e-Methods

Treatment

A total volume of 7.5 mL of the reconstituted product for any abobotulinumtoxinA dose or placebo was injected. A 2.5 mL volume was injected into the soleus muscle in a minimum of three injection sites, 1.5 mL was injected into the gastrocnemius muscle in a minimum of two injection sites and the remainder of the dose was injected into at least one other lower muscle selected by the investigator.

Retreatment

Retreatment was possible at intervals ≥12 weeks. Need for retreatment was decided by the investigator on the basis of MAS score in the GSC (decrease from baseline <1 grade), the physician-rated clinical benefit and tolerance of the previous injection. Participants not retreated at week 12 were followed-up every 4 weeks until they required retreatment or until they had completed at least 12 months of treatment (for a total treatment duration of 15 months in the open-label phase).

Analysis of binding and neutralizing antibodies

Serum antibodies to botulinum toxin A were measured with a radioimmunoprecipitation assay and positive samples were tested for neutralizing antibodies with the mouse protection assay.

Double-blind study randomization

Computer-generated randomization lists were created by an independent sponsor statistician and assigned via a 24-hour interactive voice system from an external contract research organization. A double-dummy technique was used for participant

and investigator blinding. Each treatment pack contained either three abobotulinumtoxinA 500 U vials, two vials abobotulinumtoxinA 500 U and one placebo vial, or three placebo vials. Packs and reconstitution procedure in each group were identical in appearance.

Two-step Hochberg method

Step 1: The superiority of each abobotulinumtoxinA dose to placebo was tested at a significance level of 0.05. Step 2: If the higher of the two unadjusted *p* values was <0.05, the superiority of the two abobotulinumtoxinA doses to placebo was demonstrated. If the higher was ≥0.05, the associated abobotulinumtoxinA dose was considered not superior to placebo and the lower unadjusted *p* value was compared with 0.025. If it was <0.025, the superiority of the associated abobotulinumtoxinA dose to placebo was demonstrated.

Pooling of centers

A center that had recruited fewer than six subjects was considered as a small center and pooled with another center, given the strategy below:

- If there was a small center in at least one of the single center countries, then it was pooled with the center of the closest other single center countries (geographic proximity)
- If there was only one small center in a multiple-center country, then it was pooled with the center within the same country having the closest to six recruited subjects
- If there were two small centers in a multiple-center country, then the two small centers within the country were pooled

- If there were more than two small centers in a multiple-center country, then the following 2-step procedure was applied:
  - Step 1: the smallest centers were pooled until the pooled centers reached the threshold of six recruited subjects. If there were no more small centers, the procedure was stopped. Otherwise, Step 2 was applied.
  - Step 2: if there was at least one remaining small center, the following approach was applied: (a) If there was one remaining small center then it was pooled with the center within the same country having the closest to six recruited subjects and the procedure was stopped (b) If there were two remaining small centers then the two small centers within the country were pooled and the procedure was stopped (c) If there were more than two remaining small centers then Step 1 was reiterated.

In the planned analysis of MAS scores at week 4, a significant randomized treatment by center interaction was observed. To investigate the nature of the interaction, treatment effects and standard errors by center for the 1500 U versus placebo and 1000 U versus placebo comparisons were calculated and displayed in a Galbraith plot with 99.5% confidence bounds. Centers falling outside the confidence bounds were identified as potential influential outliers. An additional exploratory analysis of MAS scores at week 4 excluding participants from centers considered as outliers was conducted (e-Results).

e-Results

Efficacy of a single injection: post-hoc analysis of primary efficacy endpoint

A post-hoc analysis of the primary efficacy endpoint (MAS was change from baseline in GSC muscle tone [MAS knee extended] after 4 weeks) was performed using a rank transform and a proportional odds model to address any concern regarding possible lack of normality in the data. Results from this were consistent with those obtained from the ANCOVA ($p = 0.2348$ and $p = 0.0039$ respectively for ABO 1000 U and ABO 1500 U).

Efficacy of a single injection: exploratory analysis of primary efficacy endpoint to investigate the effect of treatment by center

Treatment by center interaction had a significant effect on the mean changes in the MAS score in the ITT population from baseline at week 4 ($p = 0.0046$); however, an exploratory analysis excluding participants considered as outliers supported the conclusion that abobotulinumtoxinA 1500 U was superior to placebo at reducing GSC muscle tone at week 4. When these centers were excluded, the treatment by center interaction was non-significant ($p = 0.3426$). The corresponding LS mean changes (95% CI) were −0.5 (−0.6 to −0.3) for placebo, −0.5 (−0.7 to −0.4) for abobotulinumtoxinA 1000 U and −0.8 (0.9 to −0.6) for abobotulinumtoxinA 1500 U ($p = 0.0042$) supporting the conclusion that abobotulinumtoxinA 1500 U was superior to placebo at reducing muscle tone in the GSC at week 4.

Efficacy of a single injection: proportional odds ratio analysis of PGA score

To check the robustness of the rank ANCOVA analysis, a proportional odds ratio analysis was applied to the ordered PGA categorical responses. An odds ratio >1 for

abobotulinumtoxinA versus placebo indicates a positive treatment effect in favor of abobotulinumtoxinA, and an odds ratio <1 indicates a treatment effect in favor of placebo. When applied to the week 4 data, the odds ratio for abobotulinumtoxinA 1000 U versus placebo was 1.66 (95% CI 1.03–2.66; p = 0.0368) and for abobotulinumtoxinA 1500 U versus placebo it was 1.70 (95% CI 1.06–2.74; p = 0.0282).

Efficacy of a single injection: spasticity, active range of dorsiflexion and quality of life

Spasticity grades (Y) were reduced in the GSC and soleus at week 4 and the angle of catch (X_{V3}) was improved at week 1 (GSC) and week 4 (soleus) for both abobotulinumtoxinA doses versus placebo. No difference was observed for the angle of arrest (X_{V1}). The change in the active range of ankle dorsiflexion with knee extended was 3.7° (95% CI 2.0–5.3) with abobotulinumtoxinA 1500 U and 1.5° (−0.2 to 3.1) with abobotulinumtoxinA 1000 U, versus 1.6° (−0.1–3.2) with placebo (*p* = 0.07 for 1500 U and *p* = 0.94 for 1000 U vs placebo). Other changes are displayed in Table e-2. No changes occurred in SF-36 or EQ-5D between the three groups.

Effects of repeated injections: spasticity, active range of dorsiflexion and quality of life

The reductions in spasticity grade (Y) observed in the double-blind study stabilized by cycle 1 week 4. Increases in angle of arrest (X_{V1}) in the GSC across cycles stabilized by cycle 2 week 4, while X_{V3} continued to increase up to +9.5° at cycle 4 week 4, with similar findings in the soleus (Table e-2 and figure e-1). The active range of ankle dorsiflexion with the knee extended continued to increase across

cycles, with an improvement of +6.5° from baseline to cycle 4 week 4 and similar results against the soleus (Table e-2 and figure e-1).

Correlation between composite X_A (X_A against GSC + X_A against soleus) and comfortable barefoot walking speed was significant at most endpoints (Table e-8), with composite X_A explaining about a quarter of the variance in walking speed.

Effects of repeated injections: walking speed

By cycle 4 week 4, mean (standard deviation) change from baseline in participants experiencing an event within 0–2 years was 0.12 m/s (0.17) versus 0.06 m/s (0.15) for participants experiencing events >10 years prior to study (Table e-7). Among the 136 participants treated for four cycles, at baseline 0% walked >0.8 m/s, 52% walked 0.4–0.8 m/s and 48% walked <0.4 m/s. At cycle 4 last visit, 16% reached a walking speed ≥0.8 m/s, 41% walked 0.4–0.8 m/s and 43% <0.4 m/s. Only 14% of participants receiving concomitant physiotherapy reached >0.8 m/s at cycle 4 last visit versus 20% of participants not receiving physiotherapy; however, 53% of those receiving physiotherapy walked <0.4 m/s at baseline versus 39% who did not.

Safety: muscular weakness

In the double-blind study, all muscular weakness episodes in the placebo and abobotulinumtoxinA 1000 U groups were local. In the abobotulinumtoxinA 1500 U group (128 injections), there were two cases of local muscular weakness, three cases of regional weakness (bilateral leg n = 2, shoulder n = 1) and three cases of generalized muscle weakness. During the open-label extension, there were 44 cases of muscular weakness relative to 1005 injections (23 localized and 21 generalized events).

Safety: remote toxin spread

Of the five serious adverse events suggestive of remote spread effects in four participants treated with abobotulinumtoxinA 1500 U, the three cases of generalized muscle weakness and one case of dysphagia occurred during Cycle 1; one case of dysphagia occurred during Cycle 2 and the participant suffered a myocardial infarction later in the same cycle. These events were mild or moderate in intensity except one case of severe generalized muscle weakness. All four participants recovered from the events in the same treatment cycle they occurred.

Assessment of binding and neutralizing antibodies

Two participants in the placebo group, one participant in the abobotulinumtoxinA 1000 U group and one participant in the abobotulinumtoxinA 1500 U group had binding antibodies at baseline; both placebo recipients and the abobotulinumtoxinA 1000 U recipient were also positive for neutralizing antibodies at baseline. Only the participant assigned to receive abobotulinumtoxinA 1000 U had not been previously treated with botulinum toxin type A.

Table e-1. Doses of abobotulinumtoxinA administered to each muscle group across cycles, with total dose administered in the lower limb only

Muscle group	Dose injected (U)				
Dose Group/statistic		Open-label			
	Double-blind	Cycle 1	Cycle 2	Cycle 3	Cycle 4
Ankle plantar flexor muscle groups					
Medial gastrocnemius					
ABO 1000 U					
Mean (range)	122.5 (67–200)	136.7 (100–200)	142.9 (93–300)	132.0 (93–300)	123.7 (67–200)
n (%)	125 (98.4)	10 (100.0)	64 (98.5)	35 (100.0)	21 (100.0)
ABO 1500 U					
Mean (range)	183.5 (0–300)	174.4 (100–300)	174.7 (100–304)	171.8 (100–300)	168.2 (100–300)
n (%)	127 (99.2)	333 (99.4)	232 (100.0)	186 (98.4)	115 (97.5)
Lateral gastrocnemius					
ABO 1000 U					
Mean (range)	95.2 (67–200)	113.3 (67–200)	97.7 (67–200)	85.9 (67–150)	89.0 (67–150)
n (%)	108 (85.0)	10 (100.0)	61 (93.8)	33 (94.3)	21 (100.0)

Muscle group	**Dose injected (U)**				
Dose Group/statistic	**Double-blind**	**Open-label**			
		Cycle 1	**Cycle 2**	**Cycle 3**	**Cycle 4**
ABO 1500 U					
Mean (range)	145.6 (100–300)	140.9 (100–400)	140.5 (100–250)	140.6 (60–300)	142.6 (100–300)
n (%)	105 (82.0)	305 (91.0)	210 (90.5)	174 (92.1)	114 (96.6)
Soleus					
ABO 1000 U					
Mean (range)	333.3 (333–333)	416.7 (333–500)	387.2 (333–500)	351.8 (313–500)	349.2 (333–500)
n (%)	127 (100.0)	10 (100.0)	65 (100.0)	35 (100.0)	21 (100.0)
ABO 1500 U					
Mean (range)	495.3 (0–500)	499.6 (400–521)	500.0 (500–507)	496.6 (300–500)	499.2 (400–500)
n (%)	128 (100.0)	335 (100.0)	232 (100.0)	189 (100.0)	118 (100.0)
Tibialis posterior					
ABO 1000 U					
Mean (range)	196.8 (67–467)	152.4 (67–200)	174.5 (67–333)	179.3 (125–267)	159.0 (100–267)
n (%)	95 (74.8)	7 (70.0)	34 (52.3)	23 (65.7)	13 (61.9)

Muscle group	**Dose injected (U)**				
Dose Group/statistic	**Double-blind**	**Open-label**			
		Cycle 1	**Cycle 2**	**Cycle 3**	**Cycle 4**
ABO 1500 U					
Mean (range)	284.3 (100–700)	289.3 (100–700)	308.7 (100–700)	242.1 (40–700)	235.4 (100–700)
n (%)	91 (71.1)	251 (74.9)	189 (81.5)	131 (69.3)	92 (78.0)
Toe flexor muscle groups					
Flexor digitorum longus					
ABO 1000 U					
Mean (range)	136.7 (67–267)	141.7 (100–200)	141.8 (67–267)	132.0 (67–333)	136.7 (67–267)
n (%)	90 (70.9)	4 (40.0)	44 (67.7)	22 (62.9)	18 (85.7)
ABO 1500 U					
Mean (range)	220.9 (40–400)	203.4 (50–500)	191.6 (100–500)	173.4 (80–400)	166.8 (100–400)
n (%)	88 (68.8)	246 (73.4)	154 (66.4)	102 (54.0)	60 (50.8)
Flexor digitorum brevis					
ABO 1000 U					
Mean (range)	89.4 (53–133)	–	93.9 (40–133)	85.8 (33–133)	77.8 (33–133)

Muscle group	**Dose injected (U)**				
Dose Group/statistic	**Double-blind**	**Open-label**			
		Cycle 1	**Cycle 2**	**Cycle 3**	**Cycle 4**
n (%)	34 (26.8)	0	12 (18.5)	8 (22.9)	3 (14.3)
ABO 1500 U					
Mean (range)	140.8 (50–300)	129.5 (50–200)	132.0 (50–300)	121.2 (60–200)	114.8 (80–200)
n (%)*	38 (29.7)	92 (27.5)	61 (26.3)	34 (18.0)	21 (17.8)
Flexor hallucis longus					
ABO 1000 U					
Mean (range)	96.4 (53–267)	66.7 (67–67)	109.1 (53–200)	109.0 (67–133)	108.3 (67–133)
n (%)	46 (36.2)	2 (20.0)	11 (16.9)	8 (22.9)	4 (19.0)
ABO 1500 U					
Mean (range)	158.6 (60–300)	155.4 (60–340)	153.3 (80–300)	138.6 (75–200)	131.7 (60–200)
n (%)*	44 (34.4)	118 (35.2)	78 (33.6)	33 (17.5)	23 (19.5)
Flexor hallucis brevis					
ABO 1000 U					
Mean (range)	93.3 (67–133)	–	53.3 (27–67)	54.0 (33–67)	55.6 (33–67)

Muscle group	**Dose injected (U)**				
Dose Group/statistic	**Double-blind**	**Open-label**			
		Cycle 1	**Cycle 2**	**Cycle 3**	**Cycle 4**
n (%)	20 (15.7)	0	4 (6.2)	4 (11.4)	3 (14.3)
ABO 1500 U					
Mean (range)	107.9 (50–200)	117.0 (50–300)	109.3 (50–200)	97.1 (60–200)	92.2 (40–150)
n (%)*	19 (14.8)	57 (17.0)	40 (17.2)	17 (9.0)	9 (7.6)
Knee extensor muscle group					
Rectus femoris					
ABO 1000 U					
Mean (range)	210.1 (67–467)	213.3 (133–333)	237.6 (100–333)	225.0 (67–333)	257.3 (133–333)
n (%)	63 (49.6)	5 (50.0)	28 (43.1)	16 (45.7)	10 (47.6)
ABO 1500 U					
Mean (range)	350.0 (100–700)	311.9 (100–700)	291.0 (100–700)	248.8 (80–500)	243.0 (180–500)
n (%)*	50 (39.1)	142 (42.4)	84 (36.2)	49 (25.9)	20 (16.9)
Hip extensor muscle groups					
Hamstrings					

Muscle group	**Dose injected (U)**				
Dose Group/statistic	**Double-blind**	**Open-label**			
		Cycle 1	**Cycle 2**	**Cycle 3**	**Cycle 4**
Dysport 1000 U					
Mean (range)	195.8 (67–333)	175.0 (100–267)	207.7 (100–333)	183.3 (100–467)	233.3 (200–333)
n (%)	16 (12.6)	4 (40.0)	13 (20.0)	10 (28.6)	4 (19.0)
ABO 1500 U					
Mean (range)	306.3 (100–550)	305.8 (100–700)	333.6 (81–700)	283.3 (100–700)	253.8 (100–700)
n (%)*	24 (18.8)	65 (19.4)	53 (22.8)	24 (12.7)	13 (11.0)
Gluteus maximus					
ABO 1000 U					
Mean (range)	100.0 (67–133)	–	133.3 (133–133)	–	–
n (%)	2 (1.6)	0	1 (1.5)	0	0
ABO 1500 U					
Mean (range)	220.0 (100–400)	193.7 (81–400)	233.3 (200–300)	200.0 (200–200)	–
n (%)*	5 (3.9)	11 (3.3)	3 (1.3)	2 (1.1)	0
Hip adductor muscle groups					

Muscle group	**Dose injected (U)**				
Dose Group/statistic	**Double-blind**	**Open-label**			
		Cycle 1	**Cycle 2**	**Cycle 3**	**Cycle 4**
Adductor magnus					
ABO 1000 U					
Mean (range)	183.3 (133–267)	–	266.7 (267–267)	66.7 (67–67)	–
n (%)	8 (6.3)	0	1 (1.5)	1 (2.9)	0
ABO 1500 U					
Mean (range)	257.1 (200–400)	252.3 (100–400)	219.1 (100–400)	242.9 (100–500)	222.2 (100–400)
n (%)*	7 (5.5)	23 (6.9)	22 (9.5)	14 (7.4)	9 (7.6)
Gracilis					
ABO 1000 U					
Mean (range)	111.1 (67–133)	–	133.3 (67–200)	–	–
n (%)	3 (2.4)	0	2 (3.1)	0	0
ABO 1500 U					
Mean (range)	183.3 (100–200)	181.8 (100–200)	158.3 (100–200)	171.4 (100–200)	160.0 (100–200)
n (%)*	6 (4.7)	11 (3.3)	12 (5.2)	7 (3.7)	5 (4.2)

*n(%), number and percent of subjects receiving injection in the indicated muscle within each dose group. Includes subjects who received ABO 1000U in the lower limb and 500U in the upper limb during cycles 3 (98 subjects) and 4 (67 subjects). Abbreviation: ABO = abobotulinumtoxinA.

Table e-2. Additional efficacy endpoints for the double-blind phase (ITT population)

Efficacy parameters	**Placebo (n = 128)**	**ABO 1000U (n = 125)**	**ABO 1500U (n = 128)**
PGA planned analysis			
LS mean (95% CI)*	0.7 (0.5,0.9)	0.9 (0.7,1.1)	0.9 (0.7, 1.1)
p value versus placebo	–	0.0640	0.0665
PGA ranked analysis (*post-hoc*)			
LS mean†	0.6	0.8	0.8
p value versus placebo	–	0.0466	0.0406
Comfortable barefoot walking speed, m/s			
Baseline mean (SD)	0.45 (0.20)	0.44 (0.23)	0.47 (0.22)
Week 4 mean (SD)	0.50 (0.23)	0.49 (0.27)	0.52 (0.23)
LS mean (95% CI)	0.05 (0.03, 0.07)	0.05 (0.03, 0.07)	0.04 (0.03, 0.06)
p value versus placebo	–	0.7247	0.7266

Efficacy parameters	**Placebo (n = 128)**	**ABO 1000U (n = 125)**	**ABO 1500U (n = 128)**
Week 12 mean (SD)	0.49 (0.23)	0.51 (0.28)	0.54 (0.24)
LS mean (95% CI)	0.05 (0.03, 0.07)	0.07 (0.05, 0.09)	0.06 (0.04, 0.08)
p value versus placebo	–	0.2056	0.7612
MAS soleus score			
Baseline mean (SD)	3.4 (0.8)	3.4 (0.7)	3.2 (0.9)
Week 4 mean (SD)	2.9 (1.1)	2.8 (1.1)	2.5 (1.1)
LS mean (95% CI)‡	−0.4 (−0.6, −0.3)	−0.7 (−0.8, −0.5)	−0.8 (−1.0, −0.7)
p value versus placebo	–	0.0389	0.0008
Week 12 mean (SD)	3.1 (0.9)	2.9 (1.0)	2.8 (1.0)
LS mean (95% CI)‡	−0.3 (−0.6, −0.1)	−0.5 (−0.7, −0.4)	−0.6 (−0.7, −0.4)
p value versus placebo	–	0.0197	0.0067

LS means for each treatment group and treatment comparisons, as well as the *p* values, were obtained from: *an analysis of variance on visit results with treatment, botulinum toxin treatment status at

baseline, and center as covariates; [†]an analysis of variance on visit results based on ranked values with treatment, botulinum toxin treatment status at baseline, and center as covariates; [‡]an analysis of covariance on the change from baseline with treatment, baseline score, botulinum toxin treatment status at baseline, and center as covariates.

Abbreviations: ABO = abobotulinumtoxinA; CI = confidence interval; LS = least squares; MAS = Modified Ashworth Scale; PGA = Physician's Global Assessment; SD = standard deviation.

Table e-3. Passive range of motion (X_{V1}), angle of catch (X_{V3}), active ankle dorsiflexion (X_A) and spasticity grade (Y) in the GSC and soleus across cycles at baseline and week 4 of each cycle

	Tardieu Scale and active ankle dorsiflexion					
	Double-blind		Open-label			
	Baseline	Week 4	Cycle 1	Cycle 2	Cycle 3	Cycle 4
	GSC					
ABO, all doses (LL)	n = 224	n = 224	n = 341	n = 290	n = 218	n = 135
Mean X_{V1} (SD)	87.3 (9.5)	88.9 (8.9)	90.3 (8.7)	89.9 (8.6)	89.2 (9.2)	89.3 (8.6)
Mean change from baseline (SD)	–	1.6 (7.1)	2.7 (7.9)	2.4 (7.8)	2.6 (8.9)	2.7 (8.4)
Mean X_{V3} (SD)	72.2 (11.9)	77.0 (10.3)	79.6 (10.0)	79.6 (10.3)	79.7 (10.6)	80.7 (10.2)
Mean change from baseline (SD)	–	4.7 (8.3)	7.1 (10.6)	7.3 (11.1)	7.9 (12.2)	9.5 (12.4)

	Tardieu Scale and active ankle dorsiflexion					
	Double-blind		**Open-label**			
	Baseline	**Week 4**	**Cycle 1**	**Cycle 2**	**Cycle 3**	**Cycle 4**
Mean X_A (SD)	69.1 (14.3)	72.4 (13.6)	73.5 (13.3)	73.5 (13.7)	73.7 (12.5)	74.9 (11.6)
Mean change from baseline (SD)	–	3.3 (10.2)	4.1 (10.6)	4.4 (10.6)	6.0 (11.4)	6.5 (10.9)
Mean spasticity grade Y (SD)	2.6 (0.7)	2.3 (0.6)	2.1 (0.6)	2.1 (0.6)	2.1 (0.6)	2.1 (0.6)
Mean change from baseline (SD)	–	−0.3 (0.7)	−0.5 (0.8)	−0.5 (0.7)	−0.5 (0.7)	−0.5 (0.8)
	Soleus					
ABO, all doses (LL)	n = 224	n = 224	n = 341	n = 290	n = 218	n = 135
Mean X_{V1} (SD)	95.1 (9.4)	96.8 (8.9)	97.0 (9.1)	97.5 (9.6)	96.8 (9.2)	96.5 (9.2)
Mean change from baseline (SD)	–	1.7 (6.3)	1.9 (8.0)	2.8 (8.1)	2.6 (8.5)	2.4 (8.6)

	Tardieu Scale and active ankle dorsiflexion					
	Double-blind		Open-label			
	Baseline	**Week 4**	**Cycle 1**	**Cycle 2**	**Cycle 3**	**Cycle 4**
Mean X_{V3} (SD)	79.6 (10.3)	84.4 (9.3)	86.1 (9.9)	86.6 (9.8)	86.6 (9.8)	87.2 (9.9)
Mean change from baseline (SD)	–	4.7 (8.1)	6.9 (10.3)	7.5 (10.8)	7.8 (11.2)	8.8 (11.4)
Mean X_A (SD)	79.5 (13.8)	83.0 (12.4)	83.6 (12.8)	84.3 (12.1)	84.1 (12.4)	83.3 (11.9)
Mean change from baseline (SD)	–	3.5 (9.0)	4.1 (10.7)	5.0 (10.3)	5.2 (10.9)	3.8 (9.8)
Mean spasticity grade Y (SD)	2.8 (0.7)	2.3 (0.7)	2.1 (0.8)	2.1 (0.6)	2.1 (0.6)	2.1 (0.5)
Mean change from baseline (SD)	–	−0.4 (0.7)	−0.6 (0.8)	−0.6 (0.7)	−0.7 (0.8)	−0.7 (0.7)

Baseline refers to baseline of double-blind study, prior to first injection. Abbreviations: ABO = abobotulinumtoxinA; LL = lower limb; X_A = active range of motion; X_{v1} = angle of arrest; X_{v3} = angle of catch.

Table e-4. Subgroup analysis of abobotulinumtoxinA efficacy by baseline botulinum toxin type A status

	Placebo	ABO 1000U	ABO 1500U
MAS GSC score			
BoNT-A naïve	n = 81	n = 82	n = 80
Baseline mean (SD)	3.7 (0.5)	3.6 (0.5)	3.6 (0.5)
Week 4 mean (SD)	3.3 (0.8)	3.2 (0.8)	3.0 (0.9)
Mean change (SD)	−0.4 (0.7)	−0.4 (0.8)	−0.6 (0.8)
BoNT-A non-naive	n = 47	n = 43	n = 48
Baseline mean (SD)	4.1 (0.2)	4.0 (0.0)	4.0 (0.3)
Week 4 mean (SD)	3.5 (0.8)	3.2 (1.1)	3.1 (1.0)
Mean change (SD)	−0.6 (0.8)	−0.8 (1.1)	−0.9 (1.0)
PGA			
BoNT-A naïve	n = 81	n = 82	n = 79
Week 4 mean	0.7 (0.9)	0.9 (1.0)	0.9 (1.0)
BoNT-A non-naive	n = 47	n = 42	n = 46
Week 4 mean	0.8 (1.2)	1.0 (1.4)	0.8 (1.2)

Comfortable barefoot walking speed, m/s

BoNT-A naïve	n = 80	n = 82	n = 79
Baseline mean (SD)	0.434 (0.199)	0.449 (0.259)	0.461 (0.221)
Week 4 mean (SD)	0.487 (0.232)	0.500 (0.288)	0.511 (0.238)
Mean change (SD)	0.053 (0.079)	0.055 (0.120)	0.050 (0.097)
BoNT-A non-naive	n = 47	n = 43	n = 48
Baseline mean (SD)	0.469 (0.211)	0.409 (0.180)	0.488 (0.204)
Week 4 mean (SD)	0.516 (0.236)	0.461 (0.245)	0.527 (0.214)
Mean change (SD)	0.043 (0.085)	0.053 (0.106)	0.040 (0.103)

Abbreviations: ABO = abobotulinumtoxinA; BoNT-A = botulinum toxin type A; GSC = gastrocnemius–soleus complex; MAS = Modified Ashworth Scale; PGA = Physician's Global Assessment; SD = standard deviation.

Table e-5. Subgroup analysis of abobotulinumtoxinA efficacy by cause of spasticity

	Placebo	ABO 1000U	ABO 1500U
MAS GSC score			
Stroke	n = 106	n = 109	n = 116
Mean change from BL to week 4	−0.5	−0.5	−0.7
Traumatic brain injury	n = 22	n = 16	n = 12
Mean change from BL to week 4	−0.6	−0.8	−0.7
PGA			
Stroke	n = 106	n = 108	n = 114
Week 4 mean	0.7	0.9	0.9
Traumatic brain injury	n = 22	n = 16	n = 11
Week 4 mean	0.6	1.2	0.7

Abbreviations: ABO = abobotulinumtoxinA; BL = baseline; GSC = gastrocnemius–soleus complex; MAS = Modified Ashworth Scale; PGA = Physician's Global Assessment.

Table e-6. 10-metre comfortable barefoot walking speed change from baseline at week 4 versus week 12 across cycles

Visit	**ABO (all doses combined)**	
	Week 4	**Week 12**
Number of participants, n		
Double-blind	222	220
Cycle 1	335	316
Cycle 2	285	253
Cycle 3	215	150
Cycle 4	134	138
Total number of visits, n	1191	1077
LS mean (standard error)	0.073 (0.004)	0.083 (0.004)
95% CI of LS mean	0.065–0.080	0.074–0.091
Difference in LS means between weeks 4 and 12 (95% CI)	–	0.010 (0.005–0.016)
p value	–	0.0002

Abbreviations: ABO = abobotulinumtoxinA; CI = confidence interval; LS = least-squares.

Table e-7. Correlation between comfortable barefoot walking speed change from baseline and time since event (stroke or TBI in years) at baseline

Visit	**ABO (all doses combined)**	
	Week 4	**Week 12**
Double-blind, n	222	220
Pearson correlation	−0.09135	−0.1114
p value	0.1750	0.0993
Cycle 1, n	335	316
Pearson correlation	−0.075	−0.0579
p value	0.1696	0.3050
Cycle 2, n	285	253
Pearson correlation	−0.1239	−0.1514
p value	0.0366	0.0160
Cycle 3, n	215	150
Pearson correlation	−0.1220	−0.0129

p value	0.0743	0.8755
Cycle 4, n	134	–
Pearson correlation	−0.0978	–
p value	0.2611	–

Abbreviations: ABO = abobotulinumtoxinA; DB = double-blind study; SD = standard deviation.

Table e-8. Comfortable barefoot walking speed across cycles (abobotulinumtoxinA – all doses combined) by time since event (stroke or TBI)

	Comfortable barefoot walking speed, m/s			
	Time since event (stroke or TBI), years			
Visit	**0–2**	**2–5**	**5–10**	**>10**
Absolute value at baseline	n = 83	n = 70	n = 36	n = 33
Mean (SD) [range]	0.42 (0.23) [0.10–1.24]	0.45 (0.20) [0.13–0.85]	0.41 (0.21) [0.12–0.80]	0.56 (0.23) [0.10–1.14]
Change from baseline to double-blind week 4	n = 83	n = 70	n = 36	n = 33
Mean (SD) [range]	0.06 (0.11) [0.39–0.42]	0.06 (0.10) [−0.17–0.46]	0.05 (0.09) [−0.12–0.25]	0.04 (0.10) [−0.16–0.21]
Change from baseline to double-blind week 12	n = 82	n = 70	n = 35	n = 33
Mean (SD) [range]	0.08 (0.11) [−0.14–0.45]	0.07 (0.12) [−0.17–0.56]	0.06 (0.10) [−0.12 0.34]	0.05 (0.10) [−0.14–0.23]
Change from baseline to cycle 1 week 4	n = 116	n = 115	n = 54	n = 50

Mean (SD) [range]	0.07 (0.13) [−0.33–0.47]	0.08 (0.11) [−0.14–0.48]	0.06 (0.12) [−0.31–0.52]	0.04 (0.14) [−0.38–0.35)
Change from baseline to cycle 1 week 12	n = 111	n = 109	n = 51	n = 45
Mean (SD) [range]	0.08 (0.14) [−0.43–0.54]	0.09 (0.13) [−0.16–0.57]	0.07 (0.11) [−0.17–0.51]	0.06 (0.13) [−0.21–0.51]
Change from baseline to cycle 2 week 4	n = 100	n = 98	n = 46	n = 41
Mean (SD) [range]	0.10 (0.15) [−0.29–0.55]	0.08 (0.13) [−0.21–0.45]	0.04 (0.09) [−0.17–0.21]	0.05 (0.12) [−0.19–0.37]
Change from baseline to cycle 2 week 12	n = 88	n = 84	n = 43	n = 38
Mean (SD) [range]	0.12 (0.15) [−0.26–0.59]	0.09 (0.13) [−0.15–0.51]	0.06 (0.11) [−0.09–0.38]	0.05 (0.13) [−0.35–0.40]
Change from baseline to cycle 3 week 4	n = 78	n = 69	n = 35	n = 33

Mean (SD) [range]	0.11 (0.14) [−0.19–0.55]	0.07 (0.11) [−0.29–0.42]	0.04 (0.10) [−0.15–0.27]	0.05 (0.12) [−0.19–0.35)
Change from baseline to cycle 3 week 12	n = 51	n = 52	n = 27	n = 20
Mean (SD) [range]	0.12 (0.16) [−0.12–0.56)	0.06 (0.13) [−0.25–0.41]	0.07 (0.09) [−0.05–0.27]	0.10 (0.16) [−0.19–0.48]
Change from baseline to cycle 4 week 4	n = 46	n = 51	n = 21	n = 16
Mean (SD) [range]	0.12 (0.17) [−0.14–0.62]	0.08 (0.13) [−0.31–0.42]	0.07 (0.10) [−0.10–0.36)	0.06 (0.15) [−0.31–0.34]

Abbreviations: SD = standard deviation; TBI = traumatic brain injury.

Table e-9. Summary of AEs (preferred term) following abobotulinumtoxinA injections reported in ≥2% of participants at any cycle (safety population)

Preferred term, n (%) [number of events]		Double-blind		Open-label	
		Cycle 1	Cycle 2	Cycle 3	Cycle 4
Placebo	n = 130				
Muscular weakness	4 (3.1) [4]	–	–	–	–
Pain in extremity	3 (2.5) [3]	–	–	–	–
Arthralgia	1 (0.8) [1]	–	–	–	–
Fall	4 (3.3) [8]	–	–	–	–
Dysphagia	1 (0.8) [1]	–	–	–	–
Asthenia	1 (0.8) [2]	–	–	–	–

ABO 1000 U (LL)	n = 127	n = 10	n = 65	n = 133	n = 88
Muscular weakness	3 (2.4) [3]	1 (10.0) [1]	1 (1.5) [1]	5 (3.8) [5]	2 (2.3) [2]
Pain in extremity	7 (5.5) [7]	1 (10.0) [1]	2 (3.1) [3]	1 (0.8) [1]	–
Arthralgia	5 (3.9) [5]	–	1 (1.5) [1]	1 (0.8) [1]	1 (1.1) [1]
Fall	12 (9.4) [14]	1 (10.0) [1]	7 (10.8) [8]	8 (6.0) [8]	3 (3.4) [3]
Dysphagia	2 (1.6) [2]	–	–	1 (0.8) [1]	2 (2.3) [2]
Asthenia	3 (2.4) [3]	–	3 (4.6) [4]	4 (3.0) [4]	1 (1.1) [1]
ABO 1500 U (LL)	n = 128	n = 335	n = 232	n = 91	n = 51
Muscular weakness	8 (6.3) [9]	21 (6.3) [22]	11 (4.7) [11]	1 (1.1) [1]	1 (2.0) [1]
Pain in extremity	8 (6.3) [9]	10 (3.0) [10]	2 (0.9) [2]	1 (1.1) [1]	–
Arthralgia	3 (2.3) [4]	6 (1.8) [6]	5 (2.2) [6]	–	1 (2.0) [1]

Fall	8 (6.3) [9]	16 (4.8) [17]	10 (4.3) [11]	1 (1.1) [1]	2 (3.9) [3]
Dysphagia	1 (0.8) [1]	1 (0.3) [1]	6 (2.6) [6]	–	–
Asthenia	1 (0.8) [1]	9 (2.7) [9]	3 (1.3) [3]	–	–

Abbreviations: ABO = abobotulinumtoxinA; LL = lower-limb.

Table e-10. Correlation between comfortable barefoot walking speed and composite X_A at week 4 of each cycle (absolute values)

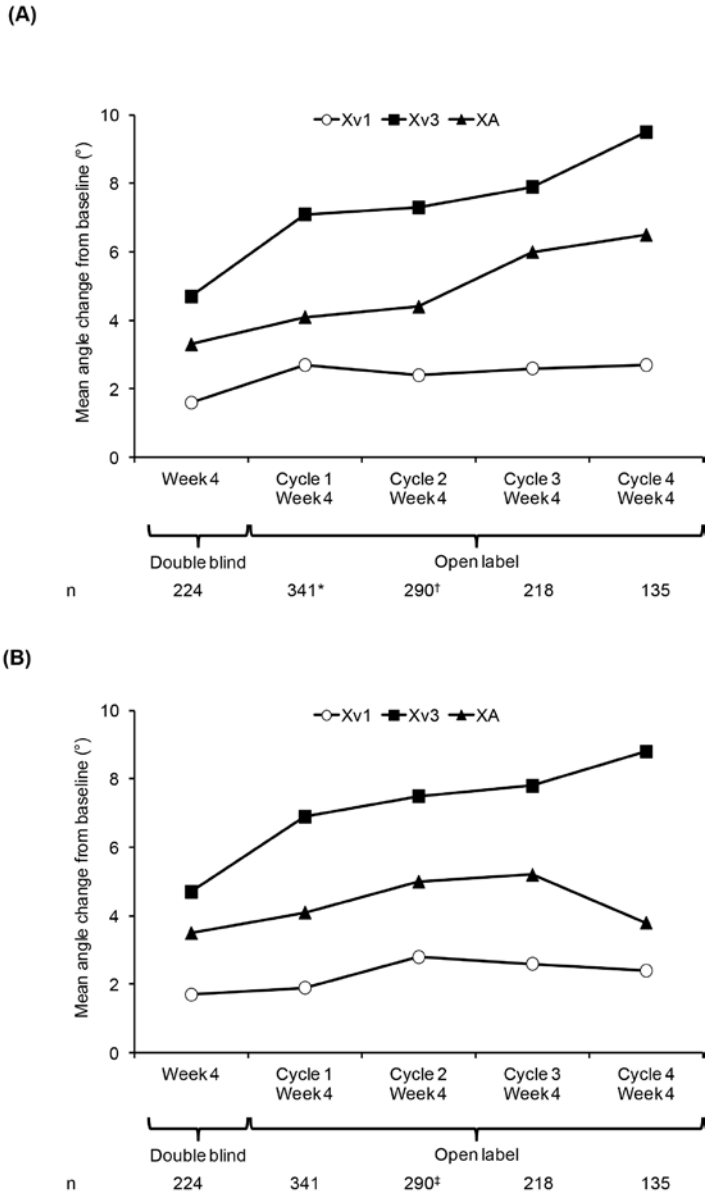
Visit	Placebo	ABO 1000 U	ABO 1500 U
Baseline, n	120	112	110
Pearson correlation	0.2027	0.3541	0.3105
p value	0.0264	0.0001	0.0010
Double-blind, n	119	111	111
Pearson correlation	0.2215	0.3831	0.2538
p value	0.0155	<0.0001	0.0072
Cycle 1, n	–	10	325
Pearson correlation	–	0.1439	0.2188
p value	–	0.6916	<0.0001
Cycle 2, n	–	63	223
Pearson correlation	–	0.0941	0.2542
p value	–	0.4633	0.0001
Cycle 3, n	–	127	88
Pearson correlation	–	0.2261	0.1287

p value	–	0.0106	0.2321
Cycle 4, n	–	83	51
Pearson correlation	–	0.1362	0.2744
p value	–	0.2197	0.0514

Abbreviations: ABO = abobotulinumtoxinA; X_A = active range of motion.

Figure legend

Figure e-1. Passive range of motion (X_{V1}), angle of catch (X_{V3}) and active ankle dorsiflexion (X_A) in the (A) GSC and (B) soleus muscle across cycles: mean change from baseline to week 4 at each cycle (abobotulinumtoxinA doses combined)



*340 for X_A; †289 for X_{V3}; ‡289 for X_{V3}. Standard deviations are available in Table e-2. GSC, gastrocnemius–soleus complex; X_A, active range of motion; X_{V1}, angle of arrest; X_{V3}, angle of catch