (94/107) female, 12.1% (13/107) male in Onabotulinumtoxin 20u group, 86.4% (19/22) female, 13.6% (3/22) male in Onabotulintoxin -placebo group. **Inclusion criteria** • Provision of written informed consent • Male or female Chinese participants who are between 18 and 65 years of age inclusive • Have moderate or severe wrinkles of vertical glabellar lines (Grade 2 or 3) at maximum frown at baseline (Day 1), as assessed by the subject using SSA • Have moderate or severe (Grade 2 or 3) vertical glabellar lines at maximum frown at baseline (Day 1), as assessed by the Investigator using ILA • Be Botulinum Toxin (BTX) naïve or have received their most recent BTX-A treatment more than 1 year prior to screening • Have a negative pregnancy test • Have an understanding of the study

NCT02450526 *(Continued)*

Exclusion criteria

- Any prior surgery affecting corrugator supercilii, prior blepharoplasty or brow lift, dermal resurfacing, or any prior cosmetic procedures or scars within 36 months
- Any prior treatment with permanent fillers in the upper face
- Any prior treatment with nonpermanent dermal fillers in the upper face within the past 3 years and/or skin abrasions/resurfacing, photo rejuvenation or skin/vascular laser intervention within the past 12 months
- Any planned facial cosmetic surgery or procedures during the study period
- Lack of capacity to frown
- Facial conditions that could affect safety or efficacy results
- History of facial nerve palsy
- Marked asymmetry; ptosis; excessive dermatochalasis; deep dermal scarring; thick sebaceous skin; photodamage etc.
- Presence of any condition that could affect the safety, conduct or outcome of the study
- Any participants who have any psychiatric illness or are taking antidepressant, anxiolytic or antipsychotic medication
- Pregnant and/or lactating female participants
- Female participants of childbearing potential not willing to use contraceptive measures throughout the course of the study
- History of drug or alcohol abuse
- Treatment with an experimental drug or device within 30 days prior to screening for this study and during the conduct of this study
- Requirement for BTX injection to site(s) for disorders other than glabellar lines
- Known allergy or hypersensitivity to BTX
- Any medical condition or laboratory finding from central laboratory results
- The participant is unable and/or unwilling to comply fully with the protocol and the study
- Mental incapacity, unwillingness or language barriers

Ethnicity:100% Asian (Chinese)

Country: China

Interventions

Intervention

- AbobotulinumtoxinA, 50 U, divided into five injections into the glabellar area. Administered in double-blind fashion at cycle 1 followed by up to 4 cycles AbobotulinumtoxinA, 50 U administered with an interval period depending on response, no less than 12 weeks between each treatment cycle

Comparator

- OnabotulinumtoxinA will be administered in treatment cycle 1 only. On Day 1, 20 U, divided into five injections into the glabellar area
- Saline solution 0.9% will be administered in treatment cycle 1 only. On Day 1, 20 U, divided into five injections into the glabellar area

Outcomes

Primary outcome

- The proportion of responders measured by the Investigator's Live Assessment (ILA) and the Subject's Self-Assessment (SSA) at maximum frown. [Time Frame: Day 29 of Cycle 1]

Secondary outcomes

- The proportion of responders with respect to Independent Reviewer's assessment of photographs of the subject's glabellar lines at maximum frown (using the Photographic Scale). [Time Frame: Day 29 of Cycle 1]
- Mean Subject's Global Assessment (SGA) score [Time Frame: Day 29 of Cycle 1]
- The proportion of responders with respect to the SGA score. [Time Frame: Day 29 of Cycle 1]

NCT02450526 *(Continued)*

Notes	Sponsor Ipsen Other study ID Y-52-52120-158. We sent an email on April,28,2019.The Ipsen company answered:"These trials have not been published unfortunately." on June, 27, 2019.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: No information Comment: we considered it unclear risk of bias
Allocation concealment (selection bias)	Unclear risk	Quote:No information Comment: we considered it unclear risk of bias
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote:No information Comment: we considered it unclear risk of bias
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote:No information Comment: we considered it unclear risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote:The authors described in the table reasons not complete the study Comment: we considered it low risk of bias
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported Comment: we considered this low risk of bias
Other bias	Unclear risk	This study was in clinical trial register site. We have contacted Ipsen pharmaceutical several times (last one January, 24, 2020) asking for publishing information. Answer- They did not have published it yet

NCT02493946

Study characteristics

Methods	Randomised clinical trial, placebo-controlled, double -blinded, 2 phases.Phase 1- Cycle 1 double-blind. Phase 2- 2-5 cycles. Start April 2015 Finish December 2016 Multicentre- Europe (France, UK Germany)
Participants	**Participants:** 190 participants randomised to the 1st phase of the study. Participants age varied- from 18-65 years: 123/126 (97.6%) in HBTX-A groups and 64/64 (100%) placebo group; > 65 years 3/126(2.42%) in HBTX-A group, and 0 in placebo group. Gender: female 115/126 (913%)in HBTX-A group and 56/64(90.6%) in placebo group.

NCT02493946 *(Continued)*

Ethnicity: Caucasian 125/126 (99.2%) in HBTX-A group and 100% in placebo group. Black 1/126(0.8%) in HBTX-A group and 0% in placebo group

Inclusion Criteria

- Provision of written informed consent prior to any study related procedures
- Male or female participants between 18 and 65 years of age
- Have moderate or severe (Grade 2 or 3) vertical glabellar lines at maximum frown at Baseline (Day 1), as assessed by the ILA using a validated 4- point photographic scale
- Have moderate or severe (Grade 2 or 3) vertical glabellar lines at maximum frown at Baseline (Day 1), as assessed by the SSA using a validated 4-point categorical scale
- Are dissatisfied or very dissatisfied (Grade 2 or 3) with their glabellar lines at Baseline (Day 1), as assessed by the subject's level of satisfaction
- Have a negative pregnancy test (for females of childbearing potential only). No childbearing potential is defined as post-menopausal for at least 1 year, surgical sterilisation at least 3 months before entering the study, or hysterectomy
- Have both the time and the ability to complete the study and comply with study instructions

Exclusion Criteria

- Previous treatment with any serotype of BTX
- Any prior treatment with permanent fillers in the upper face including the glabellar lines area
- Any prior treatment with any dermal fillers in the upper face including the glabellar lines area within the past 3 years and/or skin abrasions/resurfacing (whatever the interventional technic used) within the past 5 years, or photo rejuvenation or skin/vascular laser intervention within the past 12 months
- Any planned facial cosmetic surgery during the study
- A history of eyelid blepharoplasty or brow lifts within the past 5 years
- An inability to substantially reduce glabellar lines by physically spreading them apart or lack of capacity to frown
- An active infection or other skin problems in the upper face including the glabellar lines area (e.g. acute acne lesions or ulcers)
- Use of concomitant therapy, which in the investigator's opinion, would interfere with the evaluation of the safety or efficacy of the investigational medicinal product (IMP), including medications affecting bleeding disorders (antiplatelet agents and/or anticoagulants given for treatment or prevention of cardio/cerebro vascular diseases)
- Pregnant women, nursing mothers, or women who are planning a pregnancy during the study, or believe they may be pregnant at the start of the study Throughout the course of the study, women of childbearing potential must use a reliable form of contraception (e.g. oral contraceptives for more than 12 consecutive weeks, or spermicide and condoms)
- Treatment with an experimental drug or use of any experimental device within 30 days prior to the start of the study and during the conduct of the study.
- Known allergy or hypersensitivity to any component of BTX-A-HAC NG
- Clinically diagnosed significant anxiety disorder, or any other significant psychiatric disorder (e.g. depression) that might interfere with the participant's participation in the study
- Use of medications that affect neuromuscular transmission, such as curare-like non depolarising agents, lincosamides, polymyxins, anticholinesterases and aminoglycoside antibiotics, within the past 30 days
- A history of facial nerve palsy
- Marked facial asymmetry, ptosis, excessive dermatochalasis, deep dermal scarring, or thick sebaceous skin
- The presence of any other condition (e.g. neuromuscular disorder or other disorder that could interfere with neuromuscular function), laboratory finding or circumstance that, in the judgement of the investigator, might increase the risk to the participant or decrease the chance of obtaining satisfactory data to achieve the objectives of the study
- **Severity of the disease:** moderate-to severe glabellar lines

Interventions	**Intervention**

NCT02493946 *(Continued)*

Clostridium Botulinum Toxin Type A (BTX A HAC NG), total treatment volume 0.25 mL will be divided into 5 injections (0.05 mL per injections) injected in 5 pre-defined sites across the glabellar region. A total of 50 U of BTX-A-HAC NG will be injected/ cycle.

Comparator

The total placebo volume 0.25 mL will be divided into 5 injections (0.05 mL per injections) injected in 5 pre-defined sites across the glabellar region. Administered in Cycle 1 of the double-blind phase only.

Outcomes

Primary outcome

1. The percentage of responders at Day 29 Cycle 1 as measured by Investigator's Live Assessment (ILA) of Glabellar Lines at Maximum Frown: DB period [Time Frame: Day 29 (Cycle 1)]

Secondary outcomes

- The percentage of responders at each post-treatment visit (except Day 29 Cycle 1) as measured by the ILA at Maximum Frown: DB period Time Frame: Days 8, 57 and 85 (Cycle 1]
- The percentage of responders on Day 29 Cycle 1 who remained responders on Days 57 and 85 as Measured by the ILA at Maximum Frown: DB period [Time Frame: Days 29, 57 and 85 (Cycle 1)]
- The percentage of responders at each post-treatment visit to the study centre as measured by the ILA at Rest: DB period [Time Frame: Days 8, 29, 57 and 85 (Cycle 1)]
- The percentage of responders at each post-treatment visit to the study centre as measured by the particIpant's Self-Assessment (SSA) at Maximum Frown: DB Period [Time Frame: Days 8, 29, 57 and 85 (Cycle 1)]
- The percentage of responders at each post-treatment visit to the study centre as measured by the particIpant's level of satisfaction with theaAppearance of their Glabellar Lines: DB period [Time Frame: Days 8, 29, 57 and 85 (Cycle 1)]
- The median time to onset of treatment response based on the participant's diary card: DB period [Time Frame: Days 1 to 7 (Cycle 1)]
- Change from baseline at all post-treatment visits in the FACE-Q Satisfaction With Facial Appearance Overall Scale: DB period [Time Frame: Baseline (Day 1) and Days 8, 29, 57 and 85 (Cycle 1)]
- Change from baseline at all post-treatment visits in the FACE-Q Psychological Well-being Scale: DB period [Time Frame: Baseline (Day 1) and Days 8, 29, 57 and 85 (Cycle 1)]
- Change From baseline at all post-treatment visits in the FACE-Q Aging Appearance Appraisal Visual Analogue Scale (VAS): DB period [Time Frame: Baseline (Day 1) and Days 8, 29, 57 and 85 (Cycle 1)]
- The percentage of responders at each post-treatment visit as measured by the ILA at Maximum Frown: LT Analyses [Time Frame: Days 8, 29, 57 and 85 of Cycles 1 - 5 (up to 15 months).]
- The percentage of responders at each post-treatment visit as measured by the ILA at rest: LT Analyses [Time Frame: Days 8, 29, 57 and 85 of Cycles 1-5 (up to 15 months)]
- The percentage of responders at each post-treatment visit as measured by the SSA at Maximum Frown: LT Analyses [Time Frame: Days 8, 29, 57 and 85 of Cycles 1-5 (up to 15 months)]
- The percentage of responders at each post-treatment visit as measured by the participant's level of Satisfaction With the Appearance of their Glabellar Lines: LT Analyses [Time Frame: Days 8, 29, 57 and 85 of Cycles 1-5 (up to 15 months]
- Median time to retreatment in LT Analysis [Time Frame: Cycles 4 (up to 12 months)]
- Change from baseline at all post-treatment visits in the FACE-Q Satisfaction With Facial Appearance Overall Scale: LT Analyses [Time Frame: Days 8, 29, 57 and 85 of Cycles 1 to 3; Days 8, 29 and 85 of Cycles 4 and 5.]
- Change from baseline at all post-treatment visits in the FACE-Q Psychological Well-being Scale: LT Analyses [Time Frame: Days 8, 29, 57 and 85 of Cycles 1 to 3; Days 8, 29 and 85 of Cycles 4 and 5]
- Change from Baseline at all post-treatmentvVisits in the FACE-Q Aging Appearance Appraisal VAS: LT Analyses [Time Frame: Days 8, 29, 57 and 85 of Cycles 1 to 3; Days 8, 29 and 85 of Cycles 4 and 5]

Notes

We used only phase 1 data

Risk of bias

NCT02493946 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: no information provided.
Allocation concealment (selection bias)	Unclear risk	Comment: no information provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Subjects will first be enrolled to enter the double blind (DB) period Cycle 1" Comment: not clear who was blinded to treatment allocation.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Subjects will first be enrolled to enter the double blind (DB) period Cycle 1" Comment: not clear who was blinded to treatment allocation.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: 8/126 and 5/64 did not complete the 1st phase of the study - but no reasons given for withdrawal..
Selective reporting (reporting bias)	Low risk	Comment: All prespecified outcomes were reported
Other bias	Unclear risk	Comment: limited information about the study provided on the clinical trial website. Therefore, unable to judge if any other biases were present.

Nettar 2011

Study characteristics	
Methods	**Study design**- randomised, double-blind, split-face design in crow's feet lines **Study date**- start December 2009, end August 2010 **Study setting**- no information
Participants	**Randomised**- 90 participants, with a mean age of 54.5 years (range 31-78 years). Gender: no information **Inclusion criteria** • Men or women 18 years or older, with moderate to severe lateral orbital rhytids at maximal contraction **Exclusion criteria** • Botulinum neuromodulator treatment to the crow’s feet within the prior 6 months • Prior face-lift, brow-lift, or blepharoplasty • Prior periocular laser or chemical re-surfacing • Prior adverse reaction associated with botulinum neuromodulator • History of degenerative neuromuscular diseases **Severity of disease**- moderate to severe lateral orbital rhytids at maximal contraction **Ethnicity**- no information

Nettar 2011 *(Continued)*

Interventions	**Duration of study**- 4 weeks **Intervention** • AbobotulinumtoxinA (30 U), in one side, 0.05 mL/site, 5 points (N = 90) **Comparator** • OnabotulinumtoxinA (10 U), in the contralateral side, 0.05 mL/site, 5 points (N = 90) **Ratio**- 1:3 (OnabotulinumtoxinA:AbobotulinumtoxinA)
Outcomes	**Primary outcome** • Investigator assessment of maximal contraction at day 30 compared with day 0 **Secondary outcomes** • Patient assessment at rest and at maximal contraction at day 30 compared with day 0 and patient preference of each side's result at day 30 • Adverse events
Notes	"Dr Maas is a consultant and owns stock in both Medicis Aesthetics Inc (makers of abobotulinumtoxinA) and Allergan Inc (makers of onabotulinumtoxinA)." "Funding for this study was solicited from both Medicis Aesthetics Inc and Allergan Inc. Medicis Aesthetics Inc funded this study"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Treatment sides of the face were randomised with computer- aided software" page 381 Comment: we considered this low risk of bias
Allocation concealment (selection bias)	Unclear risk	No information Comment: we considered this unclear risk of bias due to the authors did not explain the methods used to maintain the allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Preparation of product was performed by an unblinded registered nurse who was responsible for maintaining the blind" page 381 ..."identical volumes (0.2 mL) of each were drawn into tuberculin syringes to ensure the blindness" Comment: we considered this unclear risk of bias due to no information was provided about blinding of participants
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Preparation of product was performed by an unblinded registered nurse who was responsible for maintaining the blind"....."identical volumes (0.2 mL) of each were drawn into tuberculin syringes to ensure the blindness of the injector" page 381 Comment: we considered this low risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses Comment: we considered this low risk of bias

Nettar 2011 *(Continued)*

Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported Comment: we considered this low risk of bias
Other bias	High risk	Dr Maas was stockholder of Medicia Inc. Comment: we considered this a high risk of bias

Ogilvie 2019

Study characteristics	
Methods	**Study design**- multicentre, randomised, double-blind, placebo-controlled, parallel -design,phase III in glabellar lines (Period 1) and an open-label extension (period 2) **Study date**- Start October 2014. Finished April 2016 **Study setting**- outpatients from 16 centres (9-USA, 5-Canada, 2-Europe)
Participants	**Randomised** 391 participants. Age 44.5 ±11.2 Onabotulinum group and 42.4 ±10.6 placebo group. Gender 85.9% female in OnabotulinumtoxinA group and 86.1% in placebo group. **Inclusion criteria** • Botulinum toxin–naive men and women aged at least 18 years • Moderate to severe FHL at maximum eyebrow elevation, as evaluated by the investigator **Exclusion criteria** • Any uncontrolled systemic disease, marked periocular or eyebrow asymmetry • Marked dermatochalasis • Deep dermal scarring, excessively thick sebaceous skin • Eyebrow or eyelid ptosis, eyelid folds reaching the pupil or touching the upper lash line • Known immunisation to any botulinum toxin serotype, or anticipated need for botulinum toxin treatment for another indication during the study • Had ever undergone prior periorbital, midfacial, or upper facial treatment with permanent soft-tissue fillers, synthetic implant placement, autologous fat transplantation, surgery **Ethnicity**: Caucasian 89.7% in OnabotulinumtoxinA group and 86.1% in placebo group. Asian 3.1 in OnabotulinumtoxinA group and 5% in placebo. Others 7.2% in OnabotulinumtoxinA group and 8.9% in placebo group. **Severity of the disease:**(maximum frown):Moderate 47.6% in OnabotulinumtoxinA group and 47.5% in Placebo group. Severe 52.4 % in OnabotulinumtoxinA group and 52.4% in Placebo group.
Interventions	**Duration**:Period 1- 6 months. Period 2-6 months **Intervention** OnabotulinumtoxinA 40 U (20 U in FHL and 20 U in GL) administered at 10 injection sites **Comparator** Placebo same volume in FHL and in GL) administered at 10 injection sites **Ratio**: 3:1 (OnabotulinumtoxinA: placebo)

Ogilvie 2019 *(Continued)*

Outcomes	**Primary outcome** • Proportion of mostly or very satisfied patients **Secondary outcomes** • Responders rate of FLSQ Impact domain • Responders rate FLO-11item 1, item 4, item 5, and total score
Notes	This study was funded by Allergan plc, Dublin, Ireland. Editorial support for this article was provided by Peloton Advantage, Parsippany, New Jersey, and was funded by Allergan plc. P. Ogilvie has received research support or speaking/consultant fees from Allergan plc, Evolus, Inc., Galderma, Merz Aesthetics, and Revance. A.Z. Rivkin serves as a consultant and investigator for Allergan plc and Merz Aesthetics. S. Dayan has received research support or speaking/consultant fees from Allergan plc, Galderma, Merz Aesthetics, and Valeant. S.G. Yoelin serves as a consultant and investigator for Allergan plc. B.M. Weichman was employed by Peloton Advantage, which received funding from Allergan plc for medical editing and editorial support. J.K. Garcia is an employee of Allergan plc and owns stock/options in the company. The opinions expressed in this article are those of the authors.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote:"The randomization assignment was obtained from an interactive voice/web response system, which was based on a randomization scheme prepared by Allergan Biostatistics"...Page3 Comment: we consider a low risk of bias
Allocation concealment (selection bias)	Low risk	Quote:"The randomization assignment was obtained from an interactive voice/web response system, which was based on a randomization scheme prepared by Allergan Biostatistics"...Page3 Comment: we consider a low risk of bias
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote:The study comprised a 6-month, double-blind,placebo-controlled"...Page 3 Comment: we consider unclear bias because the authors did not mention how they blinded the participants and staff
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote:The study comprised a 6-month, double-blind,placebo-controlled"...Page 3 Comment: we consider unclear bias because the authors did not mention how they blinded the participants and staff
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote:"early discontinuations were mostly attributable to personal reasons or being lost to follow-up (Figure 2...Page4 Comment: we consider unclear risk of bias because the authors did not mention the reasons of the drop-out
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported Comments: we consider low risk of bias
Other bias	Unclear risk	One of the authors was an employee of the sponsor

Park 2014

Study characteristics	
Methods	**Study design**- randomised, double-blind, split-face design in crow's feet lines and masseter **Study date**- no information **Study setting**- no information
Participants	**Randomised** 56 participants, with mean age of 43.4 years, range 23-69 years. Gender: 94.6% female, 5.4% male **Inclusion criteria** • Patients complaining of periocular wrinkles **Exclusion criteria** • Patients who had been treated with filler, BT injection, or other photo rejuvenation procedure within 6 months before enrolment • Patients were not permitted to use topical tretinoin or other retinol-containing cosmetics during and after treatment until the end of the study. • Pregnancy, active nursing • Pre-existing neuromuscular conditions • History of drug allergy or any other serious medical disorder, and medications which can be affected by BontA injection (e.g. aminoglycosides, penicillamine, quinine, calcium channel blocker, and anti-coagulant drugs, etc) **Severity of disease**- crow's feet lines, masseter **Ethnicity**- no information
Interventions	**Duration of study**- 16 weeks **Intervention** • IncobotulinumtoxinA (7.5 U), 3 points (N = 56) **Comparator** • OnabotulinumtoxinA (7.5 U), 3 points (N = 56) **Ratio**- 1:1 (IncobotulinumtoxinA:OnabotulinumtoxinA)
Outcomes	**Primary outcome** • Investigator assessment of maximal contraction at week 1 and 16. Difference of FWS by investigator week 1 and 16 **Secondary outcomes** • Onset time • Patient FWS maximum contraction in weeks 1 and 16 • Visual analogic scale by patient weeks 1, 4 and 16 • Adverse events
Notes	Quote: "Authors do not have any kind of conflict of interest regarding this study"
Risk of bias	

Park 2014 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "a randomised,double-blind" page 326 Comment: we considered this unclear risk of bias because the authors did not explain how they randomised the participants
Allocation concealment (selection bias)	Unclear risk	No information Comment: we considered this unclear risk of bias due to the authors did not explain the methods used to maintain the allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double-blind, split-face" page 326 Comment: we considered this unclear risk of bias because the authors did not explain how they blinded the participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double-blind,split-face" page 326 Comment: we considered this unclear risk of bias because the authors did not explain how they blinded the participants
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "in the periocular rhytides group 56 subjects completed the study" page 328 Comment: we considered this unclear risk of bias because the authors did not explain the reason of drop outs
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported Comment: we considered this low risk of bias
Other bias	Low risk	We considered this study at low risk of other bias

Patel 2004

Study characteristics	
Methods	**Study design**- randomised, double-blind, parallel-design in glabellar lines **Study date**- no information **Study setting**- no information
Participants	**Randomised**- 65 participants. No age or gender information **Inclusion criteria** • Presence of moderate to severe glabellar rhytids **Exclusion criteria** • Use of anticoagulant medications (i.e. coumadin) • Recent treatment of glabellar rhytids with OnabotulinumtoxinA or Zyderm II (within 6 months) • Known allergy to collagen • Inability to return for follow-up visits **Severity of disease**- moderate or severe vertical glabellar lines

Patel 2004 *(Continued)*

	Ethnicity- no information
Interventions	**Duration of study**- 12 weeks **Intervention/Comparator** • OnabotulinumtoxinA (25 U), 0.5 mL in the corrugator and procerus muscle (N = 22) • Collagen filler[Zyderm II®] = 0.7-0.75 mL, glabellar lines (N = 20) • OnabotulinumtoxinA (25 U) + collagen filler [Zyderm II®] 0.7-0.7 5mL, glabellar lines (N = 23)
Outcomes	**Primary outcome** • Investigator assessment of wrinkles maximum contraction or rest **Secondary outcomes** • Patient discomfort, • Patient satisfaction • Improvement in wrinkle severity • Adverse events
Notes	No information about conflict of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "prospectively randomised to receive" page 442 Comment: we considered this unclear risk of bias because the authors did not explain how they randomised the participants
Allocation concealment (selection bias)	Unclear risk	No information Comment: we considered this unclear risk of bias due to the authors did not explain the methods used to maintain the allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Subsequently, these study participants were randomised and blinded to 1 of 3 treatment arms." page 442 Comment: we considered this unclear risk of bias because the authors did not explain how they blinded the participant
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Patients then returned for 3 follow-up visits at 1 week, 1 month, and 3 months for an independent physician evaluation" page 443 Comment: we considered this low risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals Comment: we considered this low risk of bias
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported Comment: we considered this a low risk of bias
Other bias	Low risk	No other source of bias was found Comment: we considered this low risk of bias

Rappl 2013

Study characteristics	
Methods	**Study design**- single-centre, randomised, double-blind, placebo-controlled, parallel- design in glabellar lines **Study date**- start 2008 end 2011 **Study setting**- outpatient from one centre (Austria)
Participants	**Randomised**- 180 participants, with mean age of 40.3± 6.8 years in IncobotulinumtoxinA group; 39.7 ± 6.1 years in OnabotulinumtoxinA group; 40.7± 6.5 years in AbobotulinumtoxinA group; 40.2 ± 6.4 years total population. Gender- 51/60 (85%) female, 9/60 (15%) male in IncobotulinumtoxinA group; 50/59 (85%) female, 9/59 (15%), male in OnabotulinumtoxinA group; 51/60 (85%) female, 9/60 (15%) male in AbobotulinumtoxinA group; 152/179 (85%) female, 27/179 (15%) male total population **Inclusion criteria** • Age 20–60 years, glabellar frown lines with a score of 1–3 (mild to severe) at maximum frown on glabellar frown lines with a score of 1–3 (mild to severe) at maximum frown on the validated Merz 5-point scale • No prior BoNT/A treatment or previous treatment at least 1 year prior to the start of this study **Exclusion criteria** • Presence of very severe frown lines, • Facial asymmetry • Contraindicated medications (e.g. anticoagulants), prior allergic reaction to BontA treatment • Prior injection into the glabellar area within the last year • Infection or inflammation • Pregnancy, and breastfeeding **Severity of disease**- Quote: "26 subjects had a score of 1 on the validated Merz 5-point scale, 136 subjects had a score of 2, and 18 subjects had a score of 3" **Ethnicity**- 100% Caucasian
Interventions	**Duration of study**- 24 weeks **Intervention** • IncobotulinumtoxinA 21 U, 5U in procerus muscle, 0.21 mL (N = 60) **Comparator**- OnabotulinumtoxinA (21 U), 0.21 mL (N = 60) • AbobotulinumtoxinA (63 U), 0.25 mL (N = 60) **Ratio**- 1:1:3 (IncobotulinumtoxinA : OnabotulinumtoxinA: AbobotulinumtoxinA)
Outcomes	**Primary outcomes** • Onset • Duration evaluated by physician **Secondary outcome** • Adverse events
Notes	"Thomas Rappl has conducted speaker activities for Merz, Croma Pharma, MD-Skin Solutions, Johnson & Johnson, and Smith & Nephew. The authors report no other conflicts of interest in this work."

Rappl 2013 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Eligible subjects were assigned to groups of 60 and then randomised, using the randomizer program available at the Medical University of Graz (http:// www.randomizer.at)" page 213 Comment: we considered this low risk of bias
Allocation concealment (selection bias)	Unclear risk	Quote: "Eligible subjects were assigned to groups of 60 and then randomised, using the randomizer program available at the Medical University of Graz (http:// www.randomizer.at)" page 213 Comment: we considered this unclear risk of bias due to the authors did not reported methods for allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "In order for the injecting physician to remain blinded to the product used, an assistant prepared the products for injection using special syringes" page 213 Comment: we considered this low risk of bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "In order for the injecting physician to remain blinded to the product used, an assistant prepared the products for injection using special syringes" page 213 Comment: we considered this low risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "One female subject in the onabotulinumtoxinA group was excluded from the analysis due to failure to respond (in order to establish and compare the onset and duration of effect of the different products, it was essential that an effect was demonstrated" page 214 Comment: we considered this low risk of bias
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported Comment: we considered this low risk of bias
Other bias	Unclear risk	In figure 3 of the publication, the total dose of BontA1 and BontA2 was 23u but in the material and methods the authors described 21u Comment: we considered this unclear risk of bias, we sent an e-mail to the authors to clarify this discrepancy on November 28 2015. The author answer that 21u was the correct dose

Rivers 2015

Study characteristics

Methods	**Study design**- multicentre, randomised, double-blind, parallel-design in glabellar lines and crow's feet lines **Study date**- start July 2013, end no information **Study setting**- outpatients from eight centres

Rivers 2015 *(Continued)*

Participants	**Randomised**- 117 participants with mean age of 45.9 ± 9.66 years in onabotulinumtoxinA group, 47.1 ± 9.76 years in placebo group. Gender 48/60 (80%) females and 12/60 (20%) males in onabotulinumtoxinA group; 50/57 (87.7%) female and 7/57 (12.3%) male in placebo group **Inclusion criteria** • Age from 18 to 65 years, moderate or severe GL during maximum attempted muscle contraction (based on the FWS) • Bilaterally symmetrical CFL at maximum smile requiring treatment as determined by the investigator on Day 1 (before study treatment), no previous botulinum toxin treatment, • Women of childbearing potential required to have a negative pregnancy test result at baseline and to use a reliable form of contraception throughout study, • Ability to follow instructions and complete the study **Exclusion criteria** • Prior facial cosmetic surgery or tissue grafting/ augmentation, brow or eyelid ptosis • Excessive dermatochalasis, deep dermal scarring, or thick sebaceous skin • Inability to substantially reduce resting facial lines by physically spreading them apart • Received oral retinoid therapy within prior year • Used facial topical retinoid and/or hormone creams within prior year • Had not been on a stable regimen for ≥6 months and were unable to maintain the same regimen throughout the study **Severity of disease**- glabellar lines at maximum frown severe 24/60 (40%), moderate 36/60 (60%) in onabotulinumtocxinA; severe 30/57 (52.6%), moderate 27/57 (47.4%) in placebo group. Crow's feet lines at maximum frown severe 23/60 (38.3%), moderate 34/60 (56.7%), mild 3/60 (5%) in onabotulinumtocxinA; severe 18/57 (31.6%), moderate 38/57 (66.7%), mild 1/57 (1.8%) in placebo group **Ethnicity**- white 59/60 (98.3%) in onabotulinumtoxinA group; 56/57 (98.2%) white in placebo group
Interventions	**Duration of study**- 16 weeks **Intervention** • OnabotulinumtoxinA, (44 U), 5 injections to the glabellar area (1 in the procerus muscle, 2 in each corrugator muscle; total 20 U) and 6 injections to the crow's feet region, total 24 U (N = 60) **Comparator** Placebo 0.5 mL, 5 injections to the glabellar area (1 in the procerus muscle, 2 in each corrugator muscle) and 6 injections to the crow's feet region (N = 57)
Outcomes	**Primary outcomes** • Proportion of participants who reported being satisfied with the effect of treatment on GL at Day 60. • Participants responding "mostly satisfied" or "very satisfied" with study treatment to Item 5 of the FLSQ Follow-up Version were considered "satisfied."" **Secondary outcomes** • Outcomes for GL and CFL combined. These included the proportion of participants who reported that treatment met their expectations at Day 60 (FLSQ Item 11, "met expectations" or "better than expected") • Proportion of participants who reported satisfaction with treatment at Day 60 (FLSQ Item 5, "mostly satisfied" or "very satisfied"), • Proportion of participants who reported satisfaction with the duration of treatment effect at Day 90 (FLSQ Item 3, "mostly satisfied" or "very satisfied"). As components of participants satisfaction vary over time, 2 secondary end points were evaluated at time points considered relevant to each concept • Adverse events

Rivers 2015 *(Continued)*

Notes	Pharmaceutical support

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information available to allow a judgment Comment: we considered this unclear risk of bias
Allocation concealment (selection bias)	Unclear risk	No information available to allow a judgment Comment: we considered this unclear risk of bias
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information available to allow a judgment Comment: we considered this unclear risk of bias
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information available to allow a judgment Comment: we considered this unclear risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "The study enrolled 125 subjects (Figure 2)." and there were no losses page 953 Comment: we consider this low risk of bias
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported Comment: we consider this ow risk of bias
Other bias	High risk	Imbalance in baseline glabellar lines (more severe lines in placebo group) Comment: we consider high risk of bias

Rubin 2009

Study characteristics

Methods	**Study design**- multicentre, randomised, double-blind, placebo-controlled, parallel-design, phase III, two-three cycles (Cycle A1, A2, B, C). **Study date**- start 20 June 2005, end 11 April 2007 **Study setting**- outpatients from six centres
Participants	**Randomised**- 311 participants with a mean age of: In Cycle A1 (N = 311) mean 46.6 ± 9.72 years; Cycle A2 (N = 190) mean 46.4±9.51 years; Cycle B placebo (N = 84) 49.3 ± 9.8 years; Cycle B BontA (N = 171) 44.5 ± 8.92 years; Cycle C placebo (N = 71) mean 44.7 ± 8.73 years; Cycle C BontA (N = 71) BontA mean 44.7 ± 9.36 years. Gender Cycle A1 overall (N = 311) 269/311 (86%) female, 42/ 311 (14%) male; Cycle A2 (N = 190) 160/190 (84%) female, 30/190 (16%) male; Cycle B placebo (N = 84) 78/84 (93%) female, 6/84 (7%); Cycle B BontA (N = 171) 144/171 (84%) female, 27/171 (16%) male; Cycle C placebo (N = 71) 62/71 (87%) female, 9/71 (13%); Cycle C BontA (N = 71) BontA 60/71 (85%) female, 11/71 (15%) male

Rubin 2009 *(Continued)*

	Inclusion criteria • Male or female patients had to be 18 years or older, and female childbearing potential had to have a negative pregnant test. The patients have to have moderate to severe glabellar rhytids. (GLSS scale), at maximum frown, by investigator assessment and patient assessment **Exclusion criteria** • Previous botulinum toxin treatment to any areas of the body at any time (prior to or during the study • Prior soft tissue augmentation of glabella(e.g. collagen-type implants) within 12 months before to or during th study • Prior permanent or semi-permanent dermal fillers in the glabellar area any time, had received any dermal treatment in the glabella area for skin tightening within previous 12 months or during the study • Inability to substantially lessen glabellar lines by using physically spreading them apart. • Prior retinoid, micro dermabrasion, or prescription-level glycolic acid treatment to the glabellar area within 2 weeks prior to or during the study concurrent therapy that, in the investigator's opinion, would interfere with the evaluation of the safety or efficacy of the study medication • Any active infection in glabellar area (e.g. acute acne lesions or ulcers) • Marked facial asymmetry, ptosis, excessive dermatochalasis, deep dermal scarring, or thick sebaceous skin • Neuromuscular junctional disorders (e.g. myasthenia gravis) • Current facial palsy • Know allergy or hypersensitivity to any botulinum toxin or any component of study medication • Any other condition (e.g. neuromuscular disorder or other disorder that could interfere with neuromuscular function) or circumstance, in the judgment of the investigator, might increase patient risk or decrease the chance of obtaining satisfactory data **Severity of disease**- moderate to severe glabellar rhytids (GLSS scale), at maximum frown **Ethnicity**- Total population (N = 311) 249/311 (80%) Caucasian, 4/311 (1%) native American, 32/311 (10%) Hispanic, 9/311 (3%) African American, 13/ 311 (4%) Asian, 4/311 (1%) other
Interventions	**Duration of study**- 52 weeks **Intervention**- AbobotulinumtoxinA (50 U), 0.05 mL, 4 points(10 U/point) • Cycle A1- open-label, BontA (50U) (N = 311) • Cycle A2- moderate/severe wrinkles, open-label BontA (50 U) (N = 190) • Cycle B- moderate/severe wrinkles, randomised (2:1), BontA (50 U) (N = 255 • Cycle C- moderate/severe wrinkles, randomised (1:1), BontA (50 U) (N = 71) **Comparator**- placebo, 0.05 mL, 4 points • Cycle A1- no comparator • Cycle A2- moderate/severe wrinkles placebo (N = 94) • Cycle B- moderate/severe, randomised (2:1), placebo (N = 84) • Cycle C- moderate/severe wrinkles, randomised (1:1), placebo mL (N = 71)
Outcomes	**Primary outcome** • Day 30 post-injection in cycle C- percentage of responders rate by investigator's assessment and by patient's assessment **Secondary outcomes** • Subgroup analysis by ethnicity, gender, site at day 30 • Onset time • Duration of the treatment in the third cycle • Composite response the same response rates by investigator and patient in the same visit

Rubin 2009 *(Continued)*

- Adverse events

Notes	"Medicis Aesthetics Inc. (Scottsdale, AZ) provided Reloxin® and study funding to all of the authors"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "following one or two open-label treatments and one randomised treatment" page440 "The protocol was modified due to a randomisation error in cycle B" page 439 Comment: we considered this unclear risk of bias because the authors did not explain if participants in cycle A1 and A2 were randomised
Allocation concealment (selection bias)	Unclear risk	Quote: "in Cycle C were randomly assigns to receive either Bont-A (50) units or placebo" page 440 Comment: we considered this unclear risk of bias because the authors did not explain the methods for allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Patients were treated once during the double-blind portion of the study" page 441 Comment: we considered this unclear risk of bias due to the authors did not describe methods for blinding the participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Patients were treated once during the double-blind portion of the study" page 441 Comment: we considered this unclear risk of bias because the authors did not explain how they blinded the outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information about losses Comment: we considered this unclear risk of bias
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported Comment: we consider this low risk of bias
Other bias	Low risk	We considered this study at low risk of other bias

Rzany 2006

Study characteristics

Methods	**Study design**- multicentre, randomised, double-blind, placebo-controlled, parallel-design in forehead lines **Study date**- no information **Study setting**- outpatients from 23 centres
Participants	**Randomised**- 221 participants, with mean age of 6.6 ± 9.2 years in arm 1; 46.4 ± 8.1 years in arm 2. Gender: 98/ 109(89.9%) female in arm 1, 100/111 (90.1%) female in arm 2 **Inclusion criteria**

Rzany 2006 *(Continued)*

	• Aged 18 to 75 years; had moderate or severe vertical or diagonal glabellar wrinkles (scores of 2 or 3 on a standardised 4-point clinical scale ranging from 0 [no wrinkles] to 3 [severe wrinkles]) at maximum frown; and had mild, moderate, or severe (scores of 1, 2, or 3) vertical or diagonal glabellar wrinkles at rest • Women of childbearing potential with a negative pregnancy test result before enrolment in the study **Exclusion criteria**- no information **Severity of disease**- moderate or severe vertical or diagonal glabellar wrinkles (scores of 2 or 3 on a standardised 4-point clinical scale ranging from 0 [no wrinkles] to 3 [severe wrinkles]) at maximum frown; and had mild, moderate, or severe (scores of 1, 2, or 3) vertical or diagonal glabellar wrinkles at rest. **Ethnicity**- Quote:Quote: "Only 1 patient, in study arm 2, was not white"
Interventions	**Duration of study**- 16 weeks **Arm 1**- 3 injections (N = 110) **Intervention** • AbobotulinumtoxinA (30 U), 3 injection sites covered the medial parts of the corrugator muscles and parts of the procerus muscle (N = 73) **Comparator** • Placebo 0.05 mL/site, 3 injection sites covered the medial parts of the corrugator muscles and parts of the procerus muscle (N = 37) **Arm 2**- 5 injections (N = 111) **Intervention** • AbobotulinumtoxinA (50 U), 3 injection sites covered the medial parts of the corrugator muscles and parts of the procerus muscle and two additional ones in frontalis muscle (N = 73) **Comparator** • Placebo 0.05 mL per site, 3 injection sites covered the medial parts of the corrugator muscles and parts of the procerus muscle and two additional ones in frontalis muscle (N = 38)
Outcomes	**Primary outcome** • Percentage of responder rates at maximum glabellar frown between weeks 0 and 4 **Secondary outcomes** • Scores at maximum frown (evaluated by the committee) at weeks 0, 2, 4, 12, and 16 (data not show) • Scores at rest (evaluated by the committee) at weeks 0, 2, 4, 12, and 16 • Scores at maximum frown and at rest (evaluated by the investigator) at weeks 0, 2, 4, 12, and 16 • Subjective assessment of improvement since the first visit (evaluated by the patient) at weeks 2, 4, 12, and 16 • Assessment of patients' global satisfaction with the treatment at week 16 • Adverse events
Notes	"Financial Disclosure: Dr Rzany has received grants from Ipsen Pharma, Ettlingen, as well as from Pharma Allergan, Ettlingen, for other clinical trials not related to this study. Dr Rzany also has received honoraria from Ipsen Pharma for consulting and for conducting educational workshops. Funding/Support: This study was supported by a grant from Ipsen Pharma."
Risk of bias	

Rzany 2006 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "This was a double-blind, placebo-controlled, randomised" page 321 Comment: we considered this unclear risk of bias because the authors did not explain how they randomised the participants
Allocation concealment (selection bias)	Unclear risk	Quote: "Within each centre, patients were randomised 2:1 to receive botulinum toxin A or placebo" page 321 Comment: we considered this unclear risk of bias because the authors did not explain the methods for allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "This was a double-blind, placebo-controlled,"page 321 Comment: we considered this unclear risk of bias because the authors did not explain how they blinded the participants (patients)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "This was a double-blind, placebo-controlled" page 321 Comment: we considered this unclear risk of bias because the authors did not explain how they blinded the participants (patients)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "All but 1 patient (in study arm 1) were included in the intention-to-treat analysis." page 322 Comment: we considered this unclear risk of bias, because the authors did not explain the reason of drop outs
Selective reporting (reporting bias)	High risk	Quote: "the scores at maximum frown and at rest (evaluated by the investigator) at weeks 0, 2, 4, 12, and 16 (data not shown); the subjective assessment of improvement since the first visit (evaluated by the patient) at weeks 2, 4, 12, and 16 (data not shown)" page 322 Comment: we considered a high risk of bias. We sent an e-mail on 28 November 2015. He answer on 14 December 2015: "Concerning the data. This was an IPSEN initiated trial. All analysis was done through IPSEN. I would suggest that you contact IPSEN directly. I cced Dr. Caird in who was at that time responsible for the study."
Other bias	High risk	Pharmaceutical support: "Concerning the data. This was an IPSEN initiated trial. All analysis was done through IPSEN. I would suggest that you contact IPSEN directly. I cced Dr. Caird in who was at that time responsible for the study." Comment: we considered this high risk of bias

Rzany 2019

Study characteristics	
Methods	**Study design**- multicentre, randomised, double-blind, placebo-controlled, parallel-design, single dose for the treatment in glabellarlines **Study date**- started June 2015. Finished April 2016 **Study setting**- outpatients from 19 centres (7- USA, 5- France, 7- Germany, 2- Sweden, 1-UK, 4-Canada

Rzany 2019 *(Continued)*

Participants	Randomised 540 participants. Age: 48.8 ± 10.73 in PRA group; 49.7 ± 10.41 ONA group; 48.4 ± 10.84 in placebo group. Gender 89.8%females in PRA group; 92.3% in ONA group and 91.8% in placebo group. **Inclusion criteria** • Healthy adults, at least 18 years of age, who had moderate (GLS score = 2) to severe (GLS score = 3) glabellar lines at maximum frown, as assessed by the investigator employing the validated 4-point photo numeric GLS • In addition, patients must have answered yes to the question: "Do you find that your glabellar lines have an important psychological impact, for example, on mood, anxiety or depressive symptoms? **Exclusion criteria** • Previous treatment with botulinum toxin of any serotype in the forehead within the last 6 months or any planned treatment during the study period • Previous treatment with any facial aesthetic procedure in the glabellar area within the last 12 months • Previous insertion of permanent material in the glabellar area, any surgery in the glabellar area or any other planned facial aesthetic procedure during the study • Marked facial asymmetry, and presence or history of eyelid and/or eyebrow ptosis • Female patients of childbearing potential were required to have a negative pregnancy test and must have been willing to utilise an acceptable form of contraception **Ethnicity**: Caucasian - 67.3% PRA group, 74.4% ONA group, 73.5% placebo group. Afro-America-1.2% PRA group; 0.4% ONA group and 2.0% in placebo group. Asian- 2.4% PRA group, 2.0% ONA group, 2.0% placebo group. Multiple 0.4% PRA group, 0.4% ONA group, 0% placebo group. Other 3.3% PRA group, 0.8% ONA group, 2.0% placebo group. Missing 25.3% PRA group, 22.0% ONA group, 20.4% placebo group. **Severity of disease**: Investigator assessment maximum frown Moderate 25.3% PRA group, 28.5% ONA group, 26.5% placebo group. Severe- 74.7% PRA group, 71.5% ONA group, 73.5% placebo group
Interventions	**Duration**: 5 months (150 days) **Intervention** • PrabotulinumtoxinA 20 U, intramuscular injection (0.1 mL injected into each site, 5 sites) **Comparators** • OnabotulinumtoxinA 20 U, intramuscular injection (0.1 mL injected into each site, 5 sites) • Placebo, intramuscular injection (0.1 mL injected into each site, 5 sites) **Ratio**: 5:5:1 (PRA: ONA: Placebo)
Outcomes	**Primary outcome** • Proportion of patients classified as responders on day 30. **Secondary outcomes** • Proportion of patients with a GLS score of 0 or 1 on day 30 at maximum frown by patient assessment • Proportion of patients with at least a 1-point improvement on the SSS at day 30 (ie, a score of 1 [satisfied] or 2 [very satisfied] on day 30) • Change from baseline to day 90 in mean HADS Anxiety (HADS-A) score • Change from baseline to day 90 in mean HADS Depression (HADS-D) score • Proportion of patients with at least a 1-point improvement on the GLS from day 0 to day 2 at maximum frown by investigator assessment • Proportion of patients with at least a 1-point improvement on the GLS from day 0 to day 150 at maximum frown by investigator assessment.
Notes	It is a non -inferiority trial between PrabotulinumtoxinA and OnabotulinumtoxinA

Rzany 2019 *(Continued)*

	Sponsor Evolus, Inc Dr Avelar is Chief Medical Officer and Head of Research and Development, Evolus, Inc., Newport Beach, CA.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote:"Random numbers were generated utilizing SAS PROC PLAN (SAS Institute, Inc., Cary NC); a block randomization scheme with no stratification was employed where each block contained assignments for 5 prabotulinumtoxinA patients, 5 onabotulinumtoxinA patients, and 1 placebo patient".....Page3 Comment: we consider a low risk of bias
Allocation concealment (selection bias)	Unclear risk	Quote:"Random numbers were generated utilizing SAS PROC PLAN (SAS Institute, Inc., Cary NC); a block randomization scheme with no stratification was employed where each block contained assignments for 5 prabotulinumtoxinA patients, 5 onabotulinumtoxinA patients, and 1 placebo patient".....Page3 Comment: we consider a low risk of bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote:"Trained individuals were responsible for reconstituting the vial with 2.5 mL of saline and filling the injection syringe. The loaded syringe was then provided to the investigator while maintaining appropriate spatial separation to ensure blinding" ...Page 3 Comment: we consider a low risk of bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote:"Trained individuals were responsible for reconstituting the vial with 2.5 mL of saline and filling the injection syringe. The loaded syringe was then provided to the investigator while maintaining appropriate spatial separation to ensure blinding" ...Page 3 Comment: we consider a low risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: Figure 1 ...Page 6 Comment: we consider a low risk of bias
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported Comment: we consider a low risk of bias
Other bias	Unclear risk	An author worked for sponsor

Satler 2010

Study characteristics

Methods	**Study design**- multicentre, randomised, non-inferiority, active-controlled, parallel-design in glabellar lines

Satler 2010 *(Continued)*

	Study date- no information **Study setting**- outpatients from 20 centres
Participants	**Randomised** 381 participants, with a mean age of 41.7± 5.7 years, median 42 years, (range 22 to 50) in IncobotulinumtoxinA group; 42 ± 6.0 years, median 42 years, (range 24 to 51) in OnabotulinumtoxinA-group. Gender- 100% female **Inclusion criteria** • Women aged 18 to 50 who had moderate to severe glabellar frown lines at maximum frown (severity score of 2 or 3 on the Facial Wrinkle Scale (FWS)) as assessed by the investigator (0 = none, 1 = mild, 2 = moderate, 3 = severe) **Exclusion criteria** • Glabellar frown lines at rest according to investigator rating on the FWS • Previous treatment with botulinum toxin of any serotype in the upper third of the face within the prior 6 months and with biodegradable fillers in the glabellar area within the prior 12 months • Previous insertion of permanent material in the glabellar area • Any surgery or scars in the glabellar area • Marked facial asymmetry or ptosis of eyelid or eyebrow • Any medical condition that may put the patient at risk with exposure to botulinum toxins **Severity of disease**- Facial wrinkle score at rest, none 11/277 (4%) in IncobotulinumtoxinA group; 5/93 (5.4%) in OnabotulinumtoxinAgroup. Mild 92/277 (33.2%) in IncobotulinumtoxinA group, 32/93 (34.4%) in OnabotulinumtoxinA group. Moderate 174/277 (62.8%) in IncobotulinumtoxinA group; 56/93 (60.2%) in OnabotulinumtoxinA group. Severe 0/277 (0%) in IncobotulinumtoxinA group; 0/93 (0%) in OnabotulinumtoxinA group. Facial wrinkle scale at maximum contraction, none 0/277 (0%) in IncobotulinumtoxinA group; 0/93 (0%) in OnabotulinumtoxinA group. Mild 0/277 (0%) in IncobotulinumtoxinA group; 0/93 (0%) in OnabotulinumtoxinA group. Moderate 90/277 (32.5%) in IncobotulinumtoxinA group; 27/93 (29%) in OnabotulinumtoxinA group. Severe 187/277 (67.5%) in BIncobotulinumtoxinA group; 66/93 (71%) in OnabotulinumtoxinA group. **Ethnicity**- BontA1275/277 (99.3%) Caucasian, other 2/277 (0.7%); BontA292/93 (98.9%) Caucasian, 1/93 (1.1%) other Received at least one previous BontA treatment IncobotulinumtoxinA 84/277 (30.3%), OnabotulinumtoxinA 28/93 (30.1%)
Interventions	**Duration of study**- 12 weeks **Intervention** • IncobotulinumtoxinA (24 U), 0.15 mL (6 U)/site, in the procerus muscle, 0.125 mL (5 U) in the medial part of each corrugator muscle, and 0.1 mL (4 U) in the middle part of each corrugator muscle, 0.6 mL (N = 277) **Comparator** • OnabotulinumtoxinA (24 U), 0.15 mL (6 U)/site, in the procerus muscle, 0.125 mL (5 U) in the medial part of each corrugator muscle, and 0.1 mL (4 U) in the middle part of each corrugator muscle, 0.6mL (N = 93) **Ratio**- 1:1 (IncobotulinumtoxinA: OnabotulinumtoxinA)
Outcomes	**Primary outcome** • Percentage of responders assessed by the panel of three independent raters from standardised digital photographs (patients with an improvement of 1 point on a 4-point facial wrinkle scale) at maximum frown at week 4

Satler 2010 *(Continued)*

	Secondary outcomes • Percentage of responders assessed by the panel of three independent raters from standardised digital photographs at week 12 • Percentage of responders rate at rest at week 4 and 12 assessed by the panel of independent raters based on standardised digital photographs • Percentage of responders at weeks 4 and 12 at maximum frown and at rest (as assessed by the investigator and the patient using the FWS) • Patient global assessment • Adverse events
Notes	"This study was funded by Merz Pharmaceuticals GmbH. Editorial assistance was provided by Ogilvy 4D, Oxford, UK."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomised into two groups in a 3:1" page 2147 Comment: we considered this unclear risk of bias because the authors did not explain how they randomised the participants
Allocation concealment (selection bias)	Unclear risk	no information Comment: we considered this unclear risk of bias because the authors did not explain the methods for allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "The blinding referred to the patients and the independent rates" page 2147 Comment: we considered this unclear risk of bias due to the authors did not report the methods used for blinding the participants, including the visual aspect of interventions
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Three independent raters individually performed the assessment of the photographs" page 2147 Comment: we considered this unclear risk of bias due to the authors did not report the methods used for blinding the outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "These 381 patients had at least an observed baseline value of the primary efficacy variable and were therefore included in the FAS. Eleven patients showed major deviations from the study protocol, so the PPS comprised 370 patients (n = 277, incobotulinumtoxinA; n= 93, on- abotulinumtoxinA). Major deviations were missing efficacy measurements, time schedule deviations such as premature study termination and visits not done or done outside the visit window, taking medi- cation excluded from the study, and deviation of exclusion criteria" page 2148-9 Comment: we considered this low risk of bias
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported Comment: we considered this low risk of bias
Other bias	Low risk	We considered this study at low risk of other bias

Solish 2016

Study characteristics	
Methods	**Study design**- multicentre, randomised, dose-ranging placebo-controlled, parallel-design in glabellar lines and in forehead lines **Study date**- no information **Study setting**- outpatients from seven centres
Participants	**Randomised**- 175 participants, with mean age of 45.5 ± 9.8 years in OnabotulinumtoxinA 40u group; 47.6 ± 11 years in OnabotulinumtoxinA 30u group; 47.2 ± 8.6 years in placebo group; total population 46.8 ± 9.8 years. Gender 50/57 (87.7%) female, 7/57 (12.3%) male in OnabotulinumtoxinA 40u group; 49/59 (83.3%) female, 10/59 (16.7%) male in OnabotulinumtoxinA 30u group; 53/59 (89.7%) female, 6/57 (10.3%) male in placebo group; total population 152/175 (86.9%) female, 23/175 (13.2%)male **Inclusion criteria** • Moderate-to-severe FHL at maximum eyebrow elevation as rated by both investigator and participant FWS at day 1 before study treatment (investigator and participant ratings had to be identical at baseline) • Negative urine pregnancy test at day 1 for females of childbearing potentia **Exclusion criteria** • Concurrent or previous cosmetic botulinum toxin treatment of any serotype within the previous year • Resurfacing laser or light treatments, micro dermabrasion, or dermal peels within 3 to 6 months before enrolment • Mid-facial or periorbital treatment with nonpermanent soft-tissue fillers, or use of oral retinoids within 12 months of enrolment • Any medical condition in which exposure to botulinum toxin would pose a risk to the participant • Any other condition that might interfere with neuromuscular function **Severity of disease**- glabellar line severity (maximum frown): 25/57 (43.9%) moderate, 32/57 (56.1%) severe in OnabotulinumtoxinA 40 U group; 30/59 (50.8%) moderate, 27/59 (45.8%) severe in OnabotulinumtoxinA 30 U group; 34/59 (57.6%) moderate, 24/59 (40.7%) severe in placebo group; total population 89/175 (50.9%) moderate and 83/175 (47.4%) severe **Ethnicity**- white 55/57 (96.5%) in OnabotulinumtoxinA 40 U group; white 53/59 (89.8%) in OnabotulinumtoxinA 40 U group;52/59 (88.1%) in placebo group; total population 160/175 (91.4%)
Interventions	**Duration of study**- 24 weeks **Intervention** • OnabotulinumtoxinA- (40 U) (0.2 mL), 10 injections: 5 sites in the frontalis area (20 U, 4 U based on an injection volume of 0.1 mL) and 5 sites in the glabellar region (2 0 U,0.1 mL per site). (N = 57) • OnabotulinumtoxinA- (30 U) (0.2 mL), 10 injections: 5 sites in the frontalis area (10U, 2U of 0.05 mL) and 5 sites in the glabellar region (20 U, 0.1 mL per site). (N = 59) **Comparator** • Placebo - 0.2 mL 10 injections: 5 sites in the frontalis area (0.1 or 0.05 mL depend on the intervention group) and 5 sites in the glabellar region (0.1 mL per site). (N = 59)
Outcomes	**Primary outcome** • "None" or "mild" in investigator and participant assessment of FHL severity at maximum eyebrow elevation at day 30 using the FWS **Secondary outcomes**

Solish 2016 *(Continued)*

- Participant assessment of satisfaction with appearance of FHL measured on a 5-point scale
- Investigator and participant assessment of FHL severity at rest using the FWS with responders defined as achieving at least a 1-grade improvement from baseline
- FLO-11 psychological impact items 2, 5, and 8 (looking older than they want to look, looking less attractive than they want to look, and looking tired)
- Duration of effect based on time to return to nonresponder status from investigator-assessed FWS score;
- Participant's perception of onset of effect
- SPA
- Investigator FWS assessment of GL at maximum contraction and rest
- Adverse events.

Notes	Quote: "Dr. X. Lei, Ms. M. Bhogal, and Dr. C. Caulkins are employees of Allergan plc and receive compensation in salary, as well as stock and/or stock options. Ms. C. Somogyi, currently an employee of Kythera Pharmaceuticals, was an employee of Allergan plc at the time of this study and during manuscript preparation. The authors received research grant support from Allergan plc, Dublin, Ireland, for this study and for manuscript preparation. Funding for editorial support was provided by Allergan plc. Writing and editorial assistance was provided by SCI Scientific Communications and Information (SCI), Parsippany, NJ. Editorial assistance was provided by Beta Bowen of Allergan plc" FLO-116 and SPA5 are validated instruments developed in accordance with the US Food and Drug Administration Guidance for Industry– Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Subjects were randomised in a 1:1:1 ratio" page 411 Comment: we considered this unclear risk of bias because the authors did not explain how they randomised the participants
Allocation concealment (selection bias)	Unclear risk	no information Comment: we considered this unclear risk of bias because the authors did not explain the methods for allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "An independent drug reconstitutor/injector was used in this study to ensure maintenance of blinding of study drug and placebo" Page 411 Comment: we considered this unclear risk of bias due to the authors did not report the methods used for blinding the participants, including the visual aspect of interventions
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "An independent drug reconstitutor/injector was used in this study to ensure maintenance of blinding of study drug and placebo. A separate blinded evaluator conducted all efficacy and safety assessments." page 411 Comment: we considered this unclear risk of bias due to the authors did not report the methods used for blinding the outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	no information Comment: we consider unclear risk of bias
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported Comment: we considered a low risk of bias

Solish 2016 *(Continued)*

Other bias	Unclear risk	Quote: "However, comparison between the 30 U and placebo groups suggested a possible difference between the 2 groups in subject assessment of GL appearance at baseline" page 414 Quote: "Dr. X. Lei, Ms. M. Bhogal, and Dr. C. Caulkins are employees of Allergan plc and receive compensation in salary, as well as stock and/or stock options. Ms. C. Somogyi, currently an employee of Kythera Pharmaceuticals, was an employee of Allergan plc at the time of this study and during manuscript preparation. The authors received research grant support from Allergan plc, Dublin, Ireland, for this study and for manuscript preparation. Funding for editorial support was provided by Allergan plc. Writing and editorial assistance was provided by SCI Scientific Communications and Information (SCI), Parsippany, NJ. Editorial assistance was provided by Beta Bowen of Allergan plc" Comment: we consider unclear risk of bias because wrinkles baseline severity imbalance, and some authors were employees and stockholders of Allergan.

Solish 2018

Study characteristics	
Methods	**Study design**- multicentre, randomised, dose-ranging placebo-controlled, parallel-design in glabellar lines (BELMONT STUDY). Phase II **Study date**- no information **Study setting**- outpatients
Participants	**Randomised** 268 participants aged 30-65 years of age. Gender: 80% of participants were female **Incluion criteria**: no information **Exclusion criteria** : no information **Ethinicity**- 85% were "white" **Severity of the disease**: moderate-to-severe glabellar lines
Interventions	**Duration**: from 24 weeks to 36 weeks **Intervention** DaxibotulinumtoxinA 20U, 40 U, 60 U in the glabellar lines **Comparator** OnabotulinumtoxinA 20 U in the glabellar lines Placebo in the glabellar lines **Ratio:** (1:1:1)
Outcomes	**Primary outcome** • Proportion of participants with 1 grade change in GL severity at week 24. **Secondary outcomes** • Responders at weeks 4 and 24 for the primary endpoint • Proportion of participants with none/mild GL at these time point

Solish 2018 *(Continued)*

- Adverse events

Notes	Poster

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The BELMONT study was a randomized, "....page S106 Comment: we considered this unclear risk of bias because the authors did not explain how they randomised the participants
Allocation concealment (selection bias)	Unclear risk	Quote: "The BELMONT study was a randomized, "....page S106 Comment: we considered this unclear risk of bias because the authors did not explain how they randomised the participants
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "The BELMONT study was a randomized, "....page S10 Comment: we considered this unclear risk of bias because the authors did not explain how they blinded the participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "The BELMONT study was a randomized, "....page S10 we considered this unclear risk of bias because the authors did not explain how theey keep the participants blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: no information Comment: we consider an unclear risk of bias
Selective reporting (reporting bias)	Unclear risk	The authors did not show all the endpoints Comment: we consider an unclear risk of bias
Other bias	Unclear risk	This study is a poster

Won 2013

Study characteristics

Methods	**Study design**- multicentre, randomised, double-blind, parallel-design, active-controlled, phase III clinical trial **Study date**- no information **Study setting**- outpatient from six centres
Participants	**Randomised**- 314 participants, with mean age of 48 ± 8.8 years in NewBontA group, median 49 years (range 25-64); 47 ± 8.8 years, median 82 years, (range 27 to 64) in OnabotulinumtoxinA group. Younger than 50 years: 79/157 (50.3%) in New BontA group; 85/157 (54.1%) OnabotulinumtoxinA. Equal or older than 50 years: 78/157 (49.7%) in New BontA group; 72/157 (45.9%) in OnabotulinumtoxinA group. Gender: 135/157 (86%) female, 22/157 (14%) male in New BontA group; 124/157 (79%) female, 33/157 (21%) male in OnabotulinumtoxinAgroup. Botulinum treatment naive: New BontA 93%, OnabotulinumtoxinA 90.4% **Inclusion criteria**

Won 2013 *(Continued)*

- Eligible participants were men and women aged 20 to 65 with moderate to severe glabellar frown lines at maximum frown (severity score of 2 or 3 on the Facial Wrinkle Scale (FWS)

Exclusion criteria

- Any medical condition (e.g. myasthenia gravis, Lambert-Eaton syndrome, amyotrophic lateral sclerosis) that might have put the patient at risk with botulinum toxin
- Prior use of medications that might affect the neuromuscular junction (e.g. muscle relaxants, spectinomycin hydrochloric acid, aminoglycosides, polypeptide antibiotics, anticholinergics, benzodiazepines)
- Any allergies or hypersensitivity to the investigational drugs or their components
- Previous treatment with botulinum toxin within 3 months, other procedures that might affect glabellar and forehead lines within 6 months
- Any history of glabellar treatment (including forehead) such as a face lift and/or permanent implants or scars that might affect the treatment results
- Patients whose glabellar lines could not be satisfactorily improved with manual pressure were also excluded
- Patients were not eligible if they had dermatologic disorders or infection at potential injection sites or a history of facial nerve paralysis or ptosis
- Pregnancy or lactating women

Severity of disease- moderate to severe glabellar frown lines at maximum frown (severity score of 2 or 3 on the Facial Wrinkle Scale (FWS)

(FWS at rest) 8/142 (5.5%) none, 58/142 (40.3%) mild,38/142 (26.4%) moderate, 40/142 (27.8%) severe in New BontA group; (FWS at rest) 16/146 (10.9%) none, 48/146 (32.6%) mild, 46/146 (31.3%), 37/146 (25.2%) severe in OnabotulinumtoxinA group.

FWS at maximum contraction 0 none,0 mild, 66/142 (47.5%) moderate, 76/142 (53.5%) severe in New BontA group; OnabotulinumtoxinA (FWS at maximum contraction) 0 none, 0 mild, 66/146 (47.5%) moderate, 80/146 (53.5%) severe in OnabotulinumtoxinA group.

Ethnicity- no information

Interventions	**Duration of study**- 16 weeks **Intervention** • New BontA [Neurono®] - (20 U), 0.1 mL (4 U) in the procerus, 0.1 mL (4 U) in each medial corrugator, and 0.1 mL (4 U) in the middle of each corrugator, 0.5mL (N= 157) **Comparator** • OnabotulinumtoxinA- (20 U), 0.1 mL (4 U) in the procerus, 0.1 mL (4U) in each medial corrugator, and 0.1 mL (4 U) in the middle of each corrugator, 0.5mL (N = 157) **Ratio**- 1:1 (New BontA [Neurono®]:OnabotulinumtoxinA)
Outcomes	**Primary outcome** • Responder rate according to investigator live assessment at maximum frown at week 4, face-to-face observation **Secondary outcomes** • Responder rates according to investigator live assessment with frowning and at rest at weeks 8, 12, and 16, with additional photographic assessment by a panel of blinded raters 4 weeks after injection • Subjective satisfaction scores • Adverse events
Notes	"This study was sponsored by Medytox Inc. Dr. Woo Shun Lee was an employee of Medytox Inc., Korea."

Won 2013 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "After confirmation of eligibility, patients were randomised into two groups at a 1:1 ratio" page 173 Comment: we considered this unclear risk of bias because the authors did not explain how they randomised the participants
Allocation concealment (selection bias)	Unclear risk	Quote: "After confirmation of eligibility, patients were randomised into two groups at a 1:1 ratio" page 173 Comment: we considered this unclear risk of bias because the authors did not explain the methods for allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Each patient received a total dose of 20 U (4 U/0.1 mL) of NBoNT or OBoNT in a double-blind manner." page 173 Comment: we considered this unclear risk of bias because the authors did not explain how they blinded the participants
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Three blinded raters assessed the photographs according to the FWS." page 173 Comment: we considered this a low risk of bias
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Two hundred ninety-one of 314 patients enrolled completed the study without major deviation and therefore constituted the PP set: 142 in the NBoNT group and 146 in the OBoNT group" page 174 Comment: we considered unclear risk because the authors did not explain the drop-out reason
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported Comment: we considered a low risk of bias
Other bias	Unclear risk	Dr. Woo Shun Lee was an employee of Medytox Inc., Korea." Comment: we considered this a unclearrisk of bias

Won 2015

Study characteristics

Methods	**Study design**- multicentre, double-blinded, randomised, active-controlled parallel design **Study date**- no information **Study setting**- outpatients from three centres
Participants	**Randomised**- 268 participants, with mean age of 47.82 ± 9.15 years in DWP450 group; 47.31 ± 8.57 years in OnabotulinumtoxinA group; 47.57 ± 8.85 years total population. Gender 106/133 (79.70%) female, 27/133(20.30%) male in DWP450 group; 111/132 (84.09%) female, 21/132 (15.91%) male inOnabotulinumtoxinA group; 217/265 (81.89%) female, 48/265 (18.11%) male total population **Inclusion criteria**

Won 2015 *(Continued)*

- Participants needed to be between 20 and 65 years of age and exhibit glabellar lines of at least moderate severity at maximum frown (graded on a four-point facial wrinkle scale: 0 = none, 1 = mild, 2 = moderate, 3 = severe)

Exclusion criteria

- Any condition that could cause neuromuscular junction dysfunction (such as myasthenia gravis, Lambert–Eaton myasthenic syndrome, amyotrophic lateral sclerosis, or any systemic neuromuscular junction disorder) were excluded
- Use of aminoglycosides, curare-like agents, or muscle relaxants in the four weeks preceding the start of the study
- Previous aesthetic procedures in the six months preceding the start of the study

Severity of disease- baseline severity glabellar lines at maximum frown moderate 51/133 (38.35%) in BontA1 group, 52/132 (39.9%) in BontA2 group, 103/265 (38.87%) total population. Severe 82/133 (61.65%) in BontA1 group, 80/132 (60.61%%) in BontA2 group, 162/265 (61.13%) total population. Severity of glabellar lines at rest- mild 51/133 (38.35%) in BontA1 group, 47/132 (35.61%) in BontA2 group, 98/265 (36.98%) total population. Moderate- 26/133 (19.55%) in BontA1 group, 28/132 (21.21%) in BontA2 group, 54/265 (20.38%) total population. Severe -56/133 (42.11%) in BontA1 group, 57/132 (43.18%) in BontA2 group, 113/265 (42.64%) total population

Ethnicity- no information

Interventions

Duration of study- 16 weeks

Intervention

- DWP450 - (20U), 0.1 mL (4 U) five sites: the midline of the procerus muscle, the inferomedial aspect of each corrugator muscle, and the superior middle aspect of each corrugator (at least 1 cm above the bony orbital rim (N = 133)

Comparator

- OnabotulinumtoxinA- (20 U), 0.1 mL (4 U) five sites: the midline of the procerus muscle, the inferomedial aspect of each corrugator muscle, and the superior middle aspect of each corrugator (at least 1 cm above the bony orbital rim (N = 132)

Ratio- 1:1 (DWP450: OnabotulinumtoxinA)

Outcomes

Primary outcome

- Responder rate at maximum frown at week 4. Responder rate was defined as the percentage of participants with a score of none (0) or mild (1)

Secondary outcomes

- Responder rate at maximum frown at weeks 8, 12, and 16
- Investigator-assessed glabellar lines responder rate at rest at weeks 4, 8, 12, and 16
- Responder rate at maximal frown and at rest at weeks 4, 8, 12, and 16 using photograph assessment
- Participant-assessed degree of satisfaction and response rate of glabellar lines at weeks 4, 8, 12, and 16
- Adverse events

Notes

"Su-Young Lee and Chung-Sei Kim are employees of Daewoong Pharmaceutical. This study was sponsored by Daewoong Pharmaceutical"

Risk of bias

Bias	Authors' judgement	Support for judgement

Won 2015 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "At each centre, eligible patients were randomly assigned to either the DWP450 or OBoNT group in a 1:1 ratio using a computer-generated randomisation schedule" page 228 Comment: we considered this low risk of bias
Allocation concealment (selection bias)	Unclear risk	Quote: "At each centre, eligible patients were randomly assigned to either the DWP450 or OBoNT group in a 1:1 ratio using a computer-generated randomisation schedule" page 228 Comment: we considered this unclear risk of bias
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Investigators were blinded to medication type throughout the study." page228 Comment: we considered this unclear because the authors did not explain how they blinded the participants (patients)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "This prospective, double-blinded, randomised, active-controlled"...page 228"Three blinded independent investigators conducted photographic assessment, and all the blinded raters additionally received" page 229 Comment: we considered this low risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Of the 281 subjects screened, 268 were randomised, so that 135 were assigned to the DWP450 group and 133 to the OBoNT group. Of these, 263 completed the study, so that 265 of 268 randomised subjects composed the FAS population. The PPS1 population consisted of 263 subjects, excluding two patients who violated the visit window period and had committed concomitant medication violations. PPS2 population consisted of 245 patients, 18 of whom were excluded for the following reasons: eight for visit window violations, six for concomitant medication violations, and four for omissions of secondary efficacy endpoint assessment." page 229-30 Comment: we considered this low risk of bias
Selective reporting (reporting bias)	High risk	Patient satisfaction rate data not shown Comment: we considered this high risk of bias, we sent an e-mail on 22 November 2015. No answer
Other bias	Unclear risk	Su-Young Lee and Chung-Sei Kim are employees of Daewoong Pharmaceutical Comment: we considered this unclear risk of bias

Wu 2010

Study characteristics	
Methods	**Study design**- multicentre**,** randomised double-blind, placebo-controlled, parallel-design in glabellar lines **Study date**- no information **Study setting**- outpatient from four centres

Wu 2010 *(Continued)*

Participants	**Randomised** 227 participants, with median age of 41.7 years in BontA group, and 44.1years in placebo group. Gender: 142/170 (83.5%) female, 28/170 (16.5%) male in BontA group; 53/57 (93%) female, 4/57 (7%) male in placebo group **Inclusion criteria** • Participants were required to be aged 18 to 65 with glabellar lines of at least moderate severity at maximum frown (graded on a 4-point facial wrinkle scale: 0 = none, 1 = mild, 2 = moderate to 3 = severe) • Participants were also required to be able to complete the entire course of the study and to comply with study instructions **Exclusion criteria** • Any treatment with botulinum toxin before the study • Systemic nerve conduction junction disorder (e.g. myasthenia gravis or Eaton-Lambert syndrome) • Known allergy or sensitivity to the study medication or its components • Infection or other skin disease at injection sites • Any condition that might confound study results (e.g. marked facial asymmetry or eyelid ptosis) • Any other planned facial cosmetic or aesthetic medical treatment (e.g. face lift surgery, resurfacing, filler treatment) during the study period • Severe heart, kidney, or lung disease • Pregnancy, lactation, or participants planning a pregnancy **Severity of disease**- moderate severity at maximum frown (graded on a 4-point facial wrinkle scale: 0 = none, 1 = mild, 2 = moderate to 3 = severe) BontA (FWS at maximum frown) 86/170 (50.6%) moderate, 84/170 (49.4%) severe Placebo (FWS at maximum frown) 27/57 (47.4%) moderate, 30/57 (52.6%) severe **Ethnicity**- 100% Chinese
Interventions	**Duration**- 16 weeks **Intervention** • OnabotulinumtoxinA (20U), 4 U per site, 2 in each corrugator muscle and 1 in the procerus muscle (N = 170) **Comparator** • Placebo 0.5 mL, 2 in each corrugator muscle and 1 in the procerus muscle (N = 57)
Outcomes	**Primary outcome** • Investigator's rating of wrinkle severity at maximum frown and rest **Secondary outcome** • Participant's global assessment • Self-perception of age • Adverse events
Notes	"GlaxoSmithKline provided funding and study material."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "A total of 227 patients were randomised to receive a single treatment of 20 U of BontA or identical placebo in a ratio of 3:1" page 102-3

Wu 2010 *(Continued)*

		Comment: we considered unclear risk of bias because the authors did not explain how they allocated the participants
Allocation concealment (selection bias)	Unclear risk	Quote: "A total of 227 patients were randomised to receive a single treatment of 20U of BontA or identical placebo in a ratio of 3:1" page 102-3 Comment: we considered unclear risk of bias because the authors did not explain the methods used for allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Vials of BoNTA and placebo had identical investigational labels, which prevented identification of the contents." page 103 Comment: we considered low risk of bias
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	no information Comment: we considered unclear risk of bias because the authors did not explain how they maintained the blindness of the assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Of 258 subjects screened, 227 were randomised, with 170 in the BoNTA group and 57 in the placebo group; 222 completed the study. Reasons for discontinuation included SAEs (one breast cancer and one gastric cancer) that the investigator considered to be unrelated to the treatment, withdrawal from the study (N = 2), and loss to follow-up (n = 1)" page 104 Comment: we considered this low risk of bias
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported Comment: we considered this low risk of bias
Other bias	Low risk	We considered this study at low risk of other bias

Wu 2019

Study characteristics	
Methods	**Study design**- multicentre, randomised, double-blind, placebo-controlled, parallel design in crow's feet lines, phase III **Study date**- Started -September 2014.Finished -June 2015 **Study setting**- outpatients (nine centers in China)
Participants	**Randomised**- 417 participants were randomised in a 3:1 ratio to receive a single treatment of OnabotulinumtoxinA 24 U or placebo, with a mean age of 46.3 ± 9.64 years in OnabotulinumtoxinA group, 46.6 ± 9.39 years in placebo group. Gender, female 273/316 (86.4%) in OnabotulinumtoxinA group, 87/101 (86.1%) in placebo group. **Inclusion criteria** • Chinese females and males aged at least 18 years with moderate-to-severe bilateral CFL at maximum smile (same grade on both sides), as assessed by both the investigator and the subject using the FWS-A **Exclusion criteria** • Concurrent treatment with botulinum toxin or treatment within 1 year before enrolment • Known immunisation or hypersensitivity to botulinum toxin • Any medical condition that may result in increased subject risk

Wu 2019 *(Continued)*

- Pregnancy
- Previous surgical procedures at the treatment sites; eyebrow or eyelid ptosis; and eyelid hooding or other skin laxity unlikely to benefit from onabotulinumtoxinA treatment or likely to interfere with CFL assessments

Severity of the disease

FWS-at maximum smile(investigator rated), moderate 153/319 (48.4%) in OnabotulinumtoxinA group, 49/101 (48.5%) in placebo group. Severe 163/319 (51.6%) in OnabotulinumtoxinA group, 52/101 (51.5%) in placebo group. FWS-at maximum smile(subject rated), moderate 154/319 (48.7%) in OnabotulinumtoxinA group, 49/101 (48.5%) in placebo group. Severe 162/319 (51.3%) in OnabotulinumtoxinA group, 52/101 (51.5%) in placebo group.

Ethnicity 100% Asian

Country China

Interventions

Duration of study- 20 weeks

Intervention

- OnabotulinumtoxinA (24 U) (N = 316), 6 intramuscular injections of 0.1 mL each (3 injections per side, 4 U per injection site

Comparator-

- Placebo (N = 101), 6 intramuscular injections of 0.1 mL each (3 injections per side)

Outcomes

Primary outcomes

- Percentage of participants achieving none or mild on the Investigator's assessment of the severity of crow's feet lines (CFL) at maximum smile using the Facial Wrinkle Scale-Asian (FWS-A) [Time Frame: Day 30]
- The investigator assessed the severity of the participant's CFLs at maximum smile using the 4-point FWS-A where 0 = none, 1 = mild, 2 = moderate or 3 = severe. The percentage of participants with a score of none or mild at Day 30 is reported.

Secondary outcomes

- Percentage of participants with a ≥ 1-grade Improvement on the investigator's assessment of CFL severity at rest using the 4-point FWS-A [Time Frame: Day 30]
- The investigator assessed the severity of the participant's CFLs at rest using the 4-point Facial Wrinkle Scale where 0 = none, 1 = mild, 2 = moderate or 3 = severe among participants rated as at least mild at baseline by the Investigator. The percentages of participants with at least a 1-grade improvement are noted.
- Percentage of participants with a ≥ 1-grade improvement on the investigator's assessment of CFL severity at maximum smile on the 4-point FWS-A [Time Frame: Day 30]
- The investigator assessed the severity of the participant's CFLs at maximum smile using the 4-point Facial Wrinkle Scale where 0 = none, 1 = mild, 2 = moderate or 3 = severe. The percentages of participants with at least a 1-grade improvement are noted.
- Percentage of participants reporting their global change in appearance as very much improved or much improved using the 7-point Subject's Global Assessment of change in CFL (SGA-CFL) [Time Frame: Day 30]
- Participants assessed their global change in appearance using the 7-point SGA-CFL scale where 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, and 7 = very much worse. The percentage of participants reporting very much improved or much improved are noted.
- Percentage of participants assessing their age-related facial appearance as looking younger on the Self-Perception of Age (SPA) Questionnaire [Time Frame: Baseline, Day 30.]Participants assessed their age-related appearance according to the following on the SPA questionnaire: look my current age, look younger, and look older when compared to their baseline assessment. The percentages of par-

Wu 2019 *(Continued)*

	ticipants who reported looking younger amongst participants who rated themselves as looking their current age or older at baseline are noted. • Percentage of participants achieving none or mild on the participant's assessment of the severity of crow's feet lines (CFL) at maximum smile using the Facial Wrinkle Scale-Asian (FWS-A) [Time Frame: Day 30]. • Adverse events
Notes	Sponsor Allergan.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "At study entry, subjects were assigned a randomization number, and an interactive voice response system was used to manage the randomization and treatment assignment based on a randomization scheme prepared by Allergan Biostatistics"...page 2 Comments: we consider low risk of bias
Allocation concealment (selection bias)	Unclear risk	Quote:"This 5-month, multicenter, double-blind, randomized, parallel-group,"..page 2 Coment" we consider a unclear risk of bias, because the authors did not explain how they do concealed allocation
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Investigators and subjects were blinded to the treatment administered...page 2 Comment: we consider unclear risk of bias because the authors did not explain how they blinded the participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Investigators and subjects were blinded to the treatment administered...page 2 Comment: we consider unclear risk of bias because the authors did not explain how they blinded the participants
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote:"Reasons for discontinuation in both groups were limited to lost to follow-up (n = 4, onabotulinumtoxinA; n = 1, placebo) and personal reasons (n = 1, onabotulinumtoxinA; n = 1, placebo)."...page 3 Commenst: we consider a low risk of bias
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported Comment: we considered this low risk of bi
Other bias	Low risk	We considered this study at low risk of other bias

ABO: AbobotulinumtoxinA;**BTX:** Botulinum toxin; **CETS:** composite endpoint treatment success; **CFL:** crow's feet lines ; **FWS:** facial wrinkle scale;**GL: :** glabellar lines; **GFL:** glabellar frown lines;**HADS:** Hospital Anxiety and Depression Scale; (**HFL:** horizontal forehead lines;**ILA:** Investigator's Live Assessment; **ITT:** intention-to-treat; **LPL:** lateral periorbital lines;**MAS:** Merz Aesthetics Scales; **ONA:** nabotulinumtoxinA; **SGA:** Subject's Global Assessment; **SPA:** Self-Perception of Age; **U:** unit

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
2014-003770-16	Not randomised clinical trial
Cartier 2020	Other intervention
Hexsel 2018	Non randomised clinical trial
Mahmoud 2016	Non randomised clinical trial
NCT00752050	J&J ended plans to produce BontA
NCT00752297	J&J ended plans to produce BontA
NCT02297516	other intervention
Punga 2016	Other intervention (same units in different dilution)
Rzany 2013	Non randomised clinical trial
Wilson 2016	Other intervention- the authors assessed the BontA treatment by speckle tracking with digital image correlation. This measurement was different from all the available tools.
Zhang 2018	Other intervention

Characteristics of studies awaiting classification *[ordered by study ID]*

NCT01180348

Methods	Randomised, non-inferiority trial, split-face,active-controlled, facial wrinkles, phase III trial
Participants	192 randomised female participants, age ranging from 18 years old to 65 years old **Inclusion Criteria** • Patients who agree with all study procedures and sign for their own free will the TCLE • Adult patients were female between 18 and 65 years, regardless of social condition • Between skin phototype I and IV • With good mental and physical health • Patients who have not been treated with botulinum toxin type A • Patients who agree to abstain from physical activity for a period of 24 hours, previous and subsequent to the initiation of the study • Patients presenting at screening visit, wrinkles in the glabellar region between classes 2 and 3 of Table Wrinkles Pattern Classification, which is diagnosed Clinically by the dermatologist **Exclusion Criteria** • Patients who are in classes 0 and 1 of the Table Pattern Classification Wrinkle • Patients who have disorders or diseases that might interfere with neuromuscular function (myasthenia gravis or Lambert-Eaton syndrome) • Patients being treated with antibiotics (aminoglycosides) and muscle relaxants • Patients with pre-existing conditions such as ptosis or scars in the area to be assessed, as they may endanger the health of the patient and the results of the study • Patients who have made treatments fill in the glabellar region (retinoic acid, collagen) • Patients who have been treated in the dermatological peeling in the last three months

NCT01180348 *(Continued)*

	• Patients are using treatments cosmetics agents anti age (vitamin C pure retinoids flavonoids acid hyaluronic others) or used past 3 months • Patients with known hypersensitivity to any component of the study drug • Pregnant or lactating women **Country**: Brazil
Interventions	**Intervention**:3 applications on each side of the face in 15 predetermined sites in three regions of the face (front, glabellar, periocular). Botulift® 90 U **Comparator**: 3 applications on each side of the face in 15 predetermined sites in three regions of the face (front, glabellar, periocular).OnabotulinumtoxinA
Outcomes	**Primary Outcomes** • Overall improved assessment of hyperkinetic facial lines in a state of relaxation and maximal contraction through the Honeck's scale and photographic images obtained by equipment Visia Digital Compexton Analysis (Canfield Imaging Systems, version 4.0.2) 30 days of application • The non-inferiority of T group compared to the group Co was demonstrated in evaluations in a state of relaxation and maximal contraction in the PP analysis population, because as defined for the study, the lower limits of 95% of the mean of these assessments (-2.7% and -5.4%) are contained within the non-inferiority limit set at -10% **Secondary Outcomes** • Length of stay of the effect of botulinum toxin A (Test and Comparator) the 24-week period.The action of both treatments decreases over time and there is no significant difference between the two treatments • Safety of both botulinum toxin A. The occurrence of adverse events was similar in both groups
Notes	Sponsor Azidus Brasil We sent an email to this company (http://laboratoriobergamo.com.br/contato/) on June, 23rd, 2018. No answer.

NCT01358695

Methods	Randomised, multicentre, factorial design, placebo-controlled, masking quadruple (participant, care provider, investigator, outcomes assessor). phase II trial
Participants	111 participants, age ranging from 30 to 70 years old, both gender **Inclusion criteria** • Mild to moderate crow'sfFeet wrinkles (IGA 2-3) at rest • Moderate to severe crow's feet (IGA 3-4) on contraction • Willingness to refrain from any product affecting skin remodelling • Female participants must be not pregnant and non-lactating **Exclusion Criteria** • History of periocular surgery, brow lift or related procedures • Procedures affecting the lateral canthal region in the prior 12 months • Application of topical prescription medication to the treatment area • Female participants who are pregnant or are nursing a child **Country**: USA

NCT01358695 *(Continued)*

Interventions	**Intervention** ANT-1207 five different doses (no information about the units) **Comparator** Placebo (no information about volume)
Outcomes	**Primary outcome** • Efficacy will be assessed by Investigator's Global Assessment score [Time Frame: 2 weeks] **Secondary outcomes** • Subject Self Assessment (SSA) scale [Time Frame: 2 Weeks] • Investigator Global Assessment scale [Time Frame: Week 1, 2, 4, 8, 1]
Notes	Supported by Anterios InC. Allergan bought Anteris in 2014 Other study ID: ANT-1207-201-LCL

NCT01485601

Methods	Randomised, double-blind, multi-centre, Active-control, optimal dose-finding of MT10109, phase II trial
Participants	121 participants, age raging from 18 to 75 years old, both gender **Inclusion criteria** • Adults aged between 18 and 75 years with glabellar facial lines of at least moderate severity at maximum frown by investigator's assessment • Women of child-bearing potential must have a negative serum pregnancy test at screening **Exclusion Criteria** • Patients with an inability to substantially lessen glabellar lines by physically spreading them apart • Concurrent therapy that, in the investigator's opinion, would interfere with the evaluation of the safety or efficacy of the study medication • Patients with an anaphylactic response history to botulinum toxin type A • Patients who have been administered botulinum toxin type A within the previous 6 months • Pregnant or lactating women; • Participation in any research study involving drug administration within 90 days preceding enrolment **Country**: Australia
Interventions	**Intervention** • Single intramuscular injection of MT10109 in the glabella region, no dose information **Comparator** • Single intramuscular injection of OnabotulinumtoxinA in the glabella regio, no dose information
Outcomes	**Primary outcome** • Investigator's rating of glabellar line severity at maximum frown by live assessment. [Time Frame: at Day 30]

NCT01485601 *(Continued)*

	No secondary outcomes.
Notes	other register MT-GPRT-GL01 support Medy-tox® The title was double-blind study, but in the study descriptions it was a Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)

NCT01583478

Methods	Open-label, dose ranging, active-controlled trial
Participants	60 participants, older than 18 years old, both gender **Inclusion criteria** • Moderate to severe vertical glabellar lines at maximum frown (score of [2] or [3] by physician assessment) • Negative pregnancy test for females of childbearing potential • Time and ability to complete the study and comply with instructions, understanding of the study and contents of the informed consent **Exclusion criteria** • Previous treatment to the glabellar area with Dysport® or Botox® Cosmetic or other botulinum toxin within 90 days of entry into the study. Botulinum toxin treatment of areas other than the glabellar area at any time during the study • Patients with an ongoing treatment-related AE from any Dysport® or Botox® Cosmetic or botulinum toxin study • Inability to substantially lessen glabellar lines by physically spreading them apart • Soft tissue augmentation of the glabellar area (e.g. collagen-type implants, or hyaluronic acid fillers) at any time during the current study • Permanent or semi-permanent dermal fillers in the glabellar area at any time • Ablative skin resurfacing on the glabellar area at any time preceding the study or planning to during the current study • Upper eyelid blepharoplasty or brow-lift at any time preceding the study or planning to during the current study • Non-ablative treatments in the glabellar area for skin dyschromia e.g. Intense Pulsed Light, light-emitting diodes at any time during the current study • Non-ablative dermal treatment in the glabellar area for skin tightening (e.g. radiofrequency treatments at any time preceding the current study or plan to Have this done during the current study) • Retinoid, micro dermabrasion, or prescription-level glycolic acid treatments to the glabellar area within 2 weeks prior to study participation or during the current study, concurrent therapy that, in the investigator's opinion, would interfere with evaluation of the efficacy or safety of the medication • Active infection of the glabellar area (e.g. acute acne lesions or ulcers) • Pregnant women, nursing mothers, or women who are planning pregnancy during the study, or think they may be pregnant at the start of the study • Throughout the course of the study, women of childbearing potential must use reliable forms of contraception (e.g. abstinence, oral contraceptives for more than 12 consecutive weeks prior to enrolment, or spermicide and condoms) • Current history of chronic drug or alcohol abuse • Enrolment in any active study involving the use of investigational devices or drugs • Current facial palsy

NCT01583478 *(Continued)*

	• Marked facial asymmetry, ptosis, excessive dermatochalasis, deep dermal scarring, or thick sebaceous skin, neuromuscular junctional disorders (myasthenia gravis) • Known allergy or hypersensitivity to any botulinum toxin or any component of Dysport® or Botox® Cosmetic • Clinically-diagnosed anxiety disorder, or any other significant psychiatric disorder (e.g. depression) that, in the opinion of the investigator, might interfere with the patient's participation in the study • Concurrent use of medications that affect neuromuscular transmission, such as curare-like depolarising agents, lincosamides, polymyxins anticholinesterases affecting the striated muscle, and aminoglycoside antibiotics • Presence of any condition (e.g. neuromuscular disorder or other disorder that could interfere with neuromuscular function) or circumstance that, in the judgment of the investigator, might increase the risk to the patient or decrease the chance of obtaining satisfactory data to achieve the objectives of the study **Country**: USA
Interventions	**Treatment/comparator**: IncobotulinumtoxinA doses of 20-, 40-, 60-, 80- or 100-units divided among 5 injection points (0.25 mL total) in the glabellar region
Outcomes	**Primary Outcome** • Efficacy of escalating doses of Xeomin® in the treatment of glabellar rhytids [Time Frame: 12 months] [Designated as safety issue: no] [Investigator- and participant-assessed grading] **Secondary outcomes** • Duration of action of escalating doses of Xeomin® in the treatment of glabellar rhytids [Time Frame: 12 months] [Designated as safety issue: no] [Investigator- and participant-assessed grading] • Safety and presence of any adverse effects of Xeomin® in the treatment of glabellar rhytids [Time Frame: 12 months] [Designated as safety issue: no]
Notes	Other ID study number: ITGR-2012.This trials ended on September 30, 2015. We sent an email to Merz

NCT01791920

Methods	Double-blinded, randomised, active control comparative, multicentre-designed, phase III trial
Participants	262 participants **Inclusion Criteria** • Men and women aged between 18 and 65 • Patients attaining grade 2 or 3 in the investigator's rating of glabellar lines severity at maximum frown • Patients who voluntarily sign the informed consent • Patients who can comply with the study procedures and visit schedule **Exclusion Criteria** • Participants who had facial plastic surgery (tissue augmentation, brow lift, and dermal resurfacing)treatment within 6 months. Those who had peeling or laser therapy • Participants with skin disorders, scar or infection around glabellar region • Participants who are taking aspirin, NSAIDS or anti-coagulant • Participants with facial palsy or eyelid ptosis

NCT01791920 *(Continued)*

- Participants who diagnosed as neuromuscular junction disorder (e.g. myasthenia gravis, Lambert-Eaton Syndrome)
- Participants with history of drug intoxication, alcohol abuse and/or depressive disorder
- Participants with severe internal diseases (cardiovascular, respiratory, renal disease, liver disorder)
- Participants who have previously been treated with botulinum toxin within 3 months (Botulinum toxin type A: 3months, type B: 4 months);
- Participants who have administered following drugs within the previous 4 months: spectinomycin hydrochloride, aminoglycoside antibiotics, polypeptide antibiotics, tetracycline antibiotics, lincomycin antibiotics, muscle relaxants, anti-cholinergic agents, benzodiazepine and similar drugs, benzamide drugs Tubocurarine-type muscle relaxants
- Participants who have possibility to take the drugs listed above
- Participants who have a plan to receive facial cosmetic procedures including dermal filler, chemical peeling and dermabrasion during study period
- Participants who have glabellar lines that are unable to be improved with any physical method
- Participants who have history of hypersensitivity to botulinum toxin and other agents
- Participants who are pregnant or breast-feeding
- Participants who have a plan to be pregnant in 3months, or who are not doing contraceptive
- Participants who participated in other studies within 30 days or were not passed over 5 times of half life for investigational product
- Participants who are having trouble with acute disease
- Participants who have taken any treatment that can affect to glabellar lines and/or any lines around forehead within the previous 6 months
- Participant who are unable to communicate or follow the instructions
- Participants who are not eligible for this study based on investigator's judgement

Country: Republic of Korea

Interventions	**Intervention** • Botulinum toxin type A (Botulax®) Single administration, Day 0, 20 units **Comparator** • Botulinum toxin type A(onabotulinumtoxinA) Single administration, Day 0, 20 units
Outcomes	**Primary outcomes** • Responder rate of improvement in glabellar lines with physician's rating of line severity [Time Frame: at 4 weeks post-injection] • Improvement rate of glabellar lines at maximum frown with physician's rating of lines severity at 4weeks post injection **Secondary outcomes** • Safety evaluation in experimental drug treatment group [Time Frame: 4, 8, 12, 16 weeks post-injection] • Responder rate of improvement in glabellar lines with physician's rating of line severity [Time Frame: 8, 12, 16 weeks post-injection] • Responder rate of improvement in glabellar lines at rest with investigator's live assessment of severity [Time Frame: 4, 8, 12, 16 weeks post-injection] • Responder rate of improvement in glabellar lines at maximum frown with investigator's photo assessment [Time Frame: 4, 8, 12, 16 weeks post-injection] • Responder rate of improvement in glabellar lines at rest with investigator's photo assessment [Time Frame: 4, 8, 12, 16 weeks post injection]

NCT01791920 *(Continued)*

- Responder rate of improvement in glabellar lines with Subject's improvement assessment [Time Frame: 4, 8, 12, 16 weeks post-injection]
- Participant's satisfaction rate [Time Frame: 4, 8, 12, 16 weeks post-injection]

Notes	Sponsor Hugel We sent an email in April 2019 in the Hugel site. We did not receive any answer.

NCT01951742

Methods	Randomised, parallel-design, double-blind, dose-ranging, phase II
Participants	145 participants, age ranging from 30 to 60 years old, both gender **Inclusion Criteria** • 30 to 60 years of age • Mild to moderate crow's feet wrinkles at rest • Moderate to severe crow's feet wrinkles on contraction • Willingness to refrain from any product affecting skin remodelling • Female participants must be not pregnant and non-lactating **Exclusion Criteria** • History of periocular surgery, brow lift or related procedures • Procedures affecting the lateral canthal region in the prior 12 months • Application of topical prescription medication to the treatment area • Female participants who are pregnant or are nursing a child **Country** : USA
Interventions	**Intervention**: five different dose of ANT-1401. The units were not specified in crow's feet lines **Comparator**: placebo in crow's feet lines
Outcomes	**Primary Outcome** • IGA Scale. Week 4.Crow's Feet Wrinkle Scale **Secondary Outcomes** • Participant's self-assessment score up to 12 12 weeks • Participant's self assessment of severity of crow's feet
Notes	ANT-1401 is a BontA From Anterios Inc. I sent an email for this company on June 23, 2018

NCT02236312

Methods	Randomised, parallel-design, double-blind, phase II trial
Participants	350 participants, older than 18 years old, both gender. **Inclusion criteria**

NCT02236312 *(Continued)*

	• Moderate to very severe glabellar lines at maximum frown as assessed by the participant and the Investigator and at least mild glabellar lines at rest **Exclusion Criteria** • Any previous treatment with any botulinum toxin • Rhytids of the glabellar region that cannot be smoothed out by manually spreading the skin apart • Any previous insertion of any permanent or semi-permanent material, hyaluronic acid or collagen fillers to the glabellar region • Any history of facial surgery above the lower orbital rim • Any planned facial surgery or aesthetic procedure during the study period, ablative skin resurfacing or chemical peels above the lower orbital rim in the previous 12 months or during the study period **Country**: USA
Interventions	**Intervention:** AbobotulinumtoxinA 30 U, 45 U, and 60 U in glabellar region **Comparator**: placebo in glabellar region
Outcomes	**Primary outcome** • Reduction of glabellar frown line severity on day 14 following treatment with botulinum toxin [Time Frame: 14 Days] [Designated as safety issue: no] **Secondary outcome** • Reduction in glabellar frown line severity is derived separately for the Investigator and the participant assessment, using a validated photo scale, at maximum frown on day 14
Notes	Other study ID number: 43QM1313 Q-med. This trial finished on June 2, 2016. We resent an email on July 25, 2019

NCT02677298

Methods	Randomised, double-blind trial to assess the efficacy and safety of BoNT/A-DP in the treatment of glabellar lines in comparison with placebo, followed by an open-label extension study, phase III
Participants	700 participants, male and female. **Inclusion Criteria** • Aged ≥ 18 years or older at time of screening • Has moderate to severe glabellar frown lines at maximum frown (severity score of 2 or 3 on FWS) as determined by in-clinic assessments by both the investigator and the participant (where: 0 = 'none', 1= 'mild', 2= 'moderate', 3 = 'severe') **Exclusion criteria** • Any medical condition that may place the subject at increased risk due to exposure to botulinum toxin, including diagnosed myasthenia gravis, Eaton Lambert syndrome, amyotrophic lateral sclerosis, profound atrophy or weakness in the target muscles, or any other condition (at the investigator's discretion) that might interfere with neuromuscular function or contraindicate botulinum toxin therapy • Previous treatment with any serotype of botulinum toxin for any indication within the 12 months prior to screening, or any planned treatment with botulinum toxin of any serotype for any reason during the trial (other than the investigational treatment) • Active skin disease/infection or irritation at the treatment area

NCT02677298 *(Continued)*

	• Pregnant, breastfeeding or planning to become pregnant during the trial
Interventions	**Intervention** BoNT/A-DP- Intramuscular injection, 20 Units divided in five 0.1 mL i.m. injections into the glabellar area **Comparator** • OnabotulinumtoxinA -Intramuscular injection, 20 units divided in five 0.1 mL i.m. injections into the glabellar area • Saline solution 0.9% -Intramuscular injection, 20 units divided in five 0.1 mL i.m. injections into the glabellar area
Outcomes	**Primary outcome** • Facial Wrinkle Scale (FWS) score 0 or 1 and an improvement ≥2 points in FWS score (at maximum frown) at the week 4 relative to baseline, based on both the investigator's and the participant's in-clinic assessment [Time Frame: week 4 relative to baseline] **Secondary outcomes** • Percentage of responders at maximum frown at week 12 [Time Frame: week 12] • Percentage of responders at week 16 [Time Frame: week 16] • Proportion of participants with a ≥ 1-point reduction in FWS score at rest at week 4, based separately on the investigators' and the subjects' in-clinic assessments [Time Frame: week 4] • Percentage of responders at week 20 or later [Time Frame: week 20] • Frequency, severity and causal relationship of AEs, SAEs and AESIs [Time Frame: through study completion (60 weeks)]
Notes	Sponsor Croma-Pharma GmbH

NCT02677805

Methods	Randomised, double-blind, parallel design, placebo-controlled, phase 3 trial
Participants	200 participants, both genders **Inclusion criteria** • Aged ≥ 18 years or older at time of screening • Has moderate to severe glabellar frown lines at maximum frown (severity score of 2 or 3 on FWS) as determined by in-clinic assessments by both the investigator and the participant (where: 0= 'none', 1 = 'mild', 2 = 'moderate', 3 = 'severe') E**xclusion criteria** • Any medical condition that may place the subject at increased risk due to exposure to botulinum toxin, including diagnosed myasthenia gravis, Eaton-Lambert syndrome, amyotrophic lateral sclerosis, profound atrophy or weakness in the target muscles, or any other condition (at the investigator's discretion) that might interfere with neuromuscular function or contraindicate botulinum toxin therapy • Previous treatment with any serotype of botulinum toxin for any indication within the 12 months prior to screening, or any planned treatment with botulinum toxin of any serotype for any reason during the trial (other than the investigational treatment) • Active skin disease/infection or irritation at the treatment area • Pregnant, breastfeeding or planning to become pregnant during the trial

NCT02677805 *(Continued)*

Interventions	**Intervention** Botulinum toxin A will be administered in double-blind fashion in cycle 1. 20 units will be administered (divided in five 0.1 mL i.m. injections) into glabellar area **Comparator** Placebo will be administered in double-blind fashion in cycle 1 divided in five 0.1 mL injections into the glabellar area
Outcomes	**Primary outcome** • Facial Wrinkle Scale (FWS) score of 0 or 1 and an improvement of ≥ 2 points in FWS score (at maximum frown) at week-4 visit relative to baseline, based on both the investigators' and the participants' in-clinic assessments. [Time Frame: week 4 relative to baseline] **Secondary outcomes** • Percentage of responders at maximum frown at week 12 [Time Frame: week 12] • Percentage of responders at week 16 [Time Frame: week 16] • The proportion of participants with a ≥ 1-point reduction in FWS score at rest at week 4 based separately on the investigators' and the participants' in-clinic assessments [Time Frame: week 4] • Percentage of responders at week 20 or later [Time Frame: week 20] • Frequency, severity and causal relationship of AEs, SAes and AESIs [Time Frame: trough study completion (60 weeks)] **Country**: no information
Notes	Sponsor Croma-Pharma GmbH Other study id CPH-302-201030

NCT02882893

Methods	Randomised, active controlled, double-blind, multi-centre, phase II/III trial
Participants	238 participants **Inclusion criteria** • Male or female of at least 18 to 75 years old • Bilaterally symmetrical moderate-to-severe CFL at maximum smile on the FWS as rated by the investigator **Exclusion criteria**: no criteria **Country**: Republic of Korea
Interventions	**Intervention** • DWP450 intramuscular injection in crow's feet lines **Comparator** • OnabotulinumtoxinA intramuscular injection in crow's feet lines
Outcomes	**Primary outcome**

NCT02882893 *(Continued)*

	• Facial Wrinkle Scale(FWS) severity of Crow's feet lines (CFL) at maximum smile as assessed by investigators [Time Frame: At 4 weeks] **Secondary outcome:** no secondary outcome
Notes	Sponsor Daewoong

NCT02961673

Methods	Randomised, double-blind (participants and investigator), active-control, phase I/II trial A phase I/Ⅱ clinical trial to compare the safety and efficacy of HU-014 versus Botox® in subject with moderate to severe glabellar lines
Participants	57 participants, older than 19 years old, both gender **Inclusion Criteria** • Facial Wrinkle Scale (FWS) score > 2 when participant knits brow extremely **Exclusion Criteria** • Volunteer who has history of any diseases following (myasthenia gravis, Eaton-Lambert syndrome, amyotrophic lateral sclerosis etc.) • From screening, participant who received plastic surgery including fascioplasty, prosthesis implantation within 6 weeks • Participant who has skin disorder including infection and scar on injection site • Participant who takes a medication including skeletal muscle relaxants, aminoglycoside, lincomycin, anticholinergic drug, benzodiazepine, benzamide etc. • Participant who takes a medication including anticoagulant, antithrombotic drug except low-dose aspirin (below 325 mg/day) • Any condition that, in the view of the investigator, would interfere with study participation
Interventions	**Intervention** • Iintramuscular injection of HU-014 in the glabellar region, 5 glabellar points each 4 U/0.1 mL (Total 20 U/0. 5mL **Comparator**: • Intramuscular injection of onabotulinumtoxinA in the glabellar region, 5 glabellar points each 4 U/0.1 mL Total 20 U/0.5 mL
Outcomes	**Primary outcomes** • Assessment of Treatment-Emergent Adverse events (TEAs), Adverse Drug Reactions (ADRs) and Serious Adverse Events (SAEs) after injecting Investigational Product (Phase 1) [TimeFrame: Week 4] • Change from baseline of glabellar lines improvement rate(frown) [Time Frame: Week 4] **Secondary outcomes** • Assessment of Columbia Suicide Severity Rating Scale(C-SSRS) [Time Frame: Week 4, Week 8, Week 12] • Change from baseline of glabellar lines improvement rate (frown) [Time Frame: Week 8, Week 12] • Change from baseline of glabellar lines improvement rate (not frown) [Time Frame: Week4, Week 8, Week 12] • Efficacy outcome measure (Phase 2) by collecting Subject Satisfaction assessment [Time Frame: Week 4, Week 8, Week 12]

NCT02961673 *(Continued)*

	• Assessment of TEAs (Treatment-Emergent Adverse events), ADRs (Adverse Drug Reactions) and SAEs (Serious Adverse Events) after injecting Investigational product [Time Frame: Week 4, Week 8, Week 12]
Notes	Sponsor Huons Co., Ltd. This trial finished on April 2018

NCT03317574

Methods	Randomised, double-blind, active drug-controlled, multicentre phase Ⅰ/Ⅲ trial
Participants	250 participants **Inclusion criteria** • Male or female of at least 20 to 65 years old • Bilaterally symmetrical moderate-to-severe CFL at maximum smile on the FWS as rated by the investigator **Exclusion criteria** • Diagnosis of myasthenia gravis, Eaton-Lambert syndrome, amyotrophic lateral sclerosis • Patients with allergy or hypersensitivity to the investigational drugs or their components • Patients who have bleeding tendency or taking anti-coagulant • Female participants who are pregnant or lactating. Female participants of childbearing age who plan to get pregnant during the study period, or do not use available contraceptive methods (women of childbearing age should have negative urine pregnancy test results at baseline visit (0 weeks) prior to the first injection.) • Patients who are participating in other clinical trials or have participated in other clinical trials 30 days before screening; • Patients who are unable to communicate or follow the instructions • Patients who are not eligible for this study based on the judgment of an investigator **Country**: Republic of Korea
Interventions	**Intervention** • Meditox 24 units botulinum toxin Type A (MEDITOXIN) injected into bilateral Crow's feet line areas **Comparator** • OnabotulinumtoxinA 24 units injected into bilateral Crow's feet Line areas
Outcomes	**Primary outcome** • Percentage of participants achieving none or mild on the investigator's assessment of the severity of Crow's feet lines (CFL) at maximum smile using the Facial Wrinkle Scale(FWS) [Time Frame: 4 weeks] **Secondary outcomes:** none.
Notes	Sponsor Medy-tox Other study id MT01-KR17CFL903 This trial finished on March 27, 2019

NCT03440671

Methods	Randomised, multicentre, active control, double-blind. phase III trial
Participants	260 participant, older than 18 years old, both gender **Inclusion Criteria** • Facial Wrinkle Scale (FWS) score > 2 when participant knits brow extremely **Exclusion Criteria** • Volunteer who has history of any diseases following. (myasthenia gravis, Eaton-Lambert syndrome, amyotrophic lateral sclerosis etc.) • From screening, participant who received a plastic surgery including fascioplasty, prosthesis implantation within 6 weeks • Participant who takes medication including skeletal muscle relaxants, aminoglycoside, lincomycin, anticholinergic drug, benzodiazepine, benzamide etc • Participant who takes medication including anticoagulant, antithrombotic drug except low-dose aspirin (below 325 mg/day) • Any condition that, in the view of the investigator, would interfere with study participation **Country**: Republic of Korea
Interventions	**Intervention** • Hutox was given as an injection to 5 glabellar lines each 4 U/0.1 mL (Total 20 U/0.5 mL, I.M.) **Comparator** • OnabotulinumtoxinA injection was given an injection to 5 glabellar lines each 4 U/0.1 mL (Total 20 U/0.5 mL, I.M.)
Outcomes	**Primary outcome** • FWS(Facial Wrinkle Severity) Improvement at glabellar line [Time Frame: 4 Week] Change from baseline of glabellar lines improvement rate(frown)
Notes	Sponsor Huons Co., Ltd.

NCT03721016

Methods	Randomised, multicentre, double-blind, placebo-controlled, parallel-group study to evaluate thesSafety and efficacy of MT10109L (NivobotulinumtoxinA) for the treatment of glabellar lines With or without concurrent treatment of lateral Canthal lines, phase III trial
Participants	375participants, older than 18 years old, both genders **Inclusion Criteria** • Female participants must not be pregnant or planning to get pregnant and willing to minimise the risk of inducing pregnancy for the duration of the clinical study and follow-up period **Exclusion Criteria** • Known immunisation or hypersensitivity to any botulinum toxin serotype

NCT03721016 *(Continued)*

- Any medical condition that may put the participant at increased risk with exposure to MT10109L including diagnosed myasthenia gravis, Eaton-Lambert syndrome, amyotrophic lateral sclerosis, or any other condition that might interfere with neuromuscular function
- History of facial nerve palsy
- Any uncontrolled systemic disease
- Anticipated need for treatment with botulinum toxin of any serotype for any reason during the study (other than study intervention)
- Anticipated need for surgery or overnight hospitalisation during the study
- Prior exposure to botulinum toxin of any serotype for any reason
- Prior periorbital surgery, facial lift (full face or mid-face), thread lift, brow lift, or related procedures (eg, eyelid [blepharoplasty] and/or eyebrow surgery)
- Prior facial treatment with permanent soft tissue fillers, synthetic implantation (eg, Gore-Tex®), and/or autologous fat transplantation
- Current enrolment in an investigational drug or device study or participation in such a study within 30 days of entry into this study
- Females who are pregnant, nursing, or planning a pregnancy during the study
- Participants who plan for an extended absence away from the immediate area of the study site that would preclude them from returning for all protocol-specified study visits

Countries: USA and Canada

Interventions	**Intervention** • MT10109L- Dose 1 will be injected into the GL and placebo into the LCL: initial double-blind treatment ondDay 1, and up to 2 additional blinded treatments during the retreatment period **Comparator** • Saline solution 0.9% -Dose 1 will be injected into the GL and Placebo into the LCL: initial double-blind treatment on day 1, and up to 2 additional blinded treatments during the retreatment period.
Outcomes	**Primary outcome** • The proportion of participants with a ≥ 2-grade improvement from baseline on the Facial Wrinkle Scale With Photo numeric Guide (FWS) according to investigator and participant assessments of GL severity at maximum frown at Day 30 [Time Frame: Day 30] **Secondary outcomes** • The duration of GL treatment in participants who achieved a rating of ≥ 2-grade improvement from baseline in GL severity at maximum frown at day 30 according to investigator assessments using the FWS [Time Frame: day 1 (first treatment) to day 180] • The proportion of responders for investigator assessments of GL severity at maximum frown using the FWS [Time Frame: day 30] • The proportion of participants reporting mostly satisfied/very satisfied on the Facial Line Satisfaction Questionnaire (FLSQ) follow-up version Item 5 for GL [Time Frame: day 60] • The proportion of responders for investigator assessments of GL severity at rest using the FWS [Time Frame: day 30] • Number of patients who experienced an adverse event [Time Frame: From consent (screening visit) up to day 420] • Mean change from baseline in vital signs [Time Frame: baseline to day 360] mean change from baseline in Electrocardiogram (ECG) parameters [Time Frame: baseline to day 360] • Mean change from baseline in lab parameters [Time Frame: screening to day 120] • Number of participants with binding and neutralising antibodies [Time Frame: day 360] • Adverse events

NCT03721016 *(Continued)*

Notes	Sponsor Allergan

NCT03736928

Methods	Randomised, dose-ranging, double-blind, placebo-controlled, multicentre Study, phase II trial
Participants	401 participants, age ranging from 18 to 65 years old, both genders. **Inclusion criteria** • Moderate to severe glabellar lines at maximum frown as assessed by the Investigator using a 4-point photographic scale (0 = none, 3 = severe) • Moderate to severe glabellar lines at maximum frown as assessed by the participant using a static 4-point categorical scale (0 = none, 3 = severe) **Exclusion Criteria** • Botulinum toxin treatment in the face within 9 months prior to study treatment **Country** : USA
Interventions	**Intervention** • AbobotulinumtoxinA 50 U and 75 U intramuscular injection in glabellar lines **Comparator** • Placebo intramuscular injection in glabellar lines
Outcomes	**Primary outcome** • To determine composite responder rate at month 1 for a single dose of abobotulinumtoxinA compared to placebo [Time Frame: month 1 after treatment]
Notes	Sponsor Q-Med AB Other study id 43USD1801

NCT03806933

Methods	Randomised, double-blind, multicentre study to investigate the safety and duration of effect of different NT 201 Dose groups following the treatment of glabellar frown lines, phase II trial
Participants	240 participants, older than 18 years old, both genders. **Inclusion criteria** • Moderate (score = 2) to severe (score =3) GFL at maximum frown as assessed by investigator on the 4-point FWS • Moderate (score = 2) to severe (score =3) GFL at maximum frown as assessed byparticipant on the 4-point FWS **Exclusion criteria** • Previous treatment with Botulinum neurotoxin (BoNT) of any serotype in the facial area within the last 12 months before injection

NCT03806933 *(Continued)*

- Previous treatment with any facial cosmetic procedure (e.g. chemical peeling, photo rejuvenation, mesotherapy, photodynamic therapy, laser treatment tattooing of eyebrows) in the glabellar area within the last 12 months before injection
- Previous treatment with any biodegradable filler in the glabellar area within the last 12 months before injection
- Inability to substantially reduce GFL by physically spreading them apart as assessed by the investigator
- Excessively thick sebaceous skin or hypertrophic muscles in the upper third part of the face
- Any surgery or scars in the glabellar area
- Marked facial asymmetry
- Eyelid ptosis
- Marked brow ptosis and/or dermatochalasis
- Ongoing severe or unstable medical conditions, e.g., systemic infection, or pulmonary disease, at the discretion of the investigator

Countries: USA and Germany

Interventions	Intervention -dose-rangingIncobotulinumtoxinA, intramuscular injection into the glabellar area Open-label extension
Outcomes	**Primary outcome** • Duration of effect as defined by time between treatment and relapse to baseline status [Time Frame: From time of treatment to up to 360 days] **Secondary outcomes** • Duration of effect whereby effect is defined by a score of none (0) or mild (1) at maximum frown as assessed by the investigator according to FWS [Time Frame: From time of treatment to up to 360 days] • Duration of effect whereby effect is defined as 2-point improvement from baseline at maximum frown as assessed by the investigator according to FWS [Time Frame: From time of treatment to up to 360 days] • Percentage of subjects rated as none (0) or mild (1) at maximum frown by investigator's rating on FWS at Day 180 [Time Frame: Day 180] • Percentage of subjects rated as none (0) or mild (1) at maximum frown by subject's rating on FWS at Day 180 [Time Frame: Day 180] • Percentage of subjects rated as at least 1-point improvement compared to baseline at maximum frown by investigator's rating on FWS at Day 180 [Time Frame: Day 180] • Percentage of subjects rated as at least 1-point improvement compared to baseline at maximum frown by subject's rating on FWS Subject at Day 180 [Time Frame: Day 180]
Notes	Supported by Merz Pharmaceuticals GmbH

NCT03837561

Methods	Randomised, double-blind, active-controlled, multicentre, phase III trial
Participants	136 participants **Inclusion criteria** • Men and women aged between 18 and 65 • Participants attaining ≥ grade 2 (moderate) in the investigator's rating of the severity of glabellar lines at maximum forced frown

NCT03837561 *(Continued)*

	• Participants who voluntarily sign the informed consent **Exclusion Criteria** • Participants with allergy or hypersensitivity to the investigational drugs or their components • Participants who are participating in other clinical trials or have participated in clinical trials 30 days before screening • Participants who are not eligible for this study at the discretion of the investigator **Country**: Russia
Interventions	**Intervention** • Cunox inject 4 Units (0.1 mL) of reconstituted investigational product or the comparator intramuscularly into each of 5 sites, 2 in each corrugator muscle and 1 in the procerus muscle for a total dose of 20 Units **Comparator** • OnabotulinumtoxinA injection 4 Units (0.1 mL) of reconstituted investigational product or the comparator intramuscularly into each of 5 sites, 2 in each corrugator muscle and 1 in the procerus muscle for a total dose of 20 units.
Outcomes	**Primary outcome** • Glabellar line improvement rate at maximum frown confirmed with investigator's live assessment of glabellar line severity [Time Frame: at 4 weeks after the injection] **Secondary outcome**: no secondary outcome
Notes	Sponsor Medy-tox Other study id MT01-RU18GBL301

NCT03970876

Methods	Phase I clinical trial, participants with moderate to severe glabellar lines at maximum frown are enrolled and safety is assessed after 12 weeks of administration of 20 U of ATGC-100. In phase II clinical trial, participants with moderate to severe glabellar lines at maximum frown are enrolled, and efficacy and safety are assessed by comparing with Botox (Allergan). Phase II- randomised, double-blind, active-controlled, multicentre trial
Participants	60 participants. **Inclusion Criteria** • Healthy males and females aged between 19 and 65 years old • Participants attaining ≥ grade 2 in the investigator's rating of the severity of glabellar line at maximum frown • Participants who voluntarily signed the informed consent **Exclusion Criteria** • Participants with general neuromuscular synaptic disorders • Presence or history of eyelid and/or ptosis • Participants with noticeable facial asymmetry • Inability to substantially lessen glabellar frown lines even by physically spreading apart

NCT03970876 *(Continued)*

	• Participants who have administered the following drugs within 4 weeks prior to screening: muscle relaxants, Anti-cholinergic agents, benzodiazepine and similar drugs, Benzamide drugs, Tetracycline antibiotics, Lincomycin antibiotics, Aminoglycoside antibiotics • Participants who are taking anticoagulants and antiplatelet agents • Participants who have taken aspirin and NSAIDs within 7 days prior to administration of investigational drug • Participants with skin disorders at the injection site • Participants with previous treatment of Face Lifting, Permanent Implant, and/or Filler in glabellar region • Participants with prior filler treatments which would have interfered with the evaluation of the efficacy of the study treatment • Any other planned facial aesthetic procedure in the glabellar area during the trial period • Previous treatment with botulinum toxin in the forehead within the last 5 months or any planned treatment during the study period • A history of drug or alcohol abuse • Condition including anxiety disorder, or any other significant psychiatric disorder (e.g. depression), in the investigator's opinion
Interventions	**Intervention** • ATGC-100 will be injected to 5 glabellar lines (Each 4 U/0.1mL, Total 20 U/0.5 mL) **Comparator** • OnabotulinumtoxinA will be injected to 5 glabellar lines (Each 4 U/0.1 mL, Total 20 U/0.5 mL)
Outcomes	P**rimary outcomes** • Number of participants with treatment-related adverse events as assessed by CTCAE Version 5.0 (Phase I) [Time Frame: Up tp 12 weeks] • Glabellar line improvement rate at maximum frown confirmed with investigator's assessment (Phase II) [Time Frame: 4 weeks after the injection] S**econdary outcomes** • Glabellar line improvement rate at maximum frown confirmed with investigator's assessment (Phase II) [Time Frame: 8, 12 weeks after the injection] • Glabellar line improvement rate at rest confirmed with investigator's assessment (Phase II) [Time Frame: 4, 8, 12 weeks after the injectio] • Glabellar line improvement rate at rest confirmed with subject's assessment (Phase II) [Time Frame: 4, 8, 12 weeks after the injection] • Number of participants with treatment-related adverse events as assessed by CTCAE Version 5.0 (Phase II) [Time Frame: Up tp 12 weeks] • Adverse events **Country**: Republic of Korea
Notes	EuBiologics Co.,Ltd

NCT03985982

Methods	Randomised, double-blind, placebo-controlled trial
Participants	353 participants **Inclusion criteria**

NCT03985982 *(Continued)*

	• Ages ≥ 18 years or older at time of screening • Has moderate to severe glabellar frown lines at maximum frown (severity score of 2 or 3 on FWS) as determined by in-clinic assessments by both the investigator and the participant (where: 0 = ´none´, 1= ´mild´, 2= ´moderate´, 3= ´severe´). **Exclusion criteria** • Any medical condition that may place the subject at increased risk due to exposure to botulinum toxin, including diagnosed myasthenia gravis, Eaton-Lambert syndrome, amyotrophic lateral sclerosis, profound atrophy or weakness in the target muscles, or any other condition (at the investigator's discretion) that might interfere with neuromuscular function or contraindicate botulinum toxin therapy • Previous treatment with any serotype of botulinum toxin for any indication within the 12 months prior to screening, or any planned treatment with botulinum toxin of any serotype for any reason during the trail (other than the investigational treatment) • Active skin disease/infection or irritation at the treatment area • Pregnant, breastfeeding or planning to become pregnant during the trial **Country:** USA
Interventions	**Intervention** • OnabotulinumtoxinA -injection, 20 U, divided in five 0.1 mL i.m injections into the glabellar area **Comparator** • Placebo -divided in five 0.1 mL I.M.injections into the glabellar area
Outcomes	**Primary outcome** • Facial Wrinkle Scale (FWS) score of 0 or 1 and an improvement of ≥ 2 points in FWS score (at maximum frown) at wee= 4 visit relative to baseline, based on both the investigators´and the participants' in-clinic assessments. [Time Frame: week 4 relative to baseline] **Secondary outcomes** • Percentage of responders at maximum frown at week 12 [Time Frame: week 12] • Percentage of responders at week 16 [Time Frame: week 16] • The proportion of participants with a ≥ 1 point reduction in FWS score at rest at week 4 based separately on the investigators´and the participants' in-clinic assessments [Time Frame: week 4] • Percentage of responders at week 20 or up to week 48 [Time Frame: week 20] • Frequency, severity and causal relationship of AEs, SAes and AESIs [Time Frame: through study completion [60 weeks]
Notes	Croma-Pharma GmbH

NCT04081402

Methods	Randomised, quadruple-blind, active control, parallel arm, phase I/III trial
Participants	290 participants **Inclusion Criteria** • Bilaterally symmetrical moderate-to-severe CFL at maximum smile on the FWS as rated by the investigator **Exclusion Criteria**

NCT04081402 *(Continued)*

	• Volunteer who has history of any diseases following. (myasthenia gravis, Eaton-Lambert syndrome, amyotrophic lateral sclerosis etc.) • From screening, participants who get plasticsSurgery within 48 weeks • Participant who has skin disorder including infection and scar on injection site • Participant who takes a medication including skeletal muscle relaxants, Aminoglycoside, lincomycin, anticholinergic drug, benzodiazepine, benzamide etc. • Participant who takes a medication including anticoagulant, antithrombotic drug except low dose aspirin (below 325 mg/day) • Any condition that, in the view of the investigator, would interfere with study participation **Country** Republic of Korea
Interventions	**Intervention** • HU-014 **Comparator** • OnabotulinumtoxinA
Outcomes	**Primary outcome** • Change from baseline of Crow's feet Lines improvement rate [Time Frame: Week 4] **Secondary outcome** No information
Notes	Huons Co., Ltd.

NCT04143815

Methods	Randomised, double-blind, placebo-controlled, multicentre, dose-ranging and open-lLabel extension study
Participants	200 participants **Inclusion criteria** • Male or female over 18 years of age • Bilaterally symmetrical moderate to severe GL at maximum frown as assessed by both investigator and subject using FWS **Exclusion Criteria** • History of facial nerve paralysis • Any eyebrow or eyelid ptosis as determined by the investigator **Country** Australia
Interventions	**Intervention** • MBA-P01 -Intramuscular injection, 10 U, 20 U, 30 U **Comparator** • Placebo -intramuscular injection
Outcomes	**Primary outcome**

NCT04143815 *(Continued)*

	• Facial Wrinkle Scale(FWS) improvement [Time Frame: 4 weeks] **Secondary outcome** No information
Notes	Medy-Tox

NCT04247074

Methods	Randomised, double-blind, placebo-controlled, multicentre trial
Participants	350 participants **Inclusion Criteria** • Male or female 18 years of age or older • Moderate to severe LCL at maximum smile as assessed by the Investigator • Moderate to severe LCL at maximum smile as assessed by the participant • Moderate to severe GL at maximum frown as assessed by the Investigator • Moderate to severe GL at maximum frown as assessed by the participant **Exclusion Criteria** • Previous use of any Botulinum toxin in facial areas within 9 months prior to study treatment • Female who is pregnant, breastfeeding, or intends to conceive a child during the study • Known allergy or hypersensitivity to any component of the investigational product (QM1114-DP) **Country-** USA
Interventions	**Intervention** • QM1114-DP- intramuscular injection into either the LCL, GL, or both the LCL and GL **Comparator** • Placebo- intramuscular injection into either the LCL, GL, or both the LCL and GL
Outcomes	**Primary outcome** • Percentage of participants with a ≥ 2-grade improvement from baseline on the Glabellar Lines Investigator and participant's assessments at maximum frown at one month [Time Frame: Month 1] **Secondary outcomes** • Percentage of participants with a 0 or 1 on the Glabellar Lines Investigator scale at maximum frown [Time Frame: Baseline through Month 6] • Percentage of s participants who achieve grade 0 or 1 in Lateral Canthal Line Investigator scale at maximum smile. [Time Frame: Baseline through Month 6] • Number of participants who experienced an adverse event [Time Frame: Baseline through Month 6] • Mean change from baseline in vital signs [Time Frame: Baseline through Month 6] • Number of participants with abnormal post-baseline QTcF and QTcB intervals [Frame: Baseline through Month 6] • Number of participants with binding neutralising antibodies [Time Frame: Baseline through Month 6]

NCT04247074 *(Continued)*

Notes	Q-Med AB

NCT04249583

Methods	Randomised, double-blind, placebo-controlled, multicentre trial
Participants	300 participants **Inclusion criteria** • Male or female 18 years of age or older • Moderate to severe GL at maximum frown as assessed by the Investigator • Moderate to severe GL at maximum frown as assessed by the participant **Exclusion Criteria** • Previous use of any Botulinum toxin in facial areas within 9 months prior to study treatment • Female who is pregnant, breastfeeding, or intends to conceive a child during the study • Known allergy or hypersensitivity to any component of the investigational product (QM1114-DP) or any botulinum toxin serotype **Country** USA
Interventions	**Intervention** • QM1114-DP- intramuscular injection into glabellar lines **Comparator** • Placebo- intramuscular injection into glabella lines
Outcomes	**Primary outcome** • Percentage of participants with a ≥ 2-grade improvement from baseline on the Glabellar Lines Investigator and participant assessments at maximum frown at one month. [Time Frame: One Month] **Secondary outcome** • Percentage of participants with a 0 or 1 on the Glabellar Lines Investigator scale at maximum frown [Frame: Baseline through Month 6] • Number of participants who experienced an adverse event [Time Frame: Baseline through Month 6] • Number of participants with abnormal post-baseline QTcF and QTcB intervals [Time Frame: Baseline through Month 6] • Number of participants with binding neutralising antibodies [Time Frame: Baseline through Month 6]
Notes	Q-Med AB

NCT04281095

Methods	Randomised, double-blind, active-controlled, single-centre clinical trial
Participants	60 participants

NCT04281095 *(Continued)*

Inclusion criteria

- Male and female participants aged between 19 and 65 years
- Participants assigned a glabellar line severity grade of 2 or greater (moderate) at maximum frown assessed by the Investigator
- Participants who provide written consent to voluntarily participate in the study after receiving and understanding a detailed explanation of the study

Exclusion criteria

- Participants with diseases that may affect neuromuscular function, such as Myasthenia gravis, Lambert-Eaton syndrome, Amyotrophic lateral sclerosis, or motor neuropathy
- Participants with the history of eyelid paralysis or ptosis
- Participants with significant facial asymmetryIndividuals whose glabellar lines cannot be satisfactorily improved with physical methods since lines are not flattened even using hands
- Participants who have received medication that inhibits neuromuscular function within the 4 weeks prior to screening such as muscle relaxants, anticholinergics, benzodiazepines and similar drugs, benzamide, tetracycline antibiotics, lincomycin antibiotics, and aminoglycoside antibiotics
- Participants taking anticoagulants or antiplatelet agents (use of low-dose aspirin (325 mg/day or less) to prevent blood clotting is allowed)
- Participants who have received aspirin or NSAIDs within 7 days prior to administration of the IP
- Participants with skin abnormalities such as infection at the injection site, dermatopathy, or scars
- Participants with the history of treatment of the glabellar region (including the forehead) such as face lifting, permanent implants, or fillers
- Participants who have received other procedures that may affect the assessment of the glabellar or forehead lines during the following periods:-within 6 months of screening: facial plastic surgery such as tissue augmentation, brow lift, or dermal resurfacing; within 6 months of screening: injection of dermal fillers with hyaluronic acid as the main ingredient; within 12 months of screening: injection of dermal fillers with ingredients other than hyaluronic acid as the main ingredient
- Individuals planning a facial cosmetic procedure (skin fillers, photo rejuvenation, chemical/mechanical peeling, etc.) during the study period
- Individuals who have received a botulinum toxin preparation within 5 months prior to screening or those who are expected to receive a botulinum toxin preparation for any other purpose than the indication of this study (glabellar lines)
- Participants with the history of excessive alcohol consumption or drug addictionIndividuals with an anxiety disorder or other significant psychiatric disorders (e.g. depression), which, in the Investigator's opinion, may affect study participation or objective assessment of efficacy outcomesIndividuals who answered yes to any of the questions on the Columbia University Suicide Severity Rating Scale (C-SSRS) regarding a case within the past 12 months at the screening
- Female participants of childbearing age who do not agree to practice contraception using medically allowed contraceptive methods during the study period (hormonal contraception, IUD (intrauterine device) or IUS (intrauterine system), tubal ligation, dual protection (using a combination of male condom, female condom, cervical cap, contraceptive diaphragm, or contraceptive sponge)
- Pregnant or lactating women
- Participants who are allergic or sensitive to the IP or its components
- Individuals with concomitant illnesses that make them unsuitable for participation in the study by the Investigator such as malignant tumours, immunodeficiency (immune deficiency), kidney disease, liver disease, or lung disease
- Individuals who have participated in other clinical trials within 3 months prior to participating in this study and have received an IP or medical device during the previous clinical studies
- Individuals who are not eligible for this study for any reason as per the Investigator's discretion-Country

Country Republic of Korea

Interventions	**Intervention**

NCT04281095 *(Continued)*	• ATGC-110 -20U, intramuscular injection, glabella lines **Comparator** • OnabotulinumtoxinA -20 U, intramuscular injection, glabella lines
Outcomes	**Primary outcome** • Glabellar line improvement rate at maximum frown confirmed with investigator's live assessment [Time Frame: 0 and 4 weeks after the administration] **Secondary outcomes** • Glabellar line improvement rate at maximum frown confirmed by investigator's live assessment [Time Frame: 0, 8, 12 weeks after the administration] • Glabellar line improvement rate at rest confirmed by investigator's live assessment [Time Frame: 0, 4, 8, 12 weeks after the administration] • Glabellar line improvement rate at rest confirmed by subject's assessment [Time Frame: 0, 4, 8, 12 weeks after the administration] • Subject satisfaction rate [Time Frame: 0, 4, 8, 12 weeks after the administration] • Adverse events
Notes	ATGC Co., Ltd.

AEs: adverse events; CFL: Crow's feet lines; **FWS:** facial wrinkle scale;**IGA:** Investigator's Global Assessment;**I.M.:** intramuscular; **NSAIDs:** non-steroidal anti-inflammatory drugs; **PP:** per protocol;**SAEs:** serious adverse events; **IC:** informed consent; **U:** unit.

DATA AND ANALYSES

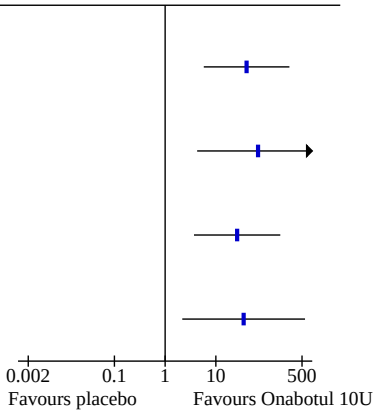
Comparison 1. OnabotulinumtoxinA 10units versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Participant assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1.1 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1.2 8 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1.3 12 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1.4 16 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.2 Physician assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.2.1 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.2.2 8 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.2.3 12 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2.4 16 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.3 Total adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

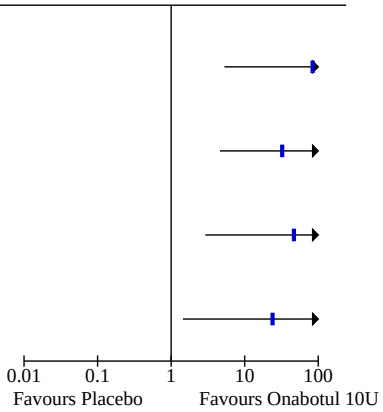
Analysis 1.1. Comparison 1: OnabotulinumtoxinA 10units versus placebo, Outcome 1: Participant assessment of success by analysing scores and scales

Study or Subgroup	OnabotulinumtoxinA 10U Events	Total	placebo Events	Total	Risk Ratio M-H, Random, 95% CI
1.1.1 4 weeks					
Harii 2008	37	44	1	48	40.36 [5.78 , 281.92]
1.1.2 8 weeks					
Harii 2008	30	43	0	48	67.93 [4.28 , 1078.29]
1.1.3 12 weeks					
Harii 2008	23	42	1	48	26.29 [3.71 , 186.39]
1.1.4 16 weeks					
Harii 2008	15	42	0	48	35.33 [2.18 , 572.97]

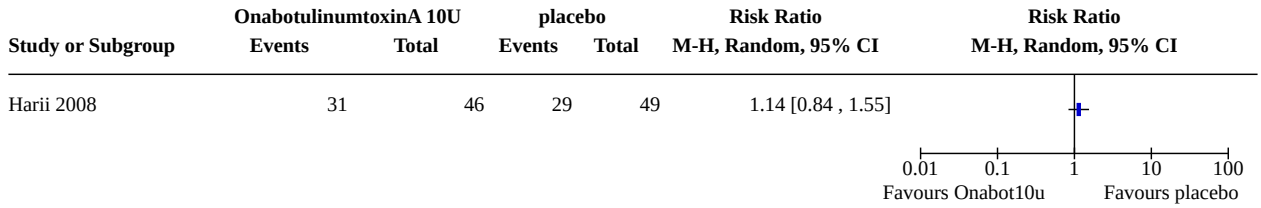


Analysis 1.2. Comparison 1: OnabotulinumtoxinA 10units versus placebo, Outcome 2: Physician assessment of success by analysing scores and scales

Study or Subgroup	OnabotulinumtoxinA 10U Events	Total	placebo Events	Total	Risk Ratio M-H, Random, 95% CI
1.2.1 4 weeks					
Harii 2008	38	44	0	48	83.84 [5.31 , 1325.05]
1.2.2 8 weeks					
Harii 2008	29	43	1	48	32.37 [4.60 , 227.65]
1.2.3 12 weeks					
Harii 2008	20	42	0	48	46.72 [2.91 , 749.60]
1.2.4 16 weeks					
Harii 2008	10	42	0	48	23.93 [1.44 , 396.41]



Analysis 1.3. Comparison 1: OnabotulinumtoxinA 10units versus placebo, Outcome 3: Total adverse events

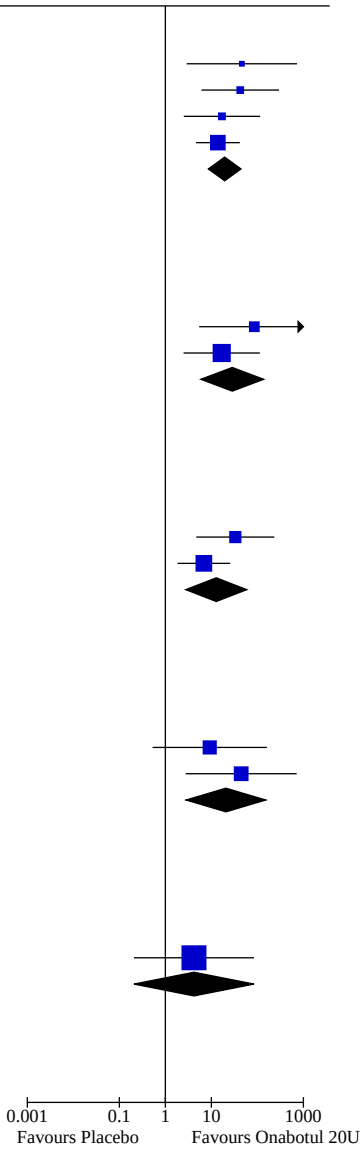


Comparison 2. OnabotulinumtoxinA 20 units versus placebo one cycle of treatment in glabellar lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Participant assessment of success by analysing scores and scales	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1.1 4 weeks	4	575	Risk Ratio (M-H, Random, 95% CI)	19.45 [8.60, 43.99]
2.1.2 8 weeks	2	204	Risk Ratio (M-H, Random, 95% CI)	28.45 [5.92, 136.74]
2.1.3 12 weeks	2	203	Risk Ratio (M-H, Random, 95% CI)	12.77 [2.78, 58.72]
2.1.4 16 weeks	2	167	Risk Ratio (M-H, Random, 95% CI)	20.71 [2.82, 151.91]
2.1.5 24 weeks	1	77	Risk Ratio (M-H, Random, 95% CI)	4.19 [0.21, 84.41]
2.2 Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)	8	1390	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.62 [1.50, 8.74]
2.3 Physician assessment of success by analysing scores and scales	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.3.1 4 weeks	7	1339	Risk Ratio (M-H, Random, 95% CI)	17.10 [10.07, 29.05]
2.3.2 8 weeks	6	1046	Risk Ratio (M-H, Random, 95% CI)	21.50 [9.68, 47.75]
2.3.3 12 weeks	6	1046	Risk Ratio (M-H, Random, 95% CI)	10.81 [5.79, 20.16]
2.3.4 16 weeks	5	933	Risk Ratio (M-H, Random, 95% CI)	15.13 [5.98, 38.27]
2.3.5 20 weeks	1	77	Risk Ratio (M-H, Random, 95% CI)	5.86 [0.31, 109.74]
2.3.6 24 weeks	1	77	Risk Ratio (M-H, Random, 95% CI)	4.19 [0.21, 84.41]
2.4 Total adverse events	8	1388	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.89, 1.45]
2.5 Duration of treatment (weeks)	1	77	Mean Difference (IV, Random, 95% CI)	18.40 [16.17, 20.63]

Analysis 2.1. Comparison 2: OnabotulinumtoxinA 20 units versus placebo one cycle of treatment in glabellar lines, Outcome 1: Participant assessment of success by analysing scores and scales

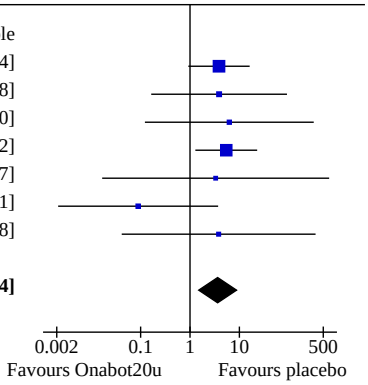
Study or Subgroup	OnabotulinumtoxinA 20U Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 4 weeks						
Carruthers 2017	27	42	0	35	8.7%	46.05 [2.91 , 728.71]
Harii 2008	38	43	1	48	17.6%	42.42 [6.08 , 295.91]
NCT02450526	84	94	1	19	18.3%	16.98 [2.52 , 114.54]
Rzany 2019	213	246	3	48	55.4%	13.85 [4.63 , 41.48]
Subtotal (95% CI)		**425**		**150**	**100.0%**	**19.45 [8.60 , 43.99]**
Total events:	362		5			
Heterogeneity: Tau² = 0.00; Chi² = 1.38, df = 3 (P = 0.71); I² = 0%						
Test for overall effect: Z = 7.13 (P < 0.00001)						
2.1.2 8 weeks						
Harii 2008	38	43	0	48	32.4%	85.75 [5.43 , 1354.69]
NCT02450526	83	94	1	19	67.6%	16.78 [2.49 , 113.19]
Subtotal (95% CI)		**137**		**67**	**100.0%**	**28.45 [5.92 , 136.74]**
Total events:	121		1			
Heterogeneity: Tau² = 0.00; Chi² = 0.93, df = 1 (P = 0.33); I² = 0%						
Test for overall effect: Z = 4.18 (P < 0.0001)						
2.1.3 12 weeks						
Harii 2008	29	42	1	48	39.4%	33.14 [4.72 , 232.95]
NCT02450526	68	94	2	19	60.6%	6.87 [1.84 , 25.65]
Subtotal (95% CI)		**136**		**67**	**100.0%**	**12.77 [2.78 , 58.72]**
Total events:	97		3			
Heterogeneity: Tau² = 0.55; Chi² = 1.76, df = 1 (P = 0.18); I² = 43%						
Test for overall effect: Z = 3.27 (P = 0.001)						
2.1.4 16 weeks						
Carruthers 2017	5	42	0	35	48.5%	9.21 [0.53 , 160.97]
Harii 2008	19	42	0	48	51.5%	44.44 [2.77 , 714.27]
Subtotal (95% CI)		**84**		**83**	**100.0%**	**20.71 [2.82 , 151.91]**
Total events:	24		0			
Heterogeneity: Tau² = 0.00; Chi² = 0.64, df = 1 (P = 0.42); I² = 0%						
Test for overall effect: Z = 2.98 (P = 0.003)						
2.1.5 24 weeks						
Carruthers 2017	2	42	0	35	100.0%	4.19 [0.21 , 84.41]
Subtotal (95% CI)		**42**		**35**	**100.0%**	**4.19 [0.21 , 84.41]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.93 (P = 0.35)						



Analysis 2.2. Comparison 2: OnabotulinumtoxinA 20 units versus placebo one cycle of treatment in glabellar lines, Outcome 2: Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

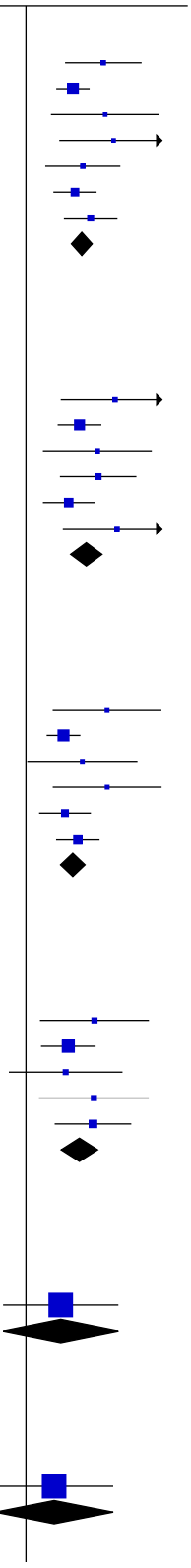
Study or Subgroup	OnabotulinumtoxinA 20U Events	Total	Placebo Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Beer 2006	0	16	0	15		Not estimable
Carruthers 2002	11	203	0	61	37.9%	3.86 [0.93 , 16.14]
Carruthers 2003b	2	202	0	71	7.7%	3.88 [0.16 , 91.98]
Carruthers 2017	1	42	0	35	5.0%	6.25 [0.12 , 320.40]
Harii 2008	7	46	1	49	37.3%	5.42 [1.28 , 22.92]
NCT02450526	1	107	0	21	2.8%	3.31 [0.02 , 657.67]
Rzany 2019	1	246	1	49	5.6%	0.09 [0.00 , 3.71]
Wu 2010	1	170	0	57	3.8%	3.80 [0.04 , 348.98]
Total (95% CI)		**1032**		**358**	**100.0%**	**3.62 [1.50 , 8.74]**
Total events:	24		2			

Heterogeneity: Chi² = 4.18, df = 6 (P = 0.65); I² = 0%
Test for overall effect: Z = 2.87 (P = 0.004)
Test for subgroup differences: Not applicable



Analysis 2.3. Comparison 2: OnabotulinumtoxinA 20 units versus placebo one cycle of treatment in glabellar lines, Outcome 3: Physician assessment of success by analysing scores and scales

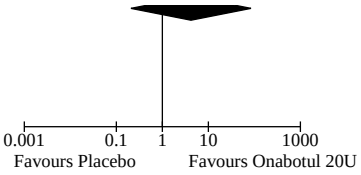
Study or Subgroup	OnabotulinumtoxinA 20U Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.3.1 4 weeks						
Carruthers 2002	170	203	1	61	7.4%	51.08 [7.31 , 357.18]
Carruthers 2003b	155	202	5	71	39.0%	10.90 [4.66 , 25.45]
Carruthers 2017	33	42	0	35	3.7%	56.09 [3.56 , 883.69]
Harii 2008	39	44	0	48	3.7%	86.02 [5.45 , 1358.84]
NCT02450526	89	94	1	19	7.7%	17.99 [2.67 , 121.28]
Rzany 2019	185	245	3	48	23.3%	12.08 [4.03 , 36.22]
Wu 2010	160	170	2	57	15.1%	26.82 [6.87 , 104.71]
Subtotal (95% CI)		**1000**		**339**	**100.0%**	**17.10 [10.07 , 29.05]**
Total events:	831		12			
Heterogeneity: Tau² = 0.00; Chi² = 5.58, df = 6 (P = 0.47); I² = 0%						
Test for overall effect: Z = 10.50 (P < 0.00001)						
2.3.2 8 weeks						
Carruthers 2002	152	203	0	61	7.7%	92.70 [5.86 , 1467.16]
Carruthers 2003b	130	202	3	71	34.8%	15.23 [5.01 , 46.32]
Carruthers 2017	22	42	0	35	7.7%	37.67 [2.37 , 599.57]
Harii 2008	36	44	1	48	14.6%	39.27 [5.62 , 274.50]
NCT02450526	87	94	2	19	27.5%	8.79 [2.37 , 32.66]
Wu 2010	151	170	0	57	7.8%	102.77 [6.50 , 1624.36]
Subtotal (95% CI)		**755**		**291**	**100.0%**	**21.50 [9.68 , 47.75]**
Total events:	578		6			
Heterogeneity: Tau² = 0.16; Chi² = 5.90, df = 5 (P = 0.32); I² = 15%						
Test for overall effect: Z = 7.53 (P < 0.00001)						
2.3.3 12 weeks						
Carruthers 2002	101	203	0	61	4.9%	61.70 [3.89 , 978.74]
Carruthers 2003b	96	202	5	71	39.4%	6.75 [2.86 , 15.91]
Carruthers 2017	10	42	0	35	4.8%	17.58 [1.07 , 289.78]
Harii 2008	28	44	0	48	4.9%	62.07 [3.90 , 987.11]
NCT02450526	72	94	2	19	19.6%	7.28 [1.95 , 27.12]
Wu 2010	125	170	3	57	26.4%	13.97 [4.63 , 42.18]
Subtotal (95% CI)		**755**		**291**	**100.0%**	**10.81 [5.79 , 20.16]**
Total events:	432		10			
Heterogeneity: Tau² = 0.07; Chi² = 5.56, df = 5 (P = 0.35); I² = 10%						
Test for overall effect: Z = 7.48 (P < 0.00001)						
2.3.4 16 weeks						
Carruthers 2002	53	203	0	61	11.2%	32.52 [2.04 , 519.07]
Carruthers 2003b	49	202	2	71	44.7%	8.61 [2.15 , 34.50]
Carruthers 2017	4	42	0	35	10.3%	7.53 [0.42 , 135.31]
Harii 2008	14	44	0	48	11.1%	31.58 [1.94 , 514.12]
Wu 2010	90	170	1	57	22.7%	30.18 [4.30 , 211.65]
Subtotal (95% CI)		**661**		**272**	**100.0%**	**15.13 [5.98 , 38.27]**
Total events:	210		3			
Heterogeneity: Tau² = 0.00; Chi² = 2.07, df = 4 (P = 0.72); I² = 0%						
Test for overall effect: Z = 5.74 (P < 0.00001)						
2.3.5 20 weeks						
Carruthers 2017	3	42	0	35	100.0%	5.86 [0.31 , 109.74]
Subtotal (95% CI)		**42**		**35**	**100.0%**	**5.86 [0.31 , 109.74]**
Total events:	3		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.18 (P = 0.24)						
2.3.6 24 weeks						
Carruthers 2017	2	42	0	35	100.0%	4.19 [0.21 , 84.41]
Subtotal (95% CI)		**42**		**35**	**100.0%**	**4.19 [0.21 , 84.41]**
Total events:	2		0			
Heterogeneity: Not applicable						



Analysis 2.3. (Continued)

Subtotal (95% CI)		42		35	100.0 %	4.19 [0.21 , 84.41]
Total events:	2		0			

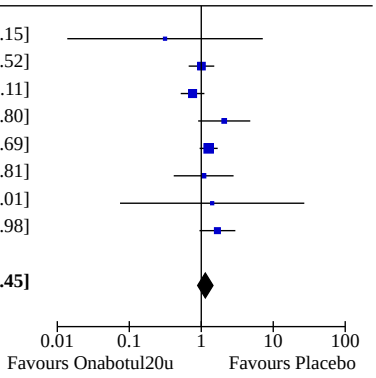
Heterogeneity: Not applicable
Test for overall effect: Z = 0.93 (P = 0.35)



Analysis 2.4. Comparison 2: OnabotulinumtoxinA 20 units versus placebo one cycle of treatment in glabellar lines, Outcome 4: Total adverse events

Study or Subgroup	OnabotulinumtoxinA 20U Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Beer 2006	0	16	1	15	0.6%	0.31 [0.01 , 7.15]
Carruthers 2002	67	203	20	61	20.7%	1.01 [0.67 , 1.52]
Carruthers 2003b	56	202	26	71	22.6%	0.76 [0.52 , 1.11]
Carruthers 2017	15	42	6	35	7.3%	2.08 [0.91 , 4.80]
Harii 2008	33	44	29	49	29.2%	1.27 [0.95 , 1.69]
NCT02450526	22	107	4	21	5.7%	1.08 [0.41 , 2.81]
Rzany 2019	3	246	0	49	0.7%	1.42 [0.07 , 27.01]
Wu 2010	55	170	11	57	13.2%	1.68 [0.94 , 2.98]
Total (95% CI)		**1030**		**358**	**100.0%**	**1.14 [0.89 , 1.45]**
Total events:	251		97			

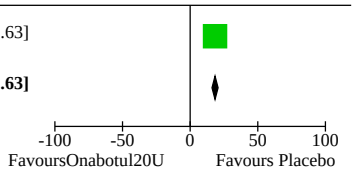
Heterogeneity: Tau² = 0.03; Chi² = 9.77, df = 7 (P = 0.20); I² = 28%
Test for overall effect: Z = 1.04 (P = 0.30)
Test for subgroup differences: Not applicable



Analysis 2.5. Comparison 2: OnabotulinumtoxinA 20 units versus placebo one cycle of treatment in glabellar lines, Outcome 5: Duration of treatment (weeks)

Study or Subgroup	OnabotulinumtoxinA 20U Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Carruthers 2017	18.8	7.13	42	0.4	1.77	35	100.0%	18.40 [16.17 , 20.63]
Total (95% CI)			**42**			**35**	**100.0%**	**18.40 [16.17 , 20.63]**

Heterogeneity: Not applicable
Test for overall effect: Z = 16.14 (P < 0.00001)
Test for subgroup differences: Not applicable



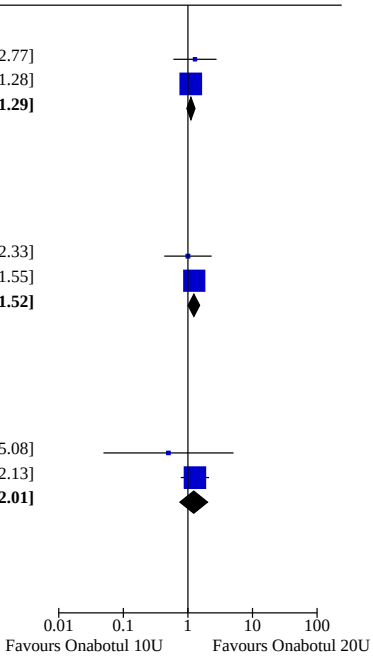
Comparison 3. OnabotulinumtoxinA 20units versus 10 units one treatment glabellar lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Participant assessment of success by analysing scores and scales	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1.1 4 weeks	2	131	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.96, 1.29]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1.2 8 weeks	2	131	Risk Ratio (M-H, Random, 95% CI)	1.24 [1.01, 1.52]
3.1.3 16 weeks	2	131	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.75, 2.01]
3.2 Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)	2	131	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.93 [0.20, 18.70]
3.3 Physician assessment of success by analysing scores and scales	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.3.1 4 weeks	2	131	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.91, 1.20]
3.3.2 8 weeks	2	131	Risk Ratio (M-H, Random, 95% CI)	1.53 [0.76, 3.10]
3.3.3 16 weeks	2	131	Risk Ratio (M-H, Random, 95% CI)	1.43 [0.76, 2.69]
3.4 Total adverse events	2	131	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.49, 2.37]

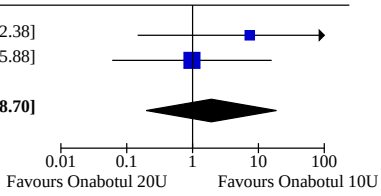
Analysis 3.1. Comparison 3: OnabotulinumtoxinA 20units versus 10 units one treatment glabellar lines, Outcome 1: Participant assessment of success by analysing scores and scales

Study or Subgroup	OnabotulinumtoxinA 20U Events	Total	OnabotulinumtoxinA 10U Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
3.1.1 4 weeks						
Carruthers 2005b	9	20	7	20	3.5%	1.29 [0.60 , 2.77]
Harii 2008	43	46	38	45	96.5%	1.11 [0.96 , 1.28]
Subtotal (95% CI)		**66**		**65**	**100.0%**	**1.11 [0.96 , 1.29]**
Total events:	52		45			
Heterogeneity: Tau² = 0.00; Chi² = 0.21, df = 1 (P = 0.65); I² = 0%						
Test for overall effect: Z = 1.45 (P = 0.15)						
3.1.2 8 weeks						
Carruthers 2005b	7	20	7	20	5.9%	1.00 [0.43 , 2.33]
Harii 2008	41	46	32	45	94.1%	1.25 [1.01 , 1.55]
Subtotal (95% CI)		**66**		**65**	**100.0%**	**1.24 [1.01 , 1.52]**
Total events:	48		39			
Heterogeneity: Tau² = 0.00; Chi² = 0.31, df = 1 (P = 0.58); I² = 0%						
Test for overall effect: Z = 2.03 (P = 0.04)						
3.1.3 16 weeks						
Carruthers 2005b	1	20	2	20	4.5%	0.50 [0.05 , 5.08]
Harii 2008	21	46	16	45	95.5%	1.28 [0.78 , 2.13]
Subtotal (95% CI)		**66**		**65**	**100.0%**	**1.23 [0.75 , 2.01]**
Total events:	22		18			
Heterogeneity: Tau² = 0.00; Chi² = 0.62, df = 1 (P = 0.43); I² = 0%						
Test for overall effect: Z = 0.83 (P = 0.41)						



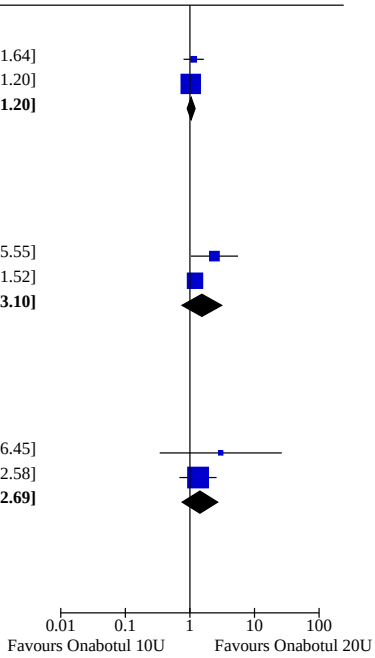
Analysis 3.2. Comparison 3: OnabotulinumtoxinA 20units versus 10 units one treatment glabellar lines, Outcome 2: Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

Study or Subgroup	OnabotulinumtoxinA 20U Events	Total	OnabotulinumtoxinA 10U Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Carruthers 2005b	1	20	0	20	33.6%	7.39 [0.15 , 372.38]
Harii 2008	1	46	1	45	66.4%	0.98 [0.06 , 15.88]
Total (95% CI)		**66**		**65**	**100.0%**	**1.93 [0.20 , 18.70]**
Total events:	2		1			
Heterogeneity: Chi² = 0.68, df = 1 (P = 0.41); I² = 0%						
Test for overall effect: Z = 0.57 (P = 0.57)						
Test for subgroup differences: Not applicable						



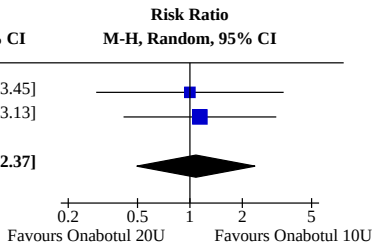
Analysis 3.3. Comparison 3: OnabotulinumtoxinA 20units versus 10 units one treatment glabellar lines, Outcome 3: Physician assessment of success by analysing scores and scales

Study or Subgroup	OnabotulinumtoxinA 20U Events	Total	OnabotulinumtoxinA 10U Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
3.3.1 4 weeks						
Carruthers 2005b	16	20	14	20	15.2%	1.14 [0.80 , 1.64]
Harii 2008	41	46	39	45	84.8%	1.03 [0.88 , 1.20]
Subtotal (95% CI)		**66**		**65**	**100.0%**	**1.05 [0.91 , 1.20]**
Total events:	57		53			
Heterogeneity: Tau² = 0.00; Chi² = 0.31, df = 1 (P = 0.58); I² = 0%						
Test for overall effect: Z = 0.61 (P = 0.54)						
3.3.2 8 weeks						
Carruthers 2005b	12	20	5	20	35.2%	2.40 [1.04 , 5.55]
Harii 2008	38	46	31	45	64.8%	1.20 [0.95 , 1.52]
Subtotal (95% CI)		**66**		**65**	**100.0%**	**1.53 [0.76 , 3.10]**
Total events:	50		36			
Heterogeneity: Tau² = 0.19; Chi² = 2.88, df = 1 (P = 0.09); I² = 65%						
Test for overall effect: Z = 1.18 (P = 0.24)						
3.3.3 16 weeks						
Carruthers 2005b	3	20	1	20	8.4%	3.00 [0.34 , 26.45]
Harii 2008	15	46	11	45	91.6%	1.33 [0.69 , 2.58]
Subtotal (95% CI)		**66**		**65**	**100.0%**	**1.43 [0.76 , 2.69]**
Total events:	18		12			
Heterogeneity: Tau² = 0.00; Chi² = 0.50, df = 1 (P = 0.48); I² = 0%						
Test for overall effect: Z = 1.11 (P = 0.27)						



Analysis 3.4. Comparison 3: OnabotulinumtoxinA 20units versus 10 units one treatment glabellar lines, Outcome 4: Total adverse events

Study or Subgroup	OnabotulinumtoxinA 20U Events	Total	OnabotulinumtoxinA 10U Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Carruthers 2005b	4	20	4	20	39.9%	1.00 [0.29 , 3.45]
Harii 2008	7	46	6	45	60.1%	1.14 [0.42 , 3.13]
Total (95% CI)		**66**		**65**	**100.0%**	**1.08 [0.49 , 2.37]**
Total events:	11		10			
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.87); I² = 0%						
Test for overall effect: Z = 0.20 (P = 0.84)						
Test for subgroup differences: Not applicable						



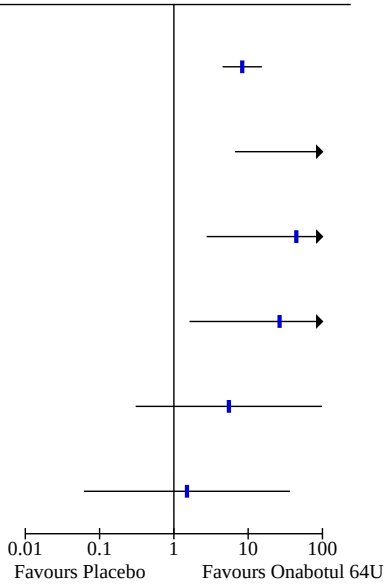
Comparison 4. OnabotulinumtoxinA 64units versus placebo one cycle of treatment, upper wrinkles

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Participant assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.1.1 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.1.2 8 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.1.3 12 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1.4 16 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.1.5 20 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.1.6 24 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.2 Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.3 Physician assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.3.1 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.3.2 8 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.3.3 12 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.3.4 16 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.3.5 20 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.3.6 24 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.4 Total adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

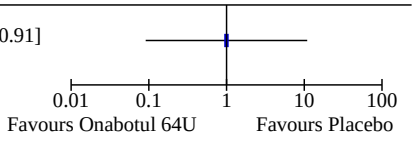
Analysis 4.1. Comparison 4: OnabotulinumtoxinA 64units versus placebo one cycle of treatment, upper wrinkles, Outcome 1: Participant assessment of success by analysing scores and scales

Study or Subgroup	Onabotulinumtoxin 64U Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 95% CI
4.1.1 4 weeks					
De Boulle 2018	167	313	10	156	8.32 [4.53 , 15.30]
4.1.2 8 weeks					
De Boulle 2018	106	313	0	156	106.50 [6.66 , 1702.48]
4.1.3 12 weeks					
De Boulle 2018	44	313	0	156	44.50 [2.76 , 717.83]
4.1.4 16 weeks					
De Boulle 2018	26	313	0	156	26.50 [1.63 , 431.99]
4.1.5 20 weeks					
De Boulle 2018	5	313	0	156	5.50 [0.31 , 98.84]
4.1.6 24 weeks					
De Boulle 2018	1	313	0	156	1.50 [0.06 , 36.61]



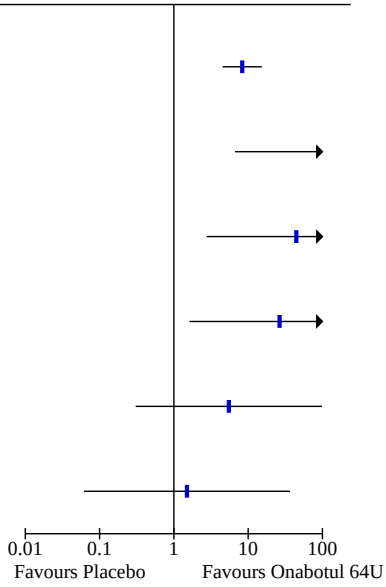
Analysis 4.2. Comparison 4: OnabotulinumtoxinA 64units versus placebo one cycle of treatment, upper wrinkles, Outcome 2: Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus

Study or Subgroup	Onabotulinumtoxin 64U Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 95% CI
De Boulle 2018	2	313	1	156	1.00 [0.09 , 10.91]



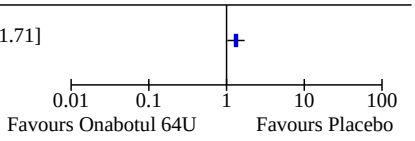
Analysis 4.3. Comparison 4: OnabotulinumtoxinA 64units versus placebo one cycle of treatment, upper wrinkles, Outcome 3: Physician assessment of success by analysing scores and scales

Study or Subgroup	Onabotulinumtoxin 64U Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 95% CI
4.3.1 4 weeks					
De Boulle 2018	167	313	10	156	8.32 [4.53 , 15.30]
4.3.2 8 weeks					
De Boulle 2018	106	313	0	156	106.50 [6.66 , 1702.48]
4.3.3 12 weeks					
De Boulle 2018	44	313	0	156	44.50 [2.76 , 717.83]
4.3.4 16 weeks					
De Boulle 2018	26	313	0	156	26.50 [1.63 , 431.99]
4.3.5 20 weeks					
De Boulle 2018	5	313	0	156	5.50 [0.31 , 98.84]
4.3.6 24 weeks					
De Boulle 2018	1	313	0	156	1.50 [0.06 , 36.61]



Analysis 4.4. Comparison 4: OnabotulinumtoxinA 64units versus placebo one cycle of treatment, upper wrinkles, Outcome 4: Total adverse events

Study or Subgroup	Onabotulinumtoxin 64U Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 95% CI
De Boulle 2018	138	313	52	156	1.32 [1.03 , 1.71]



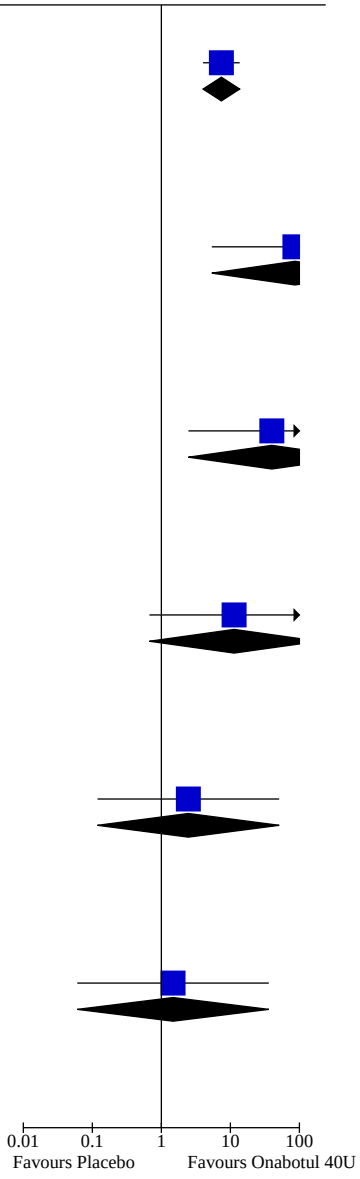
Comparison 5. OnabotulinumtoxinA 40units versus placebo one cycle of treatment, upper wrinkles

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Participant assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1.1 4 weeks	1	474	Risk Ratio (M-H, Random, 95% CI)	7.41 [4.02, 13.64]
5.1.2 8 weeks	1	474	Risk Ratio (M-H, Random, 95% CI)	86.13 [5.38, 1378.82]
5.1.3 12 weeks	1	474	Risk Ratio (M-H, Random, 95% CI)	39.87 [2.47, 644.08]
5.1.4 16 weeks	1	474	Risk Ratio (M-H, Random, 95% CI)	11.32 [0.67, 190.86]
5.1.5 20 weeks	1	474	Risk Ratio (M-H, Random, 95% CI)	2.46 [0.12, 50.95]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1.6 24 weeks	1	474	Risk Ratio (M-H, Random, 95% CI)	1.48 [0.06, 36.04]
5.2 Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5.3 Physician assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.3.1 4 weeks	1	474	Risk Ratio (M-H, Random, 95% CI)	7.41 [4.02, 13.64]
5.3.2 8 weeks	1	474	Risk Ratio (M-H, Random, 95% CI)	86.13 [5.38, 1378.82]
5.3.3 12 weeks	1	474	Risk Ratio (M-H, Random, 95% CI)	39.87 [2.47, 644.08]
5.3.4 16 weeks	1	474	Risk Ratio (M-H, Random, 95% CI)	11.32 [0.67, 190.86]
5.3.5 20 weeks	1	474	Risk Ratio (M-H, Random, 95% CI)	2.46 [0.12, 50.95]
5.3.6 24 weeks	1	474	Risk Ratio (M-H, Random, 95% CI)	1.48 [0.06, 36.04]
5.4 Total adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

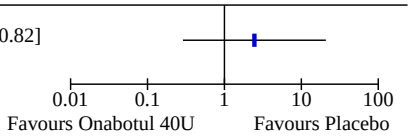
Analysis 5.1. Comparison 5: OnabotulinumtoxinA 40units versus placebo one cycle of treatment, upper wrinkles, Outcome 1: Participant assessment of success by analysing scores and scales

Study or Subgroup	OnabotulinumtoxinA 40U Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
5.1.1 4 weeks						
De Boulle 2018	151	318	10	156	100.0%	7.41 [4.02 , 13.64]
Subtotal (95% CI)		**318**		**156**	**100.0%**	**7.41 [4.02 , 13.64]**
Total events:	151		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 6.43 (P < 0.00001)						
5.1.2 8 weeks						
De Boulle 2018	87	318	0	156	100.0%	86.13 [5.38 , 1378.82]
Subtotal (95% CI)		**318**		**156**	**100.0%**	**86.13 [5.38 , 1378.82]**
Total events:	87		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.15 (P = 0.002)						
5.1.3 12 weeks						
De Boulle 2018	40	318	0	156	100.0%	39.87 [2.47 , 644.08]
Subtotal (95% CI)		**318**		**156**	**100.0%**	**39.87 [2.47 , 644.08]**
Total events:	40		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.60 (P = 0.009)						
5.1.4 16 weeks						
De Boulle 2018	11	318	0	156	100.0%	11.32 [0.67 , 190.86]
Subtotal (95% CI)		**318**		**156**	**100.0%**	**11.32 [0.67 , 190.86]**
Total events:	11		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.68 (P = 0.09)						
5.1.5 20 weeks						
De Boulle 2018	2	318	0	156	100.0%	2.46 [0.12 , 50.95]
Subtotal (95% CI)		**318**		**156**	**100.0%**	**2.46 [0.12 , 50.95]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.58 (P = 0.56)						
5.1.6 24 weeks						
De Boulle 2018	1	318	0	156	100.0%	1.48 [0.06 , 36.04]
Subtotal (95% CI)		**318**		**156**	**100.0%**	**1.48 [0.06 , 36.04]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.24 (P = 0.81)						



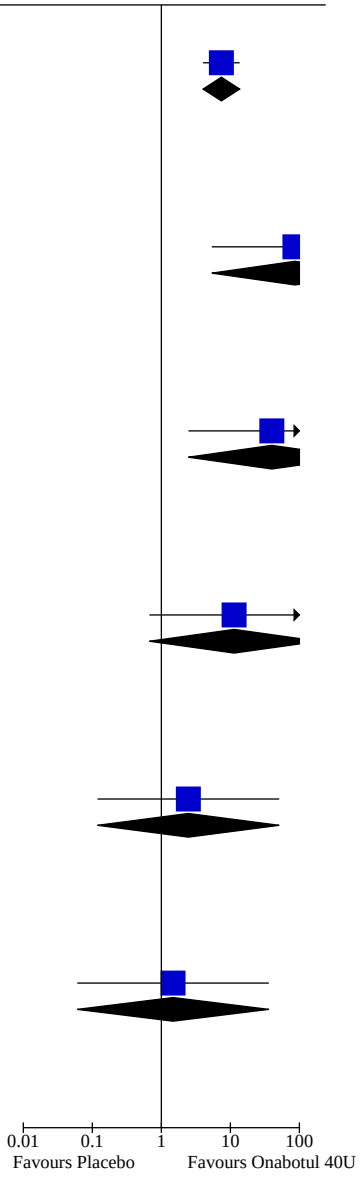
Analysis 5.2. Comparison 5: OnabotulinumtoxinA 40units versus placebo one cycle of treatment, upper wrinkles, Outcome 2: Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

Study or Subgroup	OnabotulinumtoxinA 40U Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 95% CI
De Boulle 2018	5	318	1	156	2.45 [0.29 , 20.82]



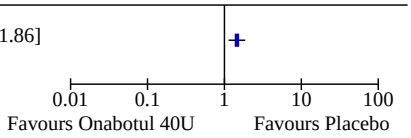
Analysis 5.3. Comparison 5: OnabotulinumtoxinA 40units versus placebo one cycle of treatment, upper wrinkles, Outcome 3: Physician assessment of success by analysing scores and scales

Study or Subgroup	OnabotulinumtoxinA 40U Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
5.3.1 4 weeks						
De Boulle 2018	151	318	10	156	100.0%	7.41 [4.02 , 13.64]
Subtotal (95% CI)		**318**		**156**	**100.0%**	**7.41 [4.02 , 13.64]**
Total events:	151		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 6.43 (P < 0.00001)						
5.3.2 8 weeks						
De Boulle 2018	87	318	0	156	100.0%	86.13 [5.38 , 1378.82]
Subtotal (95% CI)		**318**		**156**	**100.0%**	**86.13 [5.38 , 1378.82]**
Total events:	87		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.15 (P = 0.002)						
5.3.3 12 weeks						
De Boulle 2018	40	318	0	156	100.0%	39.87 [2.47 , 644.08]
Subtotal (95% CI)		**318**		**156**	**100.0%**	**39.87 [2.47 , 644.08]**
Total events:	40		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.60 (P = 0.009)						
5.3.4 16 weeks						
De Boulle 2018	11	318	0	156	100.0%	11.32 [0.67 , 190.86]
Subtotal (95% CI)		**318**		**156**	**100.0%**	**11.32 [0.67 , 190.86]**
Total events:	11		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.68 (P = 0.09)						
5.3.5 20 weeks						
De Boulle 2018	2	318	0	156	100.0%	2.46 [0.12 , 50.95]
Subtotal (95% CI)		**318**		**156**	**100.0%**	**2.46 [0.12 , 50.95]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.58 (P = 0.56)						
5.3.6 24 weeks						
De Boulle 2018	1	318	0	156	100.0%	1.48 [0.06 , 36.04]
Subtotal (95% CI)		**318**		**156**	**100.0%**	**1.48 [0.06 , 36.04]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.24 (P = 0.81)						



Analysis 5.4. Comparison 5: OnabotulinumtoxinA 40units versus placebo one cycle of treatment, upper wrinkles, Outcome 4: Total adverse events

Study or Subgroup	OnabotulinumtoxinA 40U Events	Total	Palcebo Events	Total	Risk Ratio M-H, Random, 95% CI
De Boulle 2018	154	318	52	156	1.45 [1.13 , 1.86]

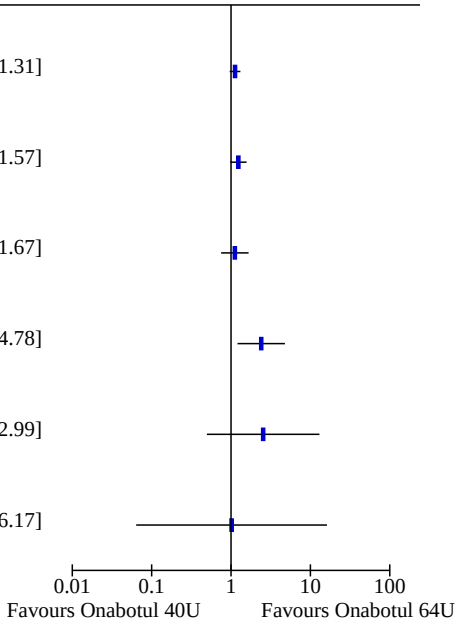


Comparison 6. OnabotulinumtoxinA 64units versus OnabotulinumoxinA 40U one cycle of treatment, upper wrinkles

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Participant assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.1.1 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.1.2 8 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.1.3 12 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.1.4 16 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.1.5 20 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.1.6 24 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.2 Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.3 Physician assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.3.1 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.3.2 8 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.3.3 12 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.3.4 16 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.3.5 20 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.3.6 24 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.4 Total adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

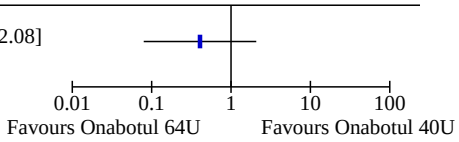
Analysis 6.1. Comparison 6: OnabotulinumtoxinA 64units versus OnabotulinumoxinA 40U one cycle of treatment, upper wrinkles, Outcome 1: Participant assessment of success by analysing scores and scales

Study or Subgroup	Onabotul 64U Events	Onabotul 64U Total	Onabotul 40U Events	Onabotul 40U Total	Risk Ratio M-H, Random, 95% CI
6.1.1 4 weeks					
De Boulle 2018	167	313	151	318	1.12 [0.96 , 1.31]
6.1.2 8 weeks					
De Boulle 2018	106	313	87	318	1.24 [0.98 , 1.57]
6.1.3 12 weeks					
De Boulle 2018	44	313	40	318	1.12 [0.75 , 1.67]
6.1.4 16 weeks					
De Boulle 2018	26	313	11	318	2.40 [1.21 , 4.78]
6.1.5 20 weeks					
De Boulle 2018	5	313	2	318	2.54 [0.50 , 12.99]
6.1.6 24 weeks					
De Boulle 2018	1	313	1	318	1.02 [0.06 , 16.17]



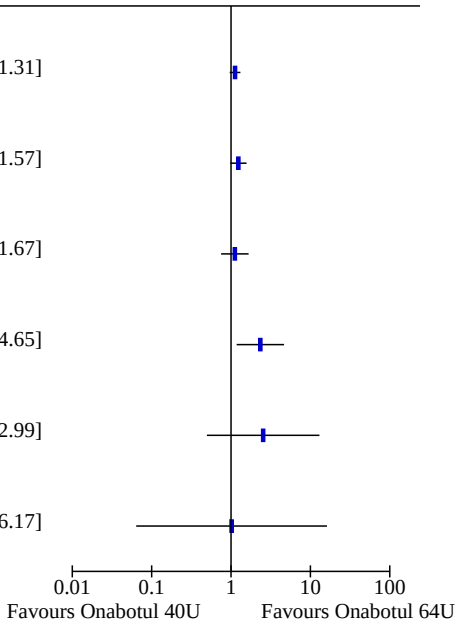
Analysis 6.2. Comparison 6: OnabotulinumtoxinA 64units versus OnabotulinumoxinA 40U one cycle of treatment, upper wrinkles, Outcome 2: Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

Study or Subgroup	Onabotul 64U Events	Onabotul 64U Total	Onabotul 40U Events	Onabotul 40U Total	Risk Ratio M-H, Random, 95% CI
De Boulle 2018	2	313	5	318	0.41 [0.08 , 2.08]



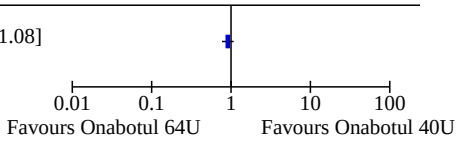
Analysis 6.3. Comparison 6: OnabotulinumtoxinA 64units versus OnabotulinumoxinA 40U one cycle of treatment, upper wrinkles, Outcome 3: Physician assessment of success by analysing scores and scales

Study or Subgroup	Onabotul 64U Events	Onabotul 64U Total	Onabotul 40U Events	Onabotul 40U Total	Risk Ratio M-H, Random, 95% CI
6.3.1 4 weeks					
De Boulle 2018	167	313	151	318	1.12 [0.96 , 1.31]
6.3.2 8 weeks					
De Boulle 2018	106	313	87	318	1.24 [0.98 , 1.57]
6.3.3 12 weeks					
De Boulle 2018	44	313	40	318	1.12 [0.75 , 1.67]
6.3.4 16 weeks					
De Boulle 2018	26	313	11	310	2.34 [1.18 , 4.65]
6.3.5 20 weeks					
De Boulle 2018	5	313	2	318	2.54 [0.50 , 12.99]
6.3.6 24 weeks					
De Boulle 2018	1	313	1	318	1.02 [0.06 , 16.17]



Analysis 6.4. Comparison 6: OnabotulinumtoxinA 64units versus OnabotulinumoxinA 40U one cycle of treatment, upper wrinkles, Outcome 4: Total adverse events

Study or Subgroup	Onabotul 64U Events	Onabotul 64U Total	Onabotul 40U Events	Onabotul 40U Total	Risk Ratio M-H, Random, 95% CI
De Boulle 2018	138	313	154	318	0.91 [0.77 , 1.08]



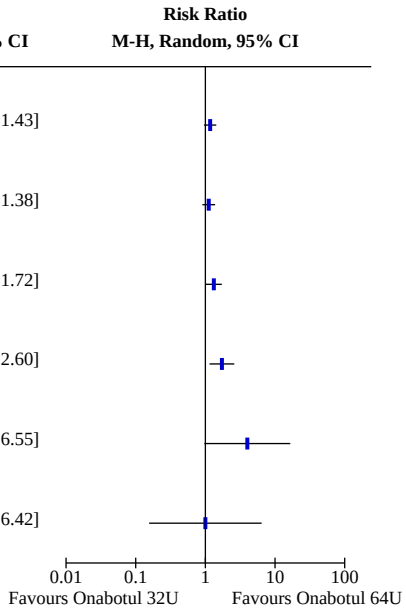
Comparison 7. OnabotulinumtoxinA 64units versus 32 units one cycle of treatment upper wrinkles

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Participant assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7.1.1 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7.1.2 8 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7.1.3 12 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7.1.4 16 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1.5 20 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7.1.6 24 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7.2 Physician assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7.2.1 4 and 8 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7.2.2 12 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7.2.3 16 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7.2.4 20 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7.3 Total adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

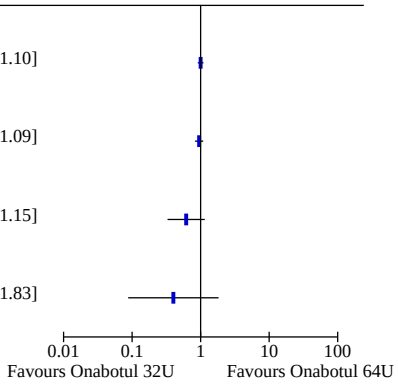
Analysis 7.1. Comparison 7: OnabotulinumtoxinA 64units versus 32 units one cycle of treatment upper wrinkles, Outcome 1: Participant assessment of success by analysing scores and scales

Study or Subgroup	OnbotulinumtoxinA 64U Events	Total	OnbotulinumtoxinA 32U Events	Total	Risk Ratio M-H, Random, 95% CI
7.1.1 4 weeks					
Carruthers 2009	20	20	17	20	1.17 [0.96 , 1.43]
7.1.2 8 weeks					
Carruthers 2009	19	20	17	20	1.12 [0.91 , 1.38]
7.1.3 12 weeks					
Carruthers 2009	20	20	15	20	1.32 [1.02 , 1.72]
7.1.4 16 weeks					
Carruthers 2009	19	20	11	20	1.73 [1.15 , 2.60]
7.1.5 20 weeks					
Carruthers 2009	8	20	2	20	4.00 [0.97 , 16.55]
7.1.6 24 weeks					
Carruthers 2009	2	20	2	20	1.00 [0.16 , 6.42]



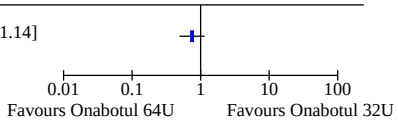
Analysis 7.2. Comparison 7: OnabotulinumtoxinA 64units versus 32 units one cycle of treatment upper wrinkles, Outcome 2: Physician assessment of success by analysing scores and scales

Study or Subgroup	OnabotulinumtoxinA 64U Events	Total	OnabotulinumtoxinA 32U Events	Total	Risk Ratio M-H, Random, 95% CI
7.2.1 4 and 8 weeks					
Carruthers 2009	20	20	20	20	1.00 [0.91 , 1.10]
7.2.2 12 weeks					
Carruthers 2009	19	20	20	20	0.95 [0.83 , 1.09]
7.2.3 16 weeks					
Carruthers 2009	8	20	13	20	0.62 [0.33 , 1.15]
7.2.4 20 weeks					
Carruthers 2009	2	20	5	20	0.40 [0.09 , 1.83]



Analysis 7.3. Comparison 7: OnabotulinumtoxinA 64units versus 32 units one cycle of treatment upper wrinkles, Outcome 3: Total adverse events

Study or Subgroup	OnabotulinumtoxinA 64U Events	Total	OnabotulinumtoxinA 32U Events	Total	Risk Ratio M-H, Random, 95% CI
Carruthers 2009	12	20	16	20	0.75 [0.49 , 1.14]

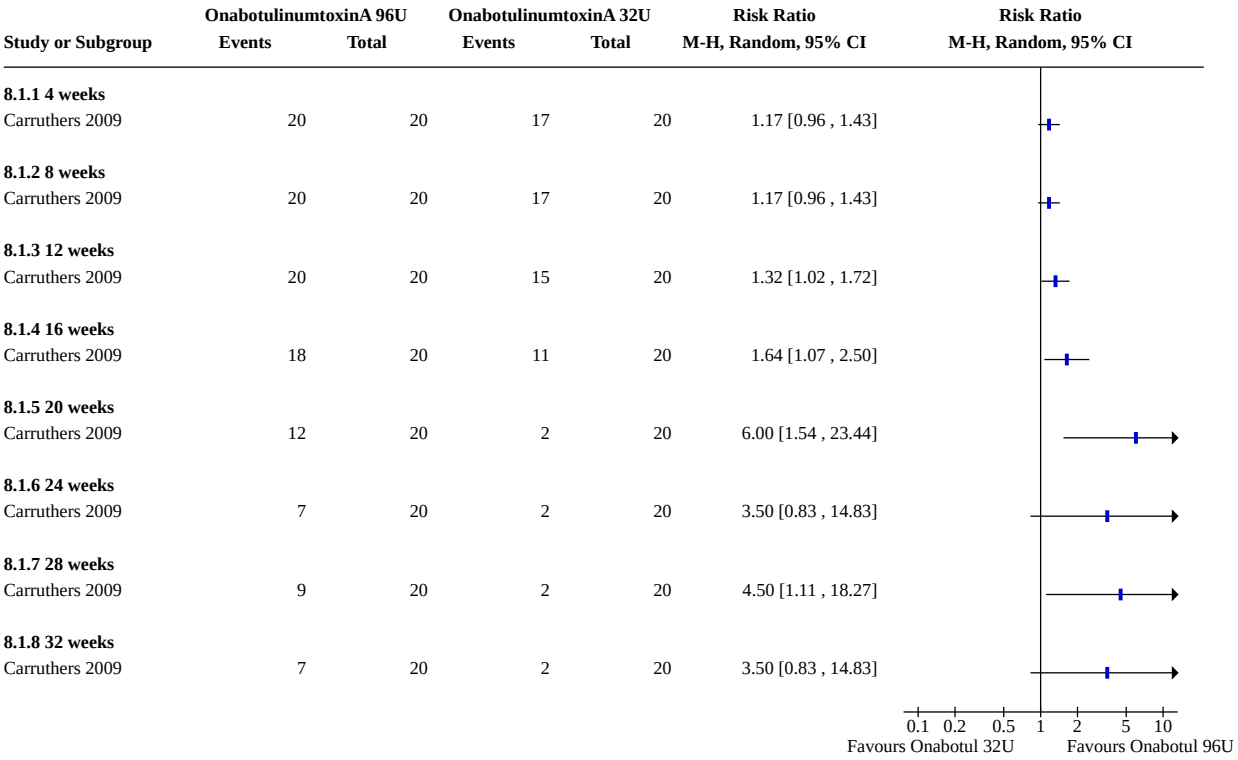


Comparison 8. OnabotulinumtoxinA 96 units versus 32 units one cycle of treatment upper wrinkles

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Participant assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8.1.1 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8.1.2 8 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8.1.3 12 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8.1.4 16 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8.1.5 20 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8.1.6 24 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8.1.7 28 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8.1.8 32 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

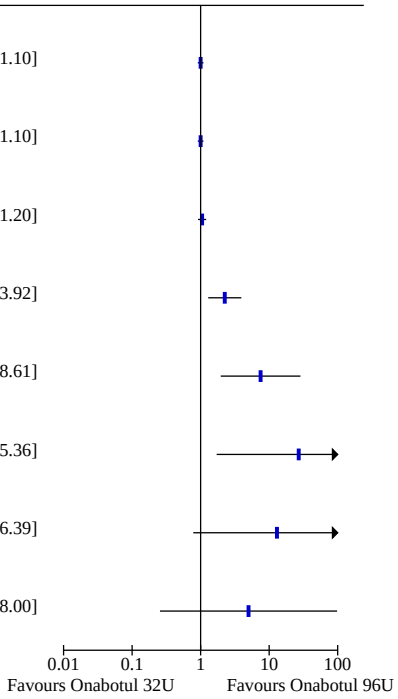
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.2 Physician assessment of success by analysing scores and scales	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8.2.1 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8.2.2 8 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8.2.3 12 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8.2.4 16 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8.2.5 20 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8.2.6 24 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8.2.7 28 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8.2.8 32 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8.3 Total adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 8.1. Comparison 8: OnabotulinumtoxinA 96 units versus 32 units one cycle of treatment upper wrinkles, Outcome 1: Participant assessment of success by analysing scores and scales



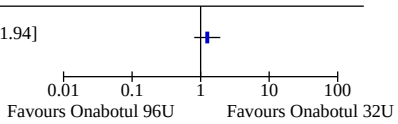
Analysis 8.2. Comparison 8: OnabotulinumtoxinA 96 units versus 32 units one cycle of treatment upper wrinkles, Outcome 2: Physician assessment of success by analysing scores and scales

Study or Subgroup	OnabotulinumtoxinA 96U Events	Total	OnabotulinumtoxinA 32U Events	Total	Risk Ratio M-H, Random, 95% CI
8.2.1 4 weeks					
Carruthers 2009	20	20	20	20	1.00 [0.91 , 1.10]
8.2.2 8 weeks					
Carruthers 2010	20	20	20	20	1.00 [0.91 , 1.10]
8.2.3 12 weeks					
Carruthers 2009	20	20	19	20	1.05 [0.92 , 1.20]
8.2.4 16 weeks					
Carruthers 2009	18	20	8	20	2.25 [1.29 , 3.92]
8.2.5 20 weeks					
Carruthers 2009	15	20	2	20	7.50 [1.97 , 28.61]
8.2.6 24 weeks					
Carruthers 2009	13	20	0	20	27.00 [1.71 , 425.36]
8.2.7 28 weeks					
Carruthers 2009	6	20	0	20	13.00 [0.78 , 216.39]
8.2.8 32 weeks					
Carruthers 2009	2	20	0	20	5.00 [0.26 , 98.00]



Analysis 8.3. Comparison 8: OnabotulinumtoxinA 96 units versus 32 units one cycle of treatment upper wrinkles, Outcome 3: Total adverse events

Study or Subgroup	OnabotulinumtoxinA 96U Events	Total	OnabotulinumtoxinA 32U Events	Total	Risk Ratio M-H, Random, 95% CI
Carruthers 2009	15	20	12	20	1.25 [0.81 , 1.94]



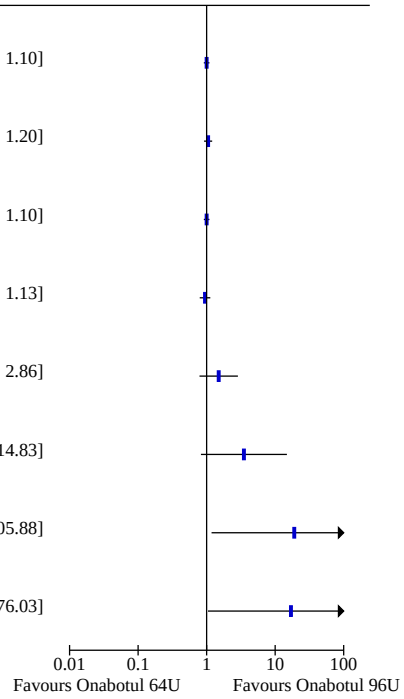
Comparison 9. OnabotulinumtoxinA 96 units versus 64 units one cycle of treatment upper wrinkles

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 Participant assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9.1.1 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9.1.2 8 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9.1.3 12 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

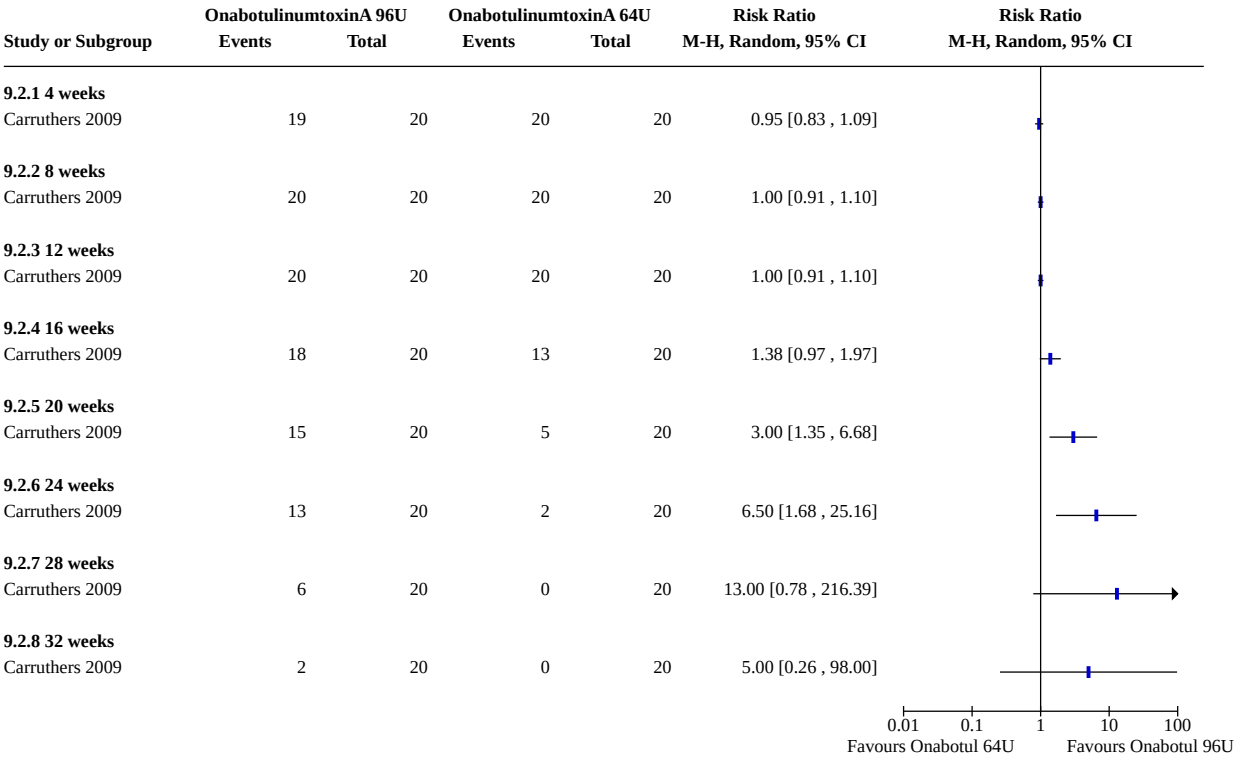
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1.4 16 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9.1.5 20 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9.1.6 24 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9.1.7 28 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9.1.8 32 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9.2 Physician assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9.2.1 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9.2.2 8 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9.2.3 12 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9.2.4 16 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9.2.5 20 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9.2.6 24 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9.2.7 28 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9.2.8 32 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9.3 Total adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 9.1. Comparison 9: OnabotulinumtoxinA 96 units versus 64 units one cycle of treatment upper wrinkles, Outcome 1: Participant assessment of success by analysing scores and scales

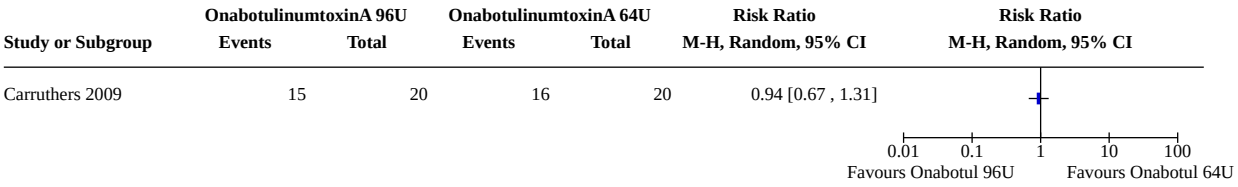
Study or Subgroup	OnabotulinumtoxinA 96U Events	Total	OnabotulinumtoxinA 64U Events	Total	Risk Ratio M-H, Random, 95% CI
9.1.1 4 weeks					
Carruthers 2009	20	20	20	20	1.00 [0.91 , 1.10]
9.1.2 8 weeks					
Carruthers 2009	20	20	19	20	1.05 [0.92 , 1.20]
9.1.3 12 weeks					
Carruthers 2009	20	20	20	20	1.00 [0.91 , 1.10]
9.1.4 16 weeks					
Carruthers 2009	18	20	19	20	0.95 [0.79 , 1.13]
9.1.5 20 weeks					
Carruthers 2009	12	20	8	20	1.50 [0.79 , 2.86]
9.1.6 24 weeks					
Carruthers 2009	7	20	2	20	3.50 [0.83 , 14.83]
9.1.7 28 weeks					
Carruthers 2009	9	20	0	20	19.00 [1.18 , 305.88]
9.1.8 32 weeks					
Carruthers 2009	8	20	0	20	17.00 [1.05 , 276.03]



Analysis 9.2. Comparison 9: OnabotulinumtoxinA 96 units versus 64 units one cycle of treatment upper wrinkles, Outcome 2: Physician assessment of success by analysing scores and scales



Analysis 9.3. Comparison 9: OnabotulinumtoxinA 96 units versus 64 units one cycle of treatment upper wrinkles, Outcome 3: Total adverse events

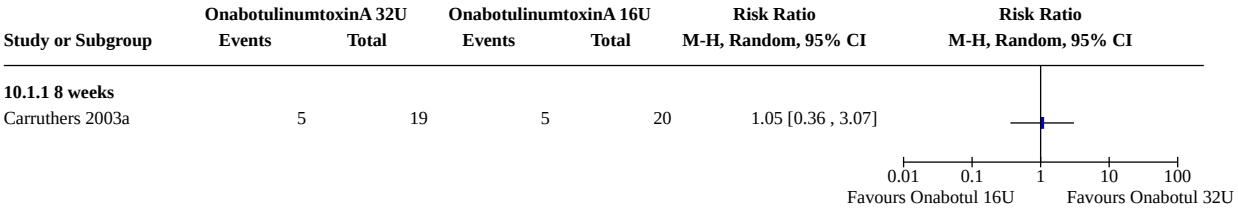


Comparison 10. OnabotulinumtoxinA 32 units versus 16 units one cycle of treatment forehead lines

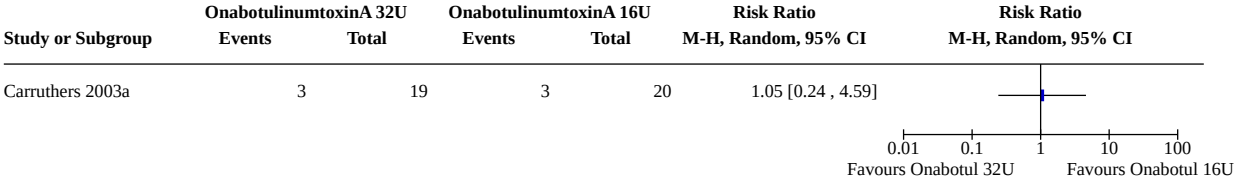
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.1 Participant assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
10.1.1 8 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
10.2 Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.3 Physician assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
10.3.1 8 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

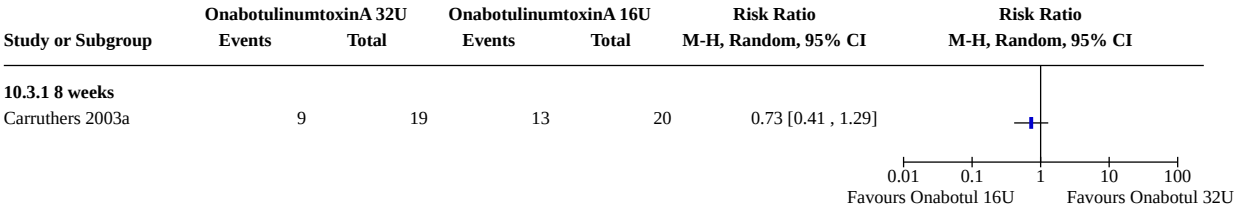
Analysis 10.1. Comparison 10: OnabotulinumtoxinA 32 units versus 16 units one cycle of treatment forehead lines, Outcome 1: Participant assessment of success by analysing scores and scales



Analysis 10.2. Comparison 10: OnabotulinumtoxinA 32 units versus 16 units one cycle of treatment forehead lines, Outcome 2: Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)



Analysis 10.3. Comparison 10: OnabotulinumtoxinA 32 units versus 16 units one cycle of treatment forehead lines, Outcome 3: Physician assessment of success by analysing scores and scales



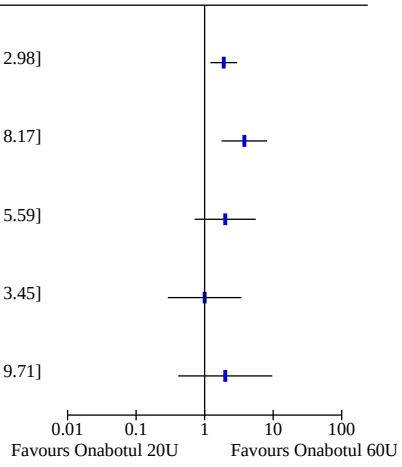
Comparison 11. OnabotulinumtoxinA 60 units versus 20 units one cycle of treatment glabellar lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.1 Physician assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.1.1 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
11.1.2 8 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
11.1.3 12 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
11.1.4 16 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
11.1.5 20 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
11.2 Total adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

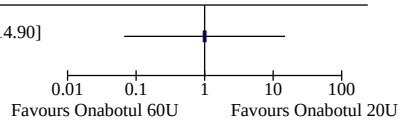
Analysis 11.1. Comparison 11: OnabotulinumtoxinA 60 units versus 20 units one cycle of treatment glabellar lines, Outcome 1: Physician assessment of success by analysing scores and scales

Study or Subgroup	OnabotulinumtoxinA 60U Events	Total	OnabotulinumtoxinA 20U Events	Total	Risk Ratio M-H, Random, 95% CI
11.1.1 4 weeks					
Carruthers 2005a	19	20	10	20	1.90 [1.21 , 2.98]
11.1.2 8 weeks					
Carruthers 2005a	19	20	5	20	3.80 [1.77 , 8.17]
11.1.3 12 weeks					
Carruthers 2005a	8	20	4	20	2.00 [0.72 , 5.59]
11.1.4 16 weeks					
Carruthers 2005a	4	20	4	20	1.00 [0.29 , 3.45]
11.1.5 20 weeks					
Carruthers 2005a	4	20	2	20	2.00 [0.41 , 9.71]



Analysis 11.2. Comparison 11: OnabotulinumtoxinA 60 units versus 20 units one cycle of treatment glabellar lines, Outcome 2: Total adverse events

Study or Subgroup	OnabotulinumtoxinA 60U Events	Total	OnabotulinumtoxinA 20U Events	Total	Risk Ratio M-H, Random, 95% CI
Carruthers 2005a	1	20	1	20	1.00 [0.07 , 14.90]

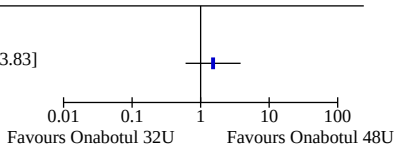


Comparison 12. OnabotulinumtoxinA 48 units versus 32 units one cycle of treatment forehead lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.1 Participant assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
12.1.1 8 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
12.2 Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
12.3 Physician assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
12.3.1 8 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

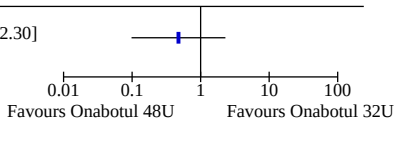
Analysis 12.1. Comparison 12: OnabotulinumtoxinA 48 units versus 32 units one cycle of treatment forehead lines, Outcome 1: Participant assessment of success by analysing scores and scales

Study or Subgroup	OnabotulinumtoxinA 48U Events	Total	OnabotulinumtoxinA 32U Events	Total	Risk Ratio M-H, Random, 95% CI
12.1.1 8 weeks					
Carruthers 2003a	8	20	5	19	1.52 [0.60 , 3.83]



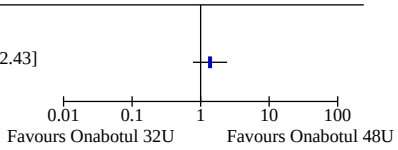
Analysis 12.2. Comparison 12: OnabotulinumtoxinA 48 units versus 32 units one cycle of treatment forehead lines, Outcome 2: Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

Study or Subgroup	OnabotulinumtoxinA 48U Events	Total	OnabotulinumtoxinA 32U Events	Total	Risk Ratio M-H, Random, 95% CI
Carruthers 2003a	2	20	4	19	0.47 [0.10 , 2.30]



Analysis 12.3. Comparison 12: OnabotulinumtoxinA 48 units versus 32 units one cycle of treatment forehead lines, Outcome 3: Physician assessment of success by analysing scores and scales

Study or Subgroup	OnabotulinumtoxinA 48U Events	Total	OnabotulinumtoxinA 32U Events	Total	Risk Ratio M-H, Random, 95% CI
12.3.1 8 weeks					
Carruthers 2003a	13	20	9	19	1.37 [0.77 , 2.43]

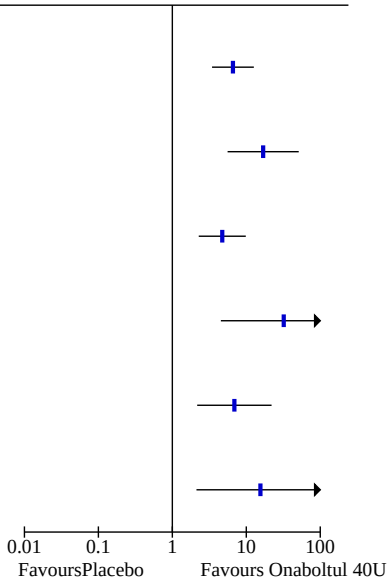


Comparison 13. OnabotulinumtoxinA 40 units versus placebo one cycle of treatment for forehead lines and glabellar lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.1 Participant assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
13.1.1 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
13.1.2 8 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
13.1.3 12 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
13.1.4 16 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
13.1.5 20 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
13.1.6 24 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
13.2 Physician assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
13.2.1 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
13.2.2 8 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
13.2.3 12 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
13.2.4 16 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
13.2.5 20 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
13.2.6 24 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
13.3 Total adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

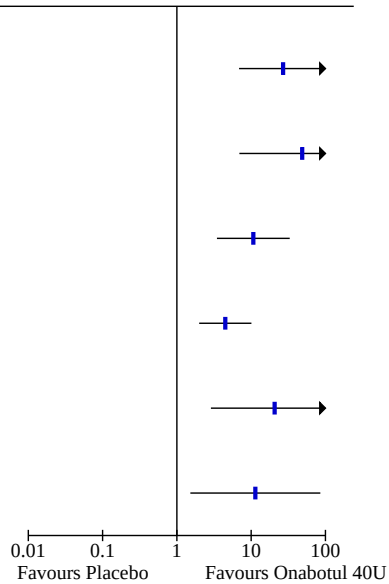
Analysis 13.1. Comparison 13: OnabotulinumtoxinA 40 units versus placebo one cycle of treatment for forehead lines and glabellar lines, Outcome 1: Participant assessment of success by analysing scores and scales

Study or Subgroup	Onabotulinumtoxin 40U Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 95% CI
13.1.1 4 weeks					
Solish 2016	51	57	8	59	6.60 [3.44 , 12.64]
13.1.2 8 weeks					
Solish 2016	49	57	3	59	16.91 [5.59 , 51.17]
13.1.3 12 weeks					
Solish 2016	32	57	7	59	4.73 [2.27 , 9.84]
13.1.4 16 weeks					
Solish 2016	31	57	1	59	32.09 [4.53 , 227.29]
13.1.5 20 weeks					
Solish 2016	20	57	3	59	6.90 [2.17 , 21.96]
13.1.6 24 weeks					
Solish 2016	15	57	1	59	15.53 [2.12 , 113.72]



Analysis 13.2. Comparison 13: OnabotulinumtoxinA 40 units versus placebo one cycle of treatment for forehead lines and glabellar lines, Outcome 2: Physician assessment of success by analysing scores and scales

Study or Subgroup	Onabotulinumtoxin 40U Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 95% CI
13.2.1 4 weeks					
Solish 2016	52	57	2	59	26.91 [6.88 , 105.34]
13.2.2 8 weeks					
Solish 2016	47	57	1	59	48.65 [6.94 , 340.90]
13.2.3 12 weeks					
Solish 2016	31	57	3	59	10.70 [3.46 , 33.04]
13.2.4 16 weeks					
Solish 2016	26	57	6	59	4.49 [2.00 , 10.08]
13.2.5 20 weeks					
Solish 2016	20	57	1	59	20.70 [2.87 , 149.20]
13.2.6 24 weeks					
Solish 2016	11	57	1	59	11.39 [1.52 , 85.36]



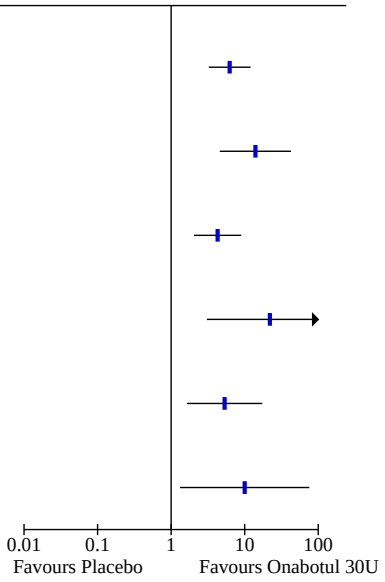
Analysis 13.3. Comparison 13: OnabotulinumtoxinA 40 units versus placebo one cycle of treatment for forehead lines and glabellar lines, Outcome 3: Total adverse events

Comparison 14. OnabotulinumtoxinA 30 units versus placebo one cycle of treatment for forehead lines and glabellar lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.1 Participant assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
14.1.1 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
14.1.2 8 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
14.1.3 12 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
14.1.4 16 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
14.1.5 20 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
14.1.6 24 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
14.2 Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
14.3 Physician assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
14.3.1 4 weeks	1	118	Risk Ratio (M-H, Random, 95% CI)	24.00 [6.11, 94.23]
14.3.2 8 weeks	1	118	Risk Ratio (M-H, Random, 95% CI)	43.00 [6.12, 302.08]
14.3.3 12 weeks	1	118	Risk Ratio (M-H, Random, 95% CI)	8.67 [2.77, 27.08]
14.3.4 16 weeks	1	118	Risk Ratio (M-H, Random, 95% CI)	3.33 [1.44, 7.71]
14.3.5 20 weeks	1	118	Risk Ratio (M-H, Random, 95% CI)	15.00 [2.05, 109.93]
14.3.6 24 weeks	1	118	Risk Ratio (M-H, Random, 95% CI)	8.00 [1.03, 61.98]
14.4 Total adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

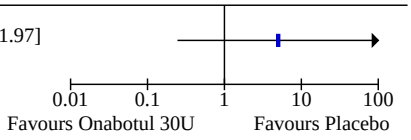
Analysis 14.1. Comparison 14: OnabotulinumtoxinA 30 units versus placebo one cycle of treatment for forehead lines and glabellar lines, Outcome 1: Participant assessment of success by analysing scores and scales

Study or Subgroup	OnabotulinumtoxinA 30U Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 95% CI
14.1.1 4 weeks					
Solish 2016	50	59	8	59	6.25 [3.25 , 12.01]
14.1.2 8 weeks					
Solish 2016	42	59	3	59	14.00 [4.59 , 42.67]
14.1.3 12 weeks					
Solish 2016	30	59	7	59	4.29 [2.05 , 8.98]
14.1.4 16 weeks					
Solish 2016	22	59	1	59	22.00 [3.06 , 157.95]
14.1.5 20 weeks					
Solish 2016	16	59	3	59	5.33 [1.64 , 17.34]
14.1.6 24 weeks					
Solish 2016	10	59	1	59	10.00 [1.32 , 75.66]



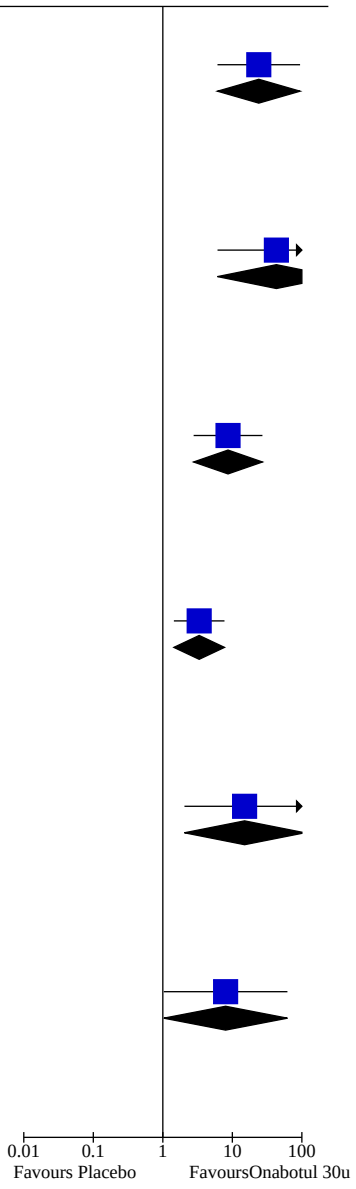
Analysis 14.2. Comparison 14: OnabotulinumtoxinA 30 units versus placebo one cycle of treatment for forehead lines and glabellar lines, Outcome 2: Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

Study or Subgroup	OnabotulinumtoxinA 30U Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 95% CI
Solish 2016	2	59	0	59	5.00 [0.25 , 101.97]



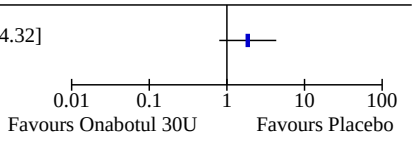
Analysis 14.3. Comparison 14: OnabotulinumtoxinA 30 units versus placebo one cycle of treatment for forehead lines and glabellar lines, Outcome 3: Physician assessment of success by analysing scores and scales

Study or Subgroup	OnabotulinumtoxinA 30u Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
14.3.1 4 weeks						
Solish 2016	48	59	2	59	100.0%	24.00 [6.11 , 94.23]
Subtotal (95% CI)		**59**		**59**	**100.0%**	**24.00 [6.11 , 94.23]**
Total events:	48		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.55 (P < 0.00001)						
14.3.2 8 weeks						
Solish 2016	43	59	1	59	100.0%	43.00 [6.12 , 302.08]
Subtotal (95% CI)		**59**		**59**	**100.0%**	**43.00 [6.12 , 302.08]**
Total events:	43		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.78 (P = 0.0002)						
14.3.3 12 weeks						
Solish 2016	26	59	3	59	100.0%	8.67 [2.77 , 27.08]
Subtotal (95% CI)		**59**		**59**	**100.0%**	**8.67 [2.77 , 27.08]**
Total events:	26		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.71 (P = 0.0002)						
14.3.4 16 weeks						
Solish 2016	20	59	6	59	100.0%	3.33 [1.44 , 7.71]
Subtotal (95% CI)		**59**		**59**	**100.0%**	**3.33 [1.44 , 7.71]**
Total events:	20		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.82 (P = 0.005)						
14.3.5 20 weeks						
Solish 2016	15	59	1	59	100.0%	15.00 [2.05 , 109.93]
Subtotal (95% CI)		**59**		**59**	**100.0%**	**15.00 [2.05 , 109.93]**
Total events:	15		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.66 (P = 0.008)						
14.3.6 24 weeks						
Solish 2016	8	59	1	59	100.0%	8.00 [1.03 , 61.98]
Subtotal (95% CI)		**59**		**59**	**100.0%**	**8.00 [1.03 , 61.98]**
Total events:	8		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.99 (P = 0.05)						



Analysis 14.4. Comparison 14: OnabotulinumtoxinA 30 units versus placebo one cycle of treatment for forehead lines and glabellar lines, Outcome 4: Total adverse events

Study or Subgroup	OnbotulinumtoxinA 30U Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 95% CI
Solish 2016	13	59	7	59	1.86 [0.80 , 4.32]

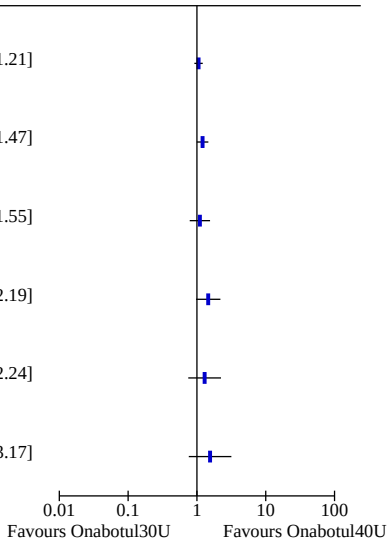


Comparison 15. OnabotulinumtoxinA 40 units versus OnabotulinumonabotulinumtoxinA 30 units one cycle of treatment for forehead lines and glabellar lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
15.1 Participant assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
15.1.1 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
15.1.2 8 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
15.1.3 12 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
15.1.4 16 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
15.1.5 20 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
15.1.6 24 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
15.2 Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
15.3 Physician assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
15.3.1 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
15.3.2 8 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
15.3.3 12 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
15.3.4 16 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
15.3.5 20 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
15.3.6 24 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
15.4 Total adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

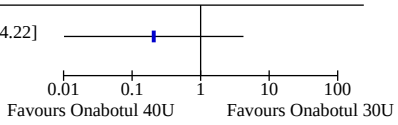
Analysis 15.1. Comparison 15: OnabotulinumtoxinA 40 units versus OnabotulinumonabotulinumtoxinA 30 units one cycle of treatment for forehead lines and glabellar lines, Outcome 1: Participant assessment of success by analysing scores and scales

Study or Subgroup	OnabotulinumtoxinA 40U Events	Total	OnabotulinumtoxinA 30U Events	Total	Risk Ratio M-H, Random, 95% CI
15.1.1 4 weeks					
Solish 2016	51	57	50	59	1.06 [0.92 , 1.21]
15.1.2 8 weeks					
Solish 2016	49	57	42	59	1.21 [1.00 , 1.47]
15.1.3 12 weeks					
Solish 2016	32	57	30	59	1.10 [0.79 , 1.55]
15.1.4 16 weeks					
Solish 2016	31	57	22	59	1.46 [0.97 , 2.19]
15.1.5 20 weeks					
Solish 2016	20	57	16	59	1.29 [0.75 , 2.24]
15.1.6 24 weeks					
Solish 2016	15	57	10	59	1.55 [0.76 , 3.17]



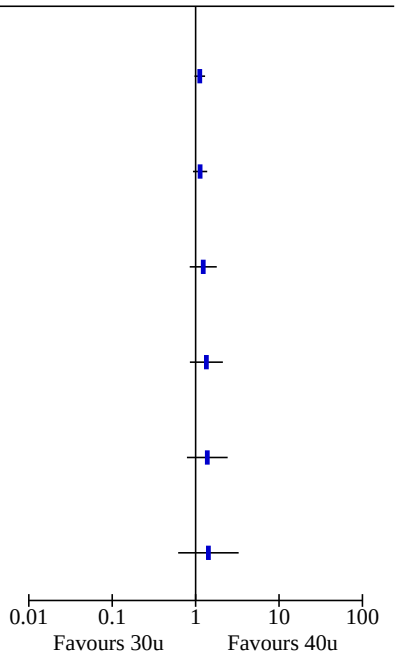
Analysis 15.2. Comparison 15: OnabotulinumtoxinA 40 units versus OnabotulinumonabotulinumtoxinA 30 units one cycle of treatment for forehead lines and glabellar lines, Outcome 2: Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

Study or Subgroup	OnabotulinumtoxinA 40U Events	Total	OnabotulinumtoxinA 30U Events	Total	Risk Ratio M-H, Random, 95% CI
Solish 2016	0	57	2	59	0.21 [0.01 , 4.22]



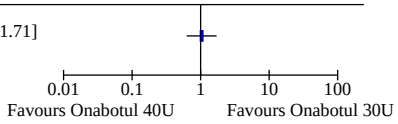
Analysis 15.3. Comparison 15: OnabotulinumtoxinA 40 units versus OnabotulinumonabotulinumtoxinA 30 units one cycle of treatment for forehead lines and glabellar lines, Outcome 3: Physician assessment of success by analysing scores and scales

Study or Subgroup	40u Events	40u Total	30u Events	30u Total	Risk Ratio M-H, Random, 95% CI
15.3.1 4 weeks					
Solish 2016	52	57	48	59	1.12 [0.97 , 1.30]
15.3.2 8 weeks					
Solish 2016	47	57	43	59	1.13 [0.93 , 1.38]
15.3.3 12 weeks					
Solish 2016	31	57	26	59	1.23 [0.85 , 1.79]
15.3.4 16 weeks					
Solish 2016	26	57	20	59	1.35 [0.85 , 2.12]
15.3.5 20 weeks					
Solish 2016	20	57	15	59	1.38 [0.79 , 2.42]
15.3.6 24 weeks					
Solish 2016	11	57	8	59	1.42 [0.62 , 3.28]



Analysis 15.4. Comparison 15: OnabotulinumtoxinA 40 units versus OnabotulinumonabotulinumtoxinA 30 units one cycle of treatment for forehead lines and glabellar lines, Outcome 4: Total adverse events

Study or Subgroup	OnabotulinumtoxinA 40U Events	OnabotulinumtoxinA 40U Total	OnabotulinumtoxinA 30U Events	OnabotulinumtoxinA 30U Total	Risk Ratio M-H, Random, 95% CI
Solish 2016	20	57	20	59	1.04 [0.63 , 1.71]

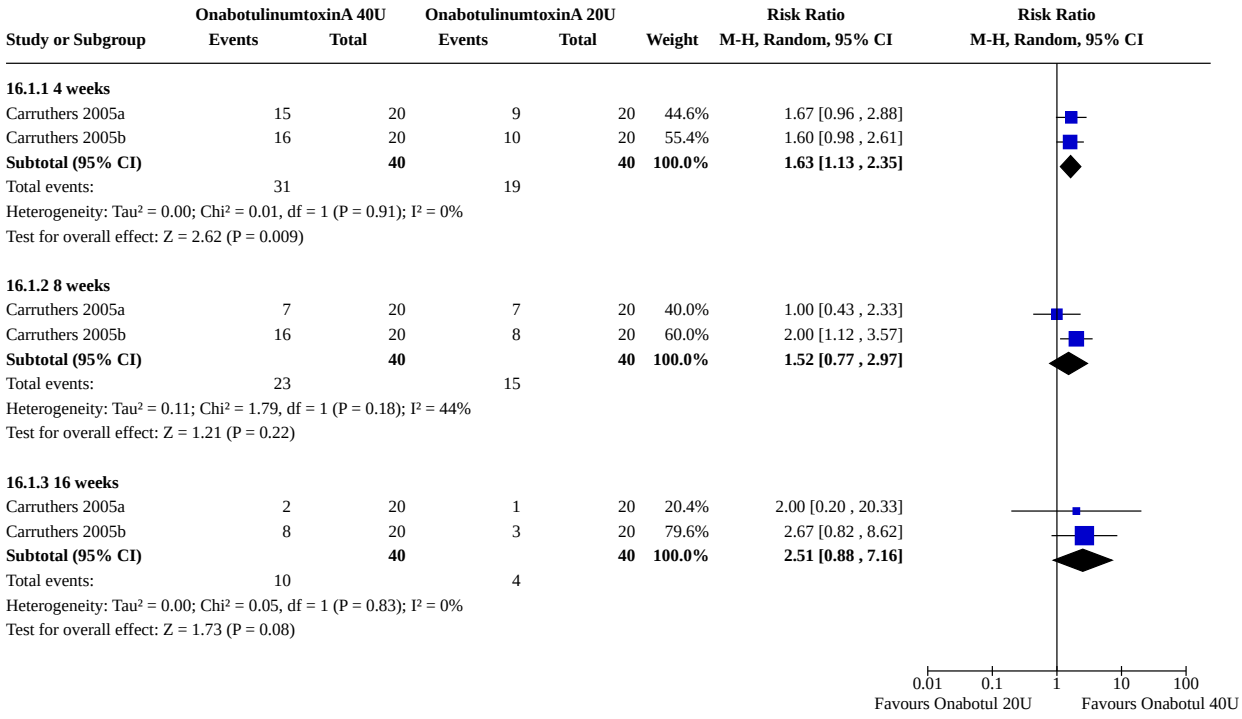


Comparison 16. OnabotulinumtoxinA 40 units versus 20 units one treatment glabellar lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16.1 Participant assessment of success by analysing scores and scales	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
16.1.1 4 weeks	2	80	Risk Ratio (M-H, Random, 95% CI)	1.63 [1.13, 2.35]
16.1.2 8 weeks	2	80	Risk Ratio (M-H, Random, 95% CI)	1.52 [0.77, 2.97]
16.1.3 16 weeks	2	80	Risk Ratio (M-H, Random, 95% CI)	2.51 [0.88, 7.16]

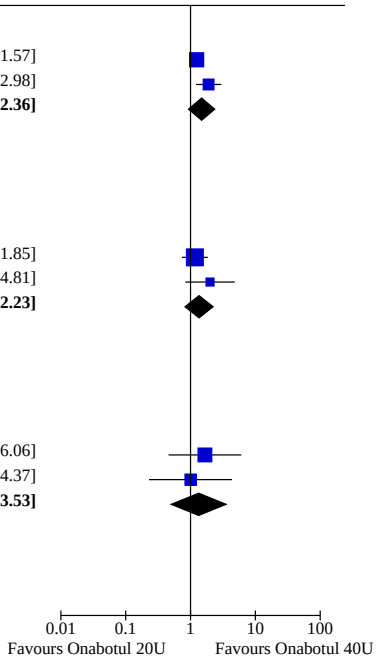
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16.2 Physician assessment of success by analysing scores and scales	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
16.2.1 4 weeks	2	80	Risk Ratio (M-H, Random, 95% CI)	1.48 [0.93, 2.36]
16.2.2 8 weeks	2	80	Risk Ratio (M-H, Random, 95% CI)	1.35 [0.82, 2.23]
16.2.3 16 weeks	2	80	Risk Ratio (M-H, Random, 95% CI)	1.34 [0.51, 3.53]
16.3 Total adverse events	2	80	Risk Ratio (M-H, Random, 95% CI)	1.93 [0.53, 7.05]

Analysis 16.1. Comparison 16: OnabotulinumtoxinA 40 units versus 20 units one treatment glabellar lines, Outcome 1: Participant assessment of success by analysing scores and scales



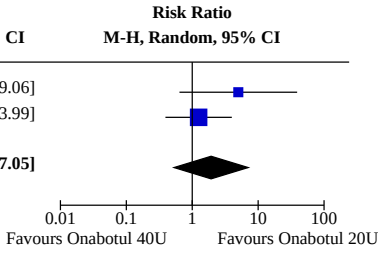
Analysis 16.2. Comparison 16: OnabotulinumtoxinA 40 units versus 20 units one treatment glabellar lines, Outcome 2: Physician assessment of success by analysing scores and scales

Study or Subgroup	OnabotulinumtoxinA 40U Events	Total	OnabotulinumtoxinA20U Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
16.2.1 4 weeks						
Carruthers 2005a	20	20	16	20	58.3%	1.24 [0.98 , 1.57]
Carruthers 2005b	19	20	10	20	41.7%	1.90 [1.21 , 2.98]
Subtotal (95% CI)		**40**		**40**	**100.0%**	**1.48 [0.93 , 2.36]**
Total events:	39		26			
Heterogeneity: Tau² = 0.08; Chi² = 3.46, df = 1 (P = 0.06); I² = 71%						
Test for overall effect: Z = 1.66 (P = 0.10)						
16.2.2 8 weeks						
Carruthers 2005a	14	20	12	20	72.4%	1.17 [0.74 , 1.85]
Carruthers 2005b	10	20	5	20	27.6%	2.00 [0.83 , 4.81]
Subtotal (95% CI)		**40**		**40**	**100.0%**	**1.35 [0.82 , 2.23]**
Total events:	24		17			
Heterogeneity: Tau² = 0.03; Chi² = 1.27, df = 1 (P = 0.26); I² = 21%						
Test for overall effect: Z = 1.19 (P = 0.23)						
16.2.3 16 weeks						
Carruthers 2005a	5	20	3	20	56.7%	1.67 [0.46 , 6.06]
Carruthers 2005b	3	20	3	20	43.3%	1.00 [0.23 , 4.37]
Subtotal (95% CI)		**40**		**40**	**100.0%**	**1.34 [0.51 , 3.53]**
Total events:	8		6			
Heterogeneity: Tau² = 0.00; Chi² = 0.26, df = 1 (P = 0.61); I² = 0%						
Test for overall effect: Z = 0.58 (P = 0.56)						



Analysis 16.3. Comparison 16: OnabotulinumtoxinA 40 units versus 20 units one treatment glabellar lines, Outcome 3: Total adverse events

Study or Subgroup	Favours Onabotul 40U Events	Total	OnabotulinumtoxinA 20U Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Carruthers 2005a	5	20	1	20	31.5%	5.00 [0.64 , 39.06]
Carruthers 2005b	5	20	4	20	68.5%	1.25 [0.39 , 3.99]
Total (95% CI)		**40**		**40**	**100.0%**	**1.93 [0.53 , 7.05]**
Total events:	10		5			
Heterogeneity: Tau² = 0.29; Chi² = 1.39, df = 1 (P = 0.24); I² = 28%						
Test for overall effect: Z = 1.00 (P = 0.32)						
Test for subgroup differences: Not applicable						

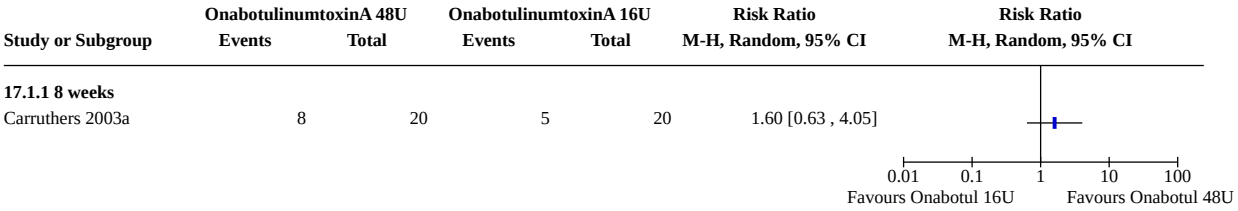


Comparison 17. OnabotulinumtoxinA 48 units versus 16 units one cycle of treatment forehead lines

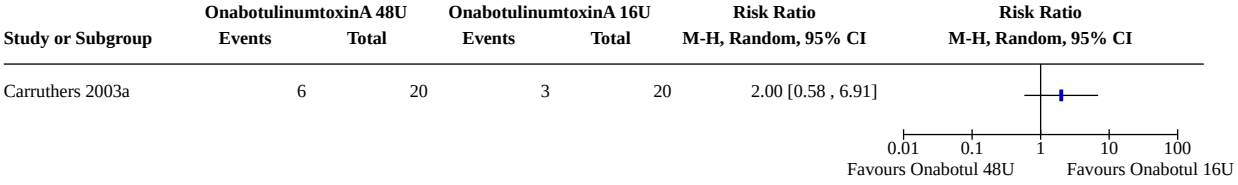
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
17.1 Participant assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
17.1.1 8 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
17.2 Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
17.3 Physician assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
17.3.1 8 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

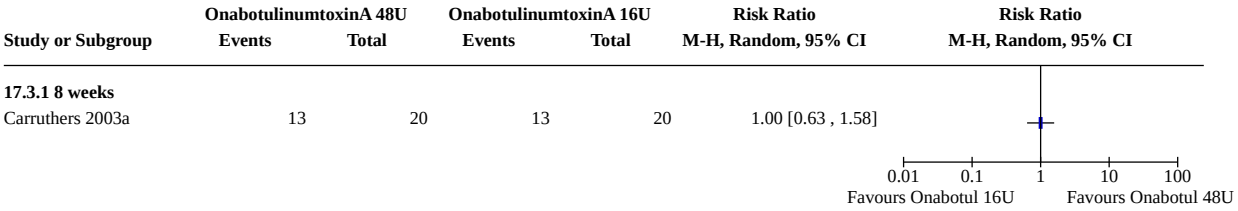
Analysis 17.1. Comparison 17: OnabotulinumtoxinA 48 units versus 16 units one cycle of treatment forehead lines, Outcome 1: Participant assessment of success by analysing scores and scales



Analysis 17.2. Comparison 17: OnabotulinumtoxinA 48 units versus 16 units one cycle of treatment forehead lines, Outcome 2: Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)



Analysis 17.3. Comparison 17: OnabotulinumtoxinA 48 units versus 16 units one cycle of treatment forehead lines, Outcome 3: Physician assessment of success by analysing scores and scales

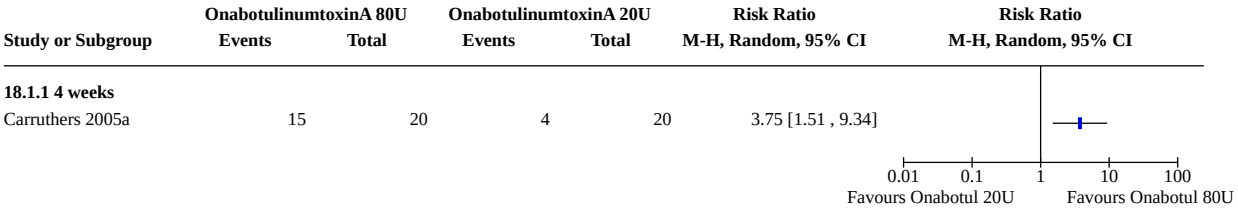


Comparison 18. OnabotulinumtoxinA 80 units versus 20 units one cycle of treatment glabellar lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
18.1 Participant assessment, maximum contraction (responder rate)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

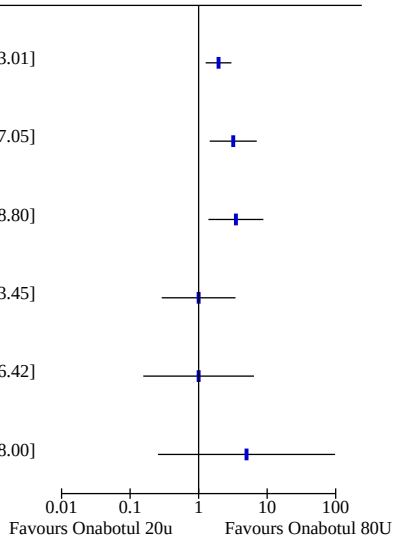
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
18.1.1 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
18.2 Physician assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
18.2.1 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
18.2.2 8 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
18.2.3 12 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
18.2.4 16 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
18.2.5 20 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
18.2.6 24 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
18.3 Total adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 18.1. Comparison 18: OnabotulinumtoxinA 80 units versus 20 units one cycle of treatment glabellar lines, Outcome 1: Participant assessment, maximum contraction (responder rate)



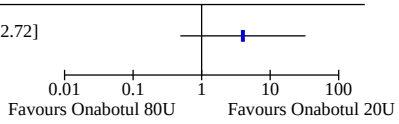
Analysis 18.2. Comparison 18: OnabotulinumtoxinA 80 units versus 20 units one cycle of treatment glabellar lines, Outcome 2: Physician assessment of success by analysing scores and scales

Study or Subgroup	OnabotulinumtoxinA 80U Events	Total	OnabotulinumtoxinA 20U Events	Total	Risk Ratio M-H, Random, 95% CI
18.2.1 4 weeks					
Carruthers 2005a	20	20	10	20	1.95 [1.27 , 3.01]
18.2.2 8 weeks					
Carruthers 2005a	16	20	5	20	3.20 [1.45 , 7.05]
18.2.3 12 weeks					
Carruthers 2005a	14	20	4	20	3.50 [1.39 , 8.80]
18.2.4 16 weeks					
Carruthers 2005a	4	20	4	20	1.00 [0.29 , 3.45]
18.2.5 20 weeks					
Carruthers 2005a	2	20	2	20	1.00 [0.16 , 6.42]
18.2.6 24 weeks					
Carruthers 2005a	2	20	0	20	5.00 [0.26 , 98.00]



Analysis 18.3. Comparison 18: OnabotulinumtoxinA 80 units versus 20 units one cycle of treatment glabellar lines, Outcome 3: Total adverse events

Study or Subgroup	OnabotulinumtoxinA 80U Events	Total	OnabotulinumtoxinA 20U Events	Total	Risk Ratio M-H, Random, 95% CI
Carruthers 2005a	4	20	1	20	4.00 [0.49 , 32.72]



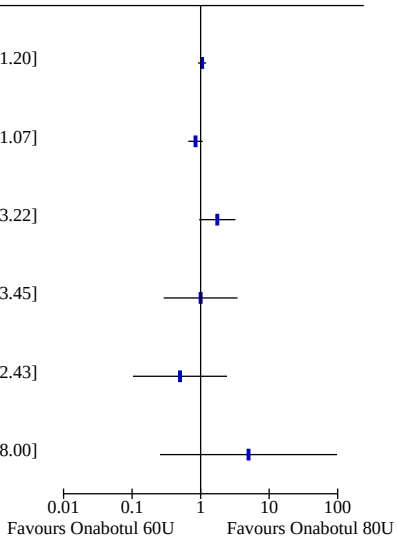
Comparison 19. OnabotulinumtoxinA 80 units versus 60 units one cycle of treatment glabellar lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
19.1 Physician assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
19.1.1 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
19.1.2 8 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
19.1.3 12 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
19.1.4 16 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
19.1.5 20 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
19.1.6 24 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
19.2 Total adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

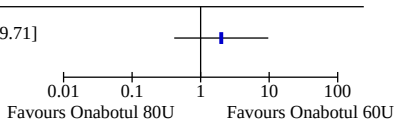
Analysis 19.1. Comparison 19: OnabotulinumtoxinA 80 units versus 60 units one cycle of treatment glabellar lines, Outcome 1: Physician assessment of success by analysing scores and scales

Study or Subgroup	OnabotulinumtoxinA 80U Events	Total	OnabotulinumtoxinA 60U Events	Total	Risk Ratio M-H, Random, 95% CI
19.1.1 4 weeks					
Carruthers 2005a	20	20	19	20	1.05 [0.92 , 1.20]
19.1.2 8 weeks					
Carruthers 2005a	16	20	19	20	0.84 [0.66 , 1.07]
19.1.3 12 weeks					
Carruthers 2005a	14	20	8	20	1.75 [0.95 , 3.22]
19.1.4 16 weeks					
Carruthers 2005a	4	20	4	20	1.00 [0.29 , 3.45]
19.1.5 20 weeks					
Carruthers 2005a	2	20	4	20	0.50 [0.10 , 2.43]
19.1.6 24 weeks					
Carruthers 2005a	2	20	0	20	5.00 [0.26 , 98.00]



Analysis 19.2. Comparison 19: OnabotulinumtoxinA 80 units versus 60 units one cycle of treatment glabellar lines, Outcome 2: Total adverse events

Study or Subgroup	OnabotulinumtoxinA 80U Events	Total	OnabotulinumtoxinA 60U Events	Total	Risk Ratio M-H, Random, 95% CI
Carruthers 2005a	4	20	2	20	2.00 [0.41 , 9.71]

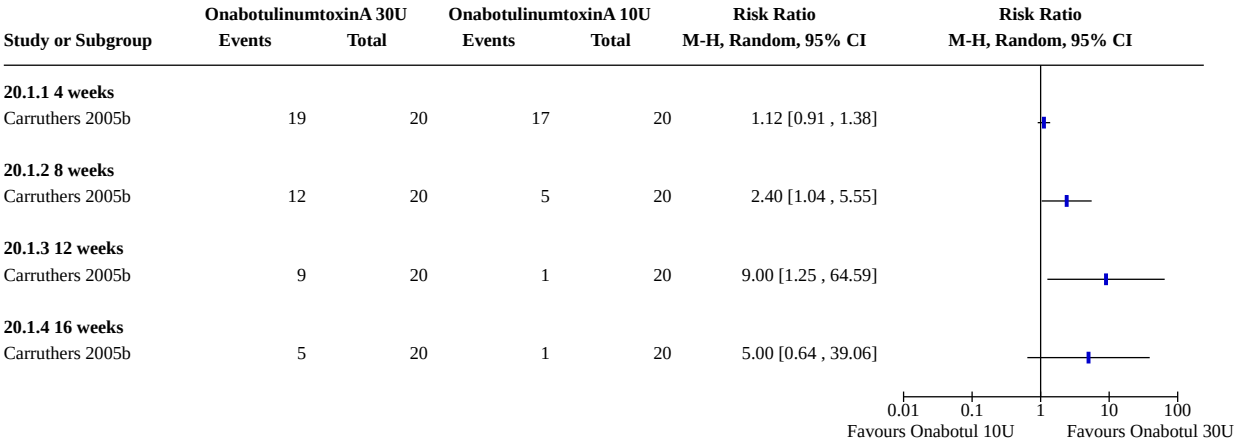


Comparison 20. OnabotulinumtoxinA 30 units versus 10 units one cycle of treatment glabellar lines

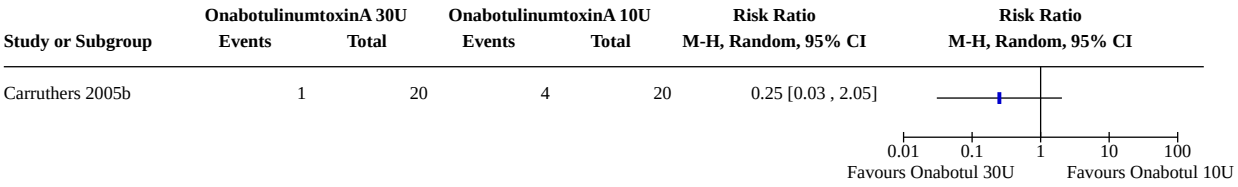
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
20.1 Physician assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
20.1.1 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
20.1.2 8 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
20.1.3 12 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
20.1.4 16 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
20.2 Total adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 20.1. Comparison 20: OnabotulinumtoxinA 30 units versus 10 units one cycle of treatment glabellar lines, Outcome 1: Physician assessment of success by analysing scores and scales



Analysis 20.2. Comparison 20: OnabotulinumtoxinA 30 units versus 10 units one cycle of treatment glabellar lines, Outcome 2: Total adverse events



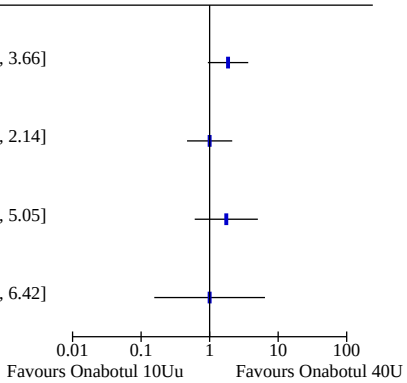
Comparison 21. OnabotulinumtoxinA 40 units versus 10 units one cycle of treatment glabellar lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
21.1 Participant assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
21.1.1 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
21.1.2 8 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
21.1.3 12 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
21.1.4 16 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
21.2 Physician assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
21.2.1 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
21.2.2 8 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
21.2.3 12 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
21.2.4 16 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
21.3 Total adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

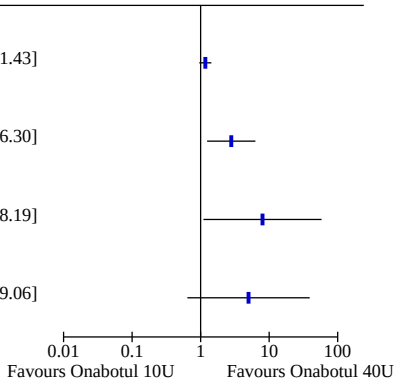
Analysis 21.1. Comparison 21: OnabotulinumtoxinA 40 units versus 10 units one cycle of treatment glabellar lines, Outcome 1: Participant assessment of success by analysing scores and scales

Study or Subgroup	OnabotulinumtoxinA 40U Events	OnabotulinumtoxinA 40U Total	OnabotulinumtoxinA 10U Events	OnabotulinumtoxinA 10U Total	Risk Ratio M-H, Random, 95% CI
21.1.1 4 weeks					
Carruthers 2005b	13	20	7	20	1.86 [0.94 , 3.66]
21.1.2 8 weeks					
Carruthers 2005b	8	20	8	20	1.00 [0.47 , 2.14]
21.1.3 12 weeks					
Carruthers 2005b	7	20	4	20	1.75 [0.61 , 5.05]
21.1.4 16 weeks					
Carruthers 2005b	2	20	2	20	1.00 [0.16 , 6.42]



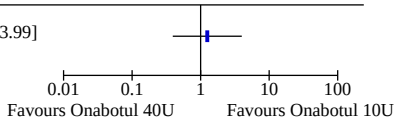
Analysis 21.2. Comparison 21: OnabotulinumtoxinA 40 units versus 10 units one cycle of treatment glabellar lines, Outcome 2: Physician assessment of success by analysing scores and scales

Study or Subgroup	OnabotulinumtoxinA 40U Events	Total	OnabotulinumtoxinA 10U Events	Total	Risk Ratio M-H, Random, 95% CI
21.2.1 4 weeks					
Carruthers 2005b	20	20	17	20	1.17 [0.96 , 1.43]
21.2.2 8 weeks					
Carruthers 2005b	14	20	5	20	2.80 [1.24 , 6.30]
21.2.3 12 weeks					
Carruthers 2005b	8	20	1	20	8.00 [1.10 , 58.19]
21.2.4 16 weeks					
Carruthers 2005b	5	20	1	20	5.00 [0.64 , 39.06]



Analysis 21.3. Comparison 21: OnabotulinumtoxinA 40 units versus 10 units one cycle of treatment glabellar lines, Outcome 3: Total adverse events

Study or Subgroup	OnabotulinumtoxinA 40U Events	Total	OnabotulinumtoxinA 10U Events	Total	Risk Ratio M-H, Random, 95% CI
Carruthers 2005b	5	20	4	20	1.25 [0.39 , 3.99]



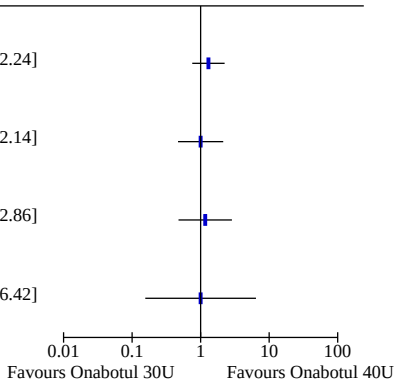
Comparison 22. OnabotulinumtoxinA 40 units versus 30 units one cycle of treatment glabellar lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
22.1 Participant assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
22.1.1 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
22.1.2 8 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
22.1.3 12 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
22.1.4 16 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
22.2 Physician assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
22.2.1 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
22.2.2 8 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
22.2.3 12 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
22.2.4 16 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
22.3 Total adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

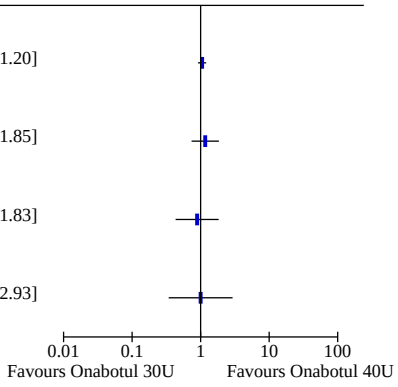
Analysis 22.1. Comparison 22: OnabotulinumtoxinA 40 units versus 30 units one cycle of treatment glabellar lines, Outcome 1: Participant assessment of success by analysing scores and scales

Study or Subgroup	OnabotulinumtoxinA 40U Events	OnabotulinumtoxinA 40U Total	OnabotulinumtoxinA 30U Events	OnabotulinumtoxinA 30U Total	Risk Ratio M-H, Random, 95% CI
22.1.1 4 weeks					
Carruthers 2005b	13	20	10	20	1.30 [0.75 , 2.24]
22.1.2 8 weeks					
Carruthers 2005b	8	20	8	20	1.00 [0.47 , 2.14]
22.1.3 12 weeks					
Carruthers 2005b	7	20	6	20	1.17 [0.48 , 2.86]
22.1.4 16 weeks					
Carruthers 2005b	2	20	2	20	1.00 [0.16 , 6.42]

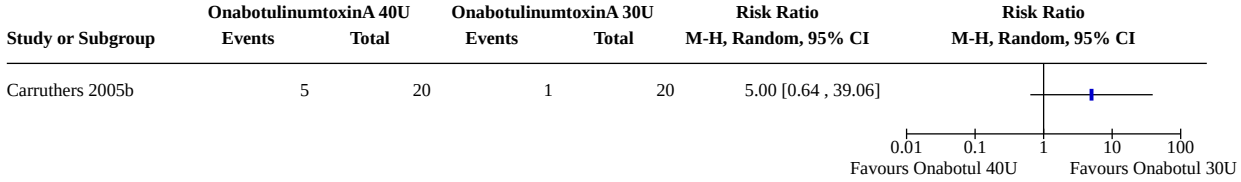


Analysis 22.2. Comparison 22: OnabotulinumtoxinA 40 units versus 30 units one cycle of treatment glabellar lines, Outcome 2: Physician assessment of success by analysing scores and scales

Study or Subgroup	OnabotulinumtoxinA 40U Events	OnabotulinumtoxinA 40U Total	OnabotulinumtoxinA 30U Events	OnabotulinumtoxinA 30U Total	Risk Ratio M-H, Random, 95% CI
22.2.1 4 weeks					
Carruthers 2005b	20	20	19	20	1.05 [0.92 , 1.20]
22.2.2 8 weeks					
Carruthers 2005b	14	20	12	20	1.17 [0.74 , 1.85]
22.2.3 12 weeks					
Carruthers 2005b	8	20	9	20	0.89 [0.43 , 1.83]
22.2.4 16 weeks					
Carruthers 2005b	5	20	5	20	1.00 [0.34 , 2.93]



Analysis 22.3. Comparison 22: OnabotulinumtoxinA 40 units versus 30 units one cycle of treatment glabellar lines, Outcome 3: Total adverse events

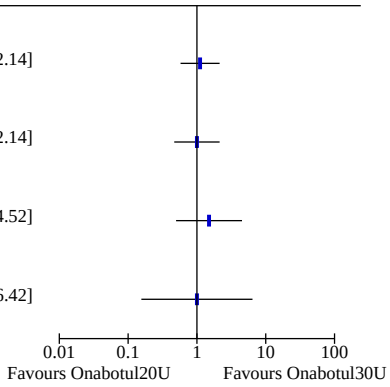


Comparison 23. OnabotulinumtoxinA 30 units versus 20 units one cycle of treatment glabellar lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
23.1 Participant assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
23.1.1 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
23.1.2 8 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
23.1.3 12 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
23.1.4 16 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
23.2 Physician assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
23.2.1 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
23.2.2 8 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
23.2.3 12 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
23.2.4 16 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
23.3 Total adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

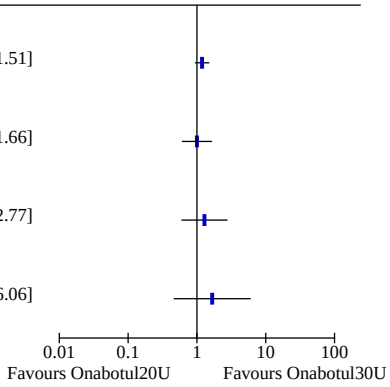
Analysis 23.1. Comparison 23: OnabotulinumtoxinA 30 units versus 20 units one cycle of treatment glabellar lines, Outcome 1: Participant assessment of success by analysing scores and scales

Study or Subgroup	OnabotulinumtoxinA 30U Events	Total	OnabotulinumtoxinA 20U Events	Total	Risk Ratio M-H, Random, 95% CI
23.1.1 4 weeks					
Carruthers 2005b	10	20	9	20	1.11 [0.58 , 2.14]
23.1.2 8 weeks					
Carruthers 2005b	8	20	8	20	1.00 [0.47 , 2.14]
23.1.3 12 weeks					
Carruthers 2005b	6	20	4	20	1.50 [0.50 , 4.52]
23.1.4 16 weeks					
Carruthers 2005b	2	20	2	20	1.00 [0.16 , 6.42]



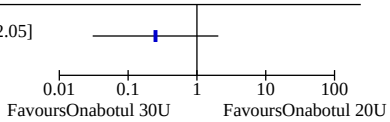
Analysis 23.2. Comparison 23: OnabotulinumtoxinA 30 units versus 20 units one cycle of treatment glabellar lines, Outcome 2: Physician assessment of success by analysing scores and scales

Study or Subgroup	OnabotulinumtoxinA 30U Events	Total	OnabotulinumtoxinA 20U Events	Total	Risk Ratio M-H, Random, 95% CI
23.2.1 4 weeks					
Carruthers 2005b	19	20	16	20	1.19 [0.93 , 1.51]
23.2.2 8 weeks					
Carruthers 2005b	12	20	12	20	1.00 [0.60 , 1.66]
23.2.3 12 weeks					
Carruthers 2005b	9	20	7	20	1.29 [0.60 , 2.77]
23.2.4 16 weeks					
Carruthers 2005b	5	20	3	20	1.67 [0.46 , 6.06]



Analysis 23.3. Comparison 23: OnabotulinumtoxinA 30 units versus 20 units one cycle of treatment glabellar lines, Outcome 3: Total adverse events

Study or Subgroup	OnabotulinumtoxinA 30U Events	Total	OnabotulinumtoxinA 20U Events	Total	Risk Ratio M-H, Random, 95% CI
Carruthers 2005b	1	20	4	20	0.25 [0.03 , 2.05]

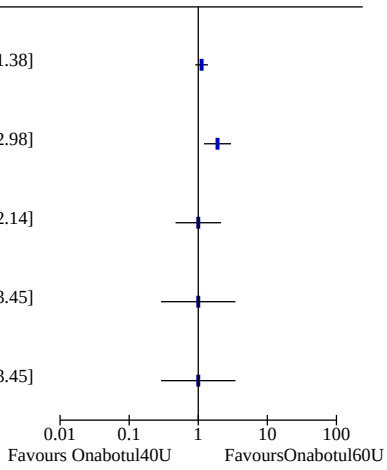


Comparison 24. OnabotulinumtoxinA 60 units versus 40 units one cycle of treatment glabellar lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
24.1 Physician assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
24.1.1 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
24.1.2 8 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
24.1.3 12 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
24.1.4 16 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
24.1.5 20 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
24.2 Total adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

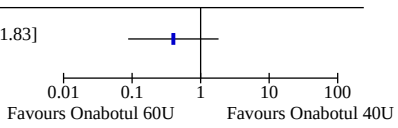
Analysis 24.1. Comparison 24: OnabotulinumtoxinA 60 units versus 40 units one cycle of treatment glabellar lines, Outcome 1: Physician assessment of success by analysing scores and scales

Study or Subgroup	OnabotulinumtoxinA 60U Events	Total	OnabotulinumtoxinA 40U Events	Total	Risk Ratio M-H, Random, 95% CI
24.1.1 4 weeks					
Carruthers 2005a	19	20	17	20	1.12 [0.91 , 1.38]
24.1.2 8 weeks					
Carruthers 2005a	19	20	10	20	1.90 [1.21 , 2.98]
24.1.3 12 weeks					
Carruthers 2005a	8	20	8	20	1.00 [0.47 , 2.14]
24.1.4 16 weeks					
Carruthers 2005a	4	20	4	20	1.00 [0.29 , 3.45]
24.1.5 20 weeks					
Carruthers 2005a	4	20	4	20	1.00 [0.29 , 3.45]



Analysis 24.2. Comparison 24: OnabotulinumtoxinA 60 units versus 40 units one cycle of treatment glabellar lines, Outcome 2: Total adverse events

Study or Subgroup	OnabotulinumtoxinA 60U Events	Total	OnabotulinumtoxinA 40U Events	Total	Risk Ratio M-H, Random, 95% CI
Carruthers 2005a	2	20	5	20	0.40 [0.09 , 1.83]

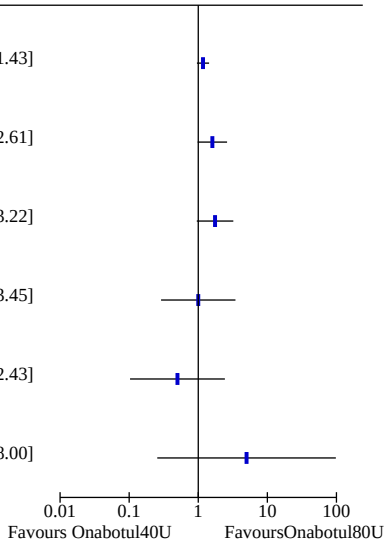


Comparison 25. OnabotulinumtoxinA 80 units versus 40 units one cycle of treatment glabellar lines

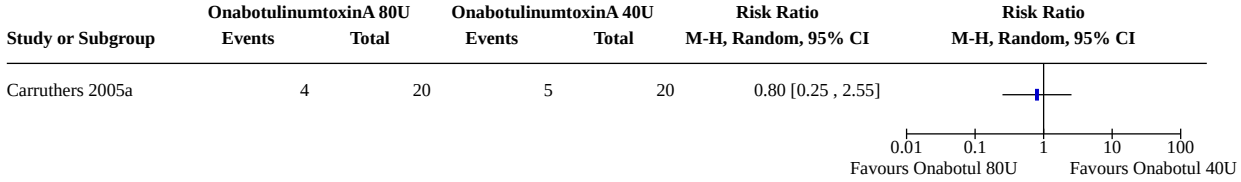
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
25.1 Physician assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
25.1.1 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
25.1.2 8 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
25.1.3 12 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
25.1.4 16 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
25.1.5 20 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
25.1.6 24 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
25.2 Total adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 25.1. Comparison 25: OnabotulinumtoxinA 80 units versus 40 units one cycle of treatment glabellar lines, Outcome 1: Physician assessment of success by analysing scores and scales

Study or Subgroup	OnabotulinumtoxinA 80U Events	OnabotulinumtoxinA 80U Total	OnabotulinumtoxinA 40U Events	OnabotulinumtoxinA 40U Total	Risk Ratio M-H, Random, 95% CI
25.1.1 4 weeks					
Carruthers 2005a	20	20	17	20	1.17 [0.96 , 1.43]
25.1.2 8 weeks					
Carruthers 2005a	16	20	10	20	1.60 [0.98 , 2.61]
25.1.3 12 weeks					
Carruthers 2005a	14	20	8	20	1.75 [0.95 , 3.22]
25.1.4 16 weeks					
Carruthers 2005a	4	20	4	20	1.00 [0.29 , 3.45]
25.1.5 20 weeks					
Carruthers 2005a	2	20	4	20	0.50 [0.10 , 2.43]
25.1.6 24 weeks					
Carruthers 2005a	2	20	0	20	5.00 [0.26 , 98.00]



Analysis 25.2. Comparison 25: OnabotulinumtoxinA 80 units versus 40 units one cycle of treatment glabellar lines, Outcome 2: Total adverse events

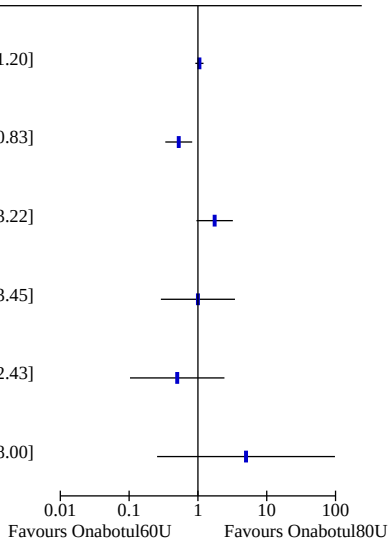


Comparison 26. OnabotulinumtoxinA 80units versus 60units one cycle of treatment glabellar lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
26.1 Physician assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
26.1.1 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
26.1.2 8 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
26.1.3 12 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
26.1.4 16 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
26.1.5 20 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
26.1.6 24 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
26.2 Total adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

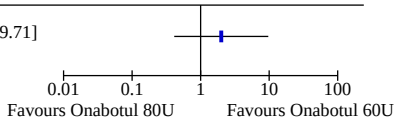
Analysis 26.1. Comparison 26: OnabotulinumtoxinA 80units versus 60units one cycle of treatment glabellar lines, Outcome 1: Physician assessment of success by analysing scores and scales

Study or Subgroup	OnabotulinumtoxinA 80U Events	Total	OnabotulinumtoxinA 60U Events	Total	Risk Ratio M-H, Random, 95% CI
26.1.1 4 weeks					
Carruthers 2005a	20	20	19	20	1.05 [0.92 , 1.20]
26.1.2 8 weeks					
Carruthers 2005a	10	20	19	20	0.53 [0.34 , 0.83]
26.1.3 12 weeks					
Carruthers 2005a	14	20	8	20	1.75 [0.95 , 3.22]
26.1.4 16 weeks					
Carruthers 2005a	4	20	4	20	1.00 [0.29 , 3.45]
26.1.5 20 weeks					
Carruthers 2005a	2	20	4	20	0.50 [0.10 , 2.43]
26.1.6 24 weeks					
Carruthers 2005a	2	20	0	20	5.00 [0.26 , 98.00]



Analysis 26.2. Comparison 26: OnabotulinumtoxinA 80units versus 60units one cycle of treatment glabellar lines, Outcome 2: Total adverse events

Study or Subgroup	OnabotulinumtoxinA 80U Events	Total	OnabotulinumtoxinA 60U Events	Total	Risk Ratio M-H, Random, 95% CI
Carruthers 2005a	4	20	2	20	2.00 [0.41 , 9.71]

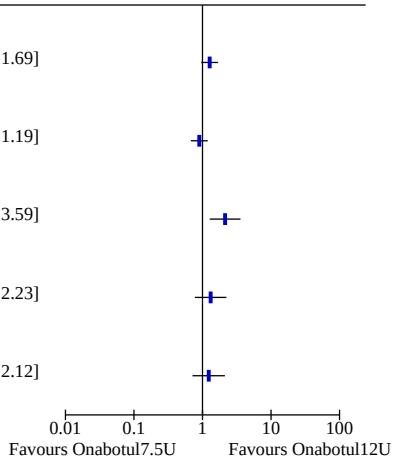


Comparison 27. OnabotulinumtoxinA 12 units versus 7.5 units one cycle of treatment perioral lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
27.1 Physician assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
27.1.1 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
27.1.2 8 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
27.1.3 12 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
27.1.4 16 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
27.1.5 20 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
27.2 Total adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

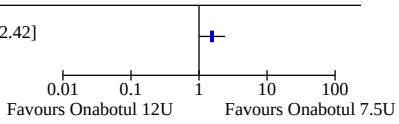
Analysis 27.1. Comparison 27: OnabotulinumtoxinA 12 units versus 7.5 units one cycle of treatment perioral lines, Outcome 1: Physician assessment of success by analysing scores and scales

Study or Subgroup	OnabotulinumtoxinA 12U Events	Total	OnabotulinumtoxinA 7.5U Events	Total	Risk Ratio M-H, Random, 95% CI
27.1.1 4 weeks					
Cohen 2012	25	29	21	31	1.27 [0.96 , 1.69]
27.1.2 8 weeks					
Cohen 2012	21	29	25	31	0.90 [0.68 , 1.19]
27.1.3 12 weeks					
Cohen 2012	22	29	11	31	2.14 [1.27 , 3.59]
27.1.4 16 weeks					
Cohen 2012	16	29	13	31	1.32 [0.78 , 2.23]
27.1.5 20 weeks					
Cohen 2012	15	29	13	31	1.23 [0.72 , 2.12]



Analysis 27.2. Comparison 27: OnabotulinumtoxinA 12 units versus 7.5 units one cycle of treatment perioral lines, Outcome 2: Total adverse events

Study or Subgroup	OnabotulinumtoxinA 12U Events	Total	OnabotulinumtoxinA 7.5U Events	Total	Risk Ratio M-H, Random, 95% CI
Cohen 2012	21	29	14	30	1.55 [1.00 , 2.42]

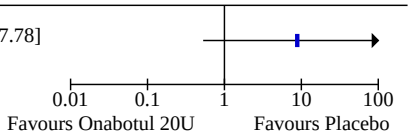


Comparison 28. OnabotulinumtoxinA 20units versus placebo in glabellar lines three cycles of treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
28.1 Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
28.2 Total adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

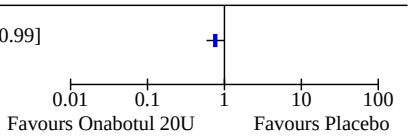
Analysis 28.1. Comparison 28: OnabotulinumtoxinA 20units versus placebo in glabellar lines three cycles of treatment, Outcome 1: Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

Study or Subgroup	OnabotulinumtoxinA 20U Events	Total	placebo Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Carruthers 2004	13	405	0	132	8.84 [0.53 , 147.78]	



Analysis 28.2. Comparison 28: OnabotulinumtoxinA 20units versus placebo in glabellar lines three cycles of treatment, Outcome 2: Total adverse events

Study or Subgroup	OnabotulinumtoxinA 20U Events	Total	placebo Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Carruthers 2004	119	405	51	132	0.76 [0.58 , 0.99]	



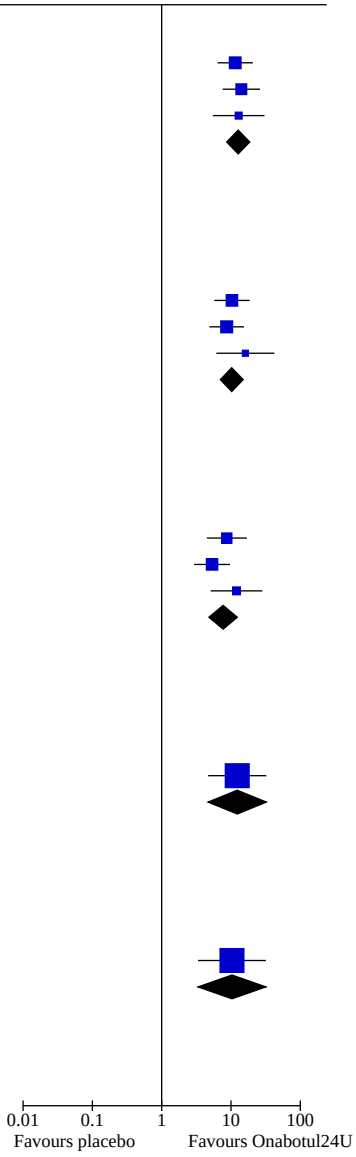
Comparison 29. OnabotulinumtoxinA24 units versus placebo one treatment in crow's feet lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
29.1 Participant assessment of success by analysing scores and scales	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
29.1.1 4 weeks	3	1474	Risk Ratio (M-H, Random, 95% CI)	12.71 [8.67, 18.63]
29.1.2 8 weeks	3	1474	Risk Ratio (M-H, Random, 95% CI)	10.25 [7.02, 14.98]
29.1.3 12 weeks	3	1474	Risk Ratio (M-H, Random, 95% CI)	7.70 [4.81, 12.33]
29.1.4 16 weeks	1	417	Risk Ratio (M-H, Random, 95% CI)	12.31 [4.68, 32.36]
29.1.5 20 weeks	1	417	Risk Ratio (M-H, Random, 95% CI)	10.33 [3.35, 31.89]
29.2 Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)	2	665	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.28 [0.12, 13.10]
29.3 Physician assessment of success by analysing scores and scales	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
29.3.1 4 weeks	4	1675	Risk Ratio (M-H, Random, 95% CI)	12.38 [8.93, 17.16]
29.3.2 8 weeks	3	1258	Risk Ratio (M-H, Random, 95% CI)	10.13 [5.34, 19.23]
29.3.3 12 weeks	3	1258	Risk Ratio (M-H, Random, 95% CI)	9.29 [5.95, 14.50]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
29.3.4 16 weeks	2	1057	Risk Ratio (M-H, Random, 95% CI)	5.46 [3.19, 9.32]
29.4 Total adverse events	2	692	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.94, 1.45]

Analysis 29.1. Comparison 29: OnabotulinumtoxinA24 units versus placebo one treatment in crow's feet lines, Outcome 1: Participant assessment of success by analysing scores and scales

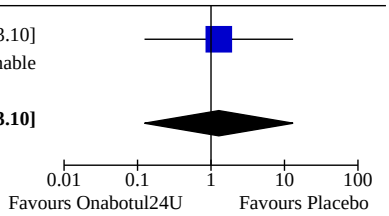
Study or Subgroup	OnabotulinumtoxinA 24U Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
29.1.1 4 weeks						
Carruthers 2014	126	222	11	223	42.3%	11.51 [6.39 , 20.71]
Moers-Carpi 2015	141	306	10	306	37.8%	14.10 [7.57 , 26.25]
Wu 2019	202	316	5	101	19.8%	12.91 [5.47 , 30.47]
Subtotal (95% CI)		**844**		**630**	**100.0%**	**12.71 [8.67 , 18.63]**
Total events:	469		26			
Heterogeneity: Tau² = 0.00; Chi² = 0.22, df = 2 (P = 0.90); I² = 0%						
Test for overall effect: Z = 13.04 (P < 0.00001)						
29.1.2 8 weeks						
Carruthers 2014	113	222	11	223	41.2%	10.32 [5.72 , 18.62]
Moers-Carpi 2015	104	306	12	306	43.3%	8.67 [4.87 , 15.42]
Wu 2019	202	316	4	101	15.5%	16.14 [6.16 , 42.32]
Subtotal (95% CI)		**844**		**630**	**100.0%**	**10.25 [7.02 , 14.98]**
Total events:	419		27			
Heterogeneity: Tau² = 0.00; Chi² = 1.26, df = 2 (P = 0.53); I² = 0%						
Test for overall effect: Z = 12.03 (P < 0.00001)						
29.1.3 12 weeks						
Carruthers 2014	78	222	9	223	35.2%	8.71 [4.48 , 16.92]
Moers-Carpi 2015	64	306	12	306	40.8%	5.33 [2.94 , 9.68]
Wu 2019	188	316	5	101	23.9%	12.02 [5.09 , 28.38]
Subtotal (95% CI)		**844**		**630**	**100.0%**	**7.70 [4.81 , 12.33]**
Total events:	330		26			
Heterogeneity: Tau² = 0.05; Chi² = 2.78, df = 2 (P = 0.25); I² = 28%						
Test for overall effect: Z = 8.49 (P < 0.00001)						
29.1.4 16 weeks						
Wu 2019	154	316	4	101	100.0%	12.31 [4.68 , 32.36]
Subtotal (95% CI)		**316**		**101**	**100.0%**	**12.31 [4.68 , 32.36]**
Total events:	154		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 5.09 (P < 0.00001)						
29.1.5 20 weeks						
Wu 2019	97	316	3	101	100.0%	10.33 [3.35 , 31.89]
Subtotal (95% CI)		**316**		**101**	**100.0%**	**10.33 [3.35 , 31.89]**
Total events:	97		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.06 (P < 0.0001)						



Analysis 29.2. Comparison 29: OnabotulinumtoxinA24 units versus placebo one treatment in crow's feet lines, Outcome 2: Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

Study or Subgroup	OnabotulinumtoxinA 24U Events	Total	Placebo Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Harii 2017	2	151	1	97	100.0%	1.28 [0.12 , 13.10]
Wu 2019	0	316	0	101		Not estimable
Total (95% CI)		**467**		**198**	**100.0%**	**1.28 [0.12 , 13.10]**
Total events:	2		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.21 (P = 0.84)
Test for subgroup differences: Not applicable



Analysis 29.3. Comparison 29: OnabotulinumtoxinA24 units versus placebo one treatment in crow's feet lines, Outcome 3: Physician assessment of success by analysing scores and scales

Study or Subgroup	OnabotulinumtoxinA 24U Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
29.3.1 4 weeks						
Carruthers 2014	149	222	12	223	34.3%	12.47 [7.14 , 21.79]
Harii 2017	71	104	8	97	23.3%	8.28 [4.21 , 16.28]
Moers-Carpi 2015	168	306	10	306	27.9%	16.80 [9.06 , 31.17]
Wu 2019	202	316	5	101	14.5%	12.91 [5.47 , 30.47]
Subtotal (95% CI)		**948**		**727**	**100.0%**	**12.38 [8.93 , 17.16]**
Total events:	590		35			

Heterogeneity: Tau² = 0.00; Chi² = 2.34, df = 3 (P = 0.50); I² = 0%
Test for overall effect: Z = 15.10 (P < 0.00001)

29.3.2 8 weeks						
Carruthers 2014	126	222	13	223	38.5%	9.74 [5.67 , 16.70]
Harii 2017	50	104	8	97	32.7%	5.83 [2.91 , 11.66]
Moers-Carpi 2015	120	306	6	306	28.9%	20.00 [8.95 , 44.71]
Subtotal (95% CI)		**632**		**626**	**100.0%**	**10.13 [5.34 , 19.23]**
Total events:	296		27			

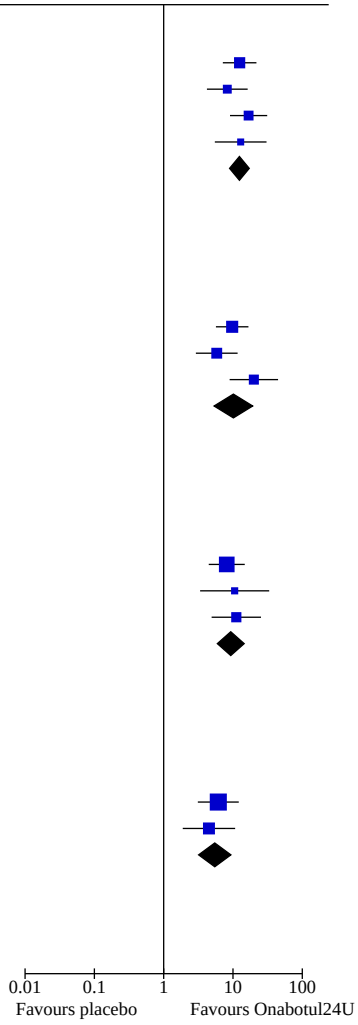
Heterogeneity: Tau² = 0.20; Chi² = 5.44, df = 2 (P = 0.07); I² = 63%
Test for overall effect: Z = 7.09 (P < 0.00001)

29.3.3 12 weeks						
Carruthers 2014	89	222	11	223	55.4%	8.13 [4.47 , 14.78]
Harii 2017	34	104	3	97	15.1%	10.57 [3.36 , 33.30]
Moers-Carpi 2015	67	306	6	306	29.5%	11.17 [4.92 , 25.36]
Subtotal (95% CI)		**632**		**626**	**100.0%**	**9.29 [5.95 , 14.50]**
Total events:	190		20			

Heterogeneity: Tau² = 0.00; Chi² = 0.44, df = 2 (P = 0.80); I² = 0%
Test for overall effect: Z = 9.81 (P < 0.00001)

29.3.4 16 weeks						
Carruthers 2014	55	222	9	223	62.1%	6.14 [3.11 , 12.11]
Moers-Carpi 2015	27	306	6	306	37.9%	4.50 [1.88 , 10.74]
Subtotal (95% CI)		**528**		**529**	**100.0%**	**5.46 [3.19 , 9.32]**
Total events:	82		15			

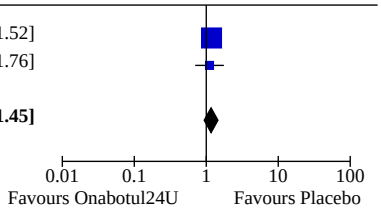
Heterogeneity: Tau² = 0.00; Chi² = 0.30, df = 1 (P = 0.58); I² = 0%
Test for overall effect: Z = 6.21 (P < 0.00001)



Analysis 29.4. Comparison 29: OnabotulinumtoxinA24 units versus placebo one treatment in crow's feet lines, Outcome 4: Total adverse events

Study or Subgroup	OnabotulinumtoxinA 24U Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Carruthers 2014	86	220	74	224	77.3%	1.18 [0.92 , 1.52]
Harii 2017	38	151	22	97	22.7%	1.11 [0.70 , 1.76]
Total (95% CI)		**371**		**321**	**100.0%**	**1.17 [0.94 , 1.45]**
Total events:	124		96			

Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 1 (P = 0.81); I² = 0%
Test for overall effect: Z = 1.38 (P = 0.17)
Test for subgroup differences: Not applicable

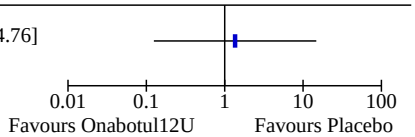


Comparison 30. OnabotulinumtoxinA 12 units versus placebo one treatment in crow's feet lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
30.1 Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
30.2 Physician assessment of success by analysing scores and scales	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
30.2.1 4 weeks	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
30.2.2 8 weeks	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
30.2.3 12 weeks	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
30.3 Total adverse events	2	657	Risk Ratio (IV, Random, 95% CI)	1.33 [0.87, 2.02]

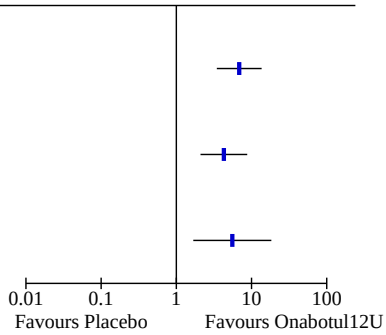
Analysis 30.1. Comparison 30: OnabotulinumtoxinA 12 units versus placebo one treatment in crow's feet lines, Outcome 1: Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

Study or Subgroup	OnabotulinumtoxinA 12U Events	Total	Placebo Events	Total	Risk Ratio IV, Random, 95% CI
Harii 2017	2	143	1	97	1.36 [0.12 , 14.76]



Analysis 30.2. Comparison 30: OnabotulinumtoxinA 12 units versus placebo one treatment in crow's feet lines, Outcome 2: Physician assessment of success by analysing scores and scales

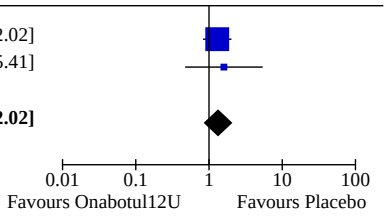
Study or Subgroup	OnabotulinumtoxinA 12U Events	Total	Placebo Events	Total	Risk Ratio IV, Random, 95% CI
30.2.1 4 weeks					
Harii 2017	56	99	8	97	6.86 [3.45 , 13.62]
30.2.2 8 weeks					
Harii 2017	35	99	8	97	4.29 [2.10 , 8.76]
30.2.3 12 weeks					
Harii 2017	17	99	3	97	5.55 [1.68 , 18.34]



Analysis 30.3. Comparison 30: OnabotulinumtoxinA 12 units versus placebo one treatment in crow's feet lines, Outcome 3: Total adverse events

Study or Subgroup	OnabotulinumtoxinA 12U Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Harii 2017	42	143	22	97	88.2%	1.29 [0.83 , 2.02]
Wu 2019	15	316	3	101	11.8%	1.60 [0.47 , 5.41]
Total (95% CI)		**459**		**198**	**100.0%**	**1.33 [0.87 , 2.02]**
Total events:	57		25			

Heterogeneity: Tau² = 0.00; Chi² = 0.10, df = 1 (P = 0.75); I² = 0%
Test for overall effect: Z = 1.32 (P = 0.19)
Test for subgroup differences: Not applicable



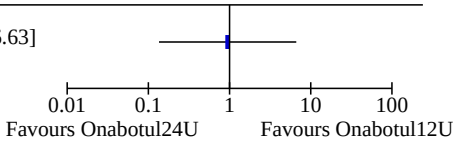
Comparison 31. OnabotulinumtoxinA 24 units versus OnabotulinumtoxinA 12 units one treatment in crow's feet lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
31.1 Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
31.2 Physician assessment of success by analysing scores and scales	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
31.2.1 4 weeks	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
31.2.2 8 weeks	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
31.2.3 12 weeks	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
31.3 Total adverse events	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected

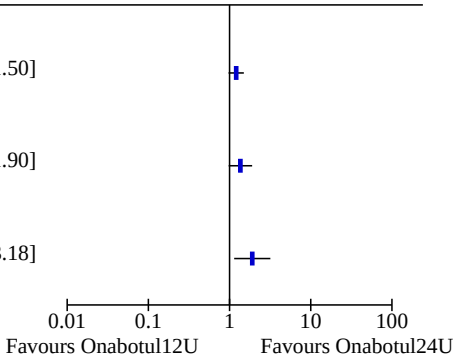
Analysis 31.1. Comparison 31: OnabotulinumtoxinA 24 units versus OnabotulinumtoxinA 12 units one treatment in crow's feet lines, Outcome 1: Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

	Onabotul24U		Onabotul12U		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	IV, Random, 95% CI	IV, Random, 95% CI
Harii 2017	2	151	2	143	0.95 [0.14 , 6.63]	



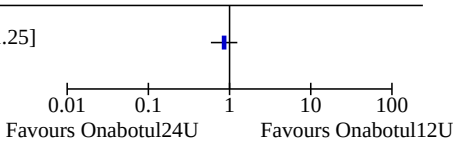
Analysis 31.2. Comparison 31: OnabotulinumtoxinA 24 units versus OnabotulinumtoxinA 12 units one treatment in crow's feet lines, Outcome 2: Physician assessment of success by analysing scores and scales

	Onabotul24U		Onabotul12U		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	IV, Random, 95% CI	IV, Random, 95% CI
31.2.1 4 weeks						
Harii 2017	71	104	56	99	1.21 [0.97 , 1.50]	
31.2.2 8 weeks						
Harii 2017	50	104	35	99	1.36 [0.97 , 1.90]	
31.2.3 12 weeks						
Harii 2017	34	104	17	99	1.90 [1.14 , 3.18]	



Analysis 31.3. Comparison 31: OnabotulinumtoxinA 24 units versus OnabotulinumtoxinA 12 units one treatment in crow's feet lines, Outcome 3: Total adverse events

	Onabotul24U		Onabotul12U		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	IV, Random, 95% CI	IV, Random, 95% CI
Harii 2017	38	151	42	143	0.86 [0.59 , 1.25]	

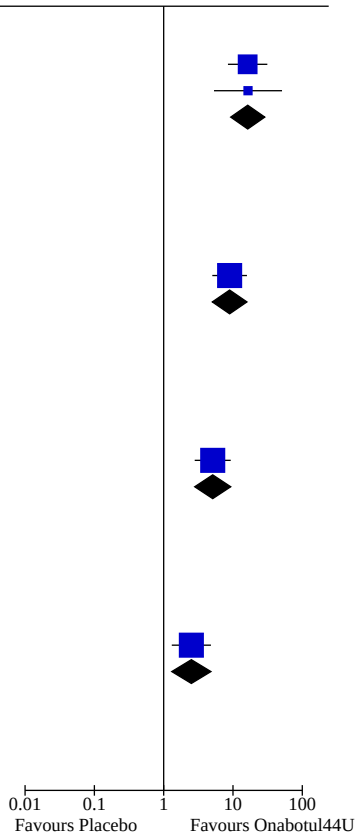


Comparison 32. OnabotulinumtoxinA 44 units versus placebo one treatments in glabellar lines and crow's feet lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
32.1 Participant assessment of success by analysing scores and scales	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
32.1.1 4 weeks	2	808	Risk Ratio (M-H, Random, 95% CI)	16.33 [9.27, 28.76]
32.1.2 8 weeks	1	611	Risk Ratio (M-H, Random, 95% CI)	8.95 [5.03, 15.90]
32.1.3 12 weeks	1	611	Risk Ratio (M-H, Random, 95% CI)	5.10 [2.80, 9.28]
32.1.4 16 weeks	1	611	Risk Ratio (M-H, Random, 95% CI)	2.51 [1.31, 4.81]
32.2 Physician assessment of success by analysing scores and scales	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
32.2.1 4 weeks	2	808	Risk Ratio (M-H, Random, 95% CI)	11.09 [4.12, 29.83]
32.2.2 8 weeks	2	808	Risk Ratio (M-H, Random, 95% CI)	9.94 [1.78, 55.44]
32.2.3 12 weeks	2	808	Risk Ratio (M-H, Random, 95% CI)	5.96 [0.60, 58.98]
32.3 Total adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

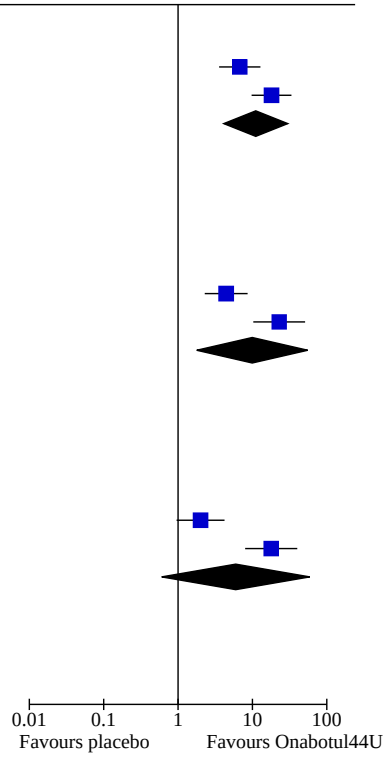
Analysis 32.1. Comparison 32: OnabotulinumtoxinA 44 units versus placebo one treatments in glabellar lines and crow's feet lines, Outcome 1: Participant assessment of success by analysing scores and scales

Study or Subgroup	OnabotulinumtoxinA 44U Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
32.1.1 4 weeks						
Moers-Carpi 2015	146	305	9	306	74.9%	16.28 [8.46 , 31.31]
Carruthers 2015	52	101	3	96	25.1%	16.48 [5.32 , 50.99]
Subtotal (95% CI)		**406**		**402**	**100.0%**	**16.33 [9.27 , 28.76]**
Total events:	198		12			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.99); I² = 0%						
Test for overall effect: Z = 9.67 (P < 0.00001)						
32.1.2 8 weeks						
Moers-Carpi 2015	107	305	12	306	100.0%	8.95 [5.03 , 15.90]
Subtotal (95% CI)		**305**		**306**	**100.0%**	**8.95 [5.03 , 15.90]**
Total events:	107		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 7.47 (P < 0.00001)						
32.1.3 12 weeks						
Moers-Carpi 2015	61	305	12	306	100.0%	5.10 [2.80 , 9.28]
Subtotal (95% CI)		**305**		**306**	**100.0%**	**5.10 [2.80 , 9.28]**
Total events:	61		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 5.34 (P < 0.00001)						
32.1.4 16 weeks						
Moers-Carpi 2015	30	305	12	306	100.0%	2.51 [1.31 , 4.81]
Subtotal (95% CI)		**305**		**306**	**100.0%**	**2.51 [1.31 , 4.81]**
Total events:	30		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.77 (P = 0.006)						



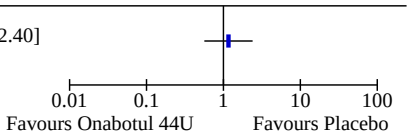
Analysis 32.2. Comparison 32: OnabotulinumtoxinA 44 units versus placebo one treatments in glabellar lines and crow's feet lines, Outcome 2: Physician assessment of success by analysing scores and scales

Study or Subgroup	44U Events	44U Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
32.2.1 4 weeks						
Carruthers 2015	64	101	9	96	49.6%	6.76 [3.57 , 12.81]
Moers-Carpi 2015	180	305	10	306	50.4%	18.06 [9.75 , 33.46]
Subtotal (95% CI)		**406**		**402**	**100.0%**	**11.09 [4.12 , 29.83]**
Total events:	244		19			
Heterogeneity: Tau² = 0.41; Chi² = 4.96, df = 1 (P = 0.03); I² = 80%						
Test for overall effect: Z = 4.76 (P < 0.00001)						
32.2.2 8 weeks						
Carruthers 2015	42	101	9	96	50.9%	4.44 [2.28 , 8.61]
Moers-Carpi 2015	137	305	6	306	49.1%	22.91 [10.27 , 51.08]
Subtotal (95% CI)		**406**		**402**	**100.0%**	**9.94 [1.78 , 55.44]**
Total events:	179		15			
Heterogeneity: Tau² = 1.40; Chi² = 10.91, df = 1 (P = 0.0010); I² = 91%						
Test for overall effect: Z = 2.62 (P = 0.009)						
32.2.3 12 weeks						
Carruthers 2015	19	101	9	96	50.2%	2.01 [0.96 , 4.22]
Moers-Carpi 2015	107	305	6	306	49.8%	17.89 [7.98 , 40.09]
Subtotal (95% CI)		**406**		**402**	**100.0%**	**5.96 [0.60 , 58.98]**
Total events:	126		15			
Heterogeneity: Tau² = 2.58; Chi² = 17.48, df = 1 (P < 0.0001); I² = 94%						
Test for overall effect: Z = 1.53 (P = 0.13)						



Analysis 32.3. Comparison 32: OnabotulinumtoxinA 44 units versus placebo one treatments in glabellar lines and crow's feet lines, Outcome 3: Total adverse events

Study or Subgroup	OnabotulinumtoxinA 44U Events	OnabotulinumtoxinA 44U Total	Placebo Events	Placebo Total	Risk Ratio M-H, Random, 95% CI
Rivers 2015	13	63	11	62	1.16 [0.56 , 2.40]

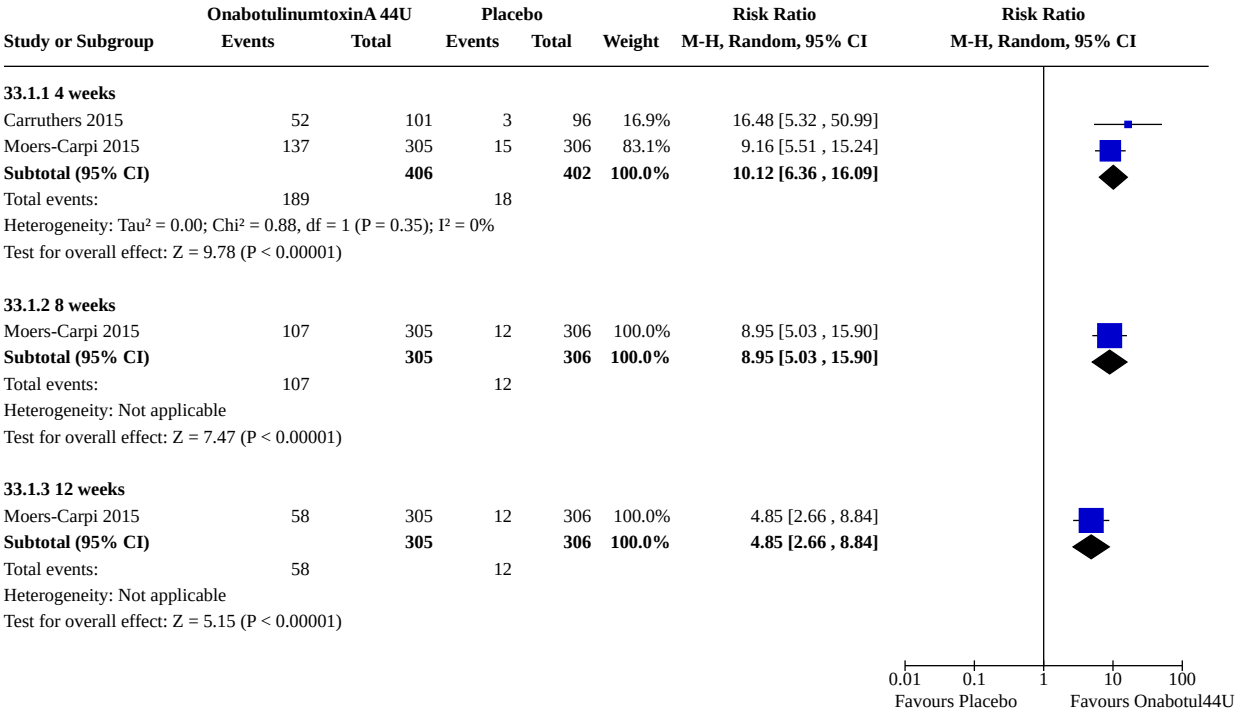


Comparison 33. OnabotulinumtoxinA 44 units versus placebo two cycles of treatments in crow's feet lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
33.1 Participant assessment of success by analysing scores and scales	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
33.1.1 4 weeks	2	808	Risk Ratio (M-H, Random, 95% CI)	10.12 [6.36, 16.09]
33.1.2 8 weeks	1	611	Risk Ratio (M-H, Random, 95% CI)	8.95 [5.03, 15.90]

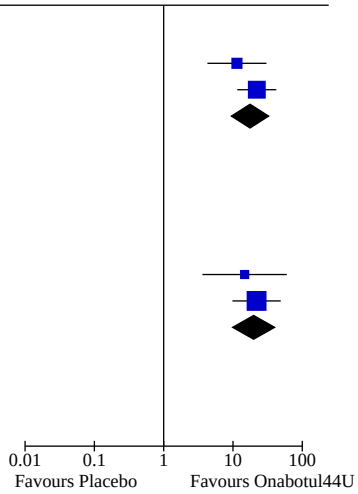
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
33.1.3 12 weeks	1	611	Risk Ratio (M-H, Random, 95% CI)	4.85 [2.66, 8.84]
33.2 Physician assessment of success by analysing scores and scales	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
33.2.1 4 weeks	2	808	Risk Ratio (M-H, Random, 95% CI)	17.63 [9.50, 32.69]
33.2.2 8 weeks	2	808	Risk Ratio (M-H, Random, 95% CI)	19.86 [9.90, 39.87]
33.3 Total adverse events	2	808	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.98, 1.30]

Analysis 33.1. Comparison 33: OnabotulinumtoxinA 44 units versus placebo two cycles of treatments in crow's feet lines, Outcome 1: Participant assessment of success by analysing scores and scales



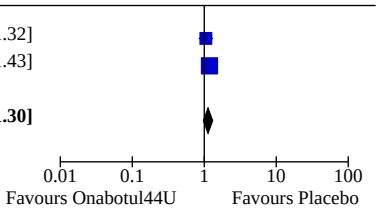
Analysis 33.2. Comparison 33: OnabotulinumtoxinA 44 units versus placebo two cycles of treatments in crow's feet lines, Outcome 2: Physician assessment of success by analysing scores and scales

Study or Subgroup	OnabotulinumtoxinA 44U Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
33.2.1 4 weeks						
Carruthers 2015	48	101	4	96	34.1%	11.41 [4.28 , 30.42]
Moers-Carpi 2015	198	305	9	306	65.9%	22.07 [11.54 , 42.23]
Subtotal (95% CI)		**406**		**402**	**100.0%**	**17.63 [9.50 , 32.69]**
Total events:	246		13			
Heterogeneity: Tau² = 0.04; Chi² = 1.23, df = 1 (P = 0.27); I² = 19%						
Test for overall effect: Z = 9.10 (P < 0.00001)						
33.2.2 8 weeks						
Carruthers 2015	31	101	2	96	24.7%	14.73 [3.62 , 59.88]
Moers-Carpi 2015	131	305	6	306	75.3%	21.90 [9.82 , 48.88]
Subtotal (95% CI)		**406**		**402**	**100.0%**	**19.86 [9.90 , 39.87]**
Total events:	162		8			
Heterogeneity: Tau² = 0.00; Chi² = 0.23, df = 1 (P = 0.63); I² = 0%						
Test for overall effect: Z = 8.41 (P < 0.00001)						



Analysis 33.3. Comparison 33: OnabotulinumtoxinA 44 units versus placebo two cycles of treatments in crow's feet lines, Outcome 3: Total adverse events

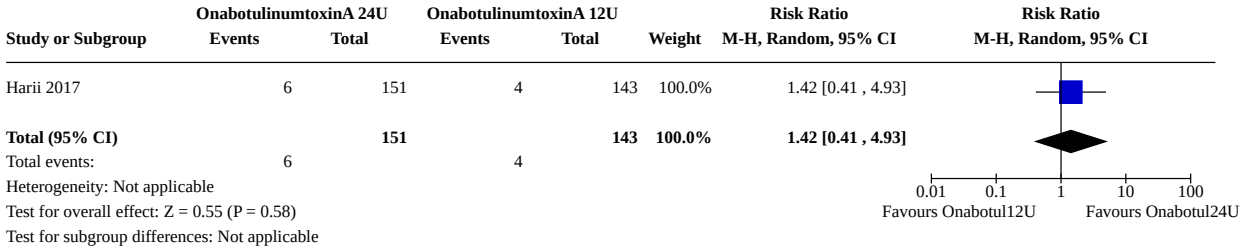
Study or Subgroup	OnabotulinumtoxinA 44U Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Carruthers 2015	62	101	56	96	40.0%	1.05 [0.84 , 1.32]
Moers-Carpi 2015	139	305	118	306	60.0%	1.18 [0.98 , 1.43]
Total (95% CI)		**406**		**402**	**100.0%**	**1.13 [0.98 , 1.30]**
Total events:	201		174			
Heterogeneity: Tau² = 0.00; Chi² = 0.61, df = 1 (P = 0.44); I² = 0%						
Test for overall effect: Z = 1.63 (P = 0.10)						
Test for subgroup differences: Not applicable						



Comparison 34. OnabotulinumtoxinA 24 units versus 12 units five cycles of treatment in crow's feet lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
34.1 Total adverse events	1	294	Risk Ratio (M-H, Random, 95% CI)	1.42 [0.41, 4.93]

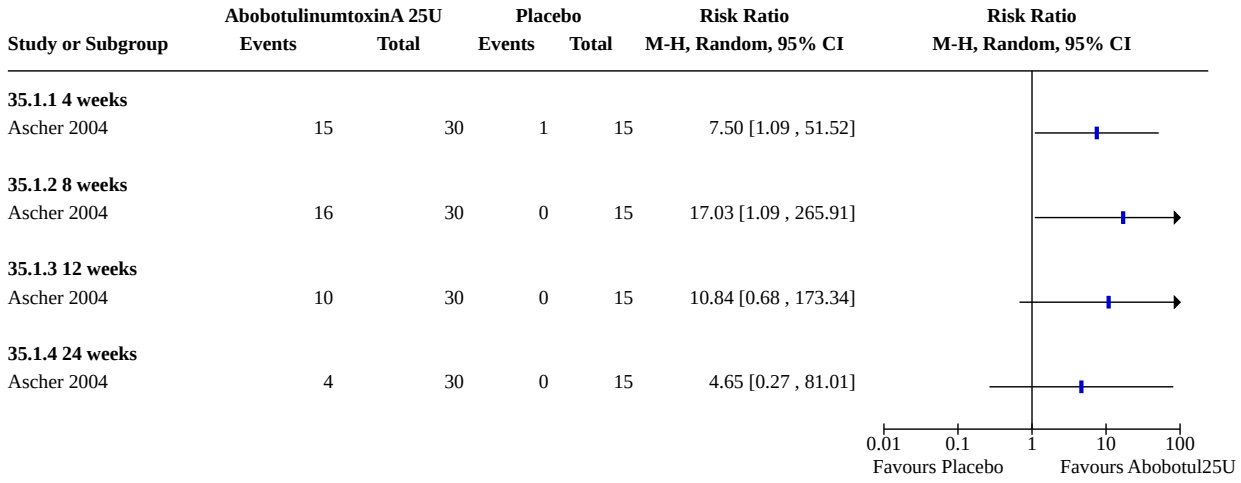
Analysis 34.1. Comparison 34: OnabotulinumtoxinA 24 units versus 12 units five cycles of treatment in crow's feet lines, Outcome 1: Total adverse events



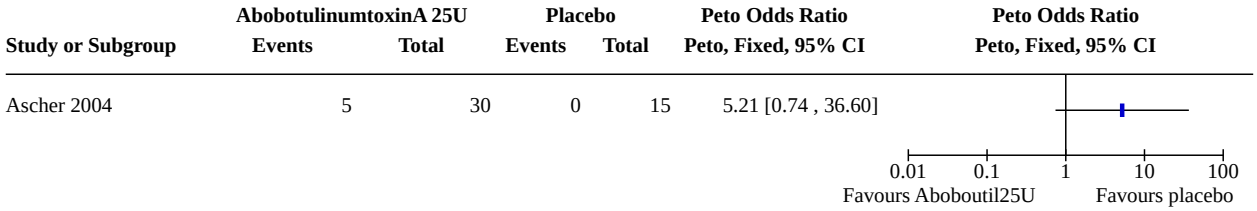
Comparison 35. AbobotulinumtoxinA 25 units versus placebo one cycle of treatment, glabellar lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
35.1 Physician assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
35.1.1 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
35.1.2 8 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
35.1.3 12 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
35.1.4 24 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
35.2 Total adverse events	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected

Analysis 35.1. Comparison 35: AbobotulinumtoxinA 25 units versus placebo one cycle of treatment, glabellar lines, Outcome 1: Physician assessment of success by analysing scores and scales



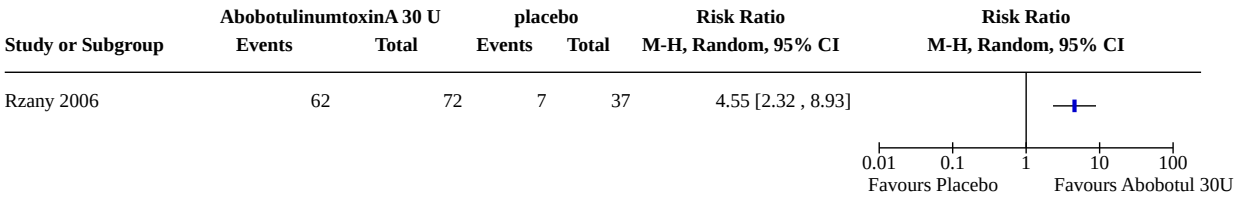
Analysis 35.2. Comparison 35: AbobotulinumtoxinA 25 units versus placebo one cycle of treatment, glabellar lines, Outcome 2: Total adverse events



Comparison 36. AbobotulinumtoxinA 30 units versus placebo one cycle of treatment in glabellar lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
36.1 Physician assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 36.1. Comparison 36: AbobotulinumtoxinA 30 units versus placebo one cycle of treatment in glabellar lines, Outcome 1: Physician assessment of success by analysing scores and scales



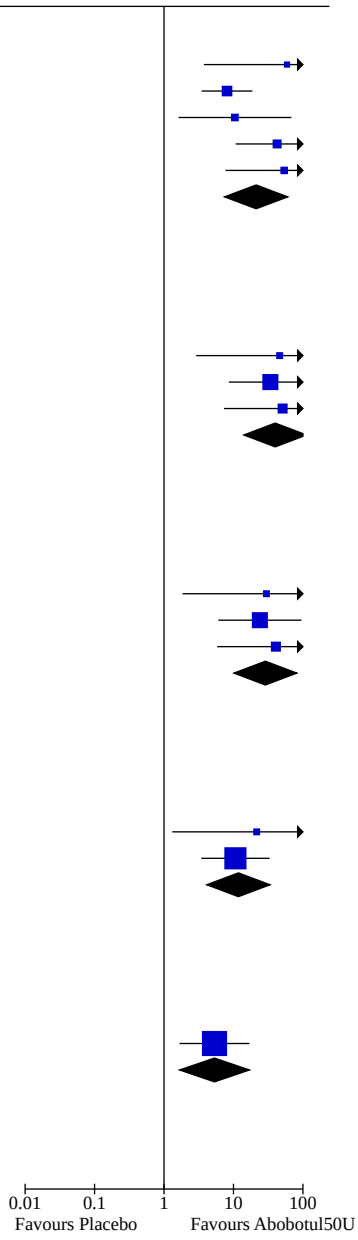
Comparison 37. AbobotulinumtoxinA 50 units versus placebo one treatment glabellar lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
37.1 Participant assessment of success by analysing scores and scales	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
37.1.1 4 weeks	5	915	Risk Ratio (M-H, Random, 95% CI)	21.22 [7.43, 60.56]
37.1.2 8 weeks	3	725	Risk Ratio (M-H, Random, 95% CI)	39.89 [14.10, 112.88]
37.1.3 12 weeks	3	725	Risk Ratio (M-H, Random, 95% CI)	28.83 [10.16, 81.81]
37.1.4 16 weeks	2	371	Risk Ratio (M-H, Random, 95% CI)	11.78 [4.12, 33.66]
37.1.5 20 weeks	1	300	Risk Ratio (M-H, Random, 95% CI)	5.33 [1.67, 16.99]
37.2 Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)	7	1294	Risk Ratio (M-H, Random, 95% CI)	3.36 [0.88, 12.87]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
37.3 Physician assessment of success by analysing scores and scales	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
37.3.1 4 weeks	7	1060	Risk Ratio (M-H, Random, 95% CI)	15.78 [8.75, 28.45]
37.3.2 8 weeks	5	802	Risk Ratio (M-H, Random, 95% CI)	30.84 [11.58, 82.12]
37.3.3 12 weeks	6	900	Risk Ratio (M-H, Random, 95% CI)	17.79 [6.70, 47.28]
37.3.4 16 weeks	2	371	Risk Ratio (M-H, Random, 95% CI)	29.88 [6.01, 148.52]
37.3.5 20 weeks	1	300	Risk Ratio (M-H, Random, 95% CI)	17.00 [2.36, 122.39]
37.4 Total adverse events	8	1471	Risk Ratio (M-H, Random, 95% CI)	1.25 [1.05, 1.49]
37.5 Duration of treatment (days)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 37.1. Comparison 37: AbobotulinumtoxinA 50 units versus placebo one treatment glabellar lines, Outcome 1: Participant assessment of success by analysing scores and scales

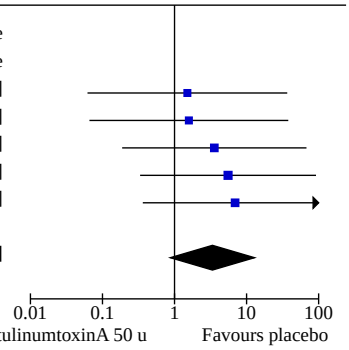
Study or Subgroup	AbobotulinumtoxinA 50U Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
37.1.1 4 weeks						
Ascher 2018	29	35	0	35	10.6%	59.00 [3.75 , 929.17]
Brandt 2009	80	105	5	53	31.5%	8.08 [3.48 , 18.73]
Kane 2009	21	22	1	11	17.5%	10.50 [1.62 , 68.19]
Monheit 2019	170	200	2	100	23.6%	42.50 [10.76 , 167.79]
NCT02450526	263	294	1	60	16.8%	53.67 [7.68 , 374.98]
Subtotal (95% CI)		**656**		**259**	**100.0%**	**21.22 [7.43 , 60.56]**
Total events:	563		9			
Heterogeneity: Tau² = 0.72; Chi² = 8.71, df = 4 (P = 0.07); I² = 54%						
Test for overall effect: Z = 5.71 (P < 0.00001)						
37.1.2 8 weeks						
Ascher 2018	22	35	0	36	14.2%	46.25 [2.91 , 734.13]
Monheit 2019	136	200	2	100	57.2%	34.00 [8.59 , 134.51]
NCT02450526	250	294	1	60	28.6%	51.02 [7.30 , 356.52]
Subtotal (95% CI)		**529**		**196**	**100.0%**	**39.89 [14.10 , 112.88]**
Total events:	408		3			
Heterogeneity: Tau² = 0.00; Chi² = 0.13, df = 2 (P = 0.94); I² = 0%						
Test for overall effect: Z = 6.95 (P < 0.00001)						
37.1.3 12 weeks						
Ascher 2018	14	35	0	36	14.1%	29.81 [1.85 , 481.21]
Monheit 2019	96	200	2	100	57.2%	24.00 [6.04 , 95.35]
NCT02450526	200	294	1	60	28.8%	40.82 [5.84 , 285.49]
Subtotal (95% CI)		**529**		**196**	**100.0%**	**28.83 [10.16 , 81.81]**
Total events:	310		3			
Heterogeneity: Tau² = 0.00; Chi² = 0.20, df = 2 (P = 0.90); I² = 0%						
Test for overall effect: Z = 6.32 (P < 0.00001)						
37.1.4 16 weeks						
Ascher 2018	10	35	0	36	14.1%	21.58 [1.31 , 354.82]
Monheit 2019	64	200	3	100	85.9%	10.67 [3.44 , 33.11]
Subtotal (95% CI)		**235**		**136**	**100.0%**	**11.78 [4.12 , 33.66]**
Total events:	74		3			
Heterogeneity: Tau² = 0.00; Chi² = 0.21, df = 1 (P = 0.65); I² = 0%						
Test for overall effect: Z = 4.60 (P < 0.00001)						
37.1.5 20 weeks						
Monheit 2019	32	200	3	100	100.0%	5.33 [1.67 , 16.99]
Subtotal (95% CI)		**200**		**100**	**100.0%**	**5.33 [1.67 , 16.99]**
Total events:	32		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.83 (P = 0.005)						



Analysis 37.2. Comparison 37: AbobotulinumtoxinA 50 units versus placebo one treatment glabellar lines, Outcome 2: Major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

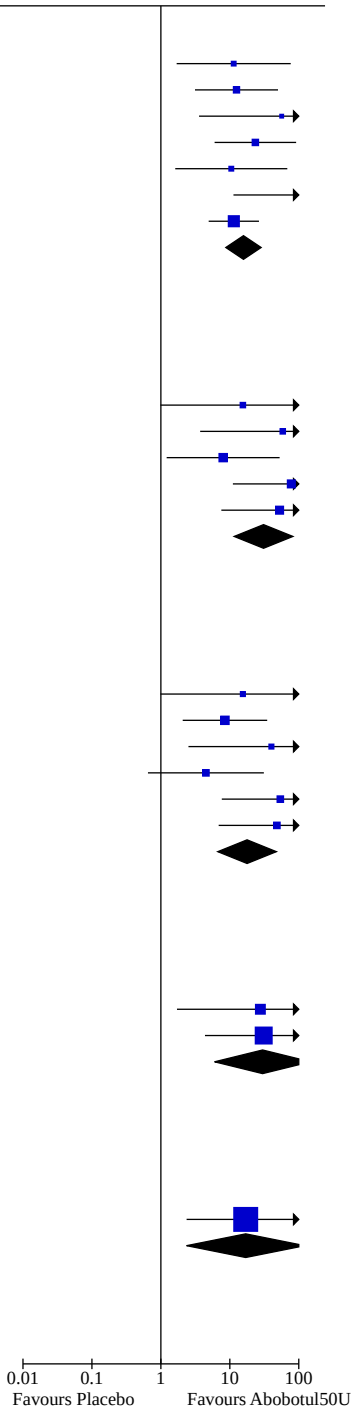
Study or Subgroup	AbobotulinumtoxinA 50U Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Ascher 2004	0	29	0	15		Not estimable
Ascher 2005	0	50	0	50		Not estimable
Monheit 2019	1	200	0	100	17.7%	1.51 [0.06 , 36.68]
Rzany 2006	1	73	0	38	17.9%	1.58 [0.07 , 37.91]
Brandt 2009	3	105	0	53	20.8%	3.57 [0.19 , 67.79]
NCT02450526	13	326	0	66	22.8%	5.53 [0.33 , 91.93]
Monheit 2007	3	95	0	94	20.7%	6.93 [0.36 , 132.29]
Total (95% CI)		**878**		**416**	**100.0%**	**3.36 [0.88 , 12.87]**
Total events:	21		0			

Heterogeneity: Tau² = 0.00; Chi² = 0.84, df = 4 (P = 0.93); I² = 0%
Test for overall effect: Z = 1.77 (P = 0.08)
Test for subgroup differences: Not applicable



Analysis 37.3. Comparison 37: AbobotulinumtoxinA 50 units versus placebo one treatment glabellar lines, Outcome 3: Physician assessment of success by analysing scores and scales

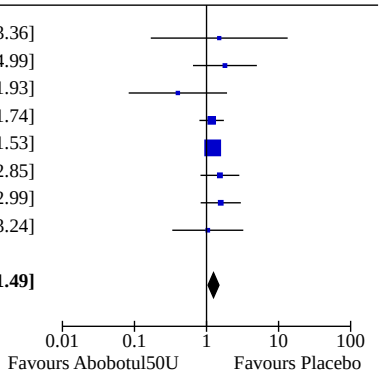
Study or Subgroup	AbobotulinumtoxinA 50U Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
37.3.1 4 weeks						
Ascher 2004	22	29	1	15	9.1%	11.38 [1.69 , 76.43]
Ascher 2005	25	50	2	50	16.5%	12.50 [3.13 , 49.98]
Ascher 2018	27	35	0	36	4.5%	56.53 [3.58 , 892.24]
Brandt 2009	93	105	2	53	17.0%	23.47 [6.02 , 91.56]
Kane 2009	21	22	1	11	9.4%	10.50 [1.62 , 68.19]
Monheit 2019	178	200	0	100	4.4%	179.39 [11.29 , 2849.58]
NCT02450526	280	294	5	60	39.0%	11.43 [4.94 , 26.46]
Subtotal (95% CI)		**735**		**325**	**100.0%**	**15.78 [8.75 , 28.45]**
Total events:	646		11			
Heterogeneity: Tau² = 0.05; Chi² = 6.46, df = 6 (P = 0.37); I² = 7%						
Test for overall effect: Z = 9.17 (P < 0.00001)						
37.3.2 8 weeks						
Ascher 2004	14	29	0	15	12.5%	15.47 [0.99 , 242.70]
Ascher 2018	28	35	0	36	12.4%	58.58 [3.71 , 923.86]
Kane 2009	16	22	1	11	26.1%	8.00 [1.21 , 52.75]
Monheit 2019	156	200	1	100	24.4%	78.00 [11.08 , 549.08]
NCT02450526	258	294	1	60	24.6%	52.65 [7.54 , 367.88]
Subtotal (95% CI)		**580**		**222**	**100.0%**	**30.84 [11.58 , 82.12]**
Total events:	472		3			
Heterogeneity: Tau² = 0.03; Chi² = 4.10, df = 4 (P = 0.39); I² = 2%						
Test for overall effect: Z = 6.86 (P < 0.00001)						
37.3.3 12 weeks						
Ascher 2004	14	29	0	15	10.4%	15.47 [0.99 , 242.70]
Ascher 2005	17	49	2	49	26.4%	8.50 [2.07 , 34.84]
Ascher 2018	19	35	0	36	10.3%	40.08 [2.51 , 639.27]
Kane 2009	9	22	1	11	17.8%	4.50 [0.65 , 31.16]
Monheit 2019	108	200	1	100	17.5%	54.00 [7.65 , 381.20]
NCT02450526	236	294	1	60	17.7%	48.16 [6.89 , 336.63]
Subtotal (95% CI)		**629**		**271**	**100.0%**	**17.79 [6.70 , 47.28]**
Total events:	403		5			
Heterogeneity: Tau² = 0.42; Chi² = 7.02, df = 5 (P = 0.22); I² = 29%						
Test for overall effect: Z = 5.77 (P < 0.00001)						
37.3.4 16 weeks						
Ascher 2018	13	35	0	36	33.1%	27.75 [1.71 , 449.60]
Monheit 2019	62	200	1	100	66.9%	31.00 [4.36 , 220.31]
Subtotal (95% CI)		**235**		**136**	**100.0%**	**29.88 [6.01 , 148.52]**
Total events:	75		1			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.95); I² = 0%						
Test for overall effect: Z = 4.15 (P < 0.0001)						
37.3.5 20 weeks						
Monheit 2019	34	200	1	100	100.0%	17.00 [2.36 , 122.39]
Subtotal (95% CI)		**200**		**100**	**100.0%**	**17.00 [2.36 , 122.39]**
Total events:	34		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.81 (P = 0.005)						



Analysis 37.4. Comparison 37: AbobotulinumtoxinA 50 units versus placebo one treatment glabellar lines, Outcome 4: Total adverse events

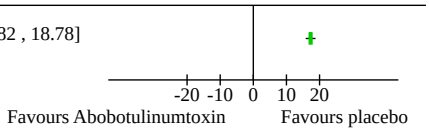
Study or Subgroup	AbobotulinumtoxinA 50U Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Ascher 2004	3	34	1	17	0.6%	1.50 [0.17 , 13.36]
Ascher 2005	9	50	5	50	2.9%	1.80 [0.65 , 4.99]
Ascher 2018	2	35	5	35	1.2%	0.40 [0.08 , 1.93]
Brandt 2009	49	105	21	53	19.9%	1.18 [0.80 , 1.74]
Monheit 2007	64	95	52	94	57.7%	1.22 [0.97 , 1.53]
Monheit 2019	23	200	15	200	7.9%	1.53 [0.82 , 2.85]
NCT02450526	70	326	9	66	7.4%	1.57 [0.83 , 2.99]
Rzany 2006	8	73	4	38	2.4%	1.04 [0.33 , 3.24]
Total (95% CI)		**918**		**553**	**100.0%**	**1.25 [1.05 , 1.49]**
Total events:	228		112			

Heterogeneity: Tau² = 0.00; Chi² = 3.74, df = 7 (P = 0.81); I² = 0%
Test for overall effect: Z = 2.51 (P = 0.01)
Test for subgroup differences: Not applicable



Analysis 37.5. Comparison 37: AbobotulinumtoxinA 50 units versus placebo one treatment glabellar lines, Outcome 5: Duration of treatment (days)

Study or Subgroup	AbobotulinumtoxinA 50U Mean	SD	Total	Placebo Mean	SD	Total	Mean Difference IV, Random, 95% CI
Ascher 2005	117	4.6	50	99.7	2.7	50	17.30 [15.82 , 18.78]

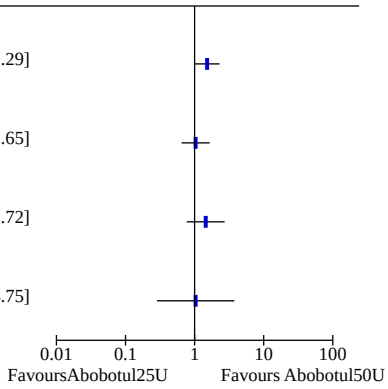


Comparison 38. AbobotulinumtoxinA 50 units versus 25 units one cycle of treatment, glabellar lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
38.1 Physician assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
38.1.1 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
38.1.2 8 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
38.1.3 12 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
38.1.4 24 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
38.2 Total adverse events	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected

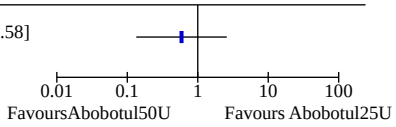
Analysis 38.1. Comparison 38: AbobotulinumtoxinA 50 units versus 25 units one cycle of treatment, glabellar lines, Outcome 1: Physician assessment of success by analysing scores and scales

Study or Subgroup	AbobotulinumtoxinA 50U Events	Total	AbobotulinumtoxinA 25U Events	Total	Risk Ratio M-H, Random, 95% CI
38.1.1 4 weeks					
Ascher 2004	22	29	15	30	1.52 [1.00 , 2.29]
38.1.2 8 weeks					
Ascher 2004	16	29	16	30	1.03 [0.65 , 1.65]
38.1.3 12 weeks					
Ascher 2004	14	29	10	30	1.45 [0.77 , 2.72]
38.1.4 24 weeks					
Ascher 2004	4	29	4	30	1.03 [0.29 , 3.75]



Analysis 38.2. Comparison 38: AbobotulinumtoxinA 50 units versus 25 units one cycle of treatment, glabellar lines, Outcome 2: Total adverse events

Study or Subgroup	AbobotulinumtoxinA 50U Events	Total	AbobotulinumtoxinA 25U Events	Total	Peto Odds Ratio Peto, Fixed, 95% CI
Ascher 2004	3	29	5	30	0.59 [0.13 , 2.58]

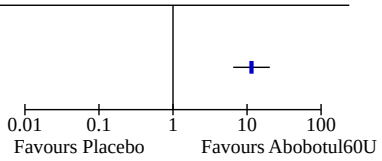


Comparison 39. AbobotulinumtoxinA 60 units versus placebo one cycle of treatment in glabellar lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
39.1 Participant assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
39.1.1 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
39.2 Physician assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
39.2.1 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

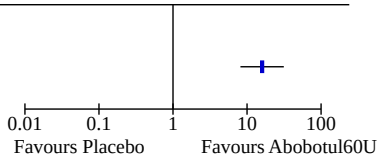
Analysis 39.1. Comparison 39: AbobotulinumtoxinA 60 units versus placebo one cycle of treatment in glabellar lines, Outcome 1: Participant assessment of success by analysing scores and scales

Study or Subgroup	AbobotulinumtoxinA 60U Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 95% CI
39.1.1 4 weeks					
Kane 2009	250	281	11	142	11.48 [6.50 , 20.29]



Analysis 39.2. Comparison 39: AbobotulinumtoxinA 60 units versus placebo one cycle of treatment in glabellar lines, Outcome 2: Physician assessment of success by analysing scores and scales

Study or Subgroup	AbobotulinumtoxinA 60U Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 95% CI
39.2.1 4 weeks					
Kane 2009	253	281	8	142	15.98 [8.14 , 31.36]

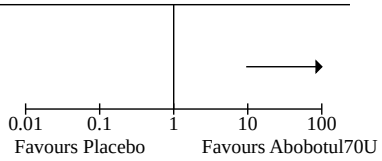


Comparison 40. AbobotulinumtoxinA 70 units versus placebo one cycle of treatment in glabellar lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
40.1 Participant assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
40.1.1 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
40.2 Physician assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
40.2.1 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

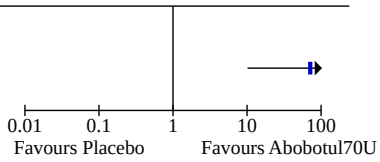
Analysis 40.1. Comparison 40: AbobotulinumtoxinA 70 units versus placebo one cycle of treatment in glabellar lines, Outcome 1: Participant assessment of success by analysing scores and scales

Study or Subgroup	ABobotulinumtoxinA 70U Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 95% CI
40.1.1 4 weeks					
Kane 2009	173	203	0	88	151.39 [9.54 , 2402.95]



Analysis 40.2. Comparison 40: AbobotulinumtoxinA 70 units versus placebo one cycle of treatment in glabellar lines, Outcome 2: Physician assessment of success by analysing scores and scales

Study or Subgroup	AbobotulinumtoxinA 70U Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 95% CI
40.2.1 4 weeks					
Kane 2009	163	201	1	88	71.36 [10.15 , 501.56]

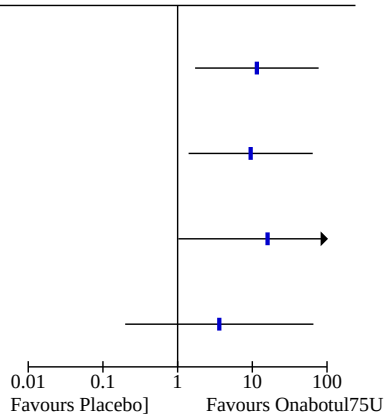


Comparison 41. AbobotulinumtoxinA 75 units versus placebo one cycle of treatment in glabellar lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
41.1 Physician assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
41.1.1 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
41.1.2 8 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
41.1.3 12 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
41.1.4 24 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 41.1. Comparison 41: AbobotulinumtoxinA 75 units versus placebo one cycle of treatment in glabellar lines, Outcome 1: Physician assessment of success by analysing scores and scales

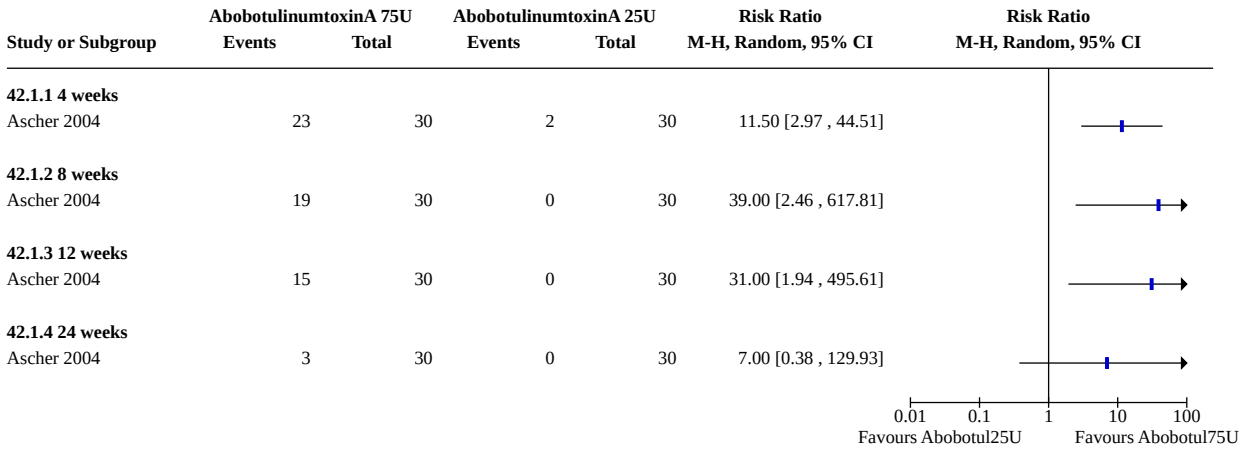
Study or Subgroup	Abobotulinumtoxin 75U Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 95% CI
41.1.1 4 weeks					
Ascher 2004	23	30	1	15	11.50 [1.71 , 77.18]
41.1.2 8 weeks					
Ascher 2004	19	30	1	15	9.50 [1.40 , 64.35]
41.1.3 12 weeks					
Ascher 2004	15	30	0	15	16.00 [1.02 , 250.48]
41.1.4 24 weeks					
Ascher 2004	3	30	0	15	3.61 [0.20 , 65.73]



Comparison 42. AbobotulinumtoxinA 75 units versus 25 units one cycle of treatment in glabellar lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
42.1 Physician assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
42.1.1 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
42.1.2 8 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
42.1.3 12 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
42.1.4 24 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 42.1. Comparison 42: AbobotulinumtoxinA 75 units versus 25 units one cycle of treatment in glabellar lines, Outcome 1: Physician assessment of success by analysing scores and scales

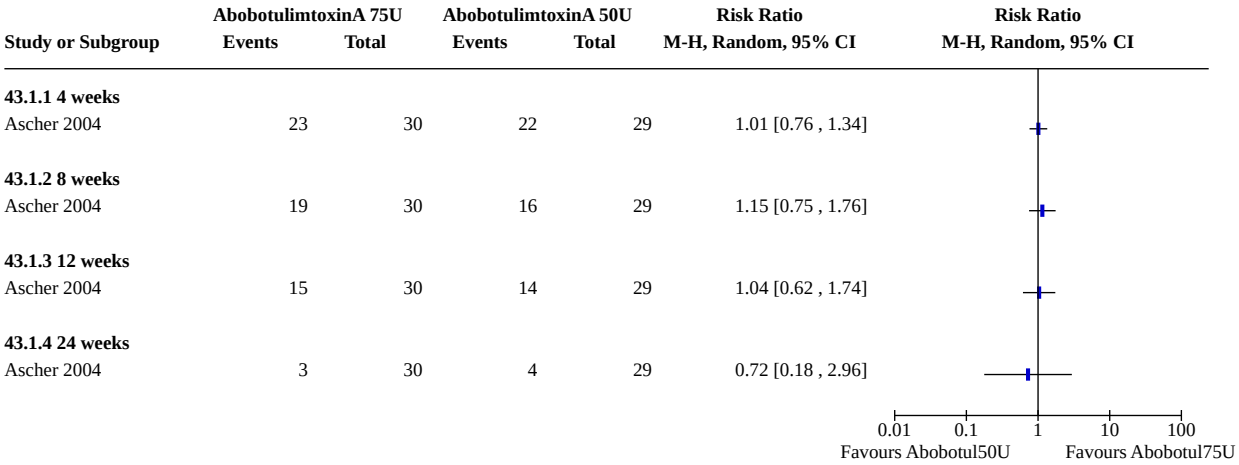


Comparison 43. AbobotulinumtoxinA 75 units versus 50 units one cycle of treatment in glabellar lines

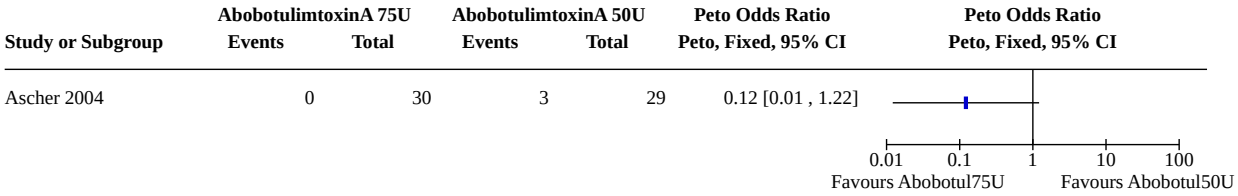
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
43.1 Physician assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
43.1.1 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
43.1.2 8 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
43.1.3 12 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
43.1.4 24 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
43.2 Total adverse events	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected

Analysis 43.1. Comparison 43: AbobotulinumtoxinA 75 units versus 50 units one cycle of treatment in glabellar lines, Outcome 1: Physician assessment of success by analysing scores and scales



Analysis 43.2. Comparison 43: AbobotulinumtoxinA 75 units versus 50 units one cycle of treatment in glabellar lines, Outcome 2: Total adverse events

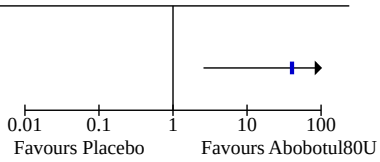


Comparison 44. AbobotulinumtoxinA 80 units versus placebo one cycle of treatment in glabellar lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
44.1 Participant assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
44.1.1 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
44.2 Physician assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
44.2.1 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

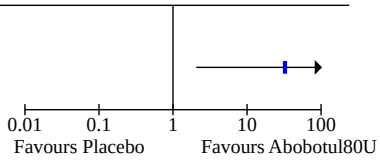
Analysis 44.1. Comparison 44: AbobotulinumtoxinA 80 units versus placebo one cycle of treatment in glabellar lines, Outcome 1: Participant assessment of success by analysing scores and scales

Study or Subgroup	AbobotulinumtoxinA 80U Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 95% CI
44.1.1 4 weeks					
Kane 2009	25	33	0	26	40.50 [2.58 , 635.35]



Analysis 44.2. Comparison 44: AbobotulinumtoxinA 80 units versus placebo one cycle of treatment in glabellar lines, Outcome 2: Physician assessment of success by analysing scores and scales

Study or Subgroup	AbobotulinumtoxinA 80U Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 95% CI
44.2.1 4 weeks					
Kane 2009	20	33	0	26	32.56 [2.06 , 514.19]

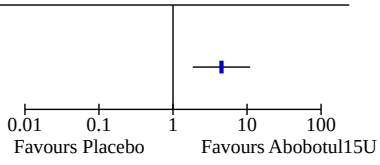


Comparison 45. AbobotulinumtoxinA 15 units versus placebo one cycle of treatment crow's feet lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
45.1 Physician assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
45.1.1 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 45.1. Comparison 45: AbobotulinumtoxinA 15 units versus placebo one cycle of treatment crow's feet lines, Outcome 1: Physician assessment of success by analysing scores and scales

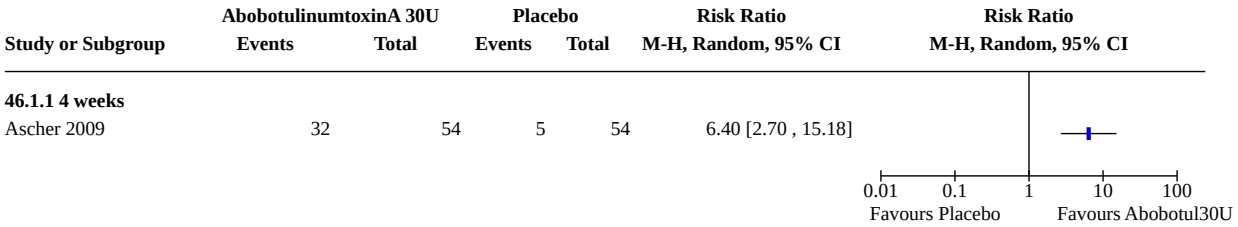
Study or Subgroup	AbobotulinumtoxinA 15U Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 95% CI
45.1.1 4 weeks					
Ascher 2009	23	55	5	54	4.52 [1.85 , 11.01]



Comparison 46. AbobotulinumtoxinA 30 units versus placebo one cycle of treatment crow's feet lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
46.1 Physician assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
46.1.1 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

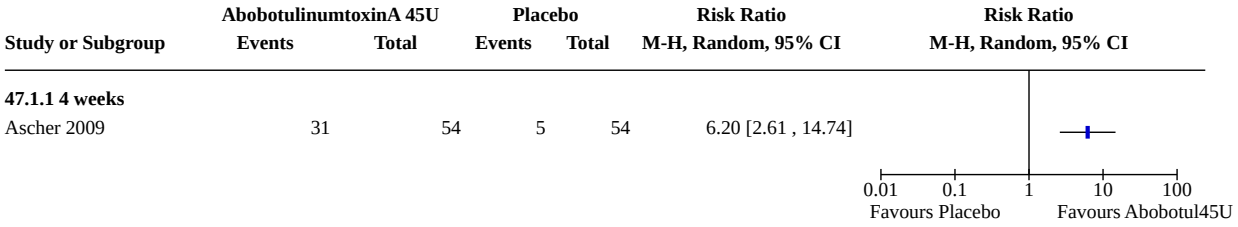
Analysis 46.1. Comparison 46: AbobotulinumtoxinA 30 units versus placebo one cycle of treatment crow's feet lines, Outcome 1: Physician assessment of success by analysing scores and scales



Comparison 47. AbobotulinumtoxinA 45 units versus placebo one cycle of treatment crow's feet lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
47.1 Physician assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
47.1.1 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 47.1. Comparison 47: AbobotulinumtoxinA 45 units versus placebo one cycle of treatment crow's feet lines, Outcome 1: Physician assessment of success by analysing scores and scales

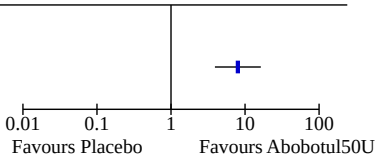


Comparison 48. AbobotulinumtoxinA 50 units versus placebo, three cycles of treatment in glabellar lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
48.1 Participant assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
48.1.1 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
48.2 Physician assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
48.2.1 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
48.3 Total adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

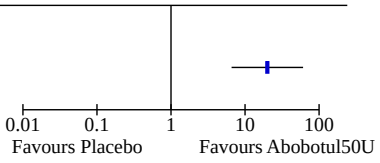
Analysis 48.1. Comparison 48: AbobotulinumtoxinA 50 units versus placebo, three cycles of treatment in glabellar lines, Outcome 1: Participant assessment of success by analysing scores and scales

Study or Subgroup	AbobotulinumtoxinA 50U Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 95% CI
48.1.1 4 weeks					
Rubin 2009	56	71	7	71	8.00 [3.92 , 16.33]



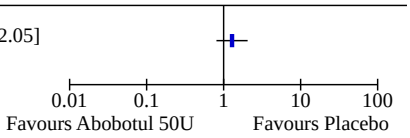
Analysis 48.2. Comparison 48: AbobotulinumtoxinA 50 units versus placebo, three cycles of treatment in glabellar lines, Outcome 2: Physician assessment of success by analysing scores and scales

Study or Subgroup	AbobotulinumtoxinA 50U Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 95% CI
48.2.1 4 weeks					
Rubin 2009	60	71	3	71	20.00 [6.58 , 60.80]



Analysis 48.3. Comparison 48: AbobotulinumtoxinA 50 units versus placebo, three cycles of treatment in glabellar lines, Outcome 3: Total adverse events

Study or Subgroup	AbobotulinumtoxinA 50U Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 95% CI
Rubin 2009	27	71	21	71	1.29 [0.81 , 2.05]

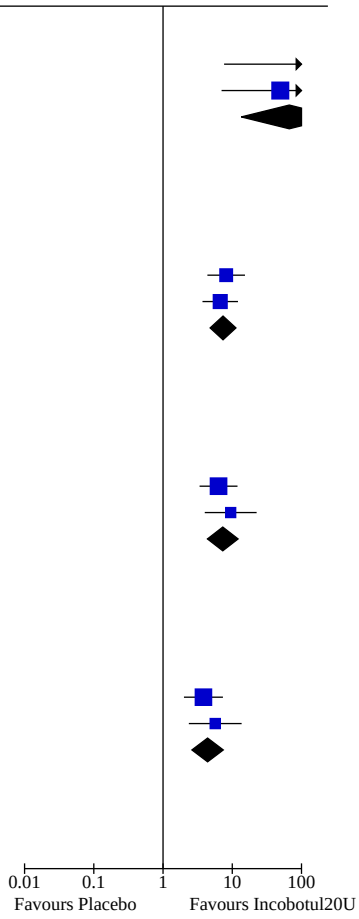


Comparison 49. IncobotulinumtoxinA 20 units versus placebo one treatment glabellar lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
49.1 Participant assessment of success by analysing scores and scales	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
49.1.1 4 weeks	2	547	Risk Ratio (M-H, Random, 95% CI)	66.57 [13.50, 328.28]
49.1.2 8 weeks	2	547	Risk Ratio (M-H, Random, 95% CI)	7.35 [4.79, 11.29]
49.1.3 12 weeks	2	547	Risk Ratio (M-H, Random, 95% CI)	7.29 [4.38, 12.13]
49.1.4 16 weeks	2	547	Risk Ratio (M-H, Random, 95% CI)	4.40 [2.61, 7.41]
49.2 Physician assessment of success by analysing scores and scales	2	547	Risk Ratio (M-H, Random, 95% CI)	134.62 [19.05, 951.45]
49.3 Total adverse events	2	547	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.90, 1.53]

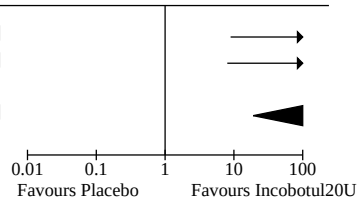
Analysis 49.1. Comparison 49: IncobotulinumtoxinA 20 units versus placebo one treatment glabellar lines, Outcome 1: Participant assessment of success by analysing scores and scales

Study or Subgroup	IncobotulinumtoxinA 20U Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
49.1.1 4 weeks						
Carruthers 2013	120	184	0	92	33.3%	121.15 [7.62 , 1926.38]
Hanke 2013	101	182	1	89	66.7%	49.39 [7.00 , 348.28]
Subtotal (95% CI)		**366**		**181**	**100.0%**	**66.57 [13.50 , 328.28]**
Total events:	221		1			
Heterogeneity: Tau² = 0.00; Chi² = 0.28, df = 1 (P = 0.59); I² = 0%						
Test for overall effect: Z = 5.16 (P < 0.00001)						
49.1.2 8 weeks						
Carruthers 2013	147	184	9	92	47.1%	8.17 [4.37 , 15.25]
Hanke 2013	137	182	10	89	52.9%	6.70 [3.71 , 12.08]
Subtotal (95% CI)		**366**		**181**	**100.0%**	**7.35 [4.79 , 11.29]**
Total events:	284		19			
Heterogeneity: Tau² = 0.00; Chi² = 0.20, df = 1 (P = 0.65); I² = 0%						
Test for overall effect: Z = 9.12 (P < 0.00001)						
49.1.3 12 weeks						
Carruthers 2013	114	184	9	92	65.1%	6.33 [3.37 , 11.90]
Hanke 2013	97	182	5	89	34.9%	9.49 [4.01 , 22.47]
Subtotal (95% CI)		**366**		**181**	**100.0%**	**7.29 [4.38 , 12.13]**
Total events:	211		14			
Heterogeneity: Tau² = 0.00; Chi² = 0.56, df = 1 (P = 0.46); I² = 0%						
Test for overall effect: Z = 7.65 (P < 0.00001)						
49.1.4 16 weeks						
Carruthers 2013	69	184	9	92	64.7%	3.83 [2.01 , 7.33]
Hanke 2013	58	182	5	89	35.3%	5.67 [2.36 , 13.64]
Subtotal (95% CI)		**366**		**181**	**100.0%**	**4.40 [2.61 , 7.41]**
Total events:	127		14			
Heterogeneity: Tau² = 0.00; Chi² = 0.50, df = 1 (P = 0.48); I² = 0%						
Test for overall effect: Z = 5.57 (P < 0.00001)						



Analysis 49.2. Comparison 49: IncobotulinumtoxinA 20 units versus placebo one treatment glabellar lines, Outcome 2: Physician assessment of success by analysing scores and scales

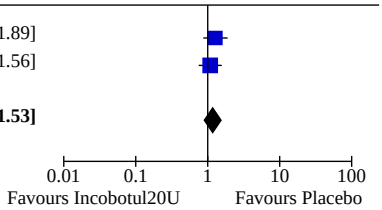
Study or Subgroup	IncobotulinumtoxinA 20U Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Carruthers 2013	141	184	0	92	50.0%	142.26 [8.95 , 2260.16]
Hanke 2013	129	182	0	89	50.0%	127.38 [8.02 , 2023.97]
Total (95% CI)		**366**		**181**	**100.0%**	**134.62 [19.05 , 951.45]**
Total events:	270		0			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.96); I² = 0%						
Test for overall effect: Z = 4.91 (P < 0.00001)						
Test for subgroup differences: Not applicable						



Analysis 49.3. Comparison 49: IncobotulinumtoxinA 20 units versus placebo one treatment glabellar lines, Outcome 3: Total adverse events

Study or Subgroup	IncobotulinumtoxinA 20U Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Carruthers 2013	64	184	25	92	47.2%	1.28 [0.87 , 1.89]
Hanke 2013	62	182	28	89	52.8%	1.08 [0.75 , 1.56]
Total (95% CI)		**366**		**181**	**100.0%**	**1.17 [0.90 , 1.53]**
Total events:	126		53			

Heterogeneity: Tau² = 0.00; Chi² = 0.38, df = 1 (P = 0.54); I² = 0%
Test for overall effect: Z = 1.16 (P = 0.24)
Test for subgroup differences: Not applicable

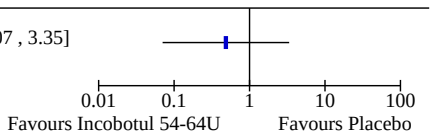


Comparison 50. IncobotulinumtoxinA 54 to 64units versus placebo one cycles of treatment glabellar lines, forehead liens, crow's feet lines

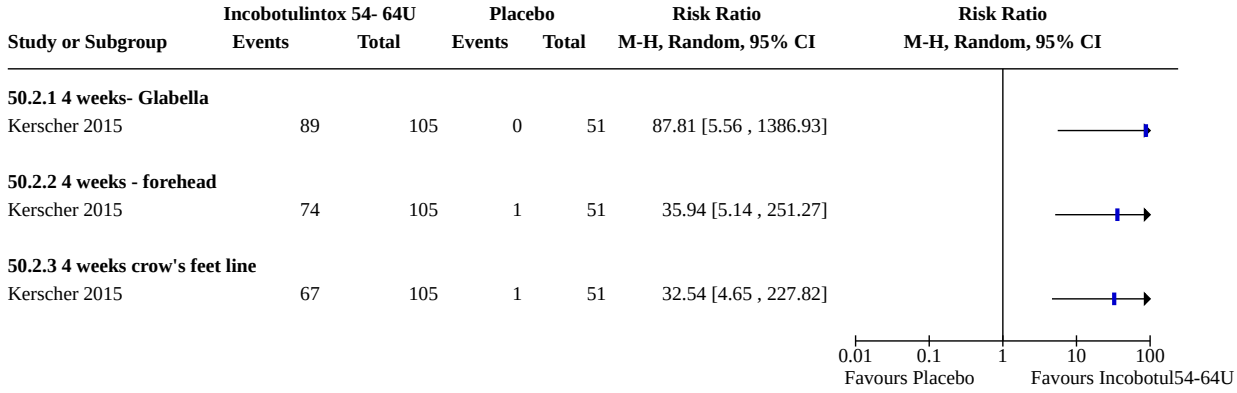
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
50.1 Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
50.2 Physician assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
50.2.1 4 weeks- Glabella	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
50.2.2 4 weeks - forehead	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
50.2.3 4 weeks crow's feet line	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
50.3 Total adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 50.1. Comparison 50: IncobotulinumtoxinA 54 to 64units versus placebo one cycles of treatment glabellar lines, forehead liens, crow's feet lines, Outcome 1: Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

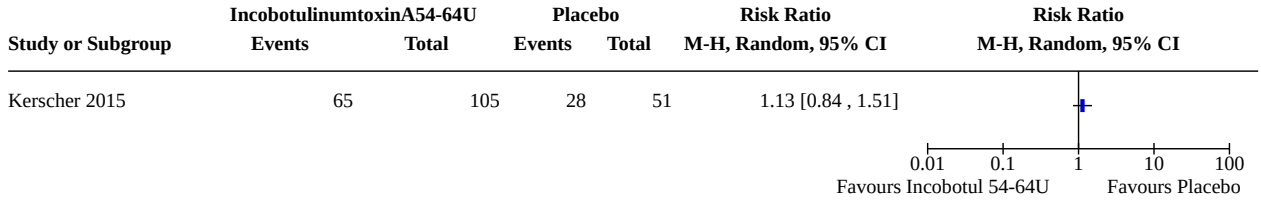
Study or Subgroup	IncobotulinumtoxinA54-64U Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 95% CI
Kerscher 2015	2	105	2	51	0.49 [0.07 , 3.35]



Analysis 50.2. Comparison 50: IncobotulinumtoxinA 54 to 64units versus placebo one cycles of treatment glabellar lines, forehead liens, crow's feet lines, Outcome 2: Physician assessment of success by analysing scores and scales



Analysis 50.3. Comparison 50: IncobotulinumtoxinA 54 to 64units versus placebo one cycles of treatment glabellar lines, forehead liens, crow's feet lines, Outcome 3: Total adverse events

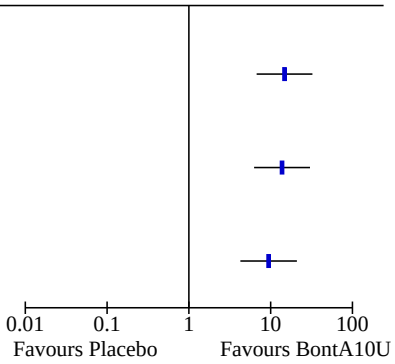


Comparison 51. HBTX-A 10 units versus placebo one cycle of treatment in glabellar lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
51.1 Participant assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
51.1.1 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
51.1.2 8 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
51.1.3 16 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
51.2 Total adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

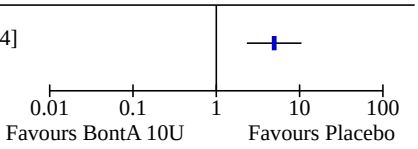
Analysis 51.1. Comparison 51: HBTX-A 10 units versus placebo one cycle of treatment in glabellar lines, Outcome 1: Participant assessment of success by analysing scores and scales

Study or Subgroup	BontA 10U Events	BontA 10U Total	Placebo Events	Placebo Total	Risk Ratio M-H, Random, 95% CI
51.1.1 4 weeks					
Feng 2015	133	183	6	122	14.78 [6.74 , 32.41]
51.1.2 8 weeks					
Feng 2015	124	183	6	122	13.78 [6.27 , 30.25]
51.1.3 16 weeks					
Feng 2015	85	183	6	122	9.44 [4.26 , 20.93]



Analysis 51.2. Comparison 51: HBTX-A 10 units versus placebo one cycle of treatment in glabellar lines, Outcome 2: Total adverse events

Study or Subgroup	BontA 10U Events	BontA 10U Total	Placebo Events	Placebo Total	Risk Ratio M-H, Random, 95% CI
Feng 2015	52	183	7	122	4.95 [2.33 , 10.54]

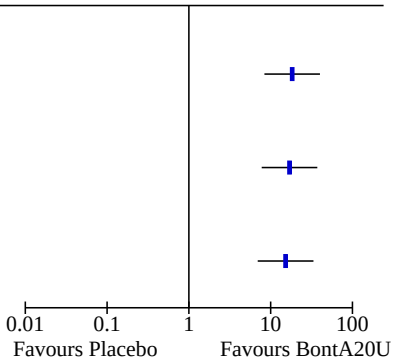


Comparison 52. HBTX-A 20 units versus placebo one cycle of treatment in glabellar lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
52.1 Participant assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
52.1.1 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
52.1.2 8 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
52.1.3 16 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
52.2 Total adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

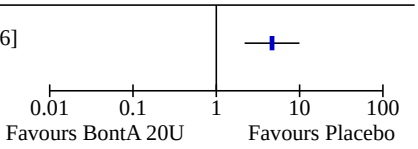
Analysis 52.1. Comparison 52: HBTX-A 20 units versus placebo one cycle of treatment in glabellar lines, Outcome 1: Participant assessment of success by analysing scores and scales

Study or Subgroup	BontA 20U Events	BontA 20U Total	Placebo Events	Placebo Total	Risk Ratio M-H, Random, 95% CI
52.1.1 4 weeks					
Feng 2015	165	183	6	122	18.33 [8.39 , 40.06]
52.1.2 8 weeks					
Feng 2015	153	183	6	122	17.00 [7.77 , 37.19]
52.1.3 16 weeks					
Feng 2015	137	183	6	122	15.22 [6.95 , 33.36]



Analysis 52.2. Comparison 52: HBTX-A 20 units versus placebo one cycle of treatment in glabellar lines, Outcome 2: Total adverse events

Study or Subgroup	BontA 20U Events	BontA 20U Total	Placebo Events	Placebo Total	Risk Ratio M-H, Random, 95% CI
Feng 2015	49	183	7	122	4.67 [2.19 , 9.96]



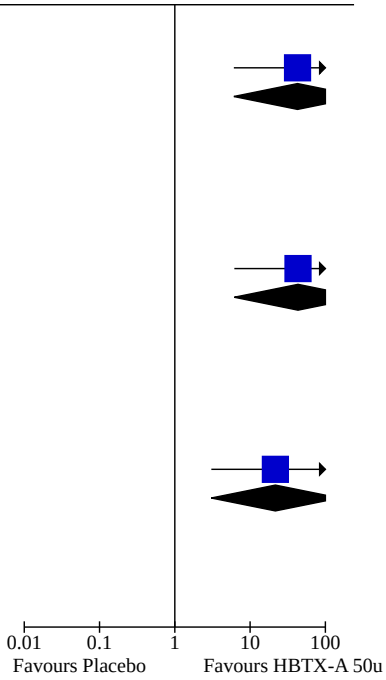
Comparison 53. HBTX-A 50 units versus placebo one cycle of treatment, glabellar lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
53.1 Participant assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
53.1.1 4 weeks	1	187	Risk Ratio (M-H, Random, 95% CI)	42.68 [6.08, 299.41]
53.1.2 8 weeks	1	182	Risk Ratio (M-H, Random, 95% CI)	43.28 [6.18, 303.19]
53.1.3 12 weeks	1	185	Risk Ratio (M-H, Random, 95% CI)	21.67 [3.06, 153.72]
53.2 Physician assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
53.2.1 4 weeks	1	185	Risk Ratio (M-H, Random, 95% CI)	49.69 [7.10, 347.71]
53.2.2 8 weeks	1	167	Risk Ratio (M-H, Random, 95% CI)	53.52 [7.65, 374.34]
53.2.3 12 weeks	1	183	Risk Ratio (M-H, Random, 95% CI)	33.17 [4.72, 233.16]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
53.3 Total adverse events	1	190	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.22 [0.02, 2.50]
53.3.1 Total adverse events	1	190	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.22 [0.02, 2.50]

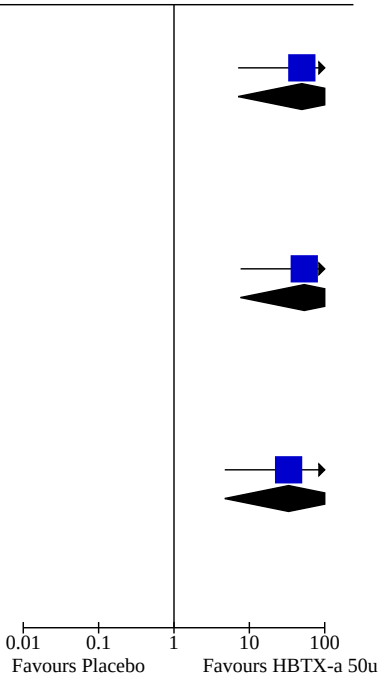
Analysis 53.1. Comparison 53: HBTX-A 50 units versus placebo one cycle of treatment, glabellar lines, Outcome 1: Participant assessment of success by analysing scores and scales

Study or Subgroup	HBTX-A 50u Events	HBTX-A 50u Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
53.1.1 4 weeks						
NCT02493946	84	124	1	63	100.0%	42.68 [6.08 , 299.41]
Subtotal (95% CI)		**124**		**63**	**100.0%**	**42.68 [6.08 , 299.41]**
Total events:	84		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.78 (P = 0.0002)						
53.1.2 8 weeks						
NCT02493946	88	122	1	60	100.0%	43.28 [6.18 , 303.19]
Subtotal (95% CI)		**122**		**60**	**100.0%**	**43.28 [6.18 , 303.19]**
Total events:	88		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.79 (P = 0.0001)						
53.1.3 12 weeks						
NCT02493946	43	123	1	62	100.0%	21.67 [3.06 , 153.72]
Subtotal (95% CI)		**123**		**62**	**100.0%**	**21.67 [3.06 , 153.72]**
Total events:	43		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.08 (P = 0.002)						



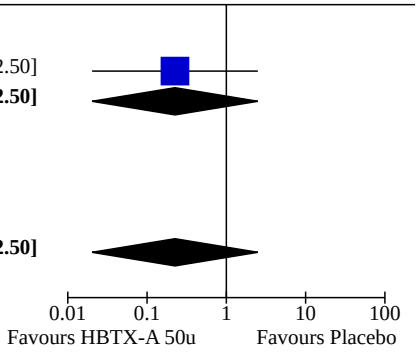
Analysis 53.2. Comparison 53: HBTX-A 50 units versus placebo one cycle of treatment, glabellar lines, Outcome 2: Physician assessment of success by analysing scores and scales

Study or Subgroup	HBTX-A 50u Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
53.2.1 4 weeks						
NCT02493946	101	124	1	61	100.0%	49.69 [7.10 , 347.71]
Subtotal (95% CI)		**124**		**61**	**100.0%**	**49.69 [7.10 , 347.71]**
Total events:	101		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.93 (P < 0.0001)						
53.2.2 8 weeks						
NCT02493946	93	106	1	61	100.0%	53.52 [7.65 , 374.34]
Subtotal (95% CI)		**106**		**61**	**100.0%**	**53.52 [7.65 , 374.34]**
Total events:	93		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.01 (P < 0.0001)						
53.2.3 12 weeks						
NCT02493946	68	123	1	60	100.0%	33.17 [4.72 , 233.16]
Subtotal (95% CI)		**123**		**60**	**100.0%**	**33.17 [4.72 , 233.16]**
Total events:	68		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.52 (P = 0.0004)						
Test for subgroup differences: Chi² = 0.13, df = 2 (P = 0.94), I² = 0%						



Analysis 53.3. Comparison 53: HBTX-A 50 units versus placebo one cycle of treatment, glabellar lines, Outcome 3: Total adverse events

Study or Subgroup	HBTX-A 50u Events	Total	Placebo Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
53.3.1 Total adverse events						
NCT02493946	1	126	2	64	100.0%	0.22 [0.02 , 2.50]
Subtotal (95% CI)		**126**		**64**	**100.0%**	**0.22 [0.02 , 2.50]**
Total events:	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.22 (P = 0.22)						
Total (95% CI)		**126**		**64**	**100.0%**	**0.22 [0.02 , 2.50]**
Total events:	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.22 (P = 0.22)						
Test for subgroup differences: Not applicable						

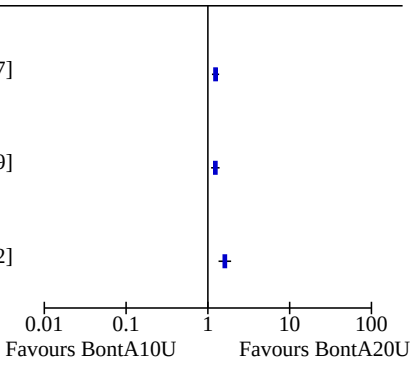


Comparison 54. HBTX-A 20 units versus 10 units one cycle of treatment in glabellar lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
54.1 Participant assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
54.1.1 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
54.1.2 8 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
54.1.3 16 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
54.2 Total adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

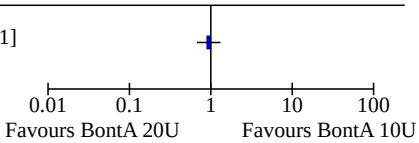
Analysis 54.1. Comparison 54: HBTX-A 20 units versus 10 units one cycle of treatment in glabellar lines, Outcome 1: Participant assessment of success by analysing scores and scales

Study or Subgroup	BontA 20U Events	BontA 20U Total	BontA 10U Events	BontA 10U Total	Risk Ratio M-H, Random, 95% CI
54.1.1 4 weeks					
Feng 2015	165	183	133	183	1.24 [1.12 , 1.37]
54.1.2 8 weeks					
Feng 2015	153	183	124	183	1.23 [1.10 , 1.39]
54.1.3 16 weeks					
Feng 2015	137	183	85	183	1.61 [1.35 , 1.92]



Analysis 54.2. Comparison 54: HBTX-A 20 units versus 10 units one cycle of treatment in glabellar lines, Outcome 2: Total adverse events

Study or Subgroup	BontA 20U Events	BontA 20U Total	BontA 10U Events	BontA 10U Total	Risk Ratio M-H, Random, 95% CI
Feng 2015	49	183	52	183	0.94 [0.68 , 1.31]

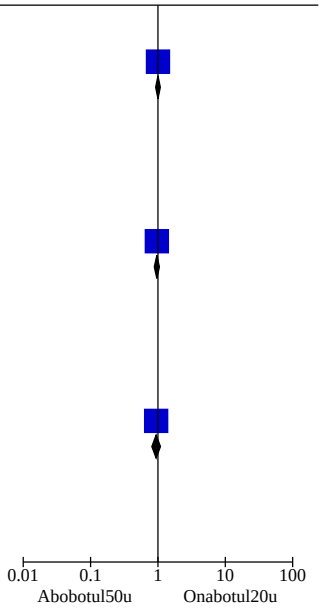


Comparison 55. AbobotulinumtoxinA 50 units versus OnabotulinumtoxinA 20 units one cycle of treatment in glabellar lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
55.1 Participant assessment success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
55.1.1 4 weeks	1	388	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.92, 1.08]
55.1.2 8 weeks	1	388	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.88, 1.05]
55.1.3 12 weeks	1	388	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.81, 1.09]
55.2 Major adverse events	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
55.2.1 Any major adverse events (eyelid ptosis, eyelid sensory disorder, s	1	433	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.65 [0.77, 9.09]
55.3 Physician assessment of success by analysing scores and scales	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
55.3.1 4 weeks	1	388	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.95, 1.06]
55.3.2 8 weeks	2	449	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.89, 1.02]
55.3.3 12 weeks	2	448	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.60, 1.40]
55.3.4 16 weeks	1	59	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.13, 1.55]
55.4 Total adverse events	2	492	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.67, 1.54]

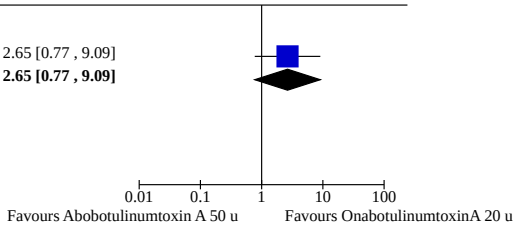
Analysis 55.1. Comparison 55: AbobotulinumtoxinA 50 units versus OnabotulinumtoxinA 20 units one cycle of treatment in glabellar lines, Outcome 1: Participant assessment success by analysing scores and scales

Study or Subgroup	AbobotulinumtoxinA 50U Events	Total	OnabotulinumtoxinA 20U Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
55.1.1 4 weeks						
NCT02450526	263	294	84	94	100.0%	1.00 [0.92 , 1.08]
Subtotal (95% CI)		**294**		**94**	**100.0%**	**1.00 [0.92 , 1.08]**
Total events:	263		84			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.03 (P = 0.98)						
55.1.2 8 weeks						
NCT02450526	250	294	83	94	100.0%	0.96 [0.88 , 1.05]
Subtotal (95% CI)		**294**		**94**	**100.0%**	**0.96 [0.88 , 1.05]**
Total events:	250		83			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.84 (P = 0.40)						
55.1.3 12 weeks						
NCT02450526	200	294	68	94	100.0%	0.94 [0.81 , 1.09]
Subtotal (95% CI)		**294**		**94**	**100.0%**	**0.94 [0.81 , 1.09]**
Total events:	200		68			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.82 (P = 0.41)						



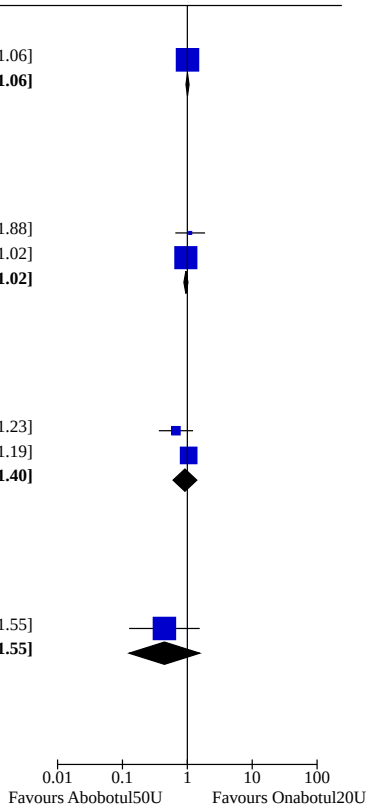
Analysis 55.2. Comparison 55: AbobotulinumtoxinA 50 units versus OnabotulinumtoxinA 20 units one cycle of treatment in glabellar lines, Outcome 2: Major adverse events

Study or Subgroup	AbobotulinumtoxinA 50U Events	Total	OnabotulinumtoxinA 20U Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
55.2.1 Any major adverse events (eyelid ptosis, eyelid sensory disorder, s						
NCT02450526	13	326	1	107	100.0%	2.65 [0.77 , 9.09]
Subtotal (95% CI)		**326**		**107**	**100.0%**	**2.65 [0.77 , 9.09]**
Total events:	13		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.55 (P = 0.12)						
Test for subgroup differences: Not applicable						



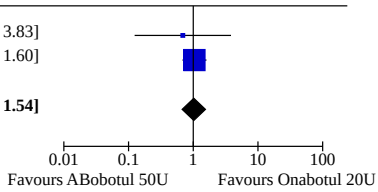
Analysis 55.3. Comparison 55: AbobotulinumtoxinA 50 units versus OnabotulinumtoxinA 20 units one cycle of treatment in glabellar lines, Outcome 3: Physician assessment of success by analysing scores and scales

Study or Subgroup	AbobotulinumtoxinA 50U Events	Total	OnabotulinumtoxinA 20U Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
55.3.1 4 weeks						
NCT02450526	280	294	89	94	100.0%	1.01 [0.95 , 1.06]
Subtotal (95% CI)		**294**		**94**	**100.0%**	**1.01 [0.95 , 1.06]**
Total events:	280		89			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.21 (P = 0.83)						
55.3.2 8 weeks						
Lowe 2006	15	30	14	31	1.8%	1.11 [0.65 , 1.88]
NCT02450526	258	294	87	94	98.2%	0.95 [0.88 , 1.02]
Subtotal (95% CI)		**324**		**125**	**100.0%**	**0.95 [0.89 , 1.02]**
Total events:	273		101			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.45$, df = 1 (P = 0.50); $I^2 = 0\%$						
Test for overall effect: Z = 1.40 (P = 0.16)						
55.3.3 12 weeks						
Lowe 2006	10	29	16	31	29.4%	0.67 [0.36 , 1.23]
NCT02450526	236	294	72	94	70.6%	1.05 [0.92 , 1.19]
Subtotal (95% CI)		**323**		**125**	**100.0%**	**0.92 [0.60 , 1.40]**
Total events:	246		88			
Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 2.22$, df = 1 (P = 0.14); $I^2 = 55\%$						
Test for overall effect: Z = 0.40 (P = 0.69)						
55.3.4 16 weeks						
Lowe 2006	3	29	7	30	100.0%	0.44 [0.13 , 1.55]
Subtotal (95% CI)		**29**		**30**	**100.0%**	**0.44 [0.13 , 1.55]**
Total events:	3		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.27 (P = 0.20)						



Analysis 55.4. Comparison 55: AbobotulinumtoxinA 50 units versus OnabotulinumtoxinA 20 units one cycle of treatment in glabellar lines, Outcome 4: Total adverse events

Study or Subgroup	AbobotulinumtoxinA 50U Events	Total	OnabotulinumtoxinA 20U Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Lowe 2006	2	29	3	30	5.8%	0.69 [0.12 , 3.83]
NCT02450526	70	326	22	107	94.2%	1.04 [0.68 , 1.60]
Total (95% CI)		**355**		**137**	**100.0%**	**1.02 [0.67 , 1.54]**
Total events:	72		25			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.21$, df = 1 (P = 0.65); $I^2 = 0\%$						
Test for overall effect: Z = 0.09 (P = 0.93)						
Test for subgroup differences: Not applicable						



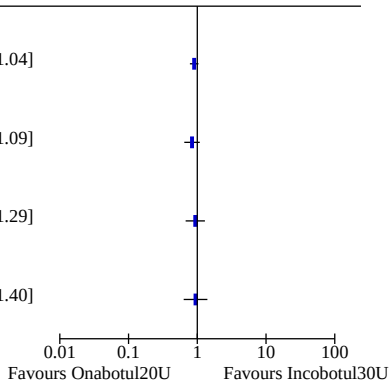
Comparison 56. IncobotulinumtoxinA 30 units versus OnabotulinumtoxinA 20 units one cycle of treatment in glabellar lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
56.1 Participant assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
56.1.1 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
56.1.2 12 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
56.1.3 14 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
56.1.4 16 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
56.2 Physician assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
56.2.1 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
56.2.2 12 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
56.2.3 14 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
56.2.4 16 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
56.3 Total adverse events	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected

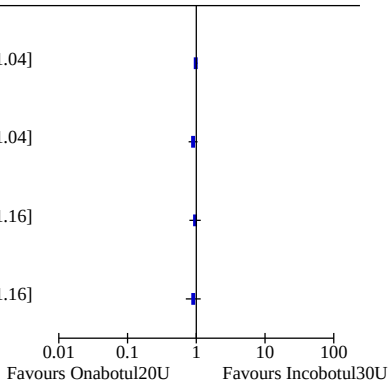
Analysis 56.1. Comparison 56: IncobotulinumtoxinA 30 units versus OnabotulinumtoxinA 20 units one cycle of treatment in glabellar lines, Outcome 1: Participant assessment of success by analysing scores and scales

Study or Subgroup	IncobotulinumtoxinA 30U Events	Total	OnabotulinumtoxinA 20U Events	Total	Risk Ratio M-H, Random, 95% CI
56.1.1 4 weeks					
Moers-Carpi 2012	82	112	91	112	0.90 [0.78 , 1.04]
56.1.2 12 weeks					
Moers-Carpi 2012	52	112	62	112	0.84 [0.65 , 1.09]
56.1.3 14 weeks					
Moers-Carpi 2012	43	112	46	112	0.93 [0.68 , 1.29]
56.1.4 16 weeks					
Moers-Carpi 2012	33	112	35	112	0.94 [0.63 , 1.40]



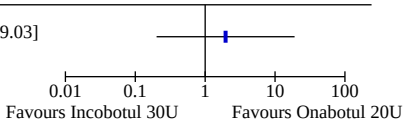
Analysis 56.2. Comparison 56: IncobotulinumtoxinA 30 units versus OnabotulinumtoxinA 20 units one cycle of treatment in glabellar lines, Outcome 2: Physician assessment of success by analysing scores and scales

Study or Subgroup	IncobotulinumtoxinA 30U Events	Total	OnabotulinumtoxinA 20U Events	Total	Risk Ratio M-H, Random, 95% CI
56.2.1 4 weeks					
Moers-Carpi 2012	106	112	108	112	0.98 [0.93 , 1.04]
56.2.2 12 weeks					
Moers-Carpi 2012	80	112	89	112	0.90 [0.77 , 1.04]
56.2.3 14 weeks					
Moers-Carpi 2012	72	112	75	112	0.96 [0.79 , 1.16]
56.2.4 16 weeks					
Moers-Carpi 2012	56	112	62	112	0.90 [0.70 , 1.16]



Analysis 56.3. Comparison 56: IncobotulinumtoxinA 30 units versus OnabotulinumtoxinA 20 units one cycle of treatment in glabellar lines, Outcome 3: Total adverse events

Study or Subgroup	IncobotulinumtoxinA 30U Events	Total	OnabotulinumtoxinA 20U Events	Total	Peto Odds Ratio Peto, Fixed, 95% CI
Moers-Carpi 2012	2	112	1	112	1.96 [0.20 , 19.03]

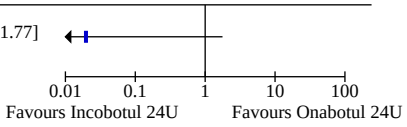


Comparison 57. IncobotulinumtoxinA 24 units versus OnabotulinumtoxinA 24 units one treatment in glabellar lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
57.1 Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
57.2 Physician assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
57.2.1 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
57.2.2 12 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
57.3 Total adverse events	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected

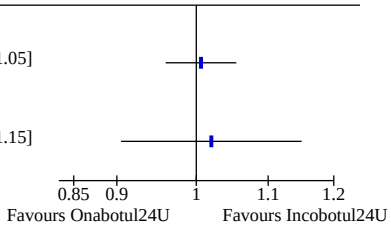
Analysis 57.1. Comparison 57: IncobotulinumtoxinA 24 units versus OnabotulinumtoxinA 24 units one treatment in glabellar lines, Outcome 1: Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

Study or Subgroup	IncobotulinumtoxinA 24U Events	Total	OnabotulinumtoxinA 24U Events	Total	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI
Satler 2010	0	284	1	97	0.02 [0.00 , 1.77]	



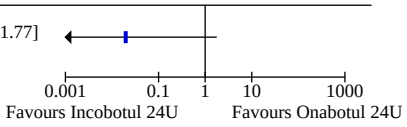
Analysis 57.2. Comparison 57: IncobotulinumtoxinA 24 units versus OnabotulinumtoxinA 24 units one treatment in glabellar lines, Outcome 2: Physician assessment of success by analysing scores and scales

Study or Subgroup	IncobotulinumtoxinA 24U Events	Total	OnabotulinumtoxinA 24U Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
57.2.1 4 weeks						
Satler 2010	274	284	93	97	1.01 [0.96 , 1.05]	
57.2.2 12 weeks						
Satler 2010	227	284	76	97	1.02 [0.91 , 1.15]	



Analysis 57.3. Comparison 57: IncobotulinumtoxinA 24 units versus OnabotulinumtoxinA 24 units one treatment in glabellar lines, Outcome 3: Total adverse events

Study or Subgroup	IncobotulinumtoxinA 24U Events	Total	OnabotulinumtoxinA 24U Events	Total	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI
Satler 2010	0	284	1	97	0.02 [0.00 , 1.77]	



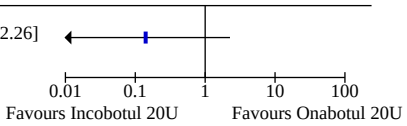
Comparison 58. IncobotulinumtoxinA 20 units versus OnabotulinumtoxinA 20 units one treatment in glabellar lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
58.1 Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
58.2 Physician assessment of success by analysing scores and scales - injector	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
58.2.1 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
58.2.2 8 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
58.2.3 12 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
58.2.4 16 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
58.3 Physician assessment of success by analysing scores and scales - independent observer	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
58.3.1 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
58.3.2 8 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
58.3.3 12 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
58.3.4 16 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
58.4 Total adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

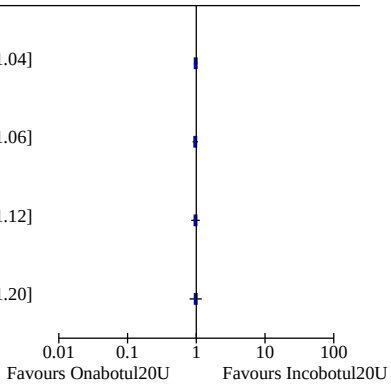
Analysis 58.1. Comparison 58: IncobotulinumtoxinA 20 units versus OnabotulinumtoxinA 20 units one treatment in glabellar lines, Outcome 1: Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

Study or Subgroup	IncobotulinumtoxinA 20U Events	IncobotulinumtoxinA 20U Total	OnabotulinumtoxinA 20U Events	OnabotulinumtoxinA 20U Total	Peto Odds Ratio Peto, Fixed, 95% CI
Kane 2015	0	122	2	128	0.14 [0.01 , 2.26]



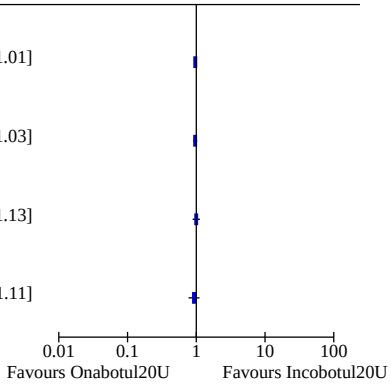
Analysis 58.2. Comparison 58: IncobotulinumtoxinA 20 units versus OnabotulinumtoxinA 20 units one treatment in glabellar lines, Outcome 2: Physician assessment of success by analysing scores and scales - injector

Study or Subgroup	IncobotulinumtoxinA 20U Events	Total	OnabotulinumtoxinA 20U Events	Total	Risk Ratio M-H, Random, 95% CI
58.2.1 4 weeks					
Kane 2015	114	122	122	128	0.98 [0.92 , 1.04]
58.2.2 8 weeks					
Kane 2015	106	122	115	128	0.97 [0.88 , 1.06]
58.2.3 12 weeks					
Kane 2015	91	122	98	128	0.97 [0.85 , 1.12]
58.2.4 16 weeks					
Kane 2015	72	122	77	128	0.98 [0.80 , 1.20]



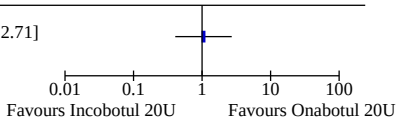
Analysis 58.3. Comparison 58: IncobotulinumtoxinA 20 units versus OnabotulinumtoxinA 20 units one treatment in glabellar lines, Outcome 3: Physician assessment of success by analysing scores and scales - independent observer

Study or Subgroup	IncobotulinumtoxinA 20U Events	Total	OnabotulinumtoxinA 20U Events	Total	Risk Ratio M-H, Random, 95% CI
58.3.1 4 weeks					
Kane 2015	117	122	127	128	0.97 [0.93 , 1.01]
58.3.2 8 weeks					
Kane 2015	111	122	121	128	0.96 [0.90 , 1.03]
58.3.3 12 weeks					
Kane 2015	98	122	103	128	1.00 [0.88 , 1.13]
58.3.4 16 weeks					
Kane 2015	76	122	86	128	0.93 [0.77 , 1.11]



Analysis 58.4. Comparison 58: IncobotulinumtoxinA 20 units versus OnabotulinumtoxinA 20 units one treatment in glabellar lines, Outcome 4: Total adverse events

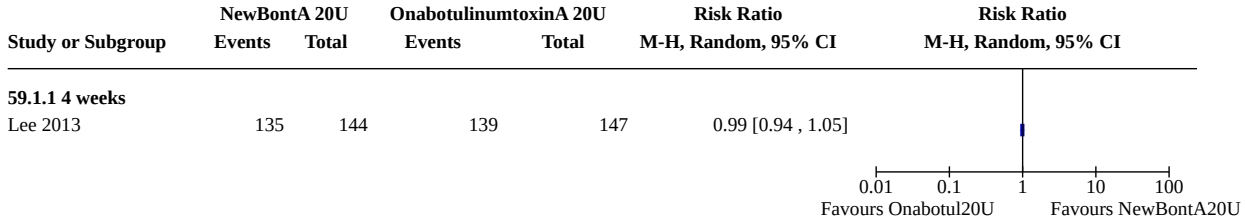
Study or Subgroup	IncobotulinumtoxinA 20U Events	Total	OnabotulinumtoxinA 20U Events	Total	Risk Ratio M-H, Random, 95% CI
Kane 2015	8	122	8	128	1.05 [0.41 , 2.71]



Comparison 59. NewBontA [Medytox®] 20 units versus OnabotulinumtoxinA 20 units one treatment in glabellar lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
59.1 Physician assessment, maximum contraction (responder rate)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
59.1.1 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 59.1. Comparison 59: NewBontA [Medytox®] 20 units versus OnabotulinumtoxinA 20 units one treatment in glabellar lines, Outcome 1: Physician assessment, maximum contraction (responder rate)



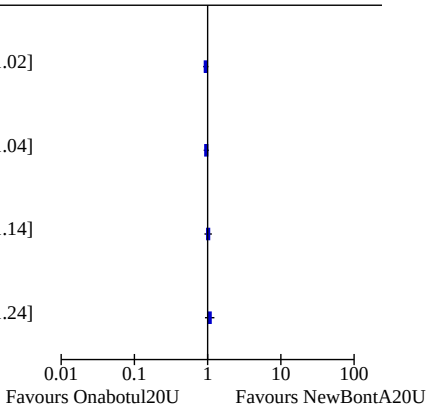
Comparison 60. NewBontA [Neuronox®] 20 units versus OnabotulinumtoxinA 20 units one treatment in glabellar lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
60.1 Participant assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
60.1.1 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
60.1.2 8 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
60.1.3 12 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
60.1.4 16 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
60.2 Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
60.3 Physician assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
60.3.1 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
60.3.2 8 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
60.3.3 12 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
60.3.4 16 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
60.4 Total adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

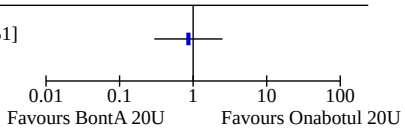
Analysis 60.1. Comparison 60: NewBontA [Neuronox®] 20 units versus OnabotulinumtoxinA 20 units one treatment in glabellar lines, Outcome 1: Participant assessment of success by analysing scores and scales

	NewBontA 20U		OnabotulinumtoxinA 20U		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Random, 95% CI
60.1.1 4 weeks						
Won 2013	134	157	142	157	0.94 [0.87 , 1.02]	
60.1.2 8 weeks						
Won 2013	136	157	142	157	0.96 [0.88 , 1.04]	
60.1.3 12 weeks						
Won 2013	124	157	122	157	1.02 [0.90 , 1.14]	
60.1.4 16 weeks						
Won 2013	112	157	105	157	1.07 [0.92 , 1.24]	

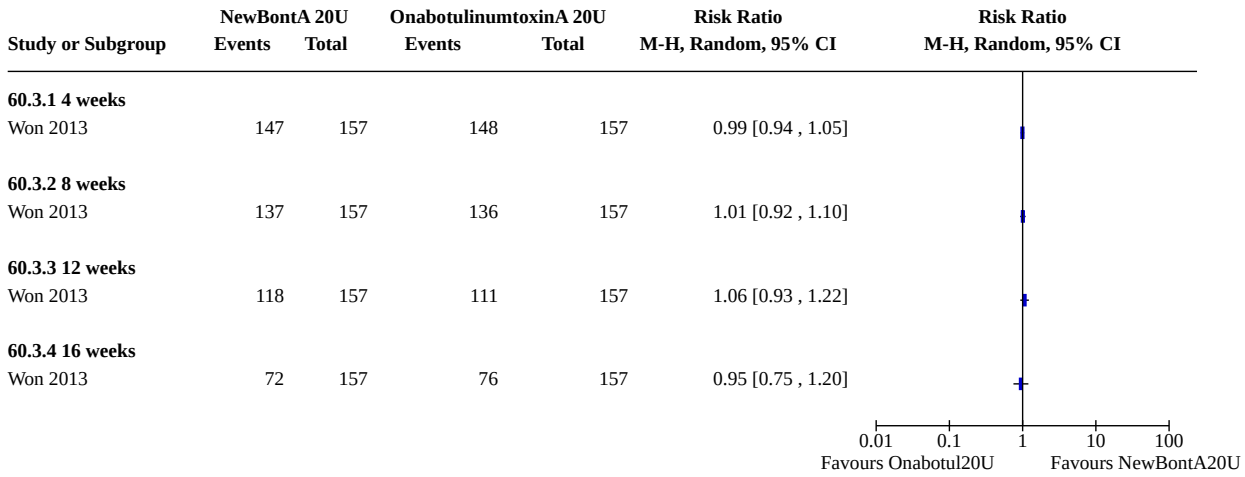


Analysis 60.2. Comparison 60: NewBontA [Neuronox®] 20 units versus OnabotulinumtoxinA 20 units one treatment in glabellar lines, Outcome 2: Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

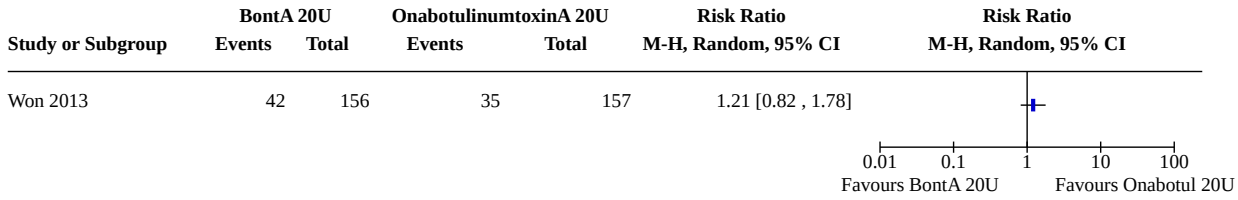
	BontA 20U		OnabotulinumtoxinA 20U		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Random, 95% CI
Won 2013	6	156	7	157	0.86 [0.30 , 2.51]	



Analysis 60.3. Comparison 60: NewBontA [Neuronox®] 20 units versus OnabotulinumtoxinA 20 units one treatment in glabellar lines, Outcome 3: Physician assessment of success by analysing scores and scales



Analysis 60.4. Comparison 60: NewBontA [Neuronox®] 20 units versus OnabotulinumtoxinA 20 units one treatment in glabellar lines, Outcome 4: Total adverse events



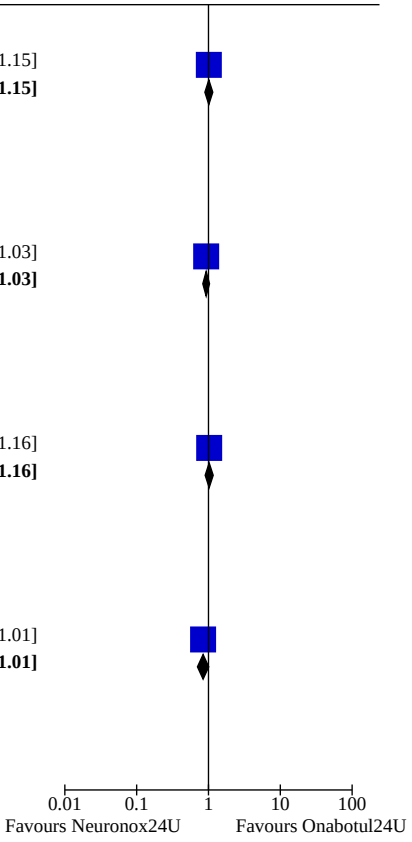
Comparison 61. NewBontA [Neuronox®] 20 units versus OnabotulinumtoxinA 20 units one treatment in crow's feet lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
61.1 Participant assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
61.1.1 4 weeks	1	220	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.89, 1.15]
61.1.2 8 weeks	1	220	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.83, 1.03]
61.1.3 12 weeks	1	220	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.90, 1.16]
61.1.4 16 weeks	1	220	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.70, 1.01]
61.2 Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
61.3 Physician assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
61.3.1 4 weeks	1	220	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.89, 1.13]
61.3.2 8 weeks	1	220	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.86, 1.11]
61.3.3 12 weeks	1	220	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.88, 1.32]
61.3.4 16 weeks	1	220	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.83, 1.56]
61.4 Total adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
61.4.1 Total adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

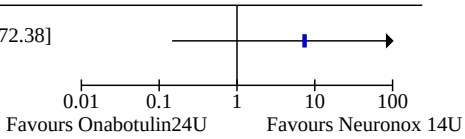
Analysis 61.1. Comparison 61: NewBontA [Neuronox®] 20 units versus OnabotulinumtoxinA 20 units one treatment in crow's feet lines, Outcome 1: Participant assessment of success by analysing scores and scales

Study or Subgroup	Neuronox® 24U Events	Total	Onabotulinum 24U Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
61.1.1 4 weeks						
Cheon 2019	90	110	89	110	100.0%	1.01 [0.89 , 1.15]
Subtotal (95% CI)		**110**		**110**	**100.0%**	**1.01 [0.89 , 1.15]**
Total events:	90		89			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.17 (P = 0.86)						
61.1.2 8 weeks						
Cheon 2019	91	110	98	110	100.0%	0.93 [0.83 , 1.03]
Subtotal (95% CI)		**110**		**110**	**100.0%**	**0.93 [0.83 , 1.03]**
Total events:	91		98			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.35 (P = 0.18)						
61.1.3 12 weeks						
Cheon 2019	90	110	88	110	100.0%	1.02 [0.90 , 1.16]
Subtotal (95% CI)		**110**		**110**	**100.0%**	**1.02 [0.90 , 1.16]**
Total events:	90		88			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.34 (P = 0.73)						
61.1.4 16 weeks						
Cheon 2019	69	110	82	110	100.0%	0.84 [0.70 , 1.01]
Subtotal (95% CI)		**110**		**110**	**100.0%**	**0.84 [0.70 , 1.01]**
Total events:	69		82			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.87 (P = 0.06)						



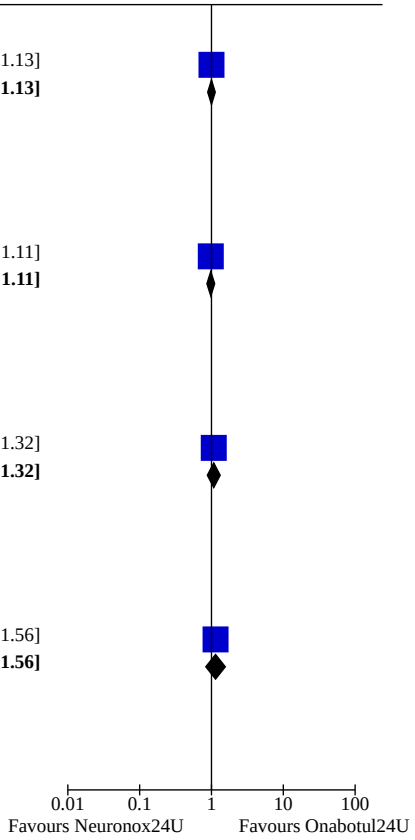
Analysis 61.2. Comparison 61: NewBontA [Neuronox®] 20 units versus OnabotulinumtoxinA 20 units one treatment in crow's feet lines, Outcome 2: Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

Study or Subgroup	Neuronox® 24U Events	Neuronox® 24U Total	Onabotulinum 24U Events	Onabotulinum 24U Total	Peto Odds Ratio Peto, Fixed, 95% CI
Cheon 2019	1	110	0	110	7.39 [0.15 , 372.38]



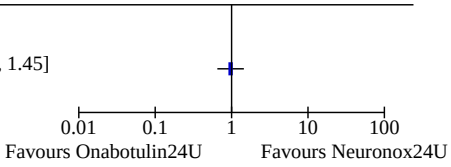
Analysis 61.3. Comparison 61: NewBontA [Neuronox®] 20 units versus OnabotulinumtoxinA 20 units one treatment in crow's feet lines, Outcome 3: Physician assessment of success by analysing scores and scales

Study or Subgroup	Neuronox® 24U Events	Neuronox® 24U Total	Onabotulinum 24U Events	Onabotulinum 24U Total	Weight	Risk Ratio M-H, Random, 95% CI
61.3.1 4 weeks						
Cheon 2019	91	110	91	110	100.0%	1.00 [0.89 , 1.13]
Subtotal (95% CI)		**110**		**110**	**100.0%**	**1.00 [0.89 , 1.13]**
Total events:	91		91			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
61.3.2 8 weeks						
Cheon 2019	89	110	91	110	100.0%	0.98 [0.86 , 1.11]
Subtotal (95% CI)		**110**		**110**	**100.0%**	**0.98 [0.86 , 1.11]**
Total events:	89		91			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.35 (P = 0.73)						
61.3.3 12 weeks						
Cheon 2019	71	110	66	110	100.0%	1.08 [0.88 , 1.32]
Subtotal (95% CI)		**110**		**110**	**100.0%**	**1.08 [0.88 , 1.32]**
Total events:	71		66			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						
61.3.4 16 weeks						
Cheon 2019	49	110	43	110	100.0%	1.14 [0.83 , 1.56]
Subtotal (95% CI)		**110**		**110**	**100.0%**	**1.14 [0.83 , 1.56]**
Total events:	49		43			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.82 (P = 0.41)						



Analysis 61.4. Comparison 61: NewBontA [Neuronox®] 20 units versus OnabotulinumtoxinA 20 units one treatment in crow's feet lines, Outcome 4: Total adverse events

Study or Subgroup	Neuronox® 24U Events	Total	Onabotulinum 24U Events	Total	Risk Ratio M-H, Random, 95% CI
61.4.1 Total adverse events					
Cheon 2019	33	110	34	110	0.97 [0.65 , 1.45]

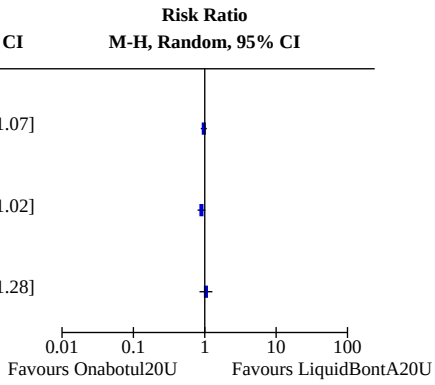


Comparison 62. Liquid BontA 20 units versus OnabotulinumtoxinA 20 units one treatment in glabellar lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
62.1 Participant assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
62.1.1 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
62.1.2 10 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
62.1.3 16 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
62.2 Physician assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
62.2.1 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
62.2.2 16 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
62.3 Total adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

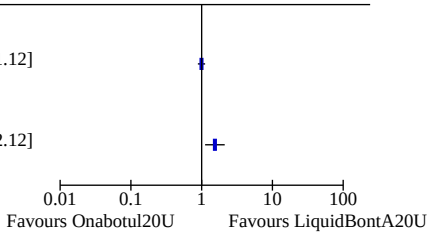
Analysis 62.1. Comparison 62: Liquid BontA 20 units versus OnabotulinumtoxinA 20 units one treatment in glabellar lines, Outcome 1: Participant assessment of success by analysing scores and scales

Study or Subgroup	Liquid BontA 20U Events	Total	OnabotulinumtoxinA 20U Events	Total	Risk Ratio M-H, Random, 95% CI
62.1.1 4 weeks					
Kim 2015	70	78	75	81	0.97 [0.88 , 1.07]
62.1.2 10 weeks					
Kim 2015	64	78	74	81	0.90 [0.79 , 1.02]
62.1.3 16 weeks					
Kim 2015	55	78	55	81	1.04 [0.84 , 1.28]



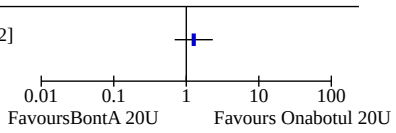
Analysis 62.2. Comparison 62: Liquid BontA 20 units versus OnabotulinumtoxinA 20 units one treatment in glabellar lines, Outcome 2: Physician assessment of success by analysing scores and scales

Study or Subgroup	Liquid BontA 20U Events	Total	OnabotulinumtoxinaA 20U Events	Total	Risk Ratio M-H, Random, 95% CI
62.2.1 4 weeks					
Kim 2015	68	78	71	81	0.99 [0.88 , 1.12]
62.2.2 16 weeks					
Kim 2015	48	77	32	79	1.54 [1.12 , 2.12]



Analysis 62.3. Comparison 62: Liquid BontA 20 units versus OnabotulinumtoxinA 20 units one treatment in glabellar lines, Outcome 3: Total adverse events

Study or Subgroup	Liquid BontA 20U Events	Total	OnabotulinumtoxinA 20U Events	Total	Risk Ratio M-H, Random, 95% CI
Kim 2015	19	84	15	84	1.27 [0.69 , 2.32]

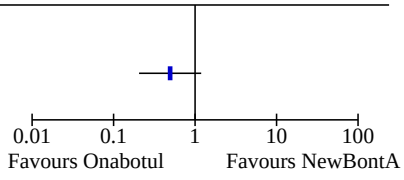


Comparison 63. NewBontA (Prosigne®) 20 units versus OnabotulinumtoxinA 20 units one treatment in glabellar lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
63.1 Physician assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
63.1.1 12 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 63.1. Comparison 63: NewBontA (Prosigne®) 20 units versus OnabotulinumtoxinA 20 units one treatment in glabellar lines, Outcome 1: Physician assessment of success by analysing scores and scales

Study or Subgroup	NewBontA 20u Events	Total	Onabotul 20u Events	Total	Risk Ratio M-H, Random, 95% CI
63.1.1 12 weeks					
Costa 2016	7	85	12	72	0.49 [0.21 , 1.19]

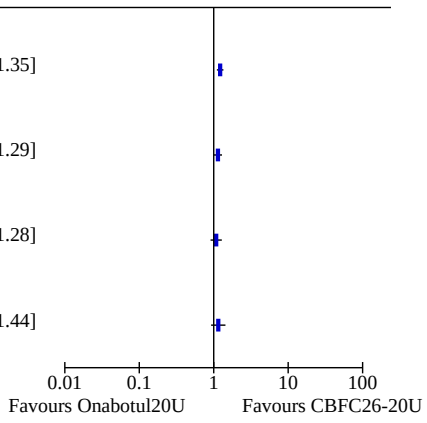


Comparison 64. CBFC26 20 units versus OnabotulinumtoxinA 20 units one treatment in glabellar lines

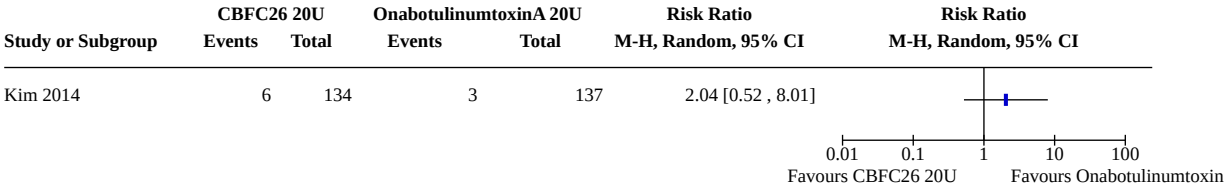
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
64.1 Participant assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
64.1.1 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
64.1.2 8 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
64.1.3 12 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
64.1.4 16 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
64.2 Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
64.3 Physician assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
64.3.1 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
64.3.2 8 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
64.3.3 12 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
64.3.4 16 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
64.4 Total adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 64.1. Comparison 64: CBFC26 20 units versus OnabotulinumtoxinA 20 units one treatment in glabellar lines, Outcome 1: Participant assessment of success by analysing scores and scales

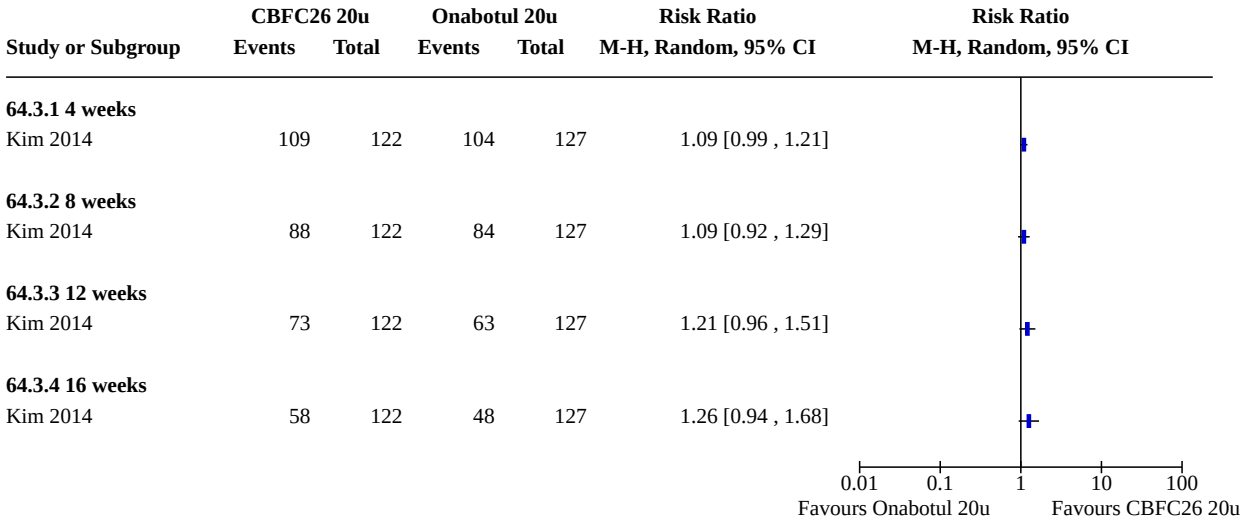
Study or Subgroup	CBFC26 20U Events	CBFC26 20U Total	OnabotulinumtoxinA 20U Events	OnabotulinumtoxinA 20U Total	Risk Ratio M-H, Random, 95% CI
64.1.1 4 weeks					
Kim 2014	116	122	99	127	1.22 [1.10 , 1.35]
64.1.2 8 weeks					
Kim 2014	104	122	95	127	1.14 [1.01 , 1.29]
64.1.3 12 weeks					
Kim 2014	85	122	82	127	1.08 [0.91 , 1.28]
64.1.4 16 weeks					
Kim 2014	73	122	66	127	1.15 [0.92 , 1.44]



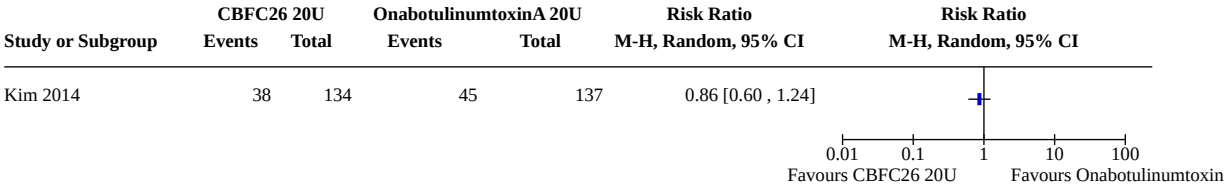
Analysis 64.2. Comparison 64: CBFC26 20 units versus OnabotulinumtoxinA 20 units one treatment in glabellar lines, Outcome 2: Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)



Analysis 64.3. Comparison 64: CBFC26 20 units versus OnabotulinumtoxinA 20 units one treatment in glabellar lines, Outcome 3: Physician assessment of success by analysing scores and scales



Analysis 64.4. Comparison 64: CBFC26 20 units versus OnabotulinumtoxinA 20 units one treatment in glabellar lines, Outcome 4: Total adverse events



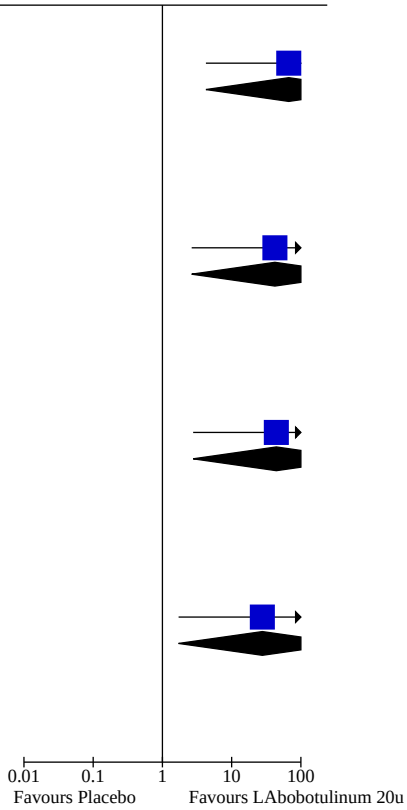
Comparison 65. Liquid AbobotulinumtoxinA 20 units versus placebo one treatment in glabellar lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
65.1 Participant assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
65.1.1 4 weeks	1	71	Risk Ratio (M-H, Random, 95% CI)	66.81 [4.25, 1050.36]
65.1.2 8 weeks	1	71	Risk Ratio (M-H, Random, 95% CI)	42.14 [2.65, 670.89]
65.1.3 12 weeks	1	71	Risk Ratio (M-H, Random, 95% CI)	44.19 [2.78, 702.51]
65.1.4 16 weeks	1	71	Risk Ratio (M-H, Random, 95% CI)	27.75 [1.71, 449.60]
65.2 Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
65.2.1 Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)	1	71	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.60 [0.15, 383.33]
65.3 Physician assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
65.3.1 4 weeks	1	71	Risk Ratio (M-H, Random, 95% CI)	66.81 [4.25, 1050.36]
65.3.2 8 weeks	1	71	Risk Ratio (M-H, Random, 95% CI)	58.58 [3.71, 923.86]
65.3.3 12 weeks	1	71	Risk Ratio (M-H, Random, 95% CI)	40.08 [2.51, 639.27]
65.3.4 16 weeks	1	71	Risk Ratio (M-H, Random, 95% CI)	19.53 [1.18, 323.24]
65.4 Total adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
65.4.1 Totl adverse events	1	71	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.41, 3.68]

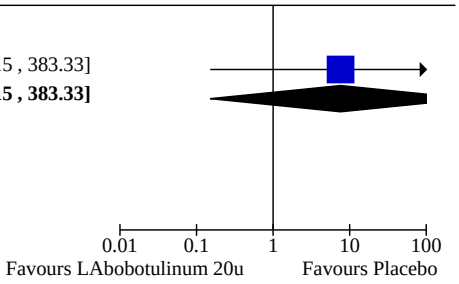
Analysis 65.1. Comparison 65: Liquid AbobotulinumtoxinA 20 units versus placebo one treatment in glabellar lines, Outcome 1: Participant assessment of success by analysing scores and scales

Study or Subgroup	LAboboutlinum20u Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
65.1.1 4 weeks						
Ascher 2018	32	35	0	36	100.0%	66.81 [4.25 , 1050.36]
Subtotal (95% CI)		**35**		**36**	**100.0%**	**66.81 [4.25 , 1050.36]**
Total events:	32		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.99 (P = 0.003)						
65.1.2 8 weeks						
Ascher 2018	20	35	0	36	100.0%	42.14 [2.65 , 670.89]
Subtotal (95% CI)		**35**		**36**	**100.0%**	**42.14 [2.65 , 670.89]**
Total events:	20		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.65 (P = 0.008)						
65.1.3 12 weeks						
Ascher 2018	21	35	0	36	100.0%	44.19 [2.78 , 702.51]
Subtotal (95% CI)		**35**		**36**	**100.0%**	**44.19 [2.78 , 702.51]**
Total events:	21		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.68 (P = 0.007)						
65.1.4 16 weeks						
Ascher 2018	13	35	0	36	100.0%	27.75 [1.71 , 449.60]
Subtotal (95% CI)		**35**		**36**	**100.0%**	**27.75 [1.71 , 449.60]**
Total events:	13		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.34 (P = 0.02)						
Test for subgroup differences: Chi² = 0.19, df = 3 (P = 0.98), I² = 0%						

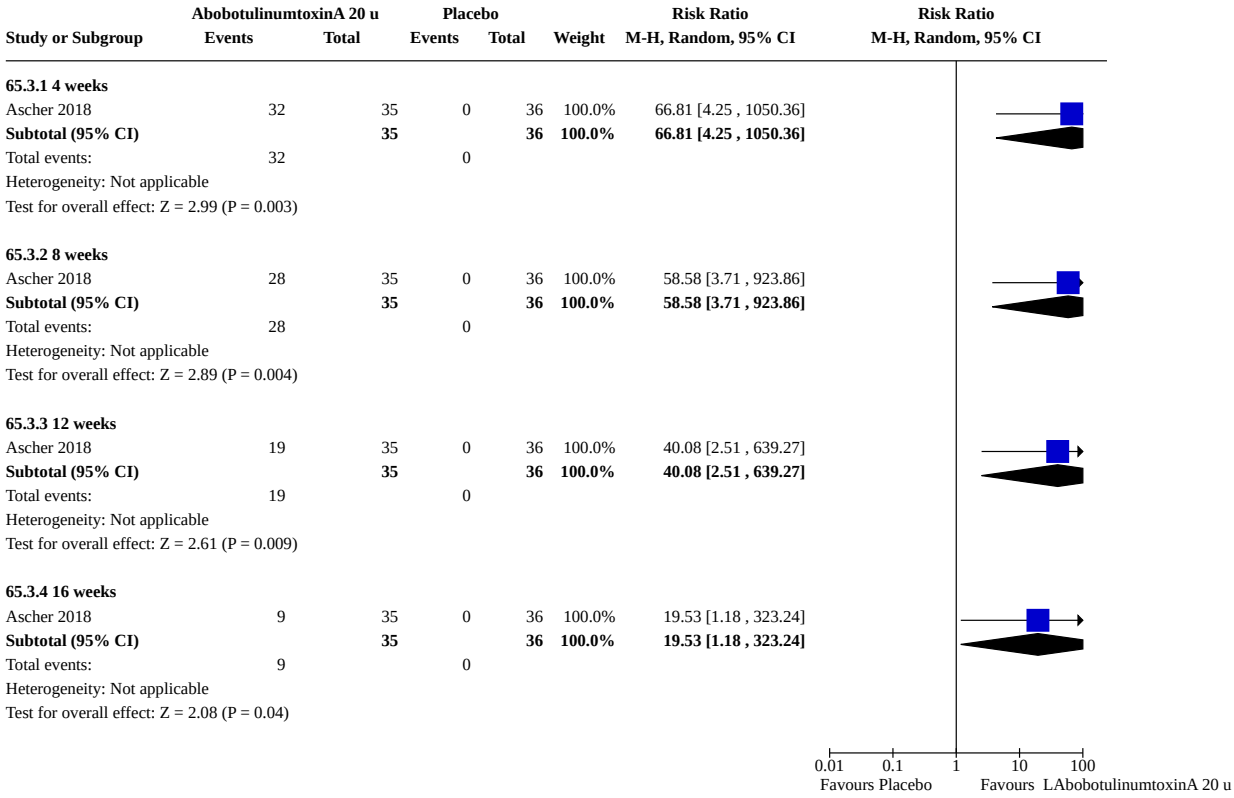


Analysis 65.2. Comparison 65: Liquid AbobotulinumtoxinA 20 units versus placebo one treatment in glabellar lines, Outcome 2: Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

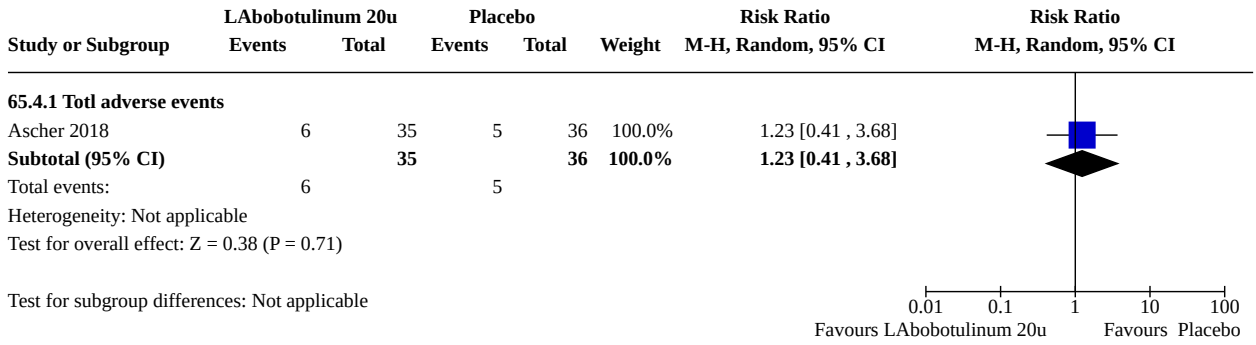
Study or Subgroup	LAbobotulinum 20u Events	Total	Placebo Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
65.2.1 Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)						
Ascher 2018	1	35	0	36	100.0%	7.60 [0.15 , 383.33]
Subtotal (95% CI)		**35**		**36**	**100.0%**	**7.60 [0.15 , 383.33]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.01 (P = 0.31)						
Test for subgroup differences: Not applicable						



Analysis 65.3. Comparison 65: Liquid AbobotulinumtoxinA 20 units versus placebo one treatment in glabellar lines, Outcome 3: Physician assessment of success by analysing scores and scales



Analysis 65.4. Comparison 65: Liquid AbobotulinumtoxinA 20 units versus placebo one treatment in glabellar lines, Outcome 4: Total adverse events



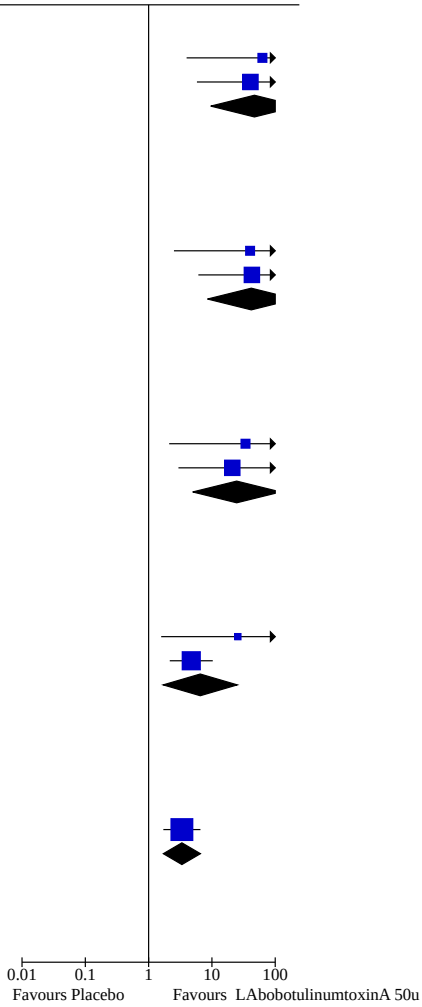
Comparison 66. Liquid AbobotulinumtoxinA 50 units versus placebo one treatment in glabellar lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
66.1 Participant assessment success by analysing scores and scales	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
66.1.1 4 weeks	2	255	Risk Ratio (M-H, Random, 95% CI)	46.95 [9.57, 230.36]
66.1.2 8 weeks	2	253	Risk Ratio (M-H, Random, 95% CI)	41.87 [8.52, 205.88]
66.1.3 12 weeks	2	254	Risk Ratio (M-H, Random, 95% CI)	24.61 [4.97, 121.91]
66.1.4 16 weeks	2	254	Risk Ratio (M-H, Random, 95% CI)	6.54 [1.70, 25.15]
66.1.5 20 weeks	1	183	Risk Ratio (M-H, Random, 95% CI)	3.35 [1.71, 6.58]
66.2 Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)	2	256	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.39 [0.07, 289.13]
66.3 Physician assessment of success by analysing scores and scales	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
66.3.1 4 weeks	2	255	Risk Ratio (M-H, Random, 95% CI)	16.73 [2.84, 98.58]
66.3.2 8 weeks	2	255	Risk Ratio (M-H, Random, 95% CI)	48.98 [9.99, 240.21]
66.3.3 12 weeks	2	255	Risk Ratio (M-H, Random, 95% CI)	35.93 [7.30, 176.90]
66.3.4 16 weeks	2	255	Risk Ratio (M-H, Random, 95% CI)	21.25 [2.95, 152.88]
66.3.5 20 weeks	1	184	Risk Ratio (M-H, Random, 95% CI)	25.86 [1.60, 417.34]
66.4 Total adverse events	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
66.4.1 Total adverse events	2	255	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.72, 1.71]

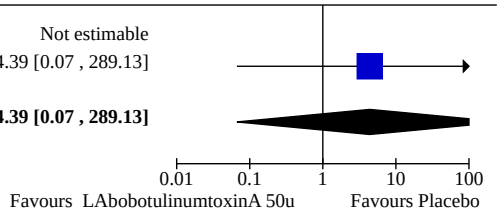
Analysis 66.1. Comparison 66: Liquid AbobotulinumtoxinA 50 units versus placebo one treatment in glabellar lines, Outcome 1: Participant assessment success by analysing scores and scales

Study or Subgroup	LAbobotulinumtoxinA 50u Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
66.1.1 4 weeks						
Ascher 2018	30	35	0	36	33.3%	62.69 [3.98 , 987.11]
Ascher 2020	84	124	1	60	66.7%	40.65 [5.80 , 284.93]
Subtotal (95% CI)		**159**		**96**	**100.0%**	**46.95 [9.57 , 230.36]**
Total events:	114		1			
Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 1 (P = 0.80); I² = 0%						
Test for overall effect: Z = 4.74 (P < 0.00001)						
66.1.2 8 weeks						
Ascher 2018	19	35	0	36	33.1%	40.08 [2.51 , 639.27]
Ascher 2020	87	122	1	60	66.9%	42.79 [6.11 , 299.78]
Subtotal (95% CI)		**157**		**96**	**100.0%**	**41.87 [8.52 , 205.88]**
Total events:	106		1			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.97); I² = 0%						
Test for overall effect: Z = 4.60 (P < 0.00001)						
66.1.3 12 weeks						
Ascher 2018	16	35	0	36	33.2%	33.92 [2.11 , 544.43]
Ascher 2020	43	123	1	60	66.8%	20.98 [2.96 , 148.68]
Subtotal (95% CI)		**158**		**96**	**100.0%**	**24.61 [4.97 , 121.91]**
Total events:	59		1			
Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 1 (P = 0.78); I² = 0%						
Test for overall effect: Z = 3.92 (P < 0.0001)						
66.1.4 16 weeks						
Ascher 2018	12	35	0	36	19.3%	25.69 [1.58 , 418.00]
Ascher 2020	58	123	6	60	80.7%	4.72 [2.16 , 10.31]
Subtotal (95% CI)		**158**		**96**	**100.0%**	**6.54 [1.70 , 25.15]**
Total events:	70		6			
Heterogeneity: Tau² = 0.43; Chi² = 1.39, df = 1 (P = 0.24); I² = 28%						
Test for overall effect: Z = 2.73 (P = 0.006)						
66.1.5 20 weeks						
Ascher 2020	55	123	8	60	100.0%	3.35 [1.71 , 6.58]
Subtotal (95% CI)		**123**		**60**	**100.0%**	**3.35 [1.71 , 6.58]**
Total events:	55		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.52 (P = 0.0004)						
Test for subgroup differences: Chi² = 17.22, df = 4 (P = 0.002), I² = 76.8%						

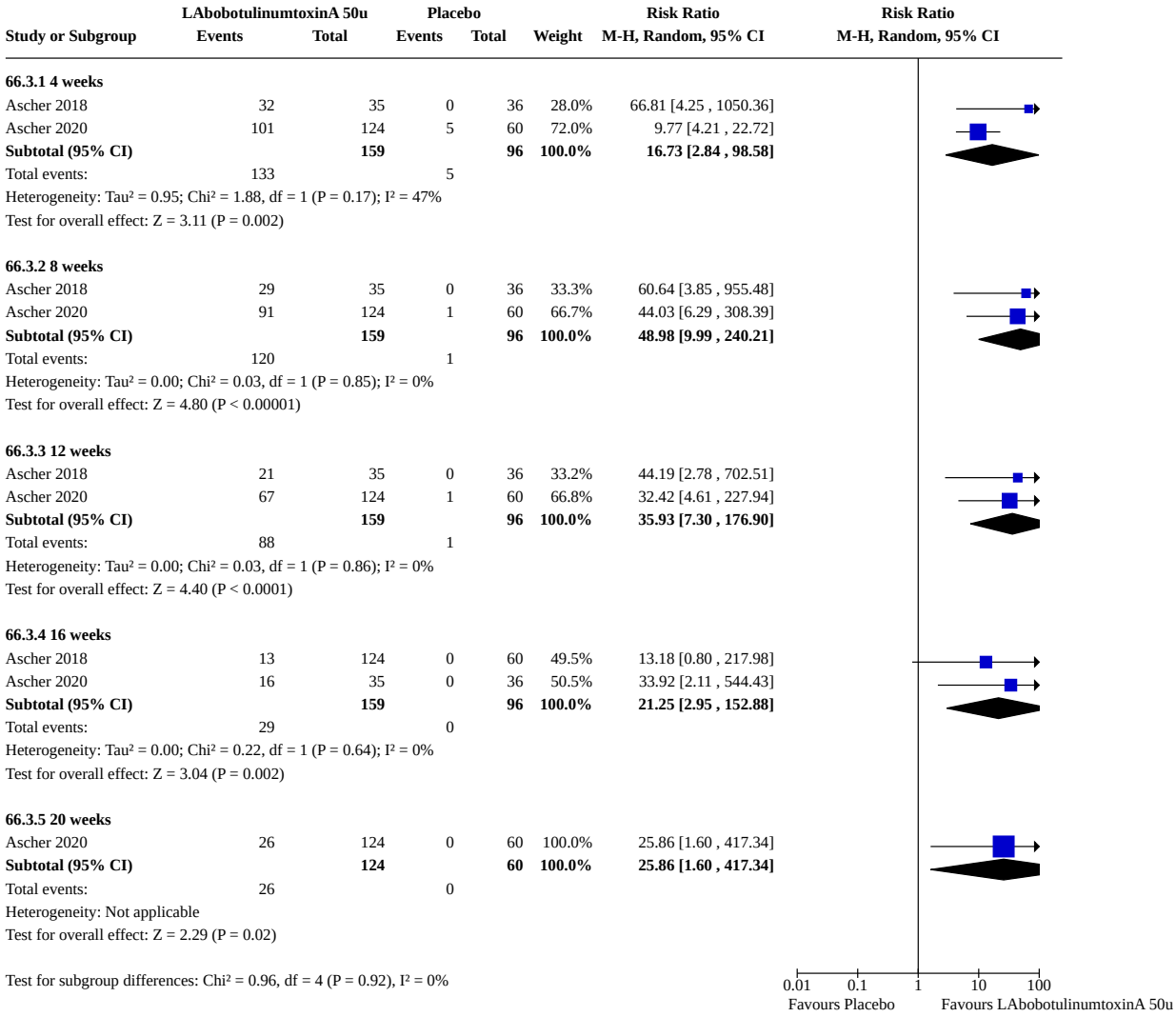


Analysis 66.2. Comparison 66: Liquid AbobotulinumtoxinA 50 units versus placebo one treatment in glabellar lines, Outcome 2: Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

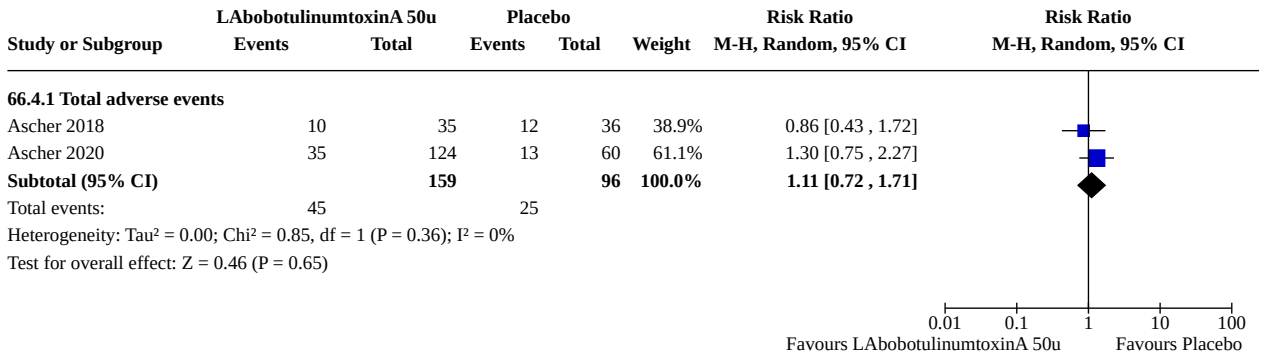
Study or Subgroup	LAbobotulinumtoxinA 50u Events	Total	Placebo Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Ascher 2018	0	35	0	36		Not estimable
Ascher 2020	1	125	0	60	100.0%	4.39 [0.07 , 289.13]
Total (95% CI)		**160**		**96**	**100.0%**	**4.39 [0.07 , 289.13]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						
Test for subgroup differences: Not applicable						



Analysis 66.3. Comparison 66: Liquid AbobotulinumtoxinA 50 units versus placebo one treatment in glabellar lines, Outcome 3: Physician assessment of success by analysing scores and scales



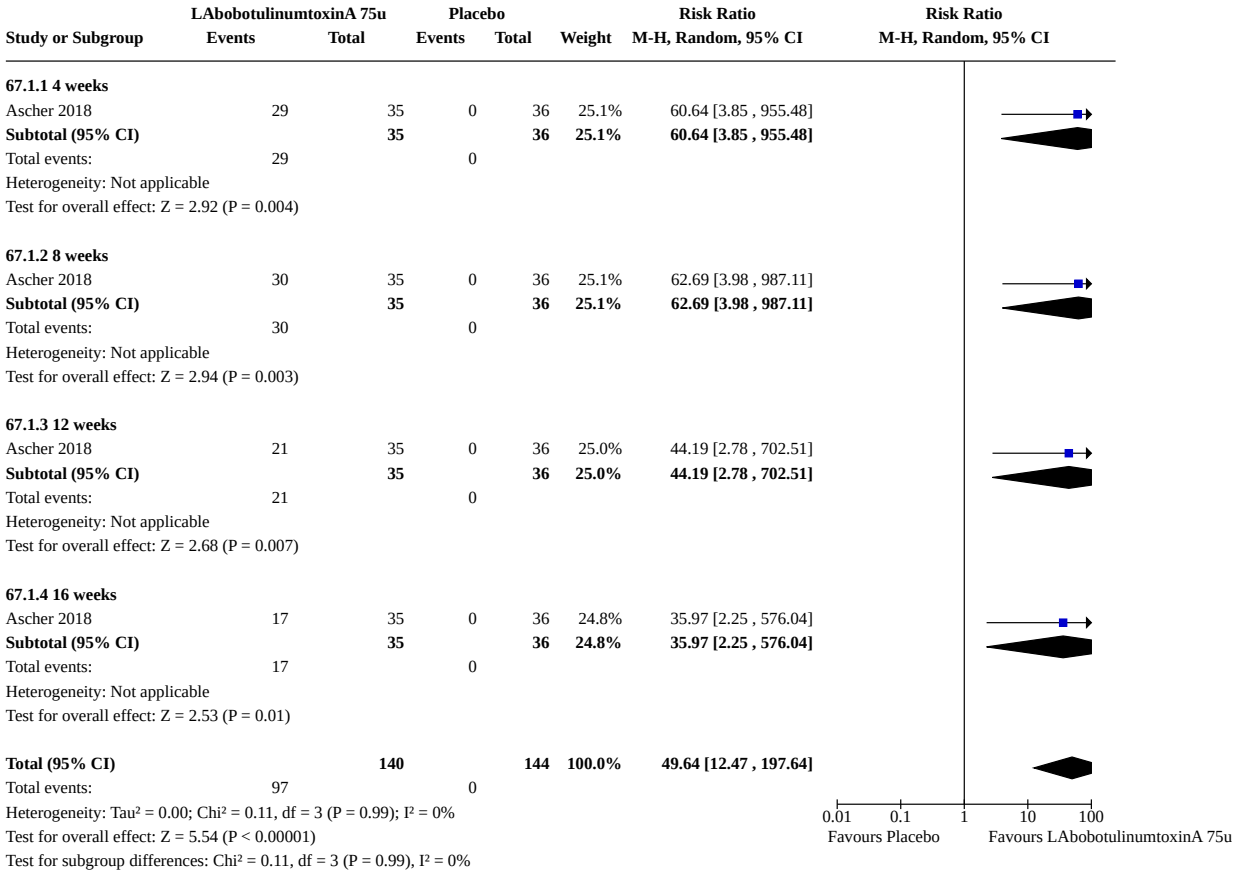
Analysis 66.4. Comparison 66: Liquid AbobotulinumtoxinA 50 units versus placebo one treatment in glabellar lines, Outcome 4: Total adverse events



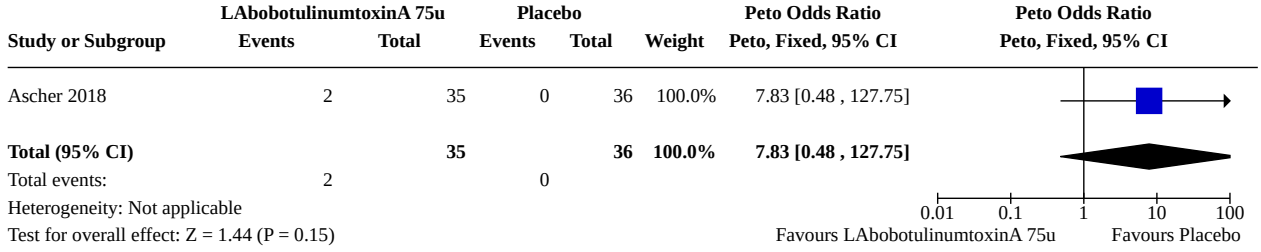
Comparison 67. Liquid AbobotulinumtoxinA 75 units versus placebo one treatment in glabellar lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
67.1 Participant assessment of success by analysing scores and scales	1	284	Risk Ratio (M-H, Random, 95% CI)	49.64 [12.47, 197.64]
67.1.1 4 weeks	1	71	Risk Ratio (M-H, Random, 95% CI)	60.64 [3.85, 955.48]
67.1.2 8 weeks	1	71	Risk Ratio (M-H, Random, 95% CI)	62.69 [3.98, 987.11]
67.1.3 12 weeks	1	71	Risk Ratio (M-H, Random, 95% CI)	44.19 [2.78, 702.51]
67.1.4 16 weeks	1	71	Risk Ratio (M-H, Random, 95% CI)	35.97 [2.25, 576.04]
67.2 Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)	1	71	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.83 [0.48, 127.75]
67.3 Physician assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
67.3.1 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
67.3.2 8 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
67.3.3 12 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
67.3.4 16 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
67.4 Total adverse events	1	71	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.24, 2.81]

Analysis 67.1. Comparison 67: Liquid AbobotulinumtoxinA 75 units versus placebo one treatment in glabellar lines, Outcome 1: Participant assessment of success by analysing scores and scales

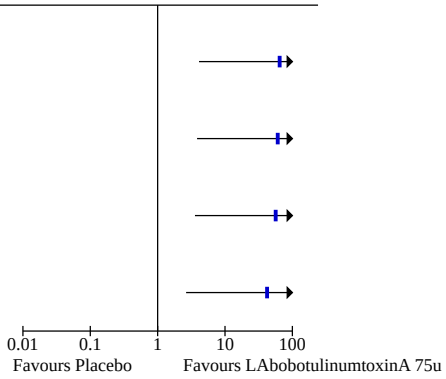


Analysis 67.2. Comparison 67: Liquid AbobotulinumtoxinA 75 units versus placebo one treatment in glabellar lines, Outcome 2: Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)



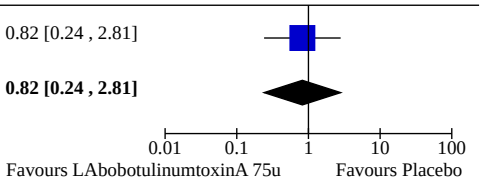
Analysis 67.3. Comparison 67: Liquid AbobotulinumtoxinA 75 units versus placebo one treatment in glabellar lines, Outcome 3: Physician assessment of success by analysing scores and scales

Study or Subgroup	LAbobotulinumtoxinA 75u Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 95% CI
67.3.1 4 weeks					
Ascher 2018	31	35	0	36	64.75 [4.12 , 1018.73]
67.3.2 8 weeks					
Ascher 2018	29	35	0	36	60.64 [3.85 , 955.48]
67.3.3 12 weeks					
Ascher 2018	27	35	0	36	56.53 [3.58 , 892.24]
67.3.4 16 weeks					
Ascher 2018	20	35	0	36	42.14 [2.65 , 670.89]



Analysis 67.4. Comparison 67: Liquid AbobotulinumtoxinA 75 units versus placebo one treatment in glabellar lines, Outcome 4: Total adverse events

Study or Subgroup	LAbobotulinumtoxinA 75u Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Ascher 2018	4	35	5	36	100.0%	0.82 [0.24 , 2.81]
Total (95% CI)		**35**		**36**	**100.0%**	**0.82 [0.24 , 2.81]**
Total events:	4		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.31 (P = 0.76)						
Test for subgroup differences: Not applicable						



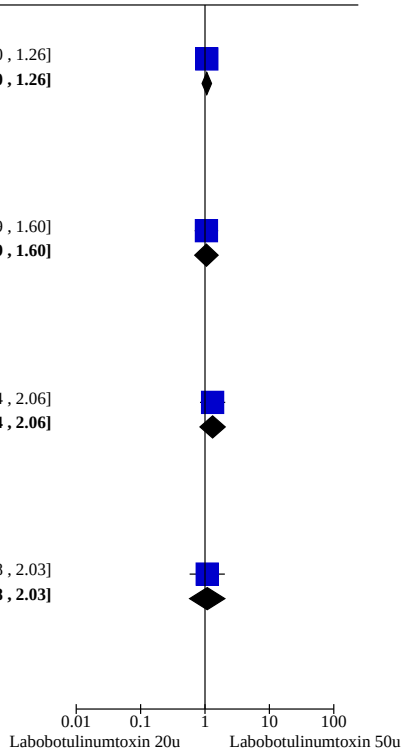
Comparison 68. Liquid AbobotulinumtoxinA 20 units versus Liquid AbobotulinumtoxinA 50 units one cycle of treatment, glabellar lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
68.1 Participant assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
68.1.1 4 weeks	1	70	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.90, 1.26]
68.1.2 8 weeks	1	70	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.69, 1.60]
68.1.3 12 weeks	1	70	Risk Ratio (M-H, Random, 95% CI)	1.31 [0.84, 2.06]
68.1.4 16 weeks	1	70	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.58, 2.03]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
68.2 Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
68.2.1 Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)	1	70	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.39 [0.15, 372.38]
68.3 Physician assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
68.3.1 4 weeks	1	70	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.90, 1.26]
68.3.2 8 weeks	1	70	Risk Ratio (M-H, Random, 95% CI)	1.47 [1.04, 2.08]
68.3.3 12 weeks	1	70	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.74, 1.90]
68.3.4 16 weeks	1	70	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.36, 1.55]
68.4 Total adverse events	1	70	Risk Ratio (M-H, Random, 95% CI)	1.50 [0.46, 4.86]
68.4.1 Total adverse events	1	70	Risk Ratio (M-H, Random, 95% CI)	1.50 [0.46, 4.86]

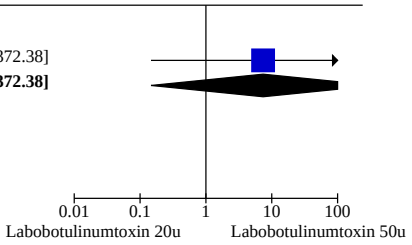
Analysis 68.1. Comparison 68: Liquid AbobotulinumtoxinA 20 units versus Liquid AbobotulinumtoxinA 50 units one cycle of treatment, glabellar lines, Outcome 1: Participant assessment of success by analysing scores and scales

Study or Subgroup	Labobotulinumtoxin 20u Events	Total	Labobotulinumtoxin 50u Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
68.1.1 4 weeks						
Ascher 2018	32	35	30	35	100.0%	1.07 [0.90 , 1.26]
Subtotal (95% CI)		**35**		**35**	**100.0%**	**1.07 [0.90 , 1.26]**
Total events:	32		30			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.75 (P = 0.45)						
68.1.2 8 weeks						
Ascher 2018	20	35	19	35	100.0%	1.05 [0.69 , 1.60]
Subtotal (95% CI)		**35**		**35**	**100.0%**	**1.05 [0.69 , 1.60]**
Total events:	20		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.24 (P = 0.81)						
68.1.3 12 weeks						
Ascher 2018	21	35	16	35	100.0%	1.31 [0.84 , 2.06]
Subtotal (95% CI)		**35**		**35**	**100.0%**	**1.31 [0.84 , 2.06]**
Total events:	21		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.18 (P = 0.24)						
68.1.4 16 weeks						
Ascher 2018	13	35	12	35	100.0%	1.08 [0.58 , 2.03]
Subtotal (95% CI)		**35**		**35**	**100.0%**	**1.08 [0.58 , 2.03]**
Total events:	13		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.25 (P = 0.80)						
Test for subgroup differences: Chi² = 0.74, df = 3 (P = 0.86), I² = 0%						



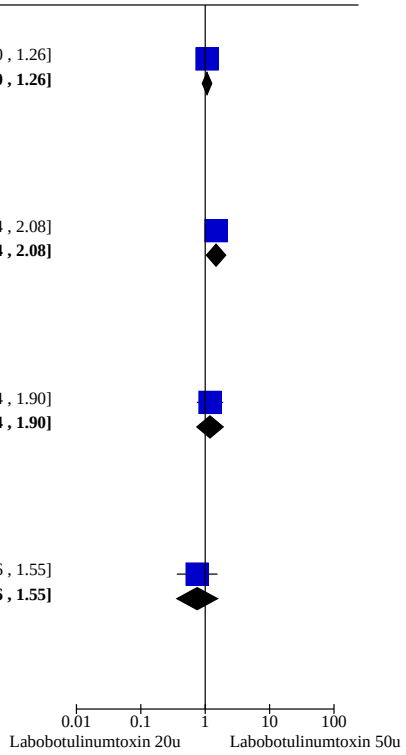
Analysis 68.2. Comparison 68: Liquid AbobotulinumtoxinA 20 units versus Liquid AbobotulinumtoxinA 50 units one cycle of treatment, glabellar lines, Outcome 2: Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

Study or Subgroup	Labobotulinumtocin20u Events	Total	Labobotukinumtoxin50u Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
68.2.1 Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)						
Ascher 2018	1	35	0	35	100.0%	7.39 [0.15 , 372.38]
Subtotal (95% CI)		**35**		**35**	**100.0%**	**7.39 [0.15 , 372.38]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.00 (P = 0.32)						
Test for subgroup differences: Not applicable						



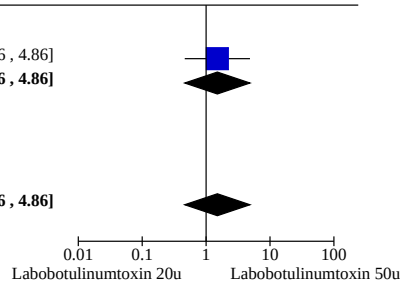
Analysis 68.3. Comparison 68: Liquid AbobotulinumtoxinA 20 units versus Liquid AbobotulinumtoxinA 50 units one cycle of treatment, glabellar lines, Outcome 3: Physician assessment of success by analysing scores and scales

Study or Subgroup	Labobotulinumtoxin 20u Events	Total	Labobotukinumtoxin50u Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
68.3.1 4 weeks						
Ascher 2018	32	35	30	35	100.0%	1.07 [0.90 , 1.26]
Subtotal (95% CI)		**35**		**35**	**100.0%**	**1.07 [0.90 , 1.26]**
Total events:	32		30			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.75 (P = 0.45)						
68.3.2 8 weeks						
Ascher 2018	28	35	19	35	100.0%	1.47 [1.04 , 2.08]
Subtotal (95% CI)		**35**		**35**	**100.0%**	**1.47 [1.04 , 2.08]**
Total events:	28		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.20 (P = 0.03)						
68.3.3 12 weeks						
Ascher 2018	19	35	16	35	100.0%	1.19 [0.74 , 1.90]
Subtotal (95% CI)		**35**		**35**	**100.0%**	**1.19 [0.74 , 1.90]**
Total events:	19		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.71 (P = 0.48)						
68.3.4 16 weeks						
Ascher 2018	9	35	12	35	100.0%	0.75 [0.36 , 1.55]
Subtotal (95% CI)		**35**		**35**	**100.0%**	**0.75 [0.36 , 1.55]**
Total events:	9		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.78 (P = 0.44)						
Test for subgroup differences: Chi² = 3.96, df = 3 (P = 0.27), I² = 24.3%						



Analysis 68.4. Comparison 68: Liquid AbobotulinumtoxinA 20 units versus Liquid AbobotulinumtoxinA 50 units one cycle of treatment, glabellar lines, Outcome 4: Total adverse events

Study or Subgroup	Labobotukinumtoxin 20u Events	Total	L abobotulinumtoxin 50u Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
68.4.1 Total adverse events						
Ascher 2018	6	35	4	35	100.0%	1.50 [0.46 , 4.86]
Subtotal (95% CI)		**35**		**35**	**100.0%**	**1.50 [0.46 , 4.86]**
Total events:	6		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
Total (95% CI)		**35**		**35**	**100.0%**	**1.50 [0.46 , 4.86]**
Total events:	6		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
Test for subgroup differences: Not applicable						

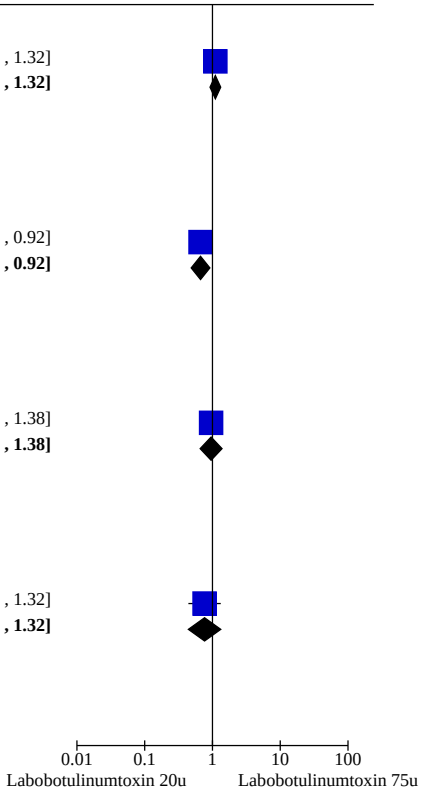


Comparison 69. Liquid AbobotulinumtoxinA 20 units versus Liquid AbobotulinumtoxinA 75 units one cycle of treatment, glabellar lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
69.1 Participant assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
69.1.1 4 weeks	1	70	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.92, 1.32]
69.1.2 8 weeks	1	70	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.49, 0.92]
69.1.3 12 weeks	1	70	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.66, 1.38]
69.1.4 16 weeks	1	70	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.44, 1.32]
69.2 Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
69.2.1 Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)	1	70	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.50 [0.05, 5.00]
69.3 Physician assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
69.3.1 4 weeks	1	70	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.88, 1.21]
69.3.2 8 weeks	1	70	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.77, 1.21]
69.3.3 12 weeks	1	70	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.49, 1.00]
69.3.4 16 weeks	1	78	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.29, 1.06]
69.4 Total adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
69.4.1 Total adverse events	1	70	Risk Ratio (M-H, Random, 95% CI)	2.50 [0.87, 7.22]

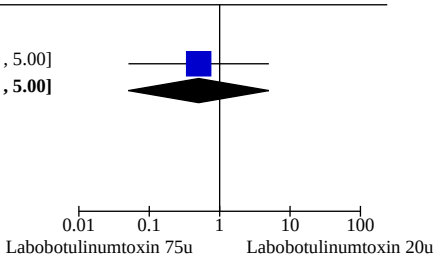
Analysis 69.1. Comparison 69: Liquid AbobotulinumtoxinA 20 units versus Liquid AbobotulinumtoxinA 75 units one cycle of treatment, glabellar lines, Outcome 1: Participant assessment of success by analysing scores and scales

Study or Subgroup	Labobotulinum 20u Events	Total	Labobotutulinum 75u Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
69.1.1 4 weeks						
Ascher 2018	32	35	29	35	100.0%	1.10 [0.92 , 1.32]
Subtotal (95% CI)		**35**		**35**	**100.0%**	**1.10 [0.92 , 1.32]**
Total events:	32		29			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.06 (P = 0.29)						
69.1.2 8 weeks						
Ascher 2018	20	35	30	35	100.0%	0.67 [0.49 , 0.92]
Subtotal (95% CI)		**35**		**35**	**100.0%**	**0.67 [0.49 , 0.92]**
Total events:	20		30			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.51 (P = 0.01)						
69.1.3 12 weeks						
Ascher 2018	21	35	22	35	100.0%	0.95 [0.66 , 1.38]
Subtotal (95% CI)		**35**		**35**	**100.0%**	**0.95 [0.66 , 1.38]**
Total events:	21		22			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.25 (P = 0.81)						
69.1.4 16 weeks						
Ascher 2018	13	35	17	35	100.0%	0.76 [0.44 , 1.32]
Subtotal (95% CI)		**35**		**35**	**100.0%**	**0.76 [0.44 , 1.32]**
Total events:	13		17			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.96 (P = 0.34)						
Test for subgroup differences: Chi² = 7.99, df = 3 (P = 0.05), I² = 62.5%						



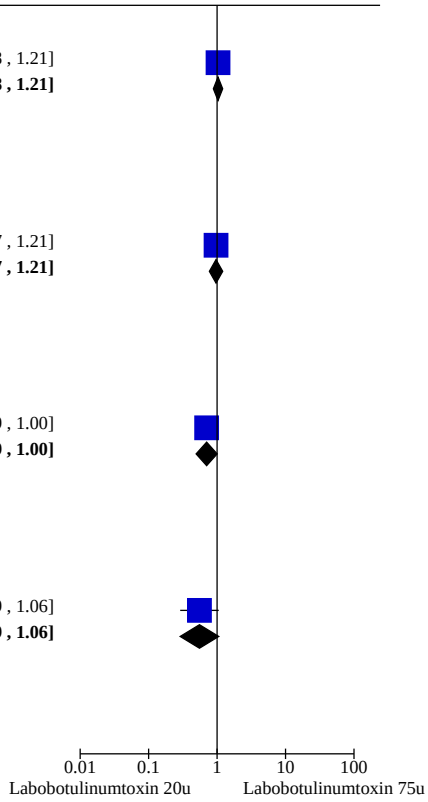
Analysis 69.2. Comparison 69: Liquid AbobotulinumtoxinA 20 units versus Liquid AbobotulinumtoxinA 75 units one cycle of treatment, glabellar lines, Outcome 2: Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

Study or Subgroup	Labobotulinum20u Events	Total	Labobotulinum 75u Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
69.2.1 Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)						
Ascher 2018	1	35	2	35	100.0%	0.50 [0.05 , 5.00]
Subtotal (95% CI)		**35**		**35**	**100.0%**	**0.50 [0.05 , 5.00]**
Total events:	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.59 (P = 0.56)						
Test for subgroup differences: Not applicable						



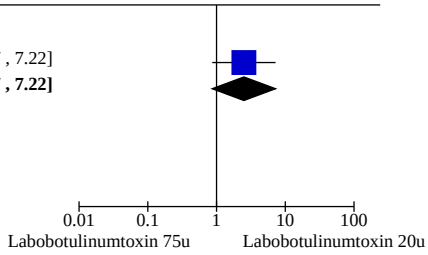
Analysis 69.3. Comparison 69: Liquid AbobotulinumtoxinA 20 units versus Liquid AbobotulinumtoxinA 75 units one cycle of treatment, glabellar lines, Outcome 3: Physician assessment of success by analysing scores and scales

Study or Subgroup	Labobotulinum 20u Events	Total	L abobotulinum 75u Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
69.3.1 4 weeks						
Ascher 2018	32	35	31	35	100.0%	1.03 [0.88 , 1.21]
Subtotal (95% CI)		**35**		**35**	**100.0%**	**1.03 [0.88 , 1.21]**
Total events:	32		31			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.40 (P = 0.69)						
69.3.2 8 weeks						
Ascher 2018	28	35	29	35	100.0%	0.97 [0.77 , 1.21]
Subtotal (95% CI)		**35**		**35**	**100.0%**	**0.97 [0.77 , 1.21]**
Total events:	28		29			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.31 (P = 0.76)						
69.3.3 12 weeks						
Ascher 2018	19	35	27	35	100.0%	0.70 [0.49 , 1.00]
Subtotal (95% CI)		**35**		**35**	**100.0%**	**0.70 [0.49 , 1.00]**
Total events:	19		27			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.95 (P = 0.05)						
69.3.4 16 weeks						
Ascher 2018	9	35	20	43	100.0%	0.55 [0.29 , 1.06]
Subtotal (95% CI)		**35**		**43**	**100.0%**	**0.55 [0.29 , 1.06]**
Total events:	9		20			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.79 (P = 0.07)						
Test for subgroup differences: Chi^2 = 6.55, df = 3 (P = 0.09), I^2 = 54.2%						



Analysis 69.4. Comparison 69: Liquid AbobotulinumtoxinA 20 units versus Liquid AbobotulinumtoxinA 75 units one cycle of treatment, glabellar lines, Outcome 4: Total adverse events

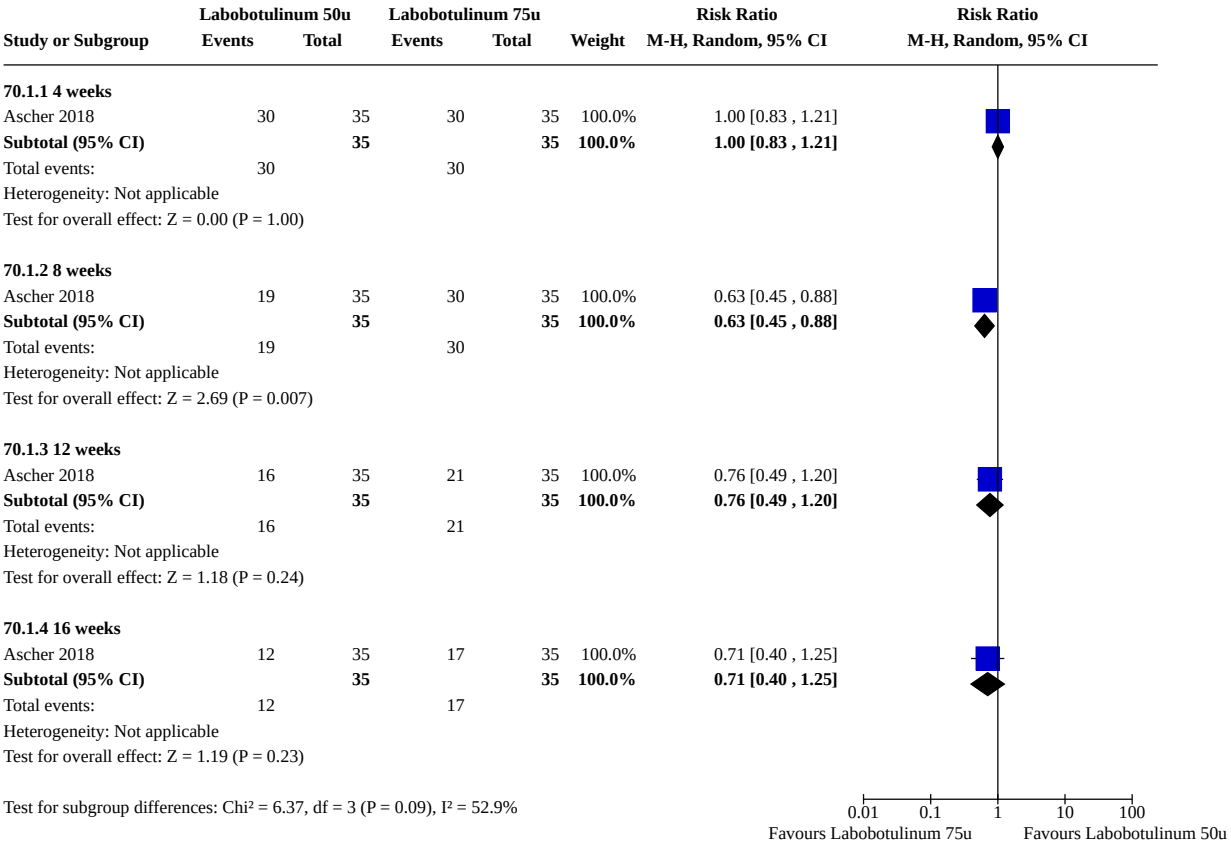
Study or Subgroup	Labobotulinum 20u Events	Total	Labobotulinum 75u Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
69.4.1 Total adverse events						
Ascher 2018	10	35	4	35	100.0%	2.50 [0.87 , 7.22]
Subtotal (95% CI)		**35**		**35**	**100.0%**	**2.50 [0.87 , 7.22]**
Total events:	10		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.69 (P = 0.09)						
Test for subgroup differences: Not applicable						



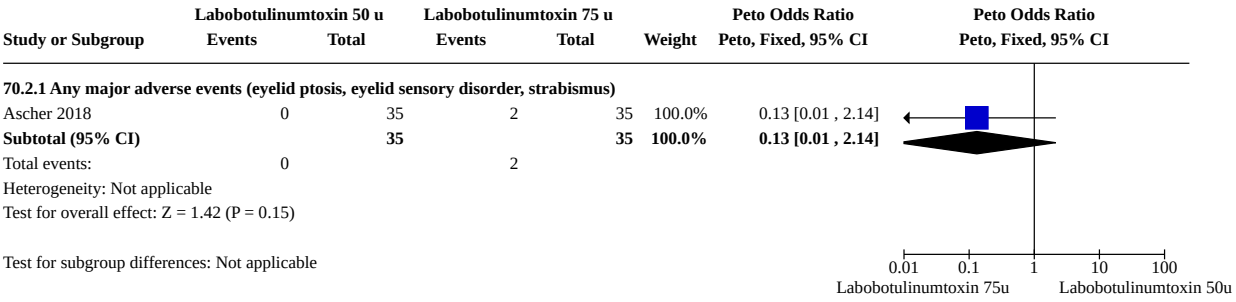
Comparison 70. Liquid AbobotulinumtoxinA 50 units versus Liquid AbobotulinumtoxinA 75 units one cycle of treatment, glabellar lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
70.1 Participant assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
70.1.1 4 weeks	1	70	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.83, 1.21]
70.1.2 8 weeks	1	70	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.45, 0.88]
70.1.3 12 weeks	1	70	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.49, 1.20]
70.1.4 16 weeks	1	70	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.40, 1.25]
70.2 Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
70.2.1 Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)	1	70	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.13 [0.01, 2.14]
70.3 Physician assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
70.3.1 4 weeks	1	70	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.81, 1.16]
70.3.2 8 weeks	1	70	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.47, 0.92]
70.3.3 12 weeks	1	70	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.40, 0.89]
70.3.4 16 weeks	1	70	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.35, 1.03]
70.4 Total adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
70.4.1 Total adverse events	1	70	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.27, 3.69]

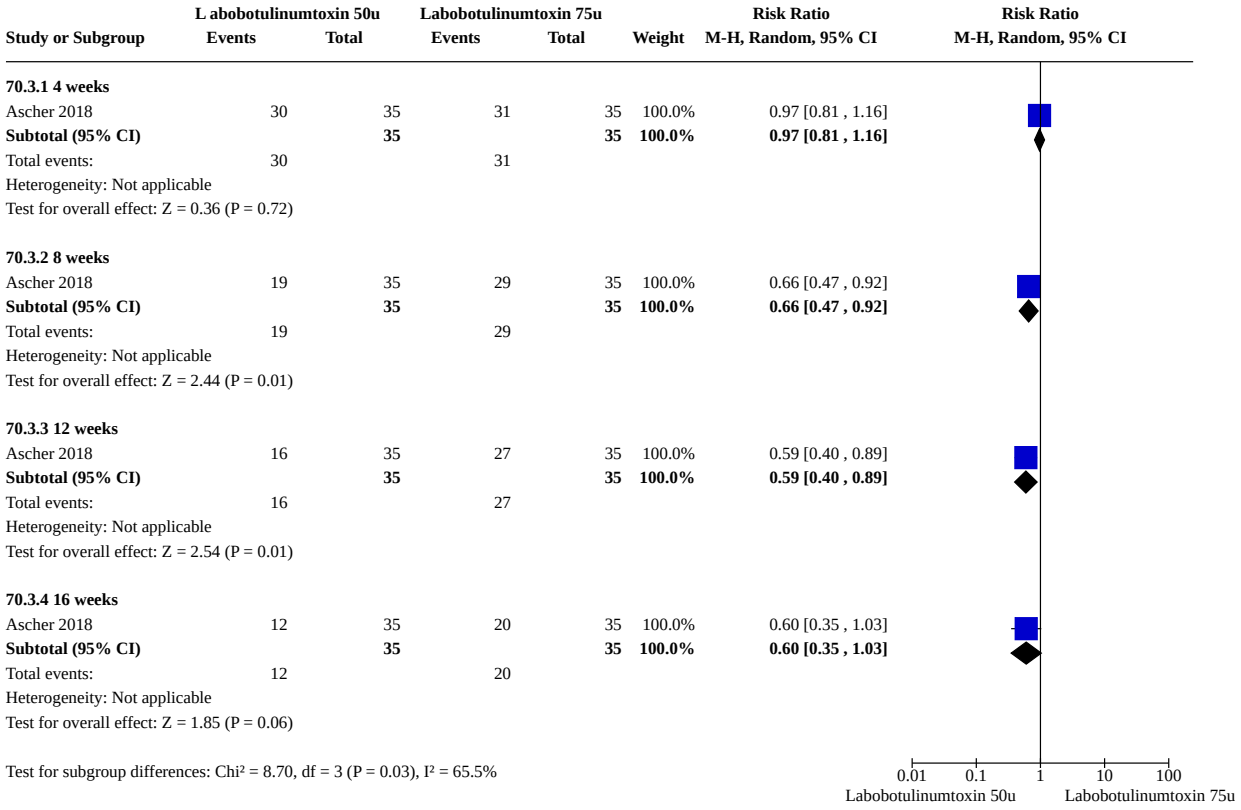
Analysis 70.1. Comparison 70: Liquid AbobotulinumtoxinA 50 units versus Liquid AbobotulinumtoxinA 75 units one cycle of treatment, glabellar lines, Outcome 1: Participant assessment of success by analysing scores and scales



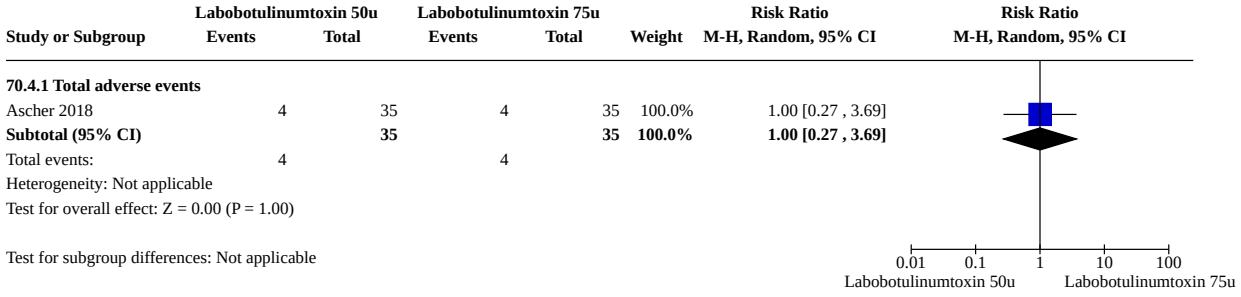
Analysis 70.2. Comparison 70: Liquid AbobotulinumtoxinA 50 units versus Liquid AbobotulinumtoxinA 75 units one cycle of treatment, glabellar lines, Outcome 2: Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)



Analysis 70.3. Comparison 70: Liquid AbobotulinumtoxinA 50 units versus Liquid AbobotulinumtoxinA 75 units one cycle of treatment, glabellar lines, Outcome 3: Physician assessment of success by analysing scores and scales



Analysis 70.4. Comparison 70: Liquid AbobotulinumtoxinA 50 units versus Liquid AbobotulinumtoxinA 75 units one cycle of treatment, glabellar lines, Outcome 4: Total adverse events



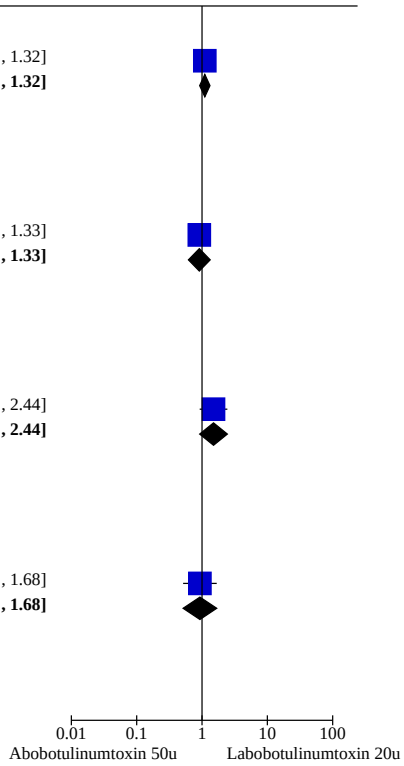
Comparison 71. Liquid AbobotulinumtoxinA 20 units versus AbobotulinumtoxinA 50 units one cycle of treatment, glabellar lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
71.1 Participant assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
71.1.1 4 weeks	1	70	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.92, 1.32]
71.1.2 8 weeks	1	70	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.62, 1.33]
71.1.3 12 weeks	1	70	Risk Ratio (M-H, Random, 95% CI)	1.50 [0.92, 2.44]
71.1.4 16 weeks	1	70	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.51, 1.68]
71.2 Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
71.2.1 Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)	1	70	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.39 [0.15, 372.38]
71.3 Physician assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
71.3.1 4 weeks	1	70	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.96, 1.46]
71.3.2 8 weeks	1	70	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.79, 1.26]
71.3.3 12 weeks	1	70	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.65, 1.54]
71.3.4 16 weeks	1	70	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.34, 1.41]
71.4 Total adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
71.4.1 Total adverse events	1	70	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.65, 13.86]

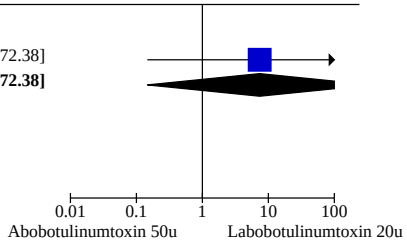
Analysis 71.1. Comparison 71: Liquid AbobotulinumtoxinA 20 units versus AbobotulinumtoxinA 50 units one cycle of treatment, glabellar lines, Outcome 1: Participant assessment of success by analysing scores and scales

Study or Subgroup	Labobtulinumtoxin 20u Events	Total	Abobotulinumtoxin 50u Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
71.1.1 4 weeks						
Ascher 2018	32	35	29	35	100.0%	1.10 [0.92 , 1.32]
Subtotal (95% CI)		**35**		**35**	**100.0%**	**1.10 [0.92 , 1.32]**
Total events:	32		29			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.06 (P = 0.29)						
71.1.2 8 weeks						
Ascher 2018	20	35	22	35	100.0%	0.91 [0.62 , 1.33]
Subtotal (95% CI)		**35**		**35**	**100.0%**	**0.91 [0.62 , 1.33]**
Total events:	20		22			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.49 (P = 0.63)						
71.1.3 12 weeks						
Ascher 2018	21	35	14	35	100.0%	1.50 [0.92 , 2.44]
Subtotal (95% CI)		**35**		**35**	**100.0%**	**1.50 [0.92 , 2.44]**
Total events:	21		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.63 (P = 0.10)						
71.1.4 16 weeks						
Ascher 2018	13	35	14	35	100.0%	0.93 [0.51 , 1.68]
Subtotal (95% CI)		**35**		**35**	**100.0%**	**0.93 [0.51 , 1.68]**
Total events:	13		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.25 (P = 0.81)						
Test for subgroup differences: Chi² = 2.81, df = 3 (P = 0.42), I² = 0%						



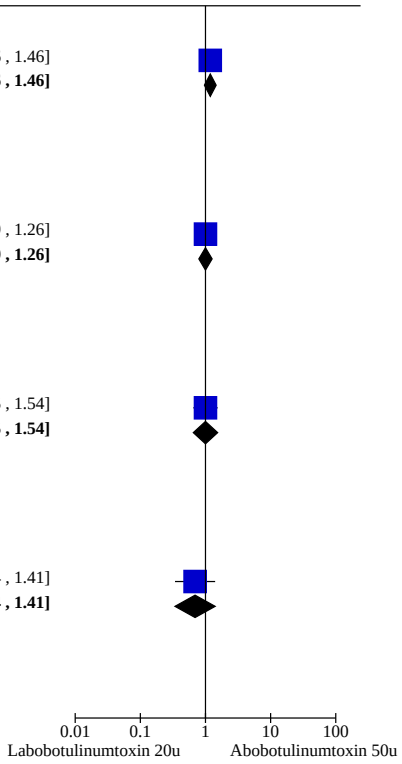
Analysis 71.2. Comparison 71: Liquid AbobotulinumtoxinA 20 units versus AbobotulinumtoxinA 50 units one cycle of treatment, glabellar lines, Outcome 2: Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

Study or Subgroup	Labobotulinumtoxin 20u Events	Total	Abobotulinumtoxin 50u Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
71.2.1 Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)						
Ascher 2018	1	35	0	35	100.0%	7.39 [0.15 , 372.38]
Subtotal (95% CI)		**35**		**35**	**100.0%**	**7.39 [0.15 , 372.38]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.00 (P = 0.32)						
Test for subgroup differences: Not applicable						



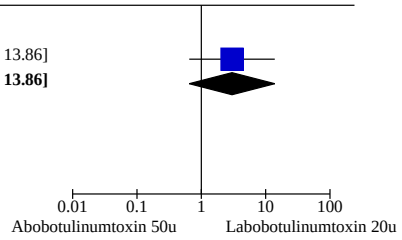
Analysis 71.3. Comparison 71: Liquid AbobotulinumtoxinA 20 units versus AbobotulinumtoxinA 50 units one cycle of treatment, glabellar lines, Outcome 3: Physician assessment of success by analysing scores and scales

Study or Subgroup	Labobotulinumtoxin 20u Events	Total	Abobotulinumtoxin 50u Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
71.3.1 4 weeks						
Ascher 2018	32	35	27	35	100.0%	1.19 [0.96 , 1.46]
Subtotal (95% CI)		**35**		**35**	**100.0%**	**1.19 [0.96 , 1.46]**
Total events:	32		27			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.61 (P = 0.11)						
71.3.2 8 weeks						
Ascher 2018	28	35	28	35	100.0%	1.00 [0.79 , 1.26]
Subtotal (95% CI)		**35**		**35**	**100.0%**	**1.00 [0.79 , 1.26]**
Total events:	28		28			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
71.3.3 12 weeks						
Ascher 2018	19	35	19	35	100.0%	1.00 [0.65 , 1.54]
Subtotal (95% CI)		**35**		**35**	**100.0%**	**1.00 [0.65 , 1.54]**
Total events:	19		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
71.3.4 16 weeks						
Ascher 2018	9	35	13	35	100.0%	0.69 [0.34 , 1.41]
Subtotal (95% CI)		**35**		**35**	**100.0%**	**0.69 [0.34 , 1.41]**
Total events:	9		13			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.02 (P = 0.31)						
Test for subgroup differences: Chi² = 2.80, df = 3 (P = 0.42), I² = 0%						



Analysis 71.4. Comparison 71: Liquid AbobotulinumtoxinA 20 units versus AbobotulinumtoxinA 50 units one cycle of treatment, glabellar lines, Outcome 4: Total adverse events

Study or Subgroup	L abobotulinumtoxin 20u Events	Total	Abobotulinum toxin 50u Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
71.4.1 Total adverse events						
Ascher 2018	6	35	2	35	100.0%	3.00 [0.65 , 13.86]
Subtotal (95% CI)		**35**		**35**	**100.0%**	**3.00 [0.65 , 13.86]**
Total events:	6		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.41 (P = 0.16)						
Test for subgroup differences: Not applicable						



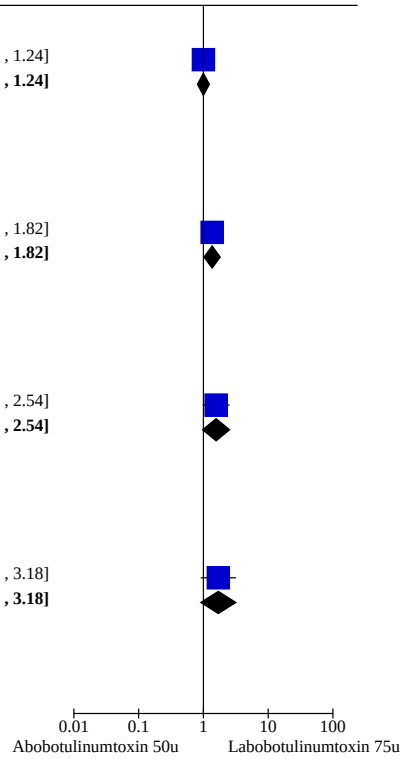
Comparison 72. Liquid AbobotulinumtoxinA 75 units versus AbobotulinumtoxinA 50 units one cycle of treatment, glabellar lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
72.1 Participant assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
72.1.1 4 weeks	1	70	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.81, 1.24]
72.1.2 8 weeks	1	70	Risk Ratio (M-H, Random, 95% CI)	1.36 [1.02, 1.82]
72.1.3 12 weeks	1	70	Risk Ratio (M-H, Random, 95% CI)	1.57 [0.97, 2.54]
72.1.4 16 weeks	1	70	Risk Ratio (M-H, Random, 95% CI)	1.70 [0.91, 3.18]
72.2 Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
72.2.1 Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)	1	70	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.61 [0.47, 124.15]
72.3 Physician assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
72.3.1 4 weeks	1	70	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.93, 1.43]
72.3.2 8 weeks	1	70	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.83, 1.30]
72.3.3 12 weeks	1	70	Risk Ratio (M-H, Random, 95% CI)	1.42 [1.00, 2.02]
72.3.4 16 weeks	1	70	Risk Ratio (M-H, Random, 95% CI)	1.54 [0.92, 2.58]
72.4 Total adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
72.4.1 Total adverse events	1	70	Risk Ratio (M-H, Random, 95% CI)	2.00 [0.39, 10.22]

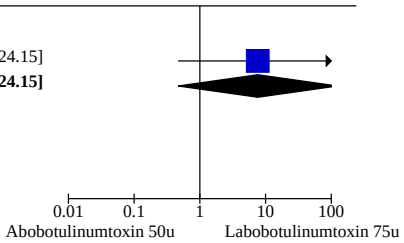
Analysis 72.1. Comparison 72: Liquid AbobotulinumtoxinA 75 units versus AbobotulinumtoxinA 50 units one cycle of treatment, glabellar lines, Outcome 1: Participant assessment of success by analysing scores and scales

Study or Subgroup	Labobotulinumtoxin 75u Events	Total	Abobotulinumtoxin 50u Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
72.1.1 4 weeks						
Ascher 2018	29	35	29	35	100.0%	1.00 [0.81 , 1.24]
Subtotal (95% CI)		**35**		**35**	**100.0%**	**1.00 [0.81 , 1.24]**
Total events:	29		29			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
72.1.2 8 weeks						
Ascher 2018	30	35	22	35	100.0%	1.36 [1.02 , 1.82]
Subtotal (95% CI)		**35**		**35**	**100.0%**	**1.36 [1.02 , 1.82]**
Total events:	30		22			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.11 (P = 0.04)						
72.1.3 12 weeks						
Ascher 2018	22	35	14	35	100.0%	1.57 [0.97 , 2.54]
Subtotal (95% CI)		**35**		**35**	**100.0%**	**1.57 [0.97 , 2.54]**
Total events:	22		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.85 (P = 0.06)						
72.1.4 16 weeks						
Ascher 2018	17	35	10	35	100.0%	1.70 [0.91 , 3.18]
Subtotal (95% CI)		**35**		**35**	**100.0%**	**1.70 [0.91 , 3.18]**
Total events:	17		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.66 (P = 0.10)						
Test for subgroup differences: Chi^2 = 5.96, df = 3 (P = 0.11), I^2 = 49.7%						



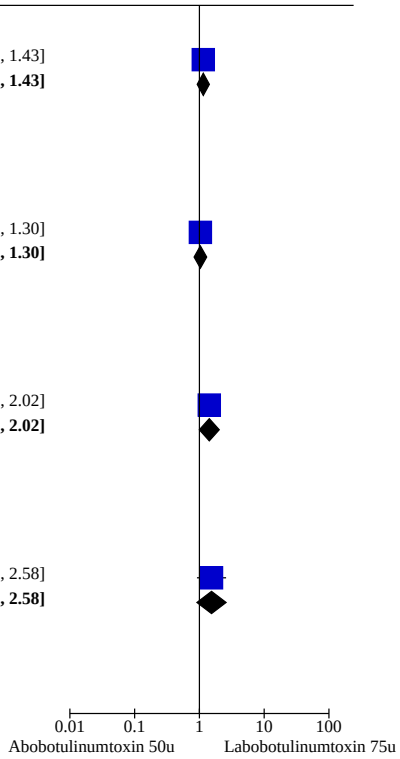
Analysis 72.2. Comparison 72: Liquid AbobotulinumtoxinA 75 units versus AbobotulinumtoxinA 50 units one cycle of treatment, glabellar lines, Outcome 2: Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

Study or Subgroup	L abobotulinumtoxin 75u Events	Total	Abobotulinumtoxin 50u Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
72.2.1 Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)						
Ascher 2018	2	35	0	35	100.0%	7.61 [0.47 , 124.15]
Subtotal (95% CI)		**35**		**35**	**100.0%**	**7.61 [0.47 , 124.15]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.42 (P = 0.15)						
Test for subgroup differences: Not applicable						



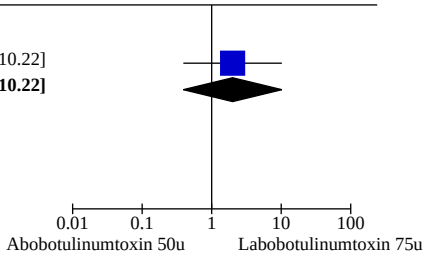
Analysis 72.3. Comparison 72: Liquid AbobotulinumtoxinA 75 units versus AbobotulinumtoxinA 50 units one cycle of treatment, glabellar lines, Outcome 3: Physician assessment of success by analysing scores and scales

Study or Subgroup	Labobotulinumtoxin 75u Events	Total	Abobotulinumtoxin 50u Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
72.3.1 4 weeks						
Ascher 2018	31	35	27	35	100.0%	1.15 [0.93 , 1.43]
Subtotal (95% CI)		**35**		**35**	**100.0%**	**1.15 [0.93 , 1.43]**
Total events:	31		27			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.25 (P = 0.21)						
72.3.2 8 weeks						
Ascher 2018	29	35	28	35	100.0%	1.04 [0.83 , 1.30]
Subtotal (95% CI)		**35**		**35**	**100.0%**	**1.04 [0.83 , 1.30]**
Total events:	29		28			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.31 (P = 0.76)						
72.3.3 12 weeks						
Ascher 2018	27	35	19	35	100.0%	1.42 [1.00 , 2.02]
Subtotal (95% CI)		**35**		**35**	**100.0%**	**1.42 [1.00 , 2.02]**
Total events:	27		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.95 (P = 0.05)						
72.3.4 16 weeks						
Ascher 2018	20	35	13	35	100.0%	1.54 [0.92 , 2.58]
Subtotal (95% CI)		**35**		**35**	**100.0%**	**1.54 [0.92 , 2.58]**
Total events:	20		13			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.63 (P = 0.10)						
Test for subgroup differences: Chi^2 = 3.40, df = 3 (P = 0.33), I^2 = 11.7%						



Analysis 72.4. Comparison 72: Liquid AbobotulinumtoxinA 75 units versus AbobotulinumtoxinA 50 units one cycle of treatment, glabellar lines, Outcome 4: Total adverse events

Study or Subgroup	Labobotulinum 75 u Events	Total	Abobtulinum 50u Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
72.4.1 Total adverse events						
Ascher 2018	4	35	2	35	100.0%	2.00 [0.39 , 10.22]
Subtotal (95% CI)		**35**		**35**	**100.0%**	**2.00 [0.39 , 10.22]**
Total events:	4		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.83 (P = 0.40)						
Test for subgroup differences: Not applicable						

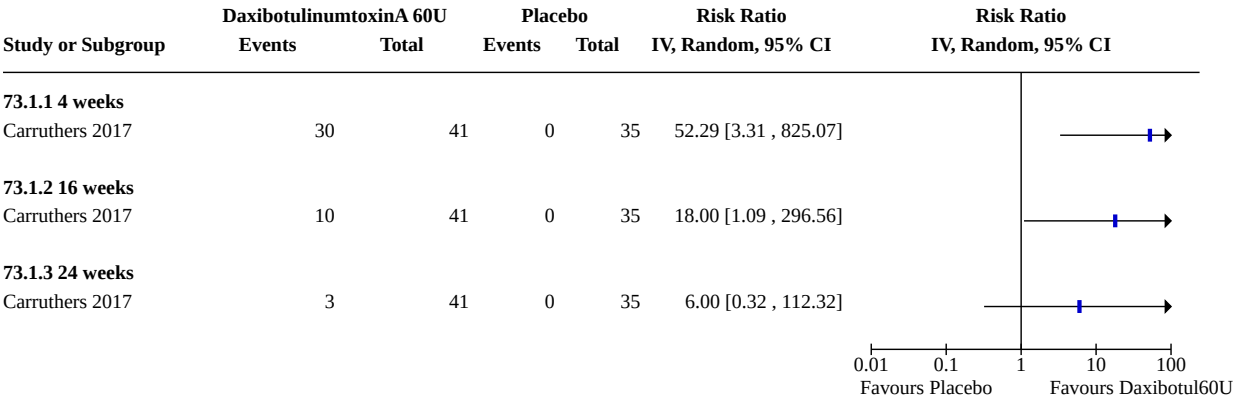


Comparison 73. DaxibotulinumtoxinA 60 units versus placebo one cycle of treatment in glabellar lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
73.1 Participants assessment of success by analysing scores and scales	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected

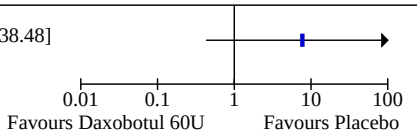
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
73.1.1 4 weeks	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
73.1.2 16 weeks	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
73.1.3 24 weeks	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
73.2 Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
73.3 Physician assessment of success by analysing scores and scales	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
73.3.1 4 weeks	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
73.3.2 8 weeks	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
73.3.3 12 weeks	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
73.3.4 16 weeks	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
73.3.5 20 weeks	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
73.3.6 24 weeks	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
73.4 Total adverse events	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
73.5 Duration of treatment	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 73.1. Comparison 73: DaxibotulinumtoxinA 60 units versus placebo one cycle of treatment in glabellar lines, Outcome 1: Participants assessment of success by analysing scores and scales



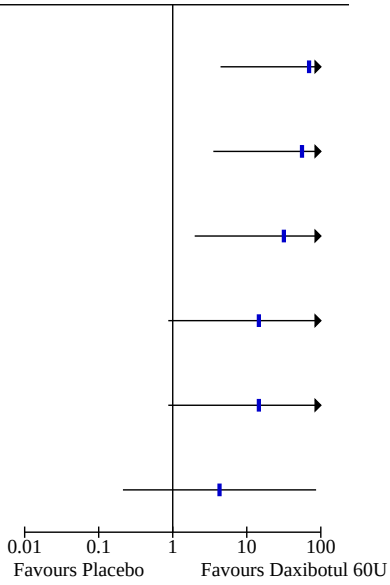
Analysis 73.2. Comparison 73: DaxibotulinumtoxinA 60 units versus placebo one cycle of treatment in glabellar lines, Outcome 2: Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

Study or Subgroup	DaxibotulinumtoxinA 60U Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 95% CI
Carruthers 2017	4	41	0	35	7.71 [0.43 , 138.48]



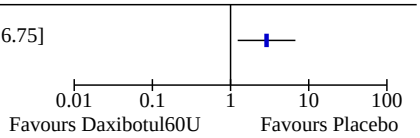
Analysis 73.3. Comparison 73: DaxibotulinumtoxinA 60 units versus placebo one cycle of treatment in glabellar lines, Outcome 3: Physician assessment of success by analysing scores and scales

Study or Subgroup	DaxibotulinumtoxinA 60U Events	Total	Placebo Events	Total	Risk Ratio IV, Random, 95% CI
73.3.1 4 weeks					
Carruthers 2017	40	41	0	35	69.43 [4.42 , 1089.43]
73.3.2 8 weeks					
Carruthers 2017	32	41	0	35	55.71 [3.54 , 877.94]
73.3.3 12 weeks					
Carruthers 2017	18	41	0	35	31.71 [1.98 , 507.90]
73.3.4 16 weeks					
Carruthers 2017	8	41	0	35	14.57 [0.87 , 243.78]
73.3.5 20 weeks					
Carruthers 2017	8	41	0	35	14.57 [0.87 , 243.78]
73.3.6 24 weeks					
Carruthers 2017	2	41	0	35	4.29 [0.21 , 86.39]

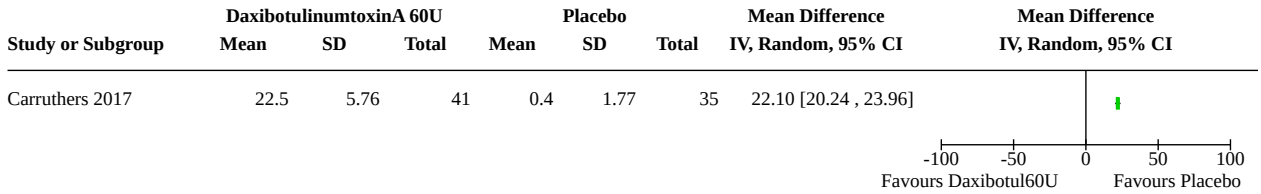


Analysis 73.4. Comparison 73: DaxibotulinumtoxinA 60 units versus placebo one cycle of treatment in glabellar lines, Outcome 4: Total adverse events

Study or Subgroup	DaxibotulinumtoxinA 60U Events	Total	Placebo Events	Total	Risk Ratio IV, Random, 95% CI
Carruthers 2017	17	53	6	54	2.89 [1.23 , 6.75]



Analysis 73.5. Comparison 73: DaxibotulinumtoxinA 60 units versus placebo one cycle of treatment in glabellar lines, Outcome 5: Duration of treatment

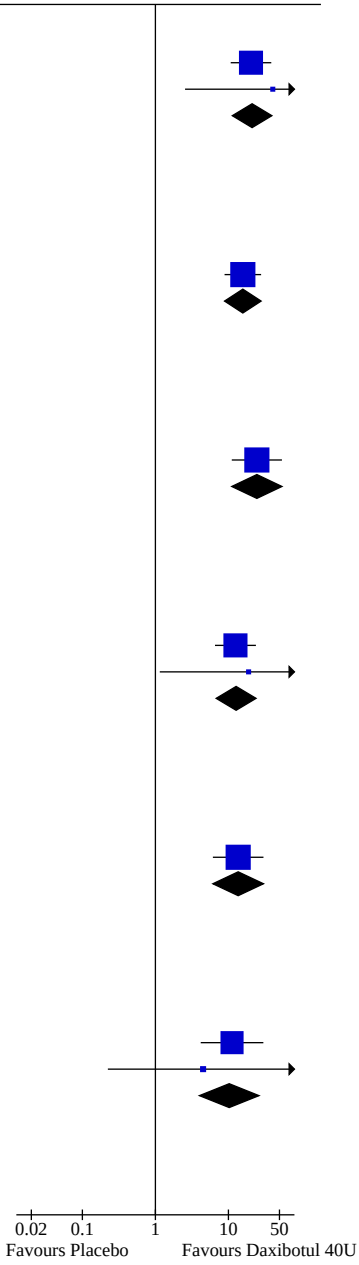


Comparison 74. DaxibotulinumtoxinA 40 units versus placebo one cycle of treatment in glabellar lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
74.1 Participant assessment of success by analysing scores and scales	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
74.1.1 4 weeks	2	683	Risk Ratio (IV, Random, 95% CI)	21.10 [11.31, 39.34]
74.1.2 8 weeks	1	609	Risk Ratio (IV, Random, 95% CI)	15.75 [8.85, 28.03]
74.1.3 12 weeks	1	609	Risk Ratio (IV, Random, 95% CI)	24.51 [11.12, 54.05]
74.1.4 16 weeks	2	683	Risk Ratio (IV, Random, 95% CI)	12.74 [6.80, 23.89]
74.1.5 20 weeks	1	609	Risk Ratio (IV, Random, 95% CI)	13.60 [6.13, 30.18]
74.1.6 24 weeks	2	683	Risk Ratio (IV, Random, 95% CI)	10.25 [4.01, 26.20]
74.2 Physician assessment of success by analysing scores and scales	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
74.2.1 4 weeks	2	683	Risk Ratio (IV, Random, 95% CI)	23.40 [12.56, 43.61]
74.2.2 8 weeks	2	683	Risk Ratio (IV, Random, 95% CI)	18.09 [10.30, 31.78]
74.2.3 12 weeks	2	683	Risk Ratio (IV, Random, 95% CI)	29.46 [13.79, 62.94]
74.2.4 16 weeks	2	683	Risk Ratio (IV, Random, 95% CI)	16.84 [9.01, 31.47]
74.2.5 20 weeks	2	683	Risk Ratio (IV, Random, 95% CI)	18.06 [8.42, 38.76]
74.2.6 24 weeks	2	683	Risk Ratio (IV, Random, 95% CI)	15.33 [6.06, 38.78]
74.3 Total adverse events	2	716	Risk Ratio (IV, Random, 95% CI)	2.23 [1.46, 3.40]
74.4 Duration of treatment effect, weeks	1	74	Mean Difference (IV, Random, 95% CI)	22.80 [20.74, 24.86]

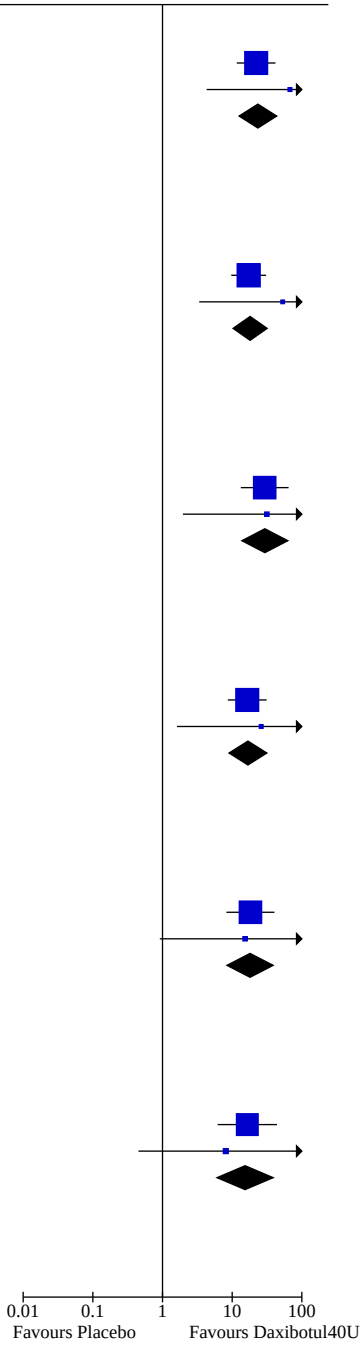
Analysis 74.1. Comparison 74: DaxibotulinumtoxinA 40 units versus placebo one cycle of treatment in glabellar lines, Outcome 1: Participant assessment of success by analysing scores and scales

Study or Subgroup	DaxibotulinumtoxinA 40U Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
74.1.1 4 weeks						
Bertucci 2020	364	405	9	204	94.9%	20.37 [10.75 , 38.62]
Carruthers 2017	22	39	0	35	5.1%	40.50 [2.55 , 643.76]
Subtotal (95% CI)		**444**		**239**	**100.0%**	**21.10 [11.31 , 39.34]**
Total events:	386		9			
Heterogeneity: Tau² = 0.00; Chi² = 0.23, df = 1 (P = 0.64); I² = 0%						
Test for overall effect: Z = 9.59 (P < 0.00001)						
74.1.2 8 weeks						
Bertucci 2020	344	405	11	204	100.0%	15.75 [8.85 , 28.03]
Subtotal (95% CI)		**405**		**204**	**100.0%**	**15.75 [8.85 , 28.03]**
Total events:	344		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 9.38 (P < 0.00001)						
74.1.3 12 weeks						
Bertucci 2020	292	405	6	204	100.0%	24.51 [11.12 , 54.05]
Subtotal (95% CI)		**405**		**204**	**100.0%**	**24.51 [11.12 , 54.05]**
Total events:	292		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 7.93 (P < 0.00001)						
74.1.4 16 weeks						
Bertucci 2020	223	405	9	204	95.0%	12.48 [6.55 , 23.78]
Carruthers 2017	10	39	0	35	5.0%	18.90 [1.15 , 311.14]
Subtotal (95% CI)		**444**		**239**	**100.0%**	**12.74 [6.80 , 23.89]**
Total events:	233		9			
Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 1 (P = 0.78); I² = 0%						
Test for overall effect: Z = 7.94 (P < 0.00001)						
74.1.5 20 weeks						
Bertucci 2020	162	405	6	204	100.0%	13.60 [6.13 , 30.18]
Subtotal (95% CI)		**405**		**204**	**100.0%**	**13.60 [6.13 , 30.18]**
Total events:	162		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 6.42 (P < 0.00001)						
74.1.6 24 weeks						
Bertucci 2020	89	405	4	204	90.2%	11.21 [4.17 , 30.09]
Carruthers 2017	2	39	0	35	9.8%	4.50 [0.22 , 90.64]
Subtotal (95% CI)		**444**		**239**	**100.0%**	**10.25 [4.01 , 26.20]**
Total events:	91		4			
Heterogeneity: Tau² = 0.00; Chi² = 0.32, df = 1 (P = 0.57); I² = 0%						
Test for overall effect: Z = 4.86 (P < 0.00001)						



Analysis 74.2. Comparison 74: DaxibotulinumtoxinA 40 units versus placebo one cycle of treatment in glabellar lines, Outcome 2: Physician assessment of success by analysing scores and scales

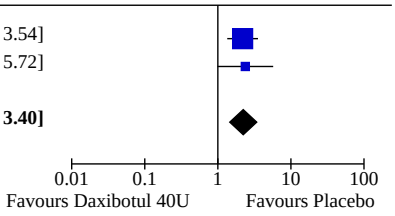
Study or Subgroup	DaxibotulinumtoxinA 40U Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
74.2.1 4 weeks						
Bertucci 2020	395	405	9	204	94.9%	22.11 [11.67 , 41.88]
Carruthers 2017	37	39	0	35	5.1%	67.50 [4.30 , 1059.74]
Subtotal (95% CI)		**444**		**239**	**100.0%**	**23.40 [12.56 , 43.61]**
Total events:	432		9			
Heterogeneity: Tau² = 0.00; Chi² = 0.60, df = 1 (P = 0.44); I² = 0%						
Test for overall effect: Z = 9.93 (P < 0.00001)						
74.2.2 8 weeks						
Bertucci 2020	377	405	11	204	95.8%	17.26 [9.71 , 30.69]
Carruthers 2017	29	39	0	35	4.2%	53.10 [3.37 , 837.88]
Subtotal (95% CI)		**444**		**239**	**100.0%**	**18.09 [10.30 , 31.78]**
Total events:	406		11			
Heterogeneity: Tau² = 0.00; Chi² = 0.61, df = 1 (P = 0.43); I² = 0%						
Test for overall effect: Z = 10.07 (P < 0.00001)						
74.2.3 12 weeks						
Bertucci 2020	349	405	6	204	92.5%	29.30 [13.31 , 64.51]
Carruthers 2017	17	39	0	35	7.5%	31.50 [1.96 , 505.13]
Subtotal (95% CI)		**444**		**239**	**100.0%**	**29.46 [13.79 , 62.94]**
Total events:	366		6			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.96); I² = 0%						
Test for overall effect: Z = 8.73 (P < 0.00001)						
74.2.4 16 weeks						
Bertucci 2020	294	405	9	204	95.0%	16.45 [8.66 , 31.25]
Carruthers 2017	14	39	0	35	5.0%	26.10 [1.61 , 421.97]
Subtotal (95% CI)		**444**		**239**	**100.0%**	**16.84 [9.01 , 31.47]**
Total events:	308		9			
Heterogeneity: Tau² = 0.00; Chi² = 0.10, df = 1 (P = 0.75); I² = 0%						
Test for overall effect: Z = 8.85 (P < 0.00001)						
74.2.5 20 weeks						
Bertucci 2020	218	405	6	204	92.6%	18.30 [8.28 , 40.46]
Carruthers 2017	8	39	0	35	7.4%	15.30 [0.92 , 255.76]
Subtotal (95% CI)		**444**		**239**	**100.0%**	**18.06 [8.42 , 38.76]**
Total events:	226		6			
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.90); I² = 0%						
Test for overall effect: Z = 7.43 (P < 0.00001)						
74.2.6 24 weeks						
Bertucci 2020	131	405	4	204	89.7%	16.50 [6.19 , 43.98]
Carruthers 2017	4	39	0	35	10.3%	8.10 [0.45 , 145.29]
Subtotal (95% CI)		**444**		**239**	**100.0%**	**15.33 [6.06 , 38.78]**
Total events:	135		4			
Heterogeneity: Tau² = 0.00; Chi² = 0.21, df = 1 (P = 0.65); I² = 0%						
Test for overall effect: Z = 5.76 (P < 0.00001)						



Analysis 74.3. Comparison 74: DaxibotulinumtoxinA 40 units versus placebo one cycle of treatment in glabellar lines, Outcome 3: Total adverse events

Study or Subgroup	DaxibotulinumtoxinA 40U Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Bertucci 2020	78	405	18	204	76.7%	2.18 [1.35 , 3.54]
Carruthers 2017	14	53	6	54	23.3%	2.38 [0.99 , 5.72]
Total (95% CI)		**458**		**258**	**100.0%**	**2.23 [1.46 , 3.40]**
Total events:	92		24			

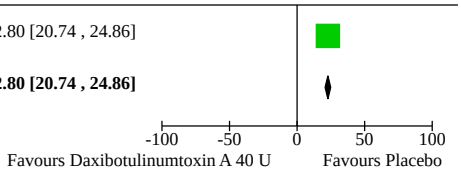
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.87); I² = 0%
Test for overall effect: Z = 3.70 (P = 0.0002)
Test for subgroup differences: Not applicable



Analysis 74.4. Comparison 74: DaxibotulinumtoxinA 40 units versus placebo one cycle of treatment in glabellar lines, Outcome 4: Duration of treatment effect, weeks

Study or Subgroup	DaxibotulinumtoxinA 40U Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Carruthers 2017	23.2	6.3	39	0.4	1.77	35	100.0%	22.80 [20.74 , 24.86]
Total (95% CI)			**39**			**35**	**100.0%**	**22.80 [20.74 , 24.86]**

Heterogeneity: Not applicable
Test for overall effect: Z = 21.67 (P < 0.00001)
Test for subgroup differences: Not applicable



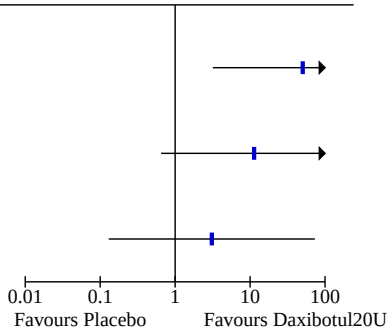
Comparison 75. DaxibotulinumtoxinA 20units versus placebo one cycle of treatment in glabellar lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
75.1 Participant assessment of success by analysing scores and scales	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
75.1.1 4 weeks	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
75.1.2 16weeks	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
75.1.3 24 weeks	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
75.2 Physician assessment of success by analysing scores and scales	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
75.2.1 4 weeks	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
75.2.2 8 weeks	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
75.2.3 12 weeks	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
75.2.4 16 weeks	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
75.2.5 20 weeks	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
75.2.6 24 weeks	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
75.3 Total adverse events	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
75.4 Duration of treatment	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

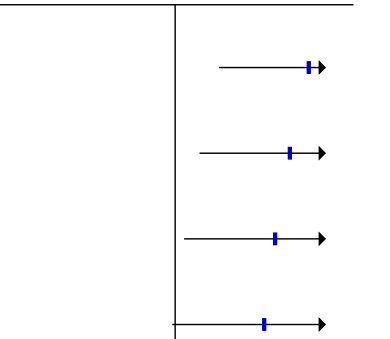
Analysis 75.1. Comparison 75: DaxibotulinumtoxinA 20units versus placebo one cycle of treatment in glabellar lines, Outcome 1: Participant assessment of success by analysing scores and scales

Study or Subgroup	DaxibotulinumtoxinA 20U Events	Total	Placebo Events	Total	Risk Ratio IV, Random, 95% CI
75.1.1 4 weeks					
Carruthers 2017	24	34	0	35	50.40 [3.19 , 797.13]
75.1.2 16weeks					
Carruthers 2017	5	34	0	35	11.31 [0.65 , 197.06]
75.1.3 24 weeks					
Carruthers 2017	1	34	0	35	3.09 [0.13 , 73.21]

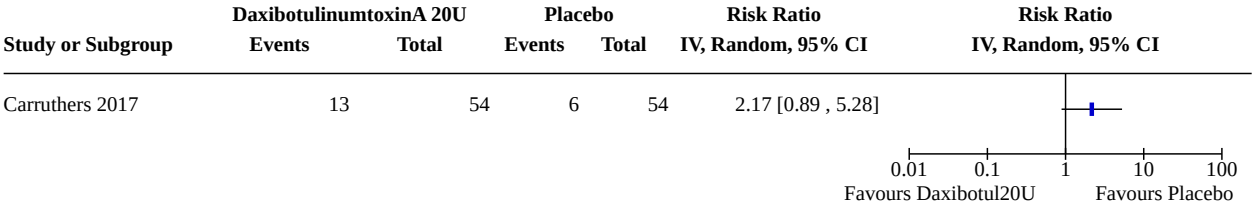


Analysis 75.2. Comparison 75: DaxibotulinumtoxinA 20units versus placebo one cycle of treatment in glabellar lines, Outcome 2: Physician assessment of success by analysing scores and scales

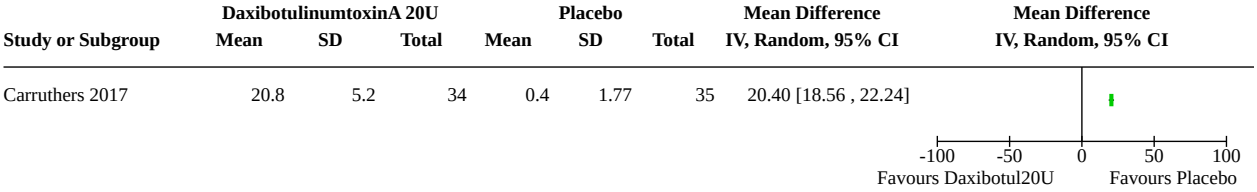
Study or Subgroup	DaxibotulinumtoxinA 20U Events	Total	Placebo Events	Total	Risk Ratio IV, Random, 95% CI
75.2.1 4 weeks					
Carruthers 2017	29	34	0	35	60.69 [3.86 , 955.19]
75.2.2 8 weeks					
Carruthers 2017	16	34	0	35	33.94 [2.12 , 544.26]
75.2.3 12 weeks					
Carruthers 2017	10	34	0	35	21.60 [1.32 , 354.72]
75.2.4 16 weeks					
Carruthers 2017	7	34	0	35	15.43 [0.92 , 260.05]
75.2.5 20 weeks					
Carruthers 2017	4	34	0	35	9.26 [0.52 , 165.65]
75.2.6 24 weeks					
Carruthers 2017	3	34	0	35	7.20 [0.39 , 134.36]



Analysis 75.3. Comparison 75: DaxibotulinumtoxinA 20units versus placebo one cycle of treatment in glabellar lines, Outcome 3: Total adverse events



Analysis 75.4. Comparison 75: DaxibotulinumtoxinA 20units versus placebo one cycle of treatment in glabellar lines, Outcome 4: Duration of treatment



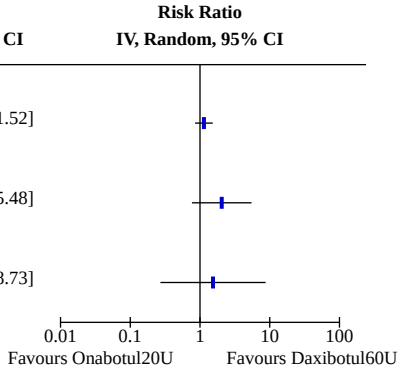
Comparison 76. DaxibotulinumtoxinA 60 units versus OnabotulinumtoxinA 20 units one cycle of treatment in glabellar lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
76.1 Participant assessment of success by analysing scores and scales	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
76.1.1 4 weeks	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
76.1.2 16 weeks	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
76.1.3 24 weeks	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
76.2 Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
76.3 Physician assessment of success by analysing scores and scales	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
76.3.1 4 weeks	1	83	Risk Ratio (IV, Random, 95% CI)	1.24 [1.05, 1.46]
76.3.2 8 weeks	1	83	Risk Ratio (IV, Random, 95% CI)	1.49 [1.07, 2.07]
76.3.3 12 weeks	1	83	Risk Ratio (IV, Random, 95% CI)	0.97 [0.60, 1.57]
76.3.4 16 weeks	1	83	Risk Ratio (IV, Random, 95% CI)	2.05 [0.67, 6.28]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
76.3.5 20 weeks	1	83	Risk Ratio (IV, Random, 95% CI)	2.73 [0.78, 9.58]
76.3.6 24 weeks	1	83	Risk Ratio (IV, Random, 95% CI)	1.02 [0.15, 6.93]
76.4 Total adverse events	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
76.5 Duration of treatment	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

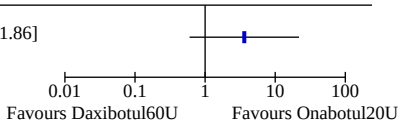
Analysis 76.1. Comparison 76: DaxibotulinumtoxinA 60 units versus OnabotulinumtoxinA 20 units one cycle of treatment in glabellar lines, Outcome 1: Participant assessment of success by analysing scores and scales

Study or Subgroup	DaxibotulinumtoxinA 60U Events	Total	OnabotulinumtoxinA 20U Events	Total	Risk Ratio IV, Random, 95% CI
76.1.1 4 weeks					
Carruthers 2017	30	41	27	42	1.14 [0.85 , 1.52]
76.1.2 16 weeks					
Carruthers 2017	10	41	5	42	2.05 [0.77 , 5.48]
76.1.3 24 weeks					
Carruthers 2017	3	41	2	42	1.54 [0.27 , 8.73]



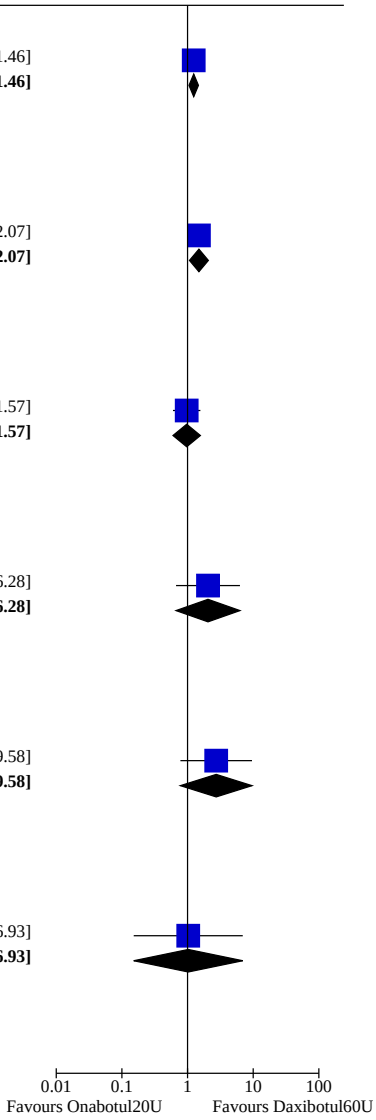
Analysis 76.2. Comparison 76: DaxibotulinumtoxinA 60 units versus OnabotulinumtoxinA 20 units one cycle of treatment in glabellar lines, Outcome 2: Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

Study or Subgroup	DaxibotulinumtoxinA 60U Events	Total	OnabotulinumtoxinA 20U Events	Total	Peto Odds Ratio Peto, Fixed, 95% CI
Carruthers 2017	4	41	1	42	3.62 [0.60 , 21.86]



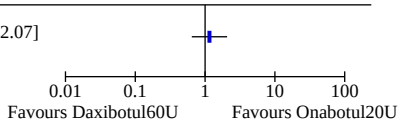
Analysis 76.3. Comparison 76: DaxibotulinumtoxinA 60 units versus OnabotulinumtoxinA 20 units one cycle of treatment in glabellar lines, Outcome 3: Physician assessment of success by analysing scores and scales

Study or Subgroup	DaxibotulinumtoxinA 60U Events	Total	OnabotulinumtoxinA 20U Events	Total	Weight	Risk Ratio IV, Random, 95% CI
76.3.1 4 weeks						
Carruthers 2017	40	41	33	42	100.0%	1.24 [1.05 , 1.46]
Subtotal (95% CI)		**41**		**42**	**100.0%**	**1.24 [1.05 , 1.46]**
Total events:	40		33			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.57 (P = 0.01)						
76.3.2 8 weeks						
Carruthers 2017	32	41	22	42	100.0%	1.49 [1.07 , 2.07]
Subtotal (95% CI)		**41**		**42**	**100.0%**	**1.49 [1.07 , 2.07]**
Total events:	32		22			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.36 (P = 0.02)						
76.3.3 12 weeks						
Carruthers 2017	18	41	19	42	100.0%	0.97 [0.60 , 1.57]
Subtotal (95% CI)		**41**		**42**	**100.0%**	**0.97 [0.60 , 1.57]**
Total events:	18		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.12 (P = 0.90)						
76.3.4 16 weeks						
Carruthers 2017	8	41	4	42	100.0%	2.05 [0.67 , 6.28]
Subtotal (95% CI)		**41**		**42**	**100.0%**	**2.05 [0.67 , 6.28]**
Total events:	8		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.25 (P = 0.21)						
76.3.5 20 weeks						
Carruthers 2017	8	41	3	42	100.0%	2.73 [0.78 , 9.58]
Subtotal (95% CI)		**41**		**42**	**100.0%**	**2.73 [0.78 , 9.58]**
Total events:	8		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.57 (P = 0.12)						
76.3.6 24 weeks						
Carruthers 2017	2	41	2	42	100.0%	1.02 [0.15 , 6.93]
Subtotal (95% CI)		**41**		**42**	**100.0%**	**1.02 [0.15 , 6.93]**
Total events:	2		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.02 (P = 0.98)						

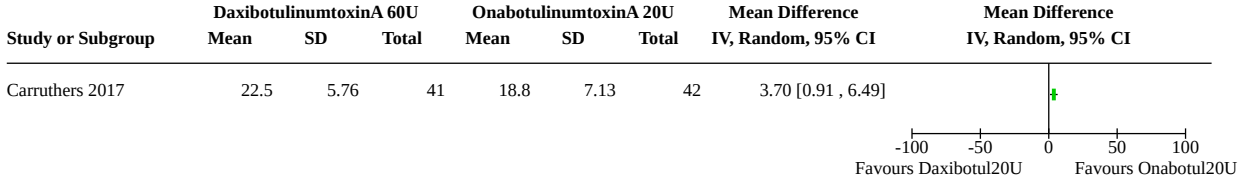


Analysis 76.4. Comparison 76: DaxibotulinumtoxinA 60 units versus OnabotulinumtoxinA 20 units one cycle of treatment in glabellar lines, Outcome 4: Total adverse events

Study or Subgroup	DaxibotulinumtoxinA 60U Events	Total	OnabotulinumtoxinA 20U Events	Total	Risk Ratio IV, Random, 95% CI
Carruthers 2017	17	53	15	54	1.15 [0.65 , 2.07]



Analysis 76.5. Comparison 76: DaxibotulinumtoxinA 60 units versus OnabotulinumtoxinA 20 units one cycle of treatment in glabellar lines, Outcome 5: Duration of treatment

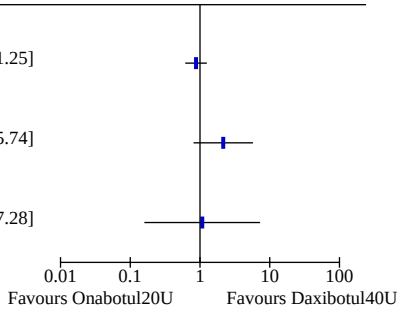


Comparison 77. DaxibotulinumtoxinA 40 units versus OnabotulinumtoxinA 20 units one cycle of treatment in glabellar lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
77.1 Participant assessment of success by analysing scores and scales	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
77.1.1 4 weeks	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
77.1.2 16 weeks	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
77.1.3 24 weeks	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
77.2 Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
77.3 Physician assessment of success by analysing scores and scales	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
77.3.1 4 weeks	1	81	Risk Ratio (IV, Random, 95% CI)	1.21 [1.01, 1.44]
77.3.2 8 weeks	1	81	Risk Ratio (IV, Random, 95% CI)	1.42 [1.01, 2.00]
77.3.3 12 weeks	1	81	Risk Ratio (IV, Random, 95% CI)	0.96 [0.59, 1.57]
77.3.4 16 weeks	1	81	Risk Ratio (IV, Random, 95% CI)	3.77 [1.36, 10.48]
77.3.5 20 weeks	1	81	Risk Ratio (IV, Random, 95% CI)	2.87 [0.82, 10.06]
77.3.6 24 weeks	1	81	Risk Ratio (IV, Random, 95% CI)	2.15 [0.42, 11.11]
77.4 Total adverse events	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
77.5 Duration of treatment	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

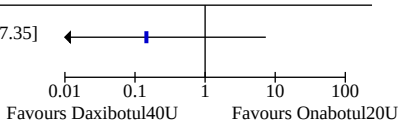
Analysis 77.1. Comparison 77: DaxibotulinumtoxinA 40 units versus OnabotulinumtoxinA 20 units one cycle of treatment in glabellar lines, Outcome 1: Participant assessment of success by analysing scores and scales

Study or Subgroup	DaxibotulinumtoxinA 40U Events	Total	OnabotulinumtoxinA 20U Events	Total	Risk Ratio IV, Random, 95% CI
77.1.1 4 weeks					
Carruthers 2017	22	39	27	42	0.88 [0.61 , 1.25]
77.1.2 16 weeks					
Carruthers 2017	10	39	5	42	2.15 [0.81 , 5.74]
77.1.3 24 weeks					
Carruthers 2017	2	39	2	42	1.08 [0.16 , 7.28]



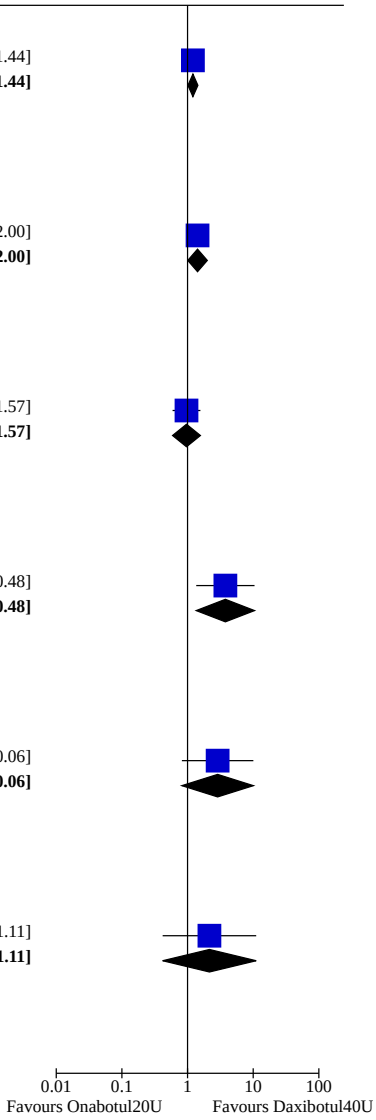
Analysis 77.2. Comparison 77: DaxibotulinumtoxinA 40 units versus OnabotulinumtoxinA 20 units one cycle of treatment in glabellar lines, Outcome 2: Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

Study or Subgroup	DaxibotulinumtoxinA 40U Events	Total	OnabotulinumtoxinA 20U Events	Total	Peto Odds Ratio Peto, Fixed, 95% CI
Carruthers 2017	0	39	1	42	0.15 [0.00 , 7.35]



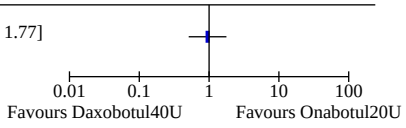
Analysis 77.3. Comparison 77: DaxibotulinumtoxinA 40 units versus OnabotulinumtoxinA 20 units one cycle of treatment in glabellar lines, Outcome 3: Physician assessment of success by analysing scores and scales

Study or Subgroup	DaxibotulinumtoxinA 40U Events	Total	OnabotulinumtoxinA 20U Events	Total	Weight	Risk Ratio IV, Random, 95% CI
77.3.1 4 weeks						
Carruthers 2017	37	39	33	42	100.0%	1.21 [1.01 , 1.44]
Subtotal (95% CI)		**39**		**42**	**100.0%**	**1.21 [1.01 , 1.44]**
Total events:	37		33			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.12 (P = 0.03)						
77.3.2 8 weeks						
Carruthers 2017	29	39	22	42	100.0%	1.42 [1.01 , 2.00]
Subtotal (95% CI)		**39**		**42**	**100.0%**	**1.42 [1.01 , 2.00]**
Total events:	29		22			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.01 (P = 0.04)						
77.3.3 12 weeks						
Carruthers 2017	17	39	19	42	100.0%	0.96 [0.59 , 1.57]
Subtotal (95% CI)		**39**		**42**	**100.0%**	**0.96 [0.59 , 1.57]**
Total events:	17		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.15 (P = 0.88)						
77.3.4 16 weeks						
Carruthers 2017	14	39	4	42	100.0%	3.77 [1.36 , 10.48]
Subtotal (95% CI)		**39**		**42**	**100.0%**	**3.77 [1.36 , 10.48]**
Total events:	14		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.54 (P = 0.01)						
77.3.5 20 weeks						
Carruthers 2017	8	39	3	42	100.0%	2.87 [0.82 , 10.06]
Subtotal (95% CI)		**39**		**42**	**100.0%**	**2.87 [0.82 , 10.06]**
Total events:	8		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.65 (P = 0.10)						
77.3.6 24 weeks						
Carruthers 2017	4	39	2	42	100.0%	2.15 [0.42 , 11.11]
Subtotal (95% CI)		**39**		**42**	**100.0%**	**2.15 [0.42 , 11.11]**
Total events:	4		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.92 (P = 0.36)						

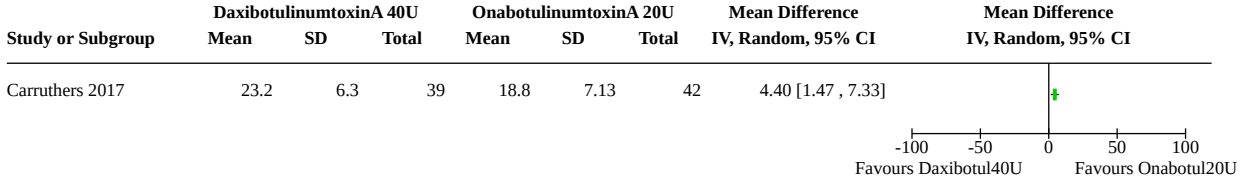


Analysis 77.4. Comparison 77: DaxibotulinumtoxinA 40 units versus OnabotulinumtoxinA 20 units one cycle of treatment in glabellar lines, Outcome 4: Total adverse events

Study or Subgroup	DaxibotulinumtoxinA 40U Events	Total	OnabotulinumtoxinA 20U Events	Total	Risk Ratio IV, Random, 95% CI
Carruthers 2017	14	53	15	54	0.95 [0.51 , 1.77]



Analysis 77.5. Comparison 77: DaxibotulinumtoxinA 40 units versus OnabotulinumtoxinA 20 units one cycle of treatment in glabellar lines, Outcome 5: Duration of treatment

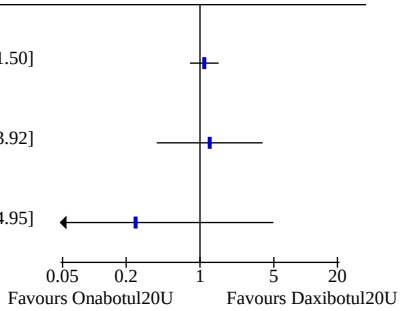


Comparison 78. DaxibotulinumtoxinA 20 units versus OnabotulinumtoxinA 20 units one cycle of treatment in glabellar lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
78.1 Participant assessment of success by analysing scores and scales	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
78.1.1 4 weeks	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
78.1.2 16 weeks	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
78.1.3 24 weeks	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
78.2 Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
78.3 Physician assessment of success by analysing scores and scales	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
78.3.1 4 weeks	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
78.3.2 8 weeks	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
78.3.3 12 weeks	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
78.3.4 16 weeks	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
78.3.5 20 weeks	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
78.3.6 24 weeks	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
78.4 Total adverse events	1	108	Risk Ratio (IV, Random, 95% CI)	0.87 [0.46, 1.64]
78.5 Duration of treatment	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

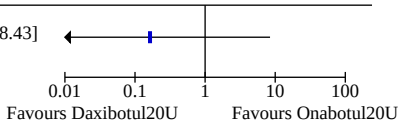
Analysis 78.1. Comparison 78: DaxibotulinumtoxinA 20 units versus OnabotulinumtoxinA 20 units one cycle of treatment in glabellar lines, Outcome 1: Participant assessment of success by analysing scores and scales

Study or Subgroup	DaxibotulinumtoxinA 20U Events	Total	OnabotulinumtoxinA 20U Events	Total	Risk Ratio IV, Random, 95% CI
78.1.1 4 weeks					
Carruthers 2017	24	34	27	42	1.10 [0.80 , 1.50]
78.1.2 16 weeks					
Carruthers 2017	5	34	5	42	1.24 [0.39 , 3.92]
78.1.3 24 weeks					
Carruthers 2017	0	34	2	42	0.25 [0.01 , 4.95]



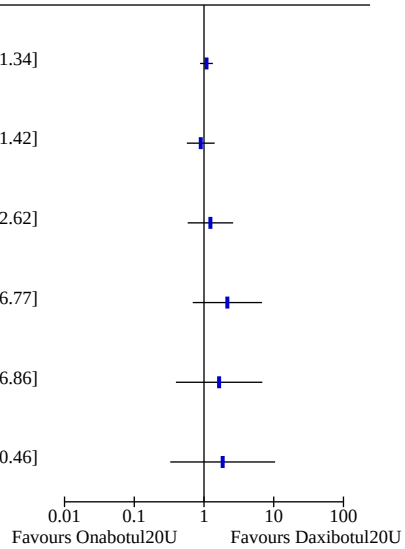
Analysis 78.2. Comparison 78: DaxibotulinumtoxinA 20 units versus OnabotulinumtoxinA 20 units one cycle of treatment in glabellar lines, Outcome 2: Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

Study or Subgroup	DaxibotulinumtoxinA 20U Events	Total	OnabotulinumtoxinA 20U Events	Total	Peto Odds Ratio Peto, Fixed, 95% CI
Carruthers 2017	0	34	1	42	0.16 [0.00 , 8.43]



Analysis 78.3. Comparison 78: DaxibotulinumtoxinA 20 units versus OnabotulinumtoxinA 20 units one cycle of treatment in glabellar lines, Outcome 3: Physician assessment of success by analysing scores and scales

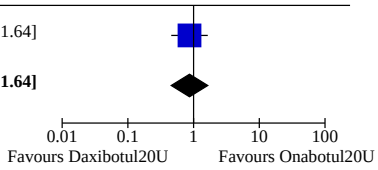
Study or Subgroup	DaxibotulinumtoxinA 20U Events	Total	OnabotulinumtoxinA 20U Events	Total	Risk Ratio IV, Random, 95% CI
78.3.1 4 weeks					
Carruthers 2017	29	34	33	42	1.09 [0.88 , 1.34]
78.3.2 8 weeks					
Carruthers 2017	16	34	22	42	0.90 [0.57 , 1.42]
78.3.3 12 weeks					
Carruthers 2017	10	34	10	42	1.24 [0.58 , 2.62]
78.3.4 16 weeks					
Carruthers 2017	7	34	4	42	2.16 [0.69 , 6.77]
78.3.5 20 weeks					
Carruthers 2017	4	34	3	42	1.65 [0.40 , 6.86]
78.3.6 24 weeks					
Carruthers 2017	3	34	2	42	1.85 [0.33 , 10.46]



Analysis 78.4. Comparison 78: DaxibotulinumtoxinA 20 units versus OnabotulinumtoxinA 20 units one cycle of treatment in glabellar lines, Outcome 4: Total adverse events

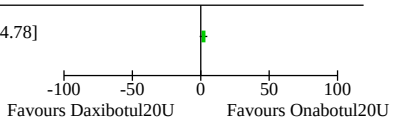
Study or Subgroup	DaxibotulinumtoxinA 20U Events	Total	OnabotulinumtoxinA 20U Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Carruthers 2017	13	54	15	54	100.0%	0.87 [0.46 , 1.64]
Total (95% CI)		**54**		**54**	**100.0%**	**0.87 [0.46 , 1.64]**
Total events:	13		15			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.44 (P = 0.66)
Test for subgroup differences: Not applicable



Analysis 78.5. Comparison 78: DaxibotulinumtoxinA 20 units versus OnabotulinumtoxinA 20 units one cycle of treatment in glabellar lines, Outcome 5: Duration of treatment

Study or Subgroup	DaxibotulinumtoxinA 20U Mean	SD	Total	OnabotulinumtoxinA 20U Mean	SD	Total	Mean Difference IV, Random, 95% CI
Carruthers 2017	20.8	5.2	34	18.8	7.13	42	2.00 [-0.78 , 4.78]

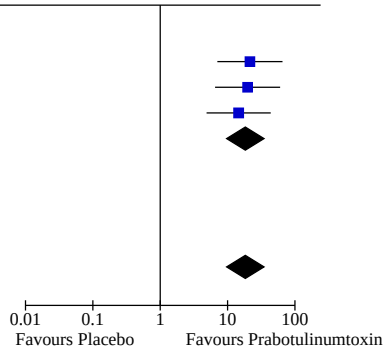


Comparison 79. PrabotulinumtoxinA 20 units versus placebo one cycle of treatment, glabellar lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
79.1 Participant assessment of success by analysing scores and scales	3	930	Risk Ratio (M-H, Random, 95% CI)	18.34 [9.68, 34.76]
79.1.1 4 weeks	3	930	Risk Ratio (M-H, Random, 95% CI)	18.34 [9.68, 34.76]
79.2 Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)	3	939	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.06, 5.65]
79.3 Physician assessment of success by analysing scores and scales	3	929	Risk Ratio (M-H, Random, 95% CI)	23.96 [9.35, 61.40]
79.3.1 4 weeks	3	929	Risk Ratio (M-H, Random, 95% CI)	23.96 [9.35, 61.40]
79.4 Total adverse events	3	948	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.91, 1.43]

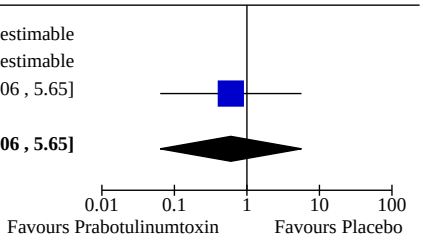
Analysis 79.1. Comparison 79: PrabotulinumtoxinA 20 units versus placebo one cycle of treatment, glabellar lines, Outcome 1: Participant assessment of success by analysing scores and scales

Study or Subgroup	PrabotulinumtoxinA 20u Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
79.1.1 4 weeks						
Beer 2019a	184	240	3	84	33.0%	21.47 [7.05 , 65.36]
Beer 2019b	183	240	3	78	33.0%	19.82 [6.52 , 60.27]
Rzany 2019	219	240	3	48	34.0%	14.60 [4.88 , 43.70]
Subtotal (95% CI)		**720**		**210**	**100.0%**	**18.34 [9.68 , 34.76]**
Total events:	586		9			
Heterogeneity: Tau² = 0.00; Chi² = 0.26, df = 2 (P = 0.88); I² = 0%						
Test for overall effect: Z = 8.92 (P < 0.00001)						
Total (95% CI)		**720**		**210**	**100.0%**	**18.34 [9.68 , 34.76]**
Total events:	586		9			
Heterogeneity: Tau² = 0.00; Chi² = 0.26, df = 2 (P = 0.88); I² = 0%						
Test for overall effect: Z = 8.92 (P < 0.00001)						
Test for subgroup differences: Not applicable						



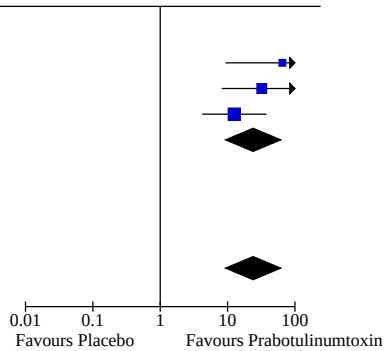
Analysis 79.2. Comparison 79: PrabotulinumtoxinA 20 units versus placebo one cycle of treatment, glabellar lines, Outcome 2: Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

Study or Subgroup	PrabotulinumtoxinA 20u Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Beer 2019a	0	246	0	84		Not estimable
Beer 2019b	0	237	0	78		Not estimable
Rzany 2019	3	245	1	49	100.0%	0.60 [0.06 , 5.65]
Total (95% CI)		**728**		**211**	**100.0%**	**0.60 [0.06 , 5.65]**
Total events:	3		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.45 (P = 0.66)						
Test for subgroup differences: Not applicable						



Analysis 79.3. Comparison 79: PrabotulinumtoxinA 20 units versus placebo one cycle of treatment, glabellar lines, Outcome 3: Physician assessment of success by analysing scores and scales

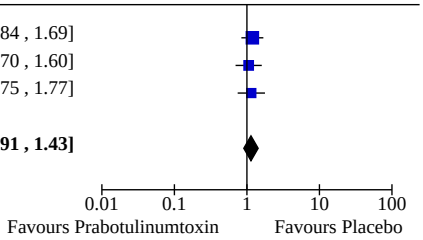
Study or Subgroup	PrabotulinumtoxinA 20u Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
79.3.1 4 weeks						
Beer 2019a	186	240	1	84	19.6%	65.10 [9.27 , 457.32]
Beer 2019b	198	240	2	78	34.2%	32.17 [8.18 , 126.53]
Rzany 2019	188	239	3	48	46.2%	12.59 [4.20 , 37.72]
Subtotal (95% CI)		**719**		**210**	**100.0%**	**23.96 [9.35 , 61.40]**
Total events:	572		6			
Heterogeneity: Tau² = 0.19; Chi² = 2.70, df = 2 (P = 0.26); I² = 26%						
Test for overall effect: Z = 6.61 (P < 0.00001)						
Total (95% CI)		**719**		**210**	**100.0%**	**23.96 [9.35 , 61.40]**
Total events:	572		6			
Heterogeneity: Tau² = 0.19; Chi² = 2.70, df = 2 (P = 0.26); I² = 26%						
Test for overall effect: Z = 6.61 (P < 0.00001)						
Test for subgroup differences: Not applicable						



Analysis 79.4. Comparison 79: PrabotulinumtoxinA 20 units versus placebo one cycle of treatment, glabellar lines, Outcome 4: Total adverse events

Study or Subgroup	PrabotulinumtoxinA 20u Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Beer 2019a	94	246	27	84	42.5%	1.19 [0.84 , 1.69]
Beer 2019b	70	246	21	78	29.9%	1.06 [0.70 , 1.60]
Rzany 2019	92	245	16	49	27.6%	1.15 [0.75 , 1.77]
Total (95% CI)		**737**		**211**	**100.0%**	**1.14 [0.91 , 1.43]**
Total events:	256		64			

Heterogeneity: Tau² = 0.00; Chi² = 0.18, df = 2 (P = 0.91); I² = 0%
Test for overall effect: Z = 1.11 (P = 0.27)
Test for subgroup differences: Not applicable

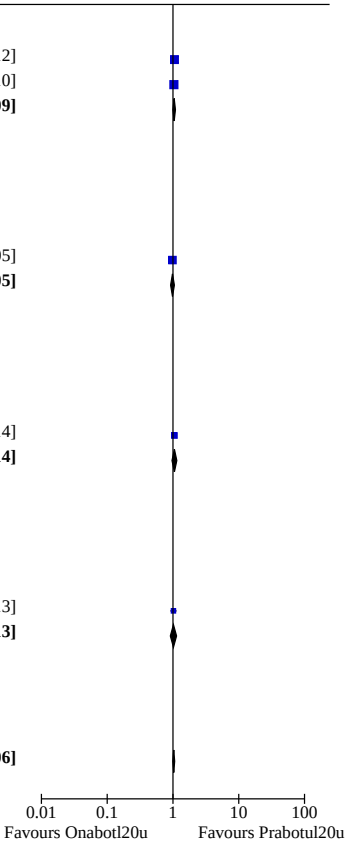


Comparison 80. PrabotulinumtoxinA 20 units versus OnabotulimtoxinA 20units one cycle of treatment, glabellar lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
80.1 Participant assessment of success by analysing scores and scales	2	1538	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.99, 1.06]
80.1.1 4 weeks	2	749	Risk Ratio (M-H, Random, 95% CI)	1.04 [1.00, 1.09]
80.1.2 8weeks	1	263	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.92, 1.05]
80.1.3 12 weeks	1	263	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.97, 1.14]
80.1.4 16 weeks	1	263	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.91, 1.13]
80.2 Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
80.3 Physician assessment of success by analysing scores and scales	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
80.3.1 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
80.4 Total adverse events	2	759	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.74, 1.13]

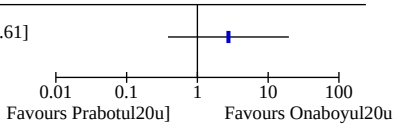
Analysis 80.1. Comparison 80: PrabotulinumtoxinA 20 units versus OnabotulimtoxinA 20units one cycle of treatment, glabellar lines, Outcome 1: Participant assessment of success by analysing scores and scales

Study or Subgroup	PrabotulinumtoxinA 20u Events	Total	OnabotulinumtoxinA 20u Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
80.1.1 4 weeks						
Rzany 2019	219	240	213	246	25.9%	1.05 [0.99 , 1.12]
Won 2015	125	131	122	132	27.0%	1.03 [0.97 , 1.10]
Subtotal (95% CI)		**371**		**378**	**52.9%**	**1.04 [1.00 , 1.09]**
Total events:	344		335			
Heterogeneity: Tau² = 0.00; Chi² = 0.23, df = 1 (P = 0.63); I² = 0%						
Test for overall effect: Z = 1.87 (P = 0.06)						
80.1.2 8weeks						
Won 2015	121	131	124	132	23.8%	0.98 [0.92 , 1.05]
Subtotal (95% CI)		**131**		**132**	**23.8%**	**0.98 [0.92 , 1.05]**
Total events:	121		124			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.50 (P = 0.61)						
80.1.3 12 weeks						
Won 2015	120	131	115	132	14.6%	1.05 [0.97 , 1.14]
Subtotal (95% CI)		**131**		**132**	**14.6%**	**1.05 [0.97 , 1.14]**
Total events:	120		115			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.18 (P = 0.24)						
80.1.4 16 weeks						
Won 2015	110	131	109	132	8.7%	1.02 [0.91 , 1.13]
Subtotal (95% CI)		**131**		**132**	**8.7%**	**1.02 [0.91 , 1.13]**
Total events:	110		109			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.30 (P = 0.76)						
Total (95% CI)		**764**		**774**	**100.0%**	**1.03 [0.99 , 1.06]**
Total events:	695		683			
Heterogeneity: Tau² = 0.00; Chi² = 2.75, df = 4 (P = 0.60); I² = 0%						
Test for overall effect: Z = 1.65 (P = 0.10)						
Test for subgroup differences: Chi² = 2.49, df = 3 (P = 0.48), I² = 0%						



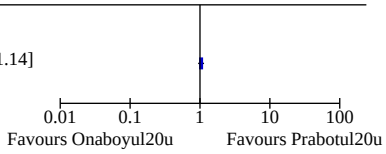
Analysis 80.2. Comparison 80: PrabotulinumtoxinA 20 units versus OnabotulimtoxinA 20units one cycle of treatment, glabellar lines, Outcome 2: Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus)

Study or Subgroup	PrabotulinumtoxinA 20u Events	Total	OnabotulinumtoxinA 20u Events	Total	Peto Odds Ratio Peto, Fixed, 95% CI
Rzany 2019	3	245	1	246	2.75 [0.38 , 19.61]



Analysis 80.3. Comparison 80: PrabotulinumtoxinA 20 units versus OnabotulimtoxinA 20units one cycle of treatment, glabellar lines, Outcome 3: Physician assessment of success by analysing scores and scales

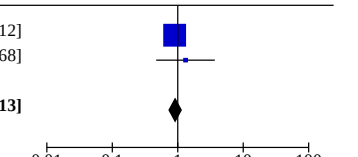
Study or Subgroup	PrabotulinumtoxinA 20u Events	Total	OnabotulinumtoxinA 20u Events	Total	Risk Ratio M-H, Random, 95% CI
80.3.1 4 weeks					
Rzany 2019	188	239	185	244	1.04 [0.94 , 1.14]



Analysis 80.4. Comparison 80: PrabotulinumtoxinA 20 units versus OnabotulimtoxinA 20units one cycle of treatment, glabellar lines, Outcome 4: Total adverse events

Study or Subgroup	PrabotulinumtoxinA 20u Events	Total	OnabotulinumtoxinA 20u Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Rzany 2019	92	245	103	246	95.7%	0.90 [0.72 , 1.12]
Won 2015	8	135	6	133	4.3%	1.31 [0.47 , 3.68]
Total (95% CI)		**380**		**379**	**100.0%**	**0.91 [0.74 , 1.13]**
Total events:	100		109			

Heterogeneity: Tau² = 0.00; Chi² = 0.51, df = 1 (P = 0.47); I² = 0%
Test for overall effect: Z = 0.85 (P = 0.40)
Test for subgroup differences: Not applicable

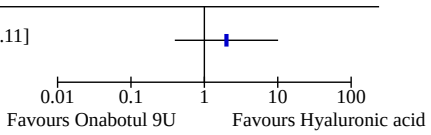


Comparison 81. OnabotulinumtoxinA 9 units versus hyaluronic acid [JUVEDERM ULTRA ® and/or JUVEDERM ULTRA PLUS®] one treatment in lips and perioral lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
81.1 Total adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 81.1. Comparison 81: OnabotulinumtoxinA 9 units versus hyaluronic acid [JUVEDERM ULTRA ® and/or JUVEDERM ULTRA PLUS®] one treatment in lips and perioral lines, Outcome 1: Total adverse events

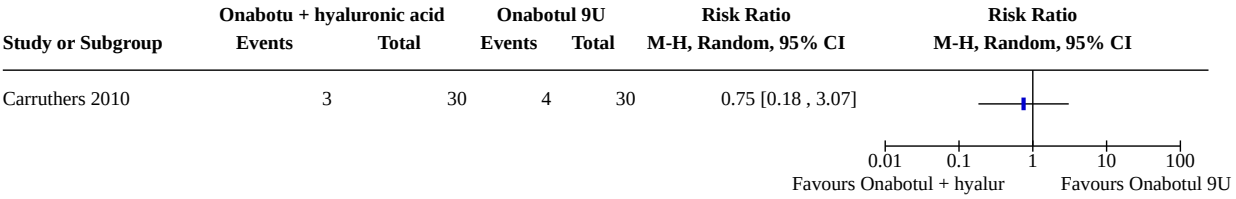
Study or Subgroup	OnabotulinumtoxinA 9U Events	Total	Hyaluronic acid Events	Total	Risk Ratio M-H, Random, 95% CI
Carruthers 2010	4	30	2	30	2.00 [0.40 , 10.11]



Comparison 82. OnabotulinumtoxinA 9 units associated with hyaluronic acid [JUVEDERM ULTRA ® and/or JUVEDERM ULTRA PLUS®] versus OnabotulinumtoxinA one treatment in lips and perioral lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
82.1 Total adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

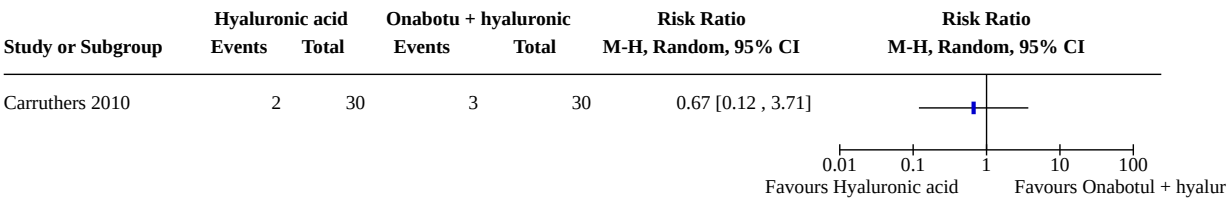
Analysis 82.1. Comparison 82: OnabotulinumtoxinA 9 units associated with hyaluronic acid [JUVEDERM ULTRA ® and/or JUVEDERM ULTRA PLUS®] versus OnabotulinumtoxinA one treatment in lips and perioral lines, Outcome 1: Total adverse events



Comparison 83. Hyaluronic acid [JUVEDERM ULTRA ® and/or JUVEDERM ULTRA PLUS®]versus OnabotulinumtoxinA 9 units associated with hyaluronic acid one treatment in lips and perioral lines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
83.1 Total adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 83.1. Comparison 83: Hyaluronic acid [JUVEDERM ULTRA ® and/or JUVEDERM ULTRA PLUS®]versus OnabotulinumtoxinA 9 units associated with hyaluronic acid one treatment in lips and perioral lines, Outcome 1: Total adverse events



APPENDICES

Appendix 1. Glossary

Term	Definition

(Continued)

Adverse event	Any undesirable harmful effect caused by medication, surgery, or other medical procedures Major adverse events will be defined when will be defined when there is partial or total loss of function of a given organ (E.g., ptosis-the patient can open her/his eyes). Total adverse events- when there is no dysfunction(pain, bruise, facial asymmetry).
Asthenotopia	Problem of vision, with pain in the eyes, back of the head and the neck
Cosmeceutical	A cosmetic pharmaceutical
Dynamic wrinkles	Wrinkles that appear only during muscle contraction, e.g. crow's feet in young people when smiling
Glabellar	Adjective for anatomical region between the eyebrows
Off-label	Term given to the use of medicine to treat a condition for which it is not licensed
Observational study	A study that describes a condition according to the presence or absence of a factor, e.g. smoking habit and lung cancer
Quasi-randomised clinical trial	Very similar to a randomised clinical trial, but the participants are not randomised to the study
Periorbicular wrinkles	Crow's feet
Randomisation	Process of selecting participants for a clinical trial; this process assures an equal chance of treatment assignment for each participant
Split-face	Some studies apply treatment X to the right side of the face and treatment Y to the left side of the face. It works like 2 separate faces
Randomised clinical trial	A type of comparative scientific research. It is the best evidence to prove causation between an intervention (e.g. drug, surgery, or devices) and outcome
Muscle tonus	The passive and continuous muscle tension at rest
Static wrinkles	Visible wrinkles not related to muscle activity (at rest or contraction) but that develop with age
Strabismus	Misalignment of the eyes. If a physician injects botulinum toxin to treat crow's feet around the eyes, the toxin can cause strabismus, because it relaxes intrinsic orbital muscles

Appendix 2. Cochrane Skin Specialised Register (CRSW)

(onabotulinum* or abobotulinum* or incobotulinum* or Botulinum* or botox or vistabel or vistabex or dysport or reloxin or azzalure or bocoture or xeomin or xeomeen or prosigne or cbtx-a or nt201 or dps refinex or pur tox) and (wrinkl* or rhytid* or glabellar or forehead or frown or marionette or crow* or ((aging or age or aged) near skin))

Appendix 3. CENTRAL (Cochrane Library) search strategy

#1 MeSH descriptor: [Botulinum Toxins] explode all trees
#2 MeSH descriptor: [Botulinum Toxins, Type A] explode all trees
#3 (onabotulinum* or abobotulinum* or incobotulinum*):ti,ab,kw
#4 (botox or vistabel or vistabex or dysport or reloxin or azzalure or bocoture or xeomin or xeomeen or prosigne or cbtx-a or nt201 or dps refinex or pur tox):ti,ab,kw
#5 {or #1-#4}
#6 MeSH descriptor: [Skin Aging] explode all trees
#7 (wrinkl* or rhytid*):ti,ab,kw
#8 ((aging or age or aged) near skin):ti,ab,kw

#9 (glabellar near line*):ti,ab,kw
#10 ((forehead or frown* or marionette*) and line*):ti,ab,kw
#11 (crow* feet):ti,ab,kw
#12 {or #6-#11}
#13 #5 and #12

Appendix 4. MEDLINE (Ovid) search strategy

1. exp Botulinum Toxins/ or exp Botulinum Toxins, Type A/
2. onabotulinum$.mp.
3. abobotulinum$.mp.
4. incobotulinum$.mp.
5. (botox or vistabel or vistabex or dysport or reloxin or azzalure or bocoture or xeomin or xeomeen or prosigne or cbtx-a or nt201 or dps refinex or pur tox).mp.
6. or/1-5
7. exp Skin Aging/
8. wrinkl$3.ti,ab.
9. rhytid$.ti,ab.
10. (glabellar adj2 line$).mp.
11. ((aging or age or aged) adj3 skin).mp.
12. forehead line$.mp.
13. frown line$.mp.
14. crow's feet.mp.
15. marionette line$.mp.
16. or/7-15
17. randomized controlled trial.pt.
18. controlled clinical trial.pt.
19. randomized.ab.
20. placebo.ab.
21. clinical trials as topic.sh.
22. randomly.ab.
23. trial.ti.
24. 17 or 18 or 19 or 20 or 21 or 22 or 23
25. exp animals/ not humans.sh.
26. 24 not 25
27. 6 and 16 and 26

[Lines 17-26: Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision); Ovid format, from section 3.6.1 in Lefebvre C, Glanville J, Briscoe S, Littlewood A, Marshall C, Metzendorf M-I, et al. Technical Supplement to Chapter 4: Searching for and selecting studies. In: Higgins JPT, Thomas J, Chandler J, Cumpston MS, Li T, Page MJ, Welch VA (eds). Cochrane Handbook for Systematic Reviews of Interventions Version 6. Cochrane, 2019. Available from: www.training.cochrane.org/handbook]

Appendix 5. Embase (Ovid) search strategy

1. botulinum toxin/ or botulinum toxin a/
2. onabotulinum$.mp.
3. abobotulinum$.mp.
4. incobotulinum$.mp.
5. (botox or vistabel or vistabex or dysport or reloxin or azzalure or bocoture or xeomin or xeomeen or prosigne or cbtx-a or nt201 or dps refinex or pur tox).mp.
6. or/1-5
7. wrinkl$3.ti,ab.
8. rhytid$.ti,ab.
9. (glabellar adj2 line$).mp.
10. ((aging or age or aged) adj3 skin).mp.
11. forehead line$.mp.
12. frown line$.mp.
13. crow's feet.mp.
14. marionette line$.mp.
15. cutaneous parameters/
16. wrinkle/
17. or/7-16

18. crossover procedure.sh.
19. double-blind procedure.sh.
20. single-blind procedure.sh.
21. (crossover$ or cross over$).tw.
22. placebo$.tw.
23. (doubl$ adj blind$).tw.
24. allocat$.tw.
25. trial.ti.
26. randomized controlled trial.sh.
27. random$.tw.
28. or/18-27
29. exp animal/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/
30. human/ or normal human/
31. 29 and 30
32. 29 not 31
33. 28 not 32
34. 6 and 17 and 33

[Lines 18-28: Based on terms suggested for identifying RCTs in Embase (section 3.6.2) in Lefebvre C, Glanville J, Briscoe S, Littlewood A, Marshall C, Metzendorf M-I, et al. Technical Supplement to Chapter 4: Searching for and selecting studies. In: Higgins JPT, Thomas J, Chandler J, Cumpston MS, Li T, Page MJ, Welch VA (eds). Cochrane Handbook for Systematic Reviews of Interventions Version 6. Cochrane, 2019. Available from: www.training.cochrane.org/handbook]

Appendix 6. LILACS search strategy

((onabotulinum$ or abobotulinum$ or incobotulinum$ or botulinum$ or botox) and (wrinkl$ or rhytid$ or skin or piel or arruga$))

In LILACS we searched using the above terms and the Controlled clinical trials topic-specific query filter.

Appendix 7. Trials register search strategies

These search terms were used for all the trials register searches:

1. botulinumtoxin A
2. facial wrinkles
3. skin ageing
4. skin aging
5. 1 and 2
6. 1 and 3
7. 1 and 4
8. 2 and 3
9. 2 and 4

WHAT'S NEW

Date	Event	Description
19 January 2022	Amended	There was a mistake in one comparison: we included the wrong study. We have now rectified this.

HISTORY

Protocol first published: Issue 9, 2014
Review first published: Issue 7, 2021

CONTRIBUTIONS OF AUTHORS

CPC and JX was the contact person with the editorial base.
CPC and RR co-ordinated contributions from the co-authors and wrote the final draft of the review.
CPC and RG screened papers against eligibility criteria.
CPC and CSC obtained data on ongoing and unpublished studies.

CPC, RG appraised the quality of papers.
CPC, RR and JX extracted data for the review and sought additional information about papers.
CPC and RR entered data into RevMan.
CPC and RR analysed and interpreted data.
CPC and MB undertook statistical analysis.
CPC and RR worked on the methods sections.
CPC, JX, and RR drafted the clinical sections of the Background and responded to the clinical comments of the referees.
CPC, RR responded to the methodology and statistics comments of the referees.
MCT was the consumer co-author and checked the review for readability and clarity, as well as ensuring outcomes are relevant to consumers.
CPC is the guarantor of the update.

Disclaimer

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DECLARATIONS OF INTEREST

Cristina Pires Camargo: nothing to declare.
Jun Xia: nothing to declare.
Caroline S Costa: nothing to declare.
Rolf Gemperli: nothing to declare.
Maria DC Tatini: nothing to declare.
Max K Bulsara: nothing to declare.
Rachel Riera: nothing to declare.

Professor Berthold Rzany, clinical referee, declared the following: "I am, or have been in the past, a speaker and advisor for IPSEN, Q-Med/Galderma and Merz." BR reports using botulinum toxin in his practice for aesthetic indications for over 20 years, and he is an author of the following included studies: Ascher 2009, Kerscher 2015, Rzany 2006, Rzany 2019, Satler 2010; and excluded study Rzany 2013.

SOURCES OF SUPPORT

Internal sources

- No sources of support provided

External sources

- The National Institute for Health Research (NIHR), UK

  The NIHR, UK, is the largest single funder of the Cochrane Skin Group.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the review version we made the following changes:

- We expanded the search for all relevant plastic and dermatologic conference proceedings, because some RCTs were published only in medical conference proceedings.
- We included an additional secondary outcome “duration of the effect of treatment”, since it was a relevant clinical question to guide decision-making.
- We changed the “Minor adverse effects (headache, haematoma, pain in the site of injection)” to “Total adverse events”. This was because most of the studies adopted major and total adverse events' categorisation.
- We changed the minimal number of participants for include studies from 20 to 50 (actually it was a typing error type of protocol version that was amended at review).
- We assessed the responder rates only during “muscle contraction”, rather than “at rest”, due to (a) for clinical practice this last approach was less relevant and (b) at label, BontA was indicated for hyperdynamic facial wrinkles.
- We performed meta-analysis only in parallel group studies, we did not include split face studies in this analysis.
- We changed the following terms: 1) “Responder rate by participant assessment” for “Participant assessment of success by analysing scores and scales”; 2) “major events” to “Any major adverse events (eyelid ptosis, eyelid sensory disorder, strabismus”; 3) “Responder rate by physician assessment” for “An assessment of the many physician scores or scales”; 4) “Any total adverse event” for “Total adverse event”; 5) “Duration of treatment effect” for “Duration of treatment”; according to editorial board suggestion.
- We were unable to assess reporting bias and perform subgroup and sensitivity analyses due to a limited number of studies.

- We planned to perform analyses using fixed-effect model by default. However, due to clinical and/or methodological heterogeneity among included studies, we used a random-effects model instead.
- We added that we would use Peto odds ratios for rare event meta-analyses.
- In our protocol we did not specify which comparisons we would create 'summary of findings tables' for. We therefore made the decision post-hoc to include six 'summary of findings tables' for the most clinically import comparisons of this review. We also specified the time points we would include (four weeks for effectiveness outcomes, and study duration for safety outcomes).

INDEX TERMS

Medical Subject Headings (MeSH)

Bias; Botulinum Toxins, Type A [adverse effects] [*therapeutic use]; Dermal Fillers [therapeutic use]; Face; Placebos [therapeutic use]; Randomized Controlled Trials as Topic; Skin Aging [*drug effects]

MeSH check words

Adult; Aged; Female; Humans; Male; Middle Aged