PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Factors affecting the health-related quality of life of patients with cervical dystonia and impact of treatment with abobotulinumtoxinA (Dysport): results from a randomized, double-blind, placebo controlled study
AUTHORS	Mordin, Margaret ; Masaquel, Catherine; Coleman Abbott, Chandra; Copley-Merriman, Catherine

VERSION 1 - REVIEW

REVIEWER	Miguel Coelho Neurology Service, Neurosciences Department, Hospital Santa Maria, Lisbon Portugal Clinical Pharmacology Unit, Instituto de Medicina Molecular, Lisbon POrtugal
REVIEW RETURNED	01-Jun-2014

GENERAL COMMENTS	ABSTRACT: results reporting correlation between TWSTRS and SF 36 should be clearer whether they concern active arm or placebo STATISTICS: the authors do not state how they have dealt with withdrawals (last observation carried forward?). Additionally, TWSTRS and SF 36 measured at different time points, week 4 and 8, are correlated and this should be discussed. The total score for SF 36 is never reported in the manuscript. REFERENCES: a new definition for dystonia is available (albaneses 13). Additionally, the authors cannot state that the AAN classified the main study as Class I and the reference is from a Toxicon publicatin and not Neurology, this is misleading. RESULTS: the results should in general be reported in a more precise and clear way. The magnitude of treatment effect of SF 36 between baseline and week 8 should be reported for each treatment arm differentely, and also the magnitude difference between treatment arms. The text describing table 3 is not clear and induces the reader in mistake; it should state which correlations concern the BoNT arm and which concern the placebo arm; table 3 should report all 8 domains. Table 2 is not informative and should be deleted. Does the treatment responder group include patients only from the BoNT arm or from both arms and if yes in which percentage. LIMITATIONS: not covered properly, namely sample size and number of withdrawals. DISCUSSION: I suggest to discuss more the results of the present study. For example, why did not Social Functioning improved if it is one domain consistently reported as affected in CD patients?

REVIEWER	Andrew Hinde

	University of Southampton United Kingdom
REVIEW RETURNED	17-Jun-2014

GENERAL COMMENTS	Research ethics. These are not addressed in this paper. As this paper reports additional results from a clinical study which was previously described in another article (Truong, et al. (2010) 'Long-term efficacy and safety of botulinum toxin type A (Dysport) in cervical dystonia', Parkinsonism Relat. Disord. 16, 316-23), then it may be that the ethical issues were dealt with in that paper. However, I think that some reference to ethical issues should be made in this paper, or to an official register entry of the Clinical Trial in question, which may be found at https://clinicaltrials.gov/ct2/show/NCT00257660?term=cervical+dystonia&rank=10. Are the study limitations discussed adequately? My question here concerns the exclusion criteria listed on p. 9, ll. 11-16. Do the authors think that these exclusion criteria might have incfluenced their results by excluding disproportionately patients who might not have experienced enhanced health-related quality of life (HRQOL) as a result of the treatment. The exclusion criteria are just listed without comment. I am especially concerned about the exclusion of those with 'suspected secondary non-responsiveness or a history of poor response to BoNT-A' as this seems likely to exclude those who might not experience a positive change in their HRQOL. The funding details are given, and the interests of the authors declared fully. However reference to the trial registration is missing, and there is no checklist. Again, it may be that the checklist was provided in the earlier paper, but this should be confirmed explicitly. Finally, on p. 12, ll. 12-13, 'Bodily Pain scores that were 33% lower (worse)' should be 'Bodily Pain scores that were 23 percentage points lower (worse)'. 71 - 48 = 23, not 33. The statistical methods used here seem reasonable. My main concern is with the exclusion criteria in the original clinical trial, and indeed with the provision of general details of that trial.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name Miguel Coelho
Institution and Country Neurology Service, Neurosciences Department, Hospital Santa Maria, Lisbon Portugal
Clinical Pharmacology Unit, Instituto de Medicina Molecular, Lisbon POrtugal
Please state any competing interests or state ‘None declared’: none declared

ABSTRACT: results reporting correlation between TWSTRS and SF 36 should be clearer whether they concern active arm or placebo [The abstract has been updated to indicate the correlations referred to are for those on active treatment [abstract -page 4]
STATISTICS: the authors do not state how they have dealt with withdrawals (last observation carried forward?). Added the following to the manuscript “Analyses were conducted on the full analysis set (i.e., all randomized subjects according to the treatment assigned at randomization) for subjects with a baseline and a week 8 SF-36 assessment.” [page 12] Additionally, TWSTRS and SF 36 measured at different time points, week 4 and 8, are correlated and this should be discussed. The total score for SF 36 is never reported in the manuscript. [The correlations are discussed in the manuscript. There is

no single Total SF-36 score, analyses focused on the 8 subscales.]
REFERENCES: a new definition for dystonia is available (albaneses 13). Additionally, the authors cannot state that the AAN classified the main study as Class I and the reference is from a Toxicon publicatin and not Neurology, this is misleading. [The Albanese 2013 article has been used to update the definition of CD in the manuscript “Dystonia, one of the most common movement disorders, with a spectrum of clinical features that range from severe generalized childhood dystonia, to adult-onset focal dystonias, to secondary dystonias and dystonias as a feature of complex neurological disorders.[1] Dystonia can be focal (localized to a single body region), or can be spread to segmental (contiguous) or multifocal (non-contiguous) regions. Dystonia is characterized by motor manifestations, primarily sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both.[1]
[page6].” We have removed reference to the AAN classifying the main study as a Class I study within our manuscript.
RESULTS: the results should in general be reported in a more precise and clear way. The magnitude of treatment effect of SF 36 between baseline and week 8 should be reported for each treatment arm differentely, and also the magnitude difference between treatment arms. [While Figure 1 presented the mean change by treatment group, and one could deduce the differential treatment group difference, we added a table (Table 2) of baseline and week 8 scores by treatment group, along with the mean change and p-value.]. The text describing table 3 is not clear and induces the reader in mistake; it should state which correlations concern the BoNT arm and which concern the placebo arm; table 3 should report all 8 domains. [Our apologies for lack of clarity regarding Table 3 and its discussion. The correlation table did include columns to present both active and placebo correlations. However, we did add the remaining 5 scales to the table and updated the discussion of table 3 for clarity. The following was included to describe table 3 findings “Table 3 presents the correlations between the TWSTRS total and domain scores at week 4 with the week 8 SF-36 domain scores. As expected, the TWSTRS was significantly correlated with the Physical Functioning, Role Physical, and Bodily Pain domain scores. The correlations between TWSTRS domain and total scores were consistently significantly correlated with the Role Physical and Bodily Pain domain scores for both treatment groups. The correlations ranged from –0.29 to –0.44 at week 4. Correlations were similar when evaluated with week 8 TWSTRS scores and week 8 SF-36 scores: –0.33 to –0.53 (week 8 correlations not shown).”[page 18]
Table 2 is not informative and should be deleted. [We have deleted the table] Does the treatment responder group include patients only from the BoNT arm or from both arms and if yes in which percentage. [The responders were clinically determined; the results present PRO scores by clinical response status (i.e.., regardless of treatment assignment). The following was added for clarity “The proportion of subjects classified as responders (achieving the predetermined 30% improvement in TWSTRS) was consistently higher for the abobotulinumtoxinA group than for the placebo group. For the abobotulinumtoxinA treatment group, 49% were classified as responders at week 4 and 58% were classified as responders at week 8. In contrast, for the placebo treated group, only 16% were classified as responders at week 4 and 26% at week 8.
Among those classified as TWSTRS responders, improvements from baseline to week 8 were observed for most of the SF-36 domains, whereas the non-responder group showed little to no change in SF-36 domains (Table 4)”[page 22]

LIMITATIONS: not covered properly, namely sample size and number of withdrawals. [The limitations have now been addressed in the article summary for the paper. We have added a study flow figure which outlines the withdrawls as well as those with PRO data at baseline and week 8. Sample size is also addressed]

DISCUSSION: I suggest to discuss more the results of the present study. For example, why did not Social Functioning improved if it is one domain consistently reported as affected in CD patients?[We elaborated the discussion [page 24]]

Reviewer: 2
Reviewer Name Andrew Hinde
Institution and Country University of Southampton
United Kingdom
Please state any competing interests or state ‘None declared’: None declared.

Research ethics. These are not addressed in this paper. As this paper reports additional results from a clinical study which was previously described in another article (Truong, et al. (2010) 'Long-term efficacy and safety of botulinum toxin type A (Dysport) in cervical dystonia', Parkinsonism Relat. Disord. 16, 316-23), then it may be that the ethical issues were dealt with in that paper. However, I think that some reference to ethical issues should be made in this paper, or to an official register entry of the Clinical Trial in question, which may be found at https://clinicaltrials.gov/ct2/show/NCT00257660?term=cervical+dystonia&rank=10.
[Reviewer #2 is correct in that much of the research ethics were dealt with in the main clinical paper. However, we did add the following to the paper “The study was conducted in accordance with the Declaration of Helsinki and was reviewed by the ethics committee responsible for each site. All patients provided written, informed, institutional review board–approved consent before participation. [page 10]

Are the study limitations discussed adequately? My question here concerns the exclusion criteria listed on p. 9, ll. 11-16. Do the authors think that these exclusion criteria might have incfluenced their results by excluding disproportionately patients who might not have experienced enhanced health-related quality of life (HRQOL) as a result of the treatment. The exclusion criteria are just listed without comment. I am especially concerned about the exclusion of those with 'suspected secondary non-responsiveness or a history of poor response to BoNT-A' as this seems likely to exclude those who might not experience a positive change in their HRQOL. [We clarified in the paper [page 9] that the key exclusion criteria were standard for efficacy trials of BoNT. We added limitations of the study to our discussion and include this point. “Our study is not without limitations that should be considered. First, the exclusion of those with suspected secondary non-responsiveness or a history of poor response to BoNT-A may have excluded those who might not experience a positive change in their health related quality of life. Secondly, the size of this study was small. Studies with a larger sample size are required to demonstrate the outcomes of abobotulinumtoxinA treatment in a study population that is more representative of the general population.” [page 25]

The funding details are given, and the interests of the authors declared fully. However reference to the trial registration is missing, and there is no checklist. Again, it may be that the checklist was provided in the earlier paper, but this should be confirmed explicitly. [We have prepared CONSORT checklist for this PRO paper; additional details may be found with the Truong publication; clinical trial registration number was added [page 28]

Finally, on p. 12, ll. 12-13, 'Bodily Pain scores that were 33% lower (worse)' should be 'Bodily Pain scores that were 23 percentage points lower (worse)'. 71 - 48 = 23, not 33. [corrected to 23% [page 13]

The statistical methods used here seem reasonable. My main concern is with the exclusion criteria in the original clinical trial, and indeed with the provision of general details of that trial. [trial details added or referenced]

VERSION 2 – REVIEW

REVIEWER	Miguel Coelho Neurology Service Department of Neurosciences Hospital de Santa Maria Lisbon,Portugal and Clinical pharmacological unit, Instituto de Medicina Molecular, Lisbon Portugal
REVIEW RETURNED	26-Aug-2014

GENERAL COMMENTS	ABSTRACT: it should be said the time points of the assessments INTRODUCTION: Did any previous trial of botulinum toxin in CD assesses QoL? This should be mentioned METHODS & STATISTICS: Despite the reply of the authors to my previous review, I still think that the summary index of SF-36 should be calculated and reported. It must be mentioned that the results of SF-36 of russian patients were compared against US norms and not russian norms. Regarding the population of interest, the efficacy analysis was performed in the per protocol population and not on the ITT population. The sentence in the results section, page 12, "received at least one dose of study medication and were included in the intent-to-treat (ITT) population" is misleading and should be deleted. A sentence adding in how many patients the SF-36 was analysed must be added and clear. RESULTS Page 22, lines 18-39: I suggest to reduce the text, as some information is repeated in similar ways. DISCUSSION: The authors say that CD is non-progressive (pp 23, line 50) whereas in the introduction that say that CD is progressive (Page 8, Line 13); please homogeneize. A limitation not adressed is the great amount of withdrawals, and this should be added because it has implications in the interpretation of the results. The lack of improvement in social functioning is not well discussed yet. FIGURES I suggest to add an * in table 2 to the domains that differ significantly between abo and placebo.

REVIEWER	Andrew Hinde Southampton Statistical Sciences Research Institute University of Southampton United Kingdom
REVIEW RETURNED	02-Sep-2014

GENERAL COMMENTS	This is a resubmission of an earlier paper to which I requested revisions. I have read the revised version and the authors' covering letter explaining the changes they have made. I am happy that all my concerns have been addressed. There are some that the authors cannot do much about, but these are now acknowledged in the paper so that readers are aware of them and can draw their own conclusions. I should like to thank the authors for the thorough and helpful way they have responded to my earlier comments. Would that all authors were so forthcoming!

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name Miguel Coelho
Institution and Country Neurology Service
Department of Neurosciences
Hospital de Santa Maria
Lisbon,Portugal
and
Clinical pharmacological unit, Instituto de Medicina Molecular, Lisbon Portugal
Please state any competing interests or state 'None declared': none declared

ABSTRACT:
it should be said the time points of the assessments Time points of the assessments were added in abstract. It now reads as follows: "Efficacy assessments included TWSTRS total (primary endpoint) and subscale scores at week 0 (baseline), at week 4 (primary), and at weeks 8 and 12 (posttreatment), a pain visual analog scale at baseline and week 4, and HRQOL assessed by the SF-36 Health Survey (SF 36) (secondary endpoint) at week 0 (baseline; prior to dosing) and at week 8 (posttreatment)"

INTRODUCTION:
Did any previous trial of botulinum toxin in CD assesses QoL? This should be mentioned We are unaware of previous trials of botulinum toxin in CD assessing QOL.

METHODS & STATISTICS:
Despite the reply of the authors to my previous review, I still think that the summary index of SF-36 should be calculated and reported. As a summary index was not previously calculated, it is beyond the authors' ability to do so at this time.
It must be mentioned that the results of SF-36 of russian patients were compared against US norms and not russian norms. The manuscript currently states that all patients were compared against US norms. Specifically, the manuscript states, "Baseline SF-36 scores for the patients with CD were lower (worse) than US population normative values[11] for patients without CD in all domains. Before treatment with either abobotulinumtoxinA or placebo, patients with CD in this study reported significantly greater impairment for all eight domains of the SF-36 relative to the age- and gender-adjusted US population normative values (Table 1)." [page. 12] However, as this reviewer requested further clarity, the methods section now reads as follows: "The unique burden of illness associated with CD was assessed by comparing patients' baseline domain scores (regardless of enrolment location) to age- and gender-adjusted SF-36 domain scores for the US population norms." [Page 11]
Regarding the population of interest, the efficacy analysis was performed in the per protocol

population and not on the ITT population. The sentence in the results section, page 12, "received at least one dose of study medication and were included in the intent-to-treat (ITT) population" is misleading and should be deleted. A sentence adding in how many patients the SF-36 was analysed must be added and clear. [Deleted suggested text and added new sentence with number of patients analyzed by the SF-36. The manuscript now reads as follows “All 116 randomized patients (abobotulinumtoxinA n = 55; placebo n = 61) received at least one dose of study medication in the double-blind phase of the study and were included in both the ITT and safety populations. Of these, 83 patients (abobotulinumtoxinA n = 45; placebo n = 38) were analysed in the HRQOL assessment.” [page 12]

RESULTS
Page 22, lines 18-39: I suggest to reduce the text, as some information is repeated in similar ways. We have reduced the text as suggested by the reviewer, it now reads as follows “Patients classified as TWSTRS responders (i.e., those with a ≥ 30% improvement in TWSTRS at week 4) reported significantly greater improvements from baseline to week 8 in five of the eight SF-36 domains compared with patients who did not respond to treatment (Table 5). Specifically, largest improvements occurred in Physical Functioning, Role Physical, Bodily Pain, Vitality, and Social Functioning (P ≤ 0.03 for all).”

DISCUSSION:
The authors say that CD is non-progressive (pp 23, line 50) whereas in the introduction that say that CD is progressive (Page 8, Line 13); please homogeneize. We have reconciled the discordance.
A limitation not adressed is the great amount of withdrawals, and this should be added because it has implications in the interpretation of the results. As requested, we have added the number of withdrawls as a study limitation [page 23]. The following was added to the manuscript “Lastly, there were quite a few withdrawals from the study, which could impact overall findings. As there were a total of 33 patients (abobotulinumtoxinA n = 10; placebo n = 23) who discontinued the study, two-thirds of whom were placebo.”
The lack of improvement in social functioning is not well discussed yet. Social functioning is addressed in the manuscript in the following way, as stated on page 16, “Patients treated with abobotulinumtoxinA reported significantly greater improvements than placebo patients from baseline to week 8 in five of the eight SF-36 domains”. In addition, as stated on page 21, “Specifically, largest improvements occurred in Physical Functioning, Role Physical, Bodily Pain, Vitality, and Social Functioning (P ≤ 0.03 for all).”

FIGURES
I suggest to add an * in table 2 to the domains that differ significantly between abo and placebo. Added asterisks where SF-36 domains differed significantly

Reviewer: 2
Reviewer Name Andrew Hinde
Institution and Country Southampton Statistical Sciences Research Institute
University of Southampton
United Kingdom
Please state any competing interests or state ‘None declared’: None declared.

This is a resubmission of an earlier paper to which I requested revisions. I have read the revised version and the authors' covering letter explaining the changes they have made.

I am happy that all my concerns have been addressed. There are some that the authors cannot do much about, but these are now acknowledged in the paper so that readers are aware of them and can

draw their own conclusions.

I should like to thank the authors for the thorough and helpful way they have responded to my earlier comments. Would that all authors were so forthcoming!

You’re welcome.