BMJ open

Factors affecting the health-related quality of life of patients with cervical dystonia and impact of treatment with abobotulinumtoxinA (Dysport)

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2014-005150
Article Type:	Research
Date Submitted by the Author:	27-Feb-2014
Complete List of Authors:	Mordin, Margaret; RTI Health Solutions, Market Access & Outcomes Strategy Masaquel, Catherine; RTI Health Solutions, Market Access & Outcomes Strategy Coleman Abbott, Chandra; Ipsen Biopharmaceuticals, Neurology Medical Affairs Copley-Merriman, Catherine; RTI Health Solutions, Market Access & Outomes Strategy
Primary Subject Heading:	Neurology
Secondary Subject Heading:	Qualitative research
Keywords:	Adult neurology < NEUROLOGY, QUALITATIVE RESEARCH, Motor neurone disease < NEUROLOGY

SCHOLARONE™
Manuscripts

For peer review only

Factors affecting the health-related quality of life of patients with cervical dystonia and impact of treatment with abobotulinumtoxinA (Dysport)

Margaret Mordin, MS, Market Access and Outcomes Strategy, RTI Health Solutions, Ann Arbor, MI, United States

Catherine Masaquel, MPH, Market Access and Outcomes Strategy, RTI Health Solutions, Ann Arbor, MI, United States

Chandra Abbott, PhD, Neurology Medical Affairs, Ipsen Biopharmaceuticals, Inc, Basking Ridge, NJ, United States

Catherine Copley-Merriman, MBA, MS, Market Access and Outcomes Strategy, RTI Health Solutions, Ann Arbor, MI, United States

Corresponding Author:

Margaret Mordin

RTI Health Solutions

3005 Boardwalk St., Suite 105

Ann Arbor, MI 48108

Telephone: +1.703.483.9009

Fax: +1.734.213.6169

E-mail: mmordin@rti.org

For peer review only

Key words: cervical dystonia, botulinum toxin type A, Dysport, spasmodic torticollis, health-related quality of life

Word Count (excluding title page, abstract, references, tables, and figure legends): ~2,815

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

ABSTRACT

Objective: To describe the health-related quality of life (HRQOL) burden of cervical dystonia (CD) and report on the HRQOL and patient perception of treatment benefits of abobotulinumtoxinA (Dysport®).

Design: The safety and efficacy of a single injection of abobotulinumtoxinA for CD treatment were evaluated in a previously reported international, multicenter, double-blind, randomized trial. HRQOL measures were assessed in the trial and have not been previously reported.

Setting: Movement disorder clinics in the United States (US) and Russia.

Participants: Patients had to have a diagnosis of CD with symptoms for at least 18 months, as well as a total Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) score of at least 30; a Severity domain score of at least 15; and a Disability domain score of at least 3. Key exclusion criteria included treatment with botulinum toxin type A (BoNT-A) or botulinum toxin type B (BoNT-B) within 16 weeks of enrollment.

Interventions: Patients were randomized to receive either 500 U abobotulinumtoxinA (n = 55) or placebo (n = 61).

Primary and secondary outcome measures: Efficacy assessments included TWSTRS total and subscale scores, a pain visual analog scale, and HRQOL assessed by the SF-36 Health Survey (SF-36).

Results: Patients with CD reported significantly greater impairment for all SF-36 domains relative to US norms. Patients treated with abobotulinumtoxinA reported significantly greater improvements in Physical Functioning, Role Physical, Bodily Pain, General Health, and Role Emotional domains than placebo patients ($P \leq 0.03$ for all). The TWSTRS was significantly correlated with Physical Function, Role Physical, and Bodily Pain scores.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Conclusions: CD has a marked impact on HRQOL. Treatment with a single abobotulinumtoxinA injection results in significant improvement in patients' HRQOL.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

ARTICLE SUMMARY

Strengths and limitations of this study

- This clinical study has been classified as class I study according to the American Academy of Neurology (AAN) Classification of Quality of Evidence for Clinical Trials.[1]
- The size of this study was small; therefore, 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.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

INTRODUCTION

Dystonia is a movement disorder characterized by patterned, directional, and often sustained muscle contractions that produce abnormal postures or repetitive movements.[2] When classified by distribution, patients are categorized as having hemidystonia or focal, segmental, multifocal, or generalized dystonia.[3] With cervical dystonia (CD), the most common form of focal dystonia, abnormal movements affect a single body region. CD is characterized by sustained involuntary muscle contraction and/or twitching of cervical musculature resulting in abnormal postures and repetitive movements of the head.[4] Depending on the particular combination of muscles involved, the following head positions can occur: torticollis (horizontal turning), laterocollis (tilting), anterocollis (flexion), and retrocollis (extension).[2] CD may be accompanied by pulling or stiffness, pain, and sensory symptoms in the affected area.[5] The diagnosis of CD is based on clinical signs and symptoms: deviation in head/neck posture; involuntary neck movements resulting in turn, tilt, and/or shoulder elevation; and neck pain.[2, 6]

Besides the clinical problems of involuntary abnormal postures and repetitive movements frequently associated with pain, patients with CD present with a wide range of social disabilities and impairments in health-related quality of life (HRQOL).[3] HRQOL is defined as the subjective perception of the impact of health status, including disease and treatment, on physical, psychological, and social functioning and well-being.

Recognizing the critical link between physical and psychological health allows a more holistic approach to patient care. By measuring HRQOL, we can ascertain the effects of a disease on individuals from the patient perspective and, thereafter, to some extent, be able to judge the

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

benefit of therapeutic interventions. With CD, several physical and emotional factors such as reduced mobility, pain, low self-esteem, embarrassment, depression, anxiety, and limited social interaction may be present. Unlike other forms of focal dystonia, pain is a predominant feature of CD and is reported in up to 75% of patients.[7] A study conducted by Degirmenci *et al*[8] evaluated anxiety and depression in dystonia patients using the Hospital Anxiety Depression (HAD) scale and assessed quality of life using the SF-36 Health Survey (SF-36), a generic HRQOL measure. Mean Anxiety and Depression subscales scores were higher in patients with dystonia when compared with the control group. Moreover, patients with dystonia had lower SF-36 scores for all domains when compared with controls.

AbobotulinumtoxinA (Dysport) 500 U was compared with placebo in an international, multicenter, double-blinded, randomized trial.[9] The study was classified as class I study according to the American Academy of Neurology (AAN) Classification of Quality of Evidence for Clinical Trials.[1] This study used the SF-36, to evaluate treatment benefit with 500 U abobotulinumtoxinA compared with placebo. As a result of the tremendous amount of research conducted using the SF-36 over the past two decades, population norms are available that can facilitate the interpretation of research results across a wide variety of patient populations, putting specific study data into “larger context.”[10] In order to understand the HRQOL impairment unique to CD, SF-36 scores for the study sample were compared with other published scores for populations with various neurological conditions. Specifically, because the HRQOL impairment of Parkinson’s disease and that of multiple sclerosis have been well established,[11] these conditions were deemed appropriate comparisons in evaluating the unique nature of HRQOL impairment due to CD.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Botulinum toxin (BoNT), a treatment with established safety and efficacy, has been recommended as first-line treatment for symptoms of CD.[1, 12] The reported benefits from BoNT are relief from pain, increased range of free movement, and improved resting posture.[13, 14] BoNT injections typically offer temporary relief and the symptoms gradually return. For CD, as for most other neurological disorders, more data exist regarding the efficacy of the Botulinum toxin type A (BoNT-A) compared with type B. BoNT-A has been shown to reduce both symptom severity and pain.[13] Currently, there are three major commercially available preparations of type A toxins: abobotulinumtoxinA (Dysport® [Ipsen Biopharm Ltd, Wrexham, UK]), onabotulinumtoxinA (Botox® [Allergan, Inc.; Irvine, CA]), and incobotulinumtoxinA (Xeomin® [Merz Pharmaceuticals GmbH; Frankfurt am Main, Germany). The potency Units of abobotulinumtoxinA are specific to the preparation and assay method utilized. They are not interchangeable with other preparations of botulinum toxin products and, therefore, units of biological activity of one BoNT product cannot be compared to or converted into units of any other botulinum toxin products assessed with any other specific assay method. Due to this, information regarding the specific benefits of a particular BoNT-A preparation and the impact on HRQOL would be valuable.

The objectives of this article are to describe the HRQOL burden of CD, as measured at baseline in a previously reported randomized, double-blind, placebo-controlled pivotal clinical study,[9] as well as report on the HRQOL and treatment benefits of abobotulinumtoxinA.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

MATERIALS AND METHODS

Study design

The study design has been reported previously.[9] Briefly, an international, multicenter, double-blind, randomized, placebo-controlled trial was conducted to evaluate the safety and efficacy of a single injection of abobotulinumtoxinA for the treatment of CD. To be eligible for study entry, patients had to have a diagnosis of CD with symptoms for at least 18 months, as well as the following Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) scores: a total score of at least 30; a Severity domain score of at least 15; and a Disability domain score of at least 3. The TWSTRS is an assessment of CD that includes a total CD rating score and three domain scores (Torticollis Severity, Disability, and Pain).

Key exclusion criteria included treatment with BoNT-A or BoNT-B within 16 weeks of enrollment, any disease of the neuromuscular junction, previous phenol injection to the neck muscles, myotomy or denervation surgery in the neck/shoulder region, cervical contracture, suspected secondary non-responsiveness or a history of poor response to BoNT-A, pure anterocollis or retrocollis, symptom remission at screening, symptoms that could interfere with TWSTRS scoring, or BoNT-A neutralizing antibodies.

Patients received an intramuscular injection of either 500 U abobotulinumtoxinA or placebo in a 1:1 ratio. Study medication was administered by intramuscular injection into two, three, or four clinically indicated neck muscles during a single dosing session at baseline.

Assessments

Assessments have been described previously.[9] The TWSTRS was determined at week 0 (baseline), at week 4 (primary), and at weeks 8 and 12 (posttreatment) by investigators trained in TWSTRS scoring. Pain was evaluated with the Pain domain of the TWSTRS and a self-reported

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

visual analog scale (VAS) assessing pain in the past 24 hours. Participants completed the pain VAS at baseline and week 4.

HRQOL was assessed using the SF-36, version 1.0. The SF-36 is a commonly used health profile that contains 36 items and includes multi-item domains to measure health status across eight dimensions: Physical Functioning, Role Limitations due to Physical Health Problems (Role Physical), Bodily Pain, Social Functioning, General Mental Health, Role Limitations due to Emotional Problems (Role Emotional), Vitality, and General Health Perceptions. Responses to questions within each domain are summed and transformed to a scale ranging from 0 to 100, with higher scores suggesting better functioning. Participants completed the SF-36 at week 0 (baseline; prior to dosing) and at week 8 (posttreatment). SF-36 scores were generated according to published algorithms.[10]

Safety assessments included incidence of treatment-emergent adverse events (TEAEs), electrocardiogram (ECG), neurological and physical examinations, and vital signs.

Statistical analyses

Burden of cervical dystonia

Population norms are available that can facilitate the interpretation of research results across a wide variety of patient populations.[10] The unique burden of illness associated with CD was assessed by comparing patients' baseline domain scores to age- and gender-adjusted SF-36 domain scores for the US population norms.[10] The 95% confidence interval was computed for the baseline SF-36 scores relative to the age- and gender-adjusted US population norms.

Baseline SF-36 scores for the study sample were compared with other published scores for populations with Parkinson's disease and multiple sclerosis. The patients with Parkinson's disease were patients attending six neurology centers in the US, with a mix of Hoehn and Yahr

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

scores representing early-, middle-, and late-stage disease.[15] The patients with multiple sclerosis were part of a longitudinal study in Ontario, Canada.[16]

Treatment effect analysis

Continuous primary (TWSTRS) and secondary variables (SF-36 domains) were analyzed using analysis of covariance (ANCOVA), controlling for treatment group, baseline score (where appropriate), treatment history (i.e., previous treatment with BoNT), and center.

Pearson correlation coefficients were calculated among the eight SF-36 domain scores and the week 4 and week 8 TWSTRS domain scores and total score by treatment group.

A responder was defined as a patient with a decrease in TWSTRS total score of at least 30% (at week 4) compared with baseline.[9] Mean SF-36 scores by TWSTRS responder status were evaluated using a *t* test. Safety assessments were based on the safety population, which included all patients who received at least one dose of study medication. Safety variables were summarised by descriptive statistics.

RESULTS

Patient disposition and demographics

All 116 randomized patients (abobotulinumtoxinA n = 55; placebo n = 61) received at least one dose of study medication and were included in the intent-to-treat (ITT) population. The mean (standard deviation [SD]) age was similar across treatment groups: 51.9 (13.4) years for the abobotulinumtoxinA group and 53.9 (12.5) years for placebo group. Similarly, both treatment groups were predominantly female (67.0% in the abobotulinumtoxinA group and 62.0% in the placebo group). All other patient demographics and baseline characteristics were similar between

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

treatment groups.[9] A total of 33 patients discontinued the study due to insufficient response, consent withdrawn, lost to follow up or other reasons.

Comparison with US population and other neurological conditions

Baseline SF-36 scores for the patients with CD were lower (worse) than US population normative values[10] 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). For example, upon study entry, patients with CD reported Role Physical impairments that were approximately 32% lower (worse) than the age- and gender-adjusted US norm (domain score of 52.4 among patients with CD vs. 76.6 for the US norm, $P < 0.05$). Similarly, patients with CD reported experiencing significantly more pain than the age- and gender-adjusted US norm upon study entry, with Bodily Pain scores that were 33% lower (worse) for patients with CD than the US norms (47.7 vs. 71.3, $P < 0.05$).

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table 1. Mean SF-36 scores for the normative US population and patients with cervical dystonia, Parkinson's disease, or multiple sclerosis

SF-36 Domain	Cervical dystonia study sample (n = 116) Mean (SD)*	US normative sample† Mean	Parkinson's disease‡ (n = 150) Mean	Multiple sclerosis§ (n = 300) Mean (SD)
Physical Functioning	67.2 (22.2)	79.7	50.4	40.5 (30.2)
Role Physical	52.4 (29.5)	76.6	31.4	24.0 (36.8)
Bodily Pain	47.7 (21.6)	71.3	59.9	59.5 (27.2)
General Health	61.4 (19.7)	68.6	51.5	51.7 (24.1)
Vitality	50.6 (18.1)	60.1	46.1	35.1 (21.7)
Social Functioning	64.8 (24.6)	82.0	62.6	57.3 (27.6)
Role Emotional	68.8 (27.1)	80.6	49.0	56.1 (44.9)
Mental Health	64.1 (18.4)	74.8	67.1	67.1 (20.8)

* Baseline domain scores significantly lower than age- and gender-adjusted general US population norm for all domains ($P < 0.05$).

† Age- and gender-adjusted US norms.[10]

‡ Damiano *et al.*[15]

§ Hopman *et al.*[16]

SD, standard deviation; SF-36, SF-36 Health Survey; US, United States.

For peer review only

Like individuals with CD, patients with Parkinson's disease and multiple sclerosis report substantial impairments in HRQOL relative to US norms (Table 1). However, each of these conditions presents with a unique profile of HRQOL impairment. Patients with CD report the greatest limitation in the Bodily Pain domain, whereas patients with Parkinson's disease report the greatest impairments in the Role Physical domain, and patients with multiple sclerosis report the greatest impairments in the Vitality domain (Table 2). Each of these neurological conditions impairs patients physically, yet the presentation of the disease manifests itself differently in terms of HRQOL impairment.

Table 2. Three most impaired SF-36 domains for patients with cervical dystonia, Parkinson's disease, or multiple sclerosis

Cervical dystonia	Parkinson's disease	Multiple sclerosis
Bodily Pain	Role Physical	Vitality
Vitality	Vitality	Physical Functioning
Role Physical	Physical Functioning	General Health

Treatment effect

Improvements from baseline to week 8 were observed for all eight SF-36 domains in the abobotulinumtoxinA group, whereas the placebo group showed some decline in Physical Functioning and little to no change in other SF-36 domains (Figure 1). The largest improvements occurred in the Role Physical and Bodily Pain domains.

Patients treated with abobotulinumtoxinA reported significantly greater improvements than placebo patients from baseline to week 8 in five of the eight SF-36 domains (Figure 1). Specifically, patients treated with abobotulinumtoxinA reported significantly greater

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

improvements in the Physical Functioning, Role Physical, Bodily Pain, General Health, and Role Emotional domains ($P \leq 0.03$ for all) than patients treated with placebo.

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 Function, Role Physical, and Bodily Pain domain scores. Across treatment groups and time periods, the correlations between TWSTRS domain and total scores were consistently significantly correlated with the Role Physical and Bodily Pain domain scores. The correlations ranged from –0.29 to –0.44 at week 4. Week 8 correlations were similar: –0.33 to –0.53.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table 3. Correlations between the week 8 SF-36 Physical Function, Role Physical, and Bodily Pain domain scores with the TWSTRS at week 4 by treatment group

	Week 4: correlation; *P*-value; n							
	Total		Disability		Severity		Pain	
	Dysport	Placebo	Dysport	Placebo	Dysport	Placebo	Dysport	Placebo
Physical Function	–0.34; 0.0278; 43	–0.19; 0.2801; 36	–0.34; 0.0257; 44	–0.03; 0.8978; 36	–0.35; 0.0223; 43	–0.31; 0.0694; 36	–0.13; 0.3969; 44	–0.10; 0.55; 36
Role Physical	–0.34; 0.0295; 42	–0.34; 0.0422; 36	–0.34; 0.0270; 43	–0.27; 0.1069; 36	–0.35; 0.0229; 42	–0.37; 0.0255; 36	–0.12; 0.4265; 43	–0.18; 0.2811; 36
Bodily Pain	–0.41; 0.00080; 40	–0.35; 0.0345; 36	–0.31; 0.0523; 41	–0.29; 0.0871; 36	–0.20; 0.2133; 40	–0.44; 0.0076; 36	–0.53; 0.0003; 41	–0.14; 0.4296; 36

Note: Correlations are negative as the TWSTRS and SF-36 are scored in opposite directions.

SF-36, SF-36 Health Survey; TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Improvements from baseline to week 8 were observed for most of the SF-36 domains in the TWSTRS responder group, whereas the non-responder group showed little to no change in SF-36 domains (Table 4). The largest improvements occurred in the Role Physical and Bodily Pain domains. 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 4). Specifically, responders reported significantly greater improvements in Physical Functioning, Role Physical, Bodily Pain, Vitality, and Social Functioning ($P \leq 0.03$ for all) than patients considered non-responsive to treatment.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table 4. Mean change in SF-36 scores by TWSTRS response status

	TWSTRS Responder Status			
	Mean Change in SF-36			
SF-36 Domain	TWSTRS Non-responder (n = 47)	TWSTRS responder (n = 36)	Difference (responder – non-responder)	*P*-value
Physical Functioning	–0.6	9.1	9.7	0.0091
Role Physical	3.5	19.3	15.8	0.0020
Bodily Pain	1.8	17.6	15.8	0.0005
General Health	–1.5	3.3	4.8	0.0552
Vitality	0.8	11.1	10.3	0.0067
Social Functioning	2.8	14.3	11.5	0.0251
Role Emotional	2.8	12.5	9.7	0.0665
Mental Health	3.9	8.5	4.6	0.1691

SF-36, SF-36 Health Survey.

For peer review only

DISCUSSION

Although CD is usually non-progressive and limited to involuntary muscle spasms of the neck, its detrimental effect on health status is comparable to progressive and generalized conditions clinically perceived to be of greater severity (such as multiple sclerosis and

Parkinson's disease). Camfield[17] conducted a survey of 150 patients with CD that included the SF-36 and the Beck anxiety and depression indexes. Patients with CD had lower scores in all eight SF-36 domains compared with controls in the United Kingdom (UK), particularly in the Role Physical (41.6 vs. 85.8), Bodily Pain (54.6 vs. 81.5), and General Health (46.2 vs. 73.5) domains. Domain scores were comparable to data from patients with mild to moderate multiple sclerosis and moderate epilepsy. Our results are similar to those of Camfield[17], and support the implication that CD has a significant impact on health status that is comparable with other neurological disorders of high morbidity. CD appears to have a disproportionate negative impact on patients' physical role limitation, despite their good physical functioning. One possible explanation is that pain limits such activities. Another possibility is that patients with CD consciously limit activities that make their dystonia visible to others to avoid mockery.[18]

A few studies have investigated the impact of CD on HRQOL and factors modifying a patient's ability to cope with this disease. Slawek *et al*[19] conducted an HRQOL survey study in 101 patients previously treated with BoNT-A using the TWSTRS, a pain VAS (0-100%), the SF-36, and the Montgomery-Åsberg Depression Rating Scale (MADRS). The patients' baseline SF-36 scores were worse than those of healthy controls in all eight SF-36 domains. Improvements were observed 4 weeks after the single BoNT-A injections in all SF-36 domains, and in the VAS, TWSTRS, and MADRS scores. The TWSTRS results did not correlate with any of the SF-36 domains. Longer treatment with BoNT-A was associated with better scores. Hefter *et al*[20, 21] conducted a prospective, open-label study of abobotulinumtoxinA in 516 de novo CD patients using the TWSTRS, the Craniocervical Dystonia Questionnaire (CDQ-24), patient diaries, and a global assessment of pain. In contrast with the SF-36, which is a general measure of HRQOL, the CDQ-24 is a disease-specific questionnaire that evaluates HRQOL in patients with CD.[22]

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

The CDQ-24 has five subscales: Stigma, Emotional Wellbeing, Pain, Activities of Daily Living, and Social/Family Life. At week 4, significant improvements were observed in CDQ-24 total and subscale scores that were sustained up to week 12. Significant reductions in patient diary item scores for activities of daily living, pain, and pain duration at week 4 and 12 were observed. Sixty-six percent of patients reported pain relief (less or no pain) at week 4 and 74% at week 12. Improvements in quality of life and pain intensity for up to 12 weeks in patients with CD were observed after treatment with abobotulinumtoxinA.

Likewise, in our findings, patients treated with abobotulinumtoxinA reported significantly greater improvements in TWSTRS total mean scores at weeks 4, 8, and 12 ($P \leq 0.019$) compared with placebo.[9] Improvements from baseline to week 8 were observed for all eight SF-36 domains in the abobotulinumtoxinA group, whereas the placebo group either stayed the same or became worse (with a decline in physical functioning). In this study, the SF-36 results did correlate with the TWSTRS for the Role Physical and Bodily Pain domains across treatment groups and time periods. AbobotulinumtoxinA was well tolerated in this study, as previously published.[9]

CONCLUSION

CD has a marked impact on HRQOL for patients. Patients with CD report significantly worse functioning than that of their peers (age- and gender-adjusted US normative values). Results from this prospective, randomized controlled trial support the ability of abobotulinumtoxinA 500 U to provide efficacy in reducing motor symptoms in conjunction with significant improvements in HRQOL for patients.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

ACKNOWLEDGMENTS

All authors were involved in the analysis and interpretation of the data, manuscript writing, review and critique. All authors approved the final manuscript. The authors wish to acknowledge Jean Hubble, MD, formerly of Ipsen Biopharmaceuticals, Inc., for her clinical contributions to this paper; and Stephen Chang, PhD, formerly of Ipsen Biopharmaceuticals, Inc., for conduct of the statistical analyses of the trial data reported in this manuscript. Rosemarie Kelly, PhD, consultant to Ipsen, provided critical review of the manuscript.

COMPETING INTERESTS

Chandra Abbott is an employee of Ipsen Biopharmaceuticals, Inc. Margaret Mordin, Catherine Masaquel, and Catherine Copley-Merriman, employees of RTI Health Solutions, were contracted by Ipsen Biopharmaceuticals, Inc. to perform and report on the research described here.

FUNDING

This work was supported by Ipsen Biopharmaceuticals, Inc.

CONTRIBUTORSHIP

All authors meet the ICMJE criteria for authorship.

DATA SHARING

No additional data are available.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

REFERENCES

1. Hallett M, Albanese A, Dressler D, *et al*. Evidence-based review and assessment of botulinum neurotoxin for the treatment of movement disorders. *Toxicon* 2013;**67**:94–114.

2. Geyer HL, Bressman SB. The diagnosis of dystonia. *Lancet Neurol* 2006;**5**:780–90.

3. Pekmezovic T, Svetel M, Ivanovic N, *et al*. Quality of life in patients with focal dystonia. *Clin Neurol Neurosurg* 2009;**111**:161–64.

4. Van Zandijcke M. Cervical dystonia (spasmodic torticollis). Some aspects of the natural history. *Acta Neurol Belg* 1995;**95**:210–15.

5. Kutvonen O, Dastidar P, Nurmikko T. Pain in spasmodic torticollis. *Pain* 1997;**69**:279–86.

6. Chan J, Brin MF, Fahn S. Idiopathic cervical dystonia: clinical characteristics. *Mov Disord* 1991;**6**:119–26.

7. Ben-Shlomo Y, Camfield L, Warner T. What are the determinants of quality of life in people with cervical dystonia? *J Neurol Neurosurg Psychiatry* 2002;**72**:608–14.

8. Degirmenci Y, Oyekcin DG, Bakar C, *et al*. Anxiety and depression in primary and secondary dystonia: A burden on health related quality of life. *Neurology, Psychiatry, and Brain Research* 2013;**19**:80-5.

9. Truong D, Brodsky, Lew M, *et al*. Long-term efficacy and safety of botulinum toxin type A (Dysport) in cervical dystonia. *Parkinsonism Relat Disord* 2010;**16**:316–23.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

10. Ware JE, Snow KK, Kosinski M, *et al*. SF-36 Health Survey: manual and interpretation guide. Boston: The Health Institute, New England Medical Center, 1993.

11. Welsh M. Parkinson's disease and quality of life: issues and challenges beyond motor symptoms. *Neurol Clin* 2004;**22**:S141–8.

12. Simpson DM, Blitzer A, Brashear A, *et al*. Assessment: botulinum neurotoxin for the treatment of movement disorders (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2008;**70**:1699–706.

13. Costa J, Espirito-Santo C, Borges A, *et al*. Botulinum toxin type A therapy for cervical dystonia. *Cochrane Database Syst Rev* 2005;CD003633.

14. Jankovic J, Brin MF. Therapeutic uses of botulinum toxin. *N Engl J Med* 1991;**324**:1186–94.

15. Damiano AM, McGrath MM, Willian MK, *et al*. Evaluation of a measurement strategy for Parkinson's disease: assessing patient health-related quality of life. *Qual Life Res* 2000;**9**:87–100.

16. Hopman W, Coo H, Edgar C, *et al*., Factors Associated with Health-Related Quality of Life in Multiple Sclerosis. *Can J Neurol Sci* 2007;**34**:160–6.

17. Camfield L. Quality of life in cervical dystonia. *Mov Disord* 2000;**15**(suppl).

18. Camfield L, Ben-Shlomo Y, Warner TT; Epidemiological Study of Dystonia in Europe Collaborative Group. Impact of cervical dystonia on quality of life. *Mov Disord* 2002;**17**:838–45.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

19. Slawek J, Friedman A, Potulska A, *et al*. Factors affecting the health-related quality of life of patients with cervical dystonia and the impact of botulinum toxin type A injections. *Funct Neurol* 2007;**22**:95–100.

20. Hefter H, Benecke R, Erbguth F, *et al*. An open-label cohort study of the improvement of quality of life and pain in de novo cervical dystonia patients after injections with 500 U botulinum toxin A (Dysport). *BMJ Open* 2013;**3**:e001853.doi:10.1136/bmjopen-2012-001853.

21. Hefter H, Kupsch A, Mungersdorf M, *et al*; on behalf of the Dysport Cervical Dystonia Study Group. A botulinum toxin A treatment algorithm for de novo management of torticollis and laterocollis. *BMJ Open* 2011;**2**:e000196.doi:10.1136/bmjopen-2011-000196.

22. Müller J, Wissel J, Kemmler G, *et al*. Craniocervical dystonia questionnaire (CDQ-24): development and validation of a disease-specific quality of life instrument. *J Neurol Neurosurg Psychiatry* 2004;**75**:749–53.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

FIGURE LEGEND

Figure 1. Mean (SE) change in SF-36 scores at week 8

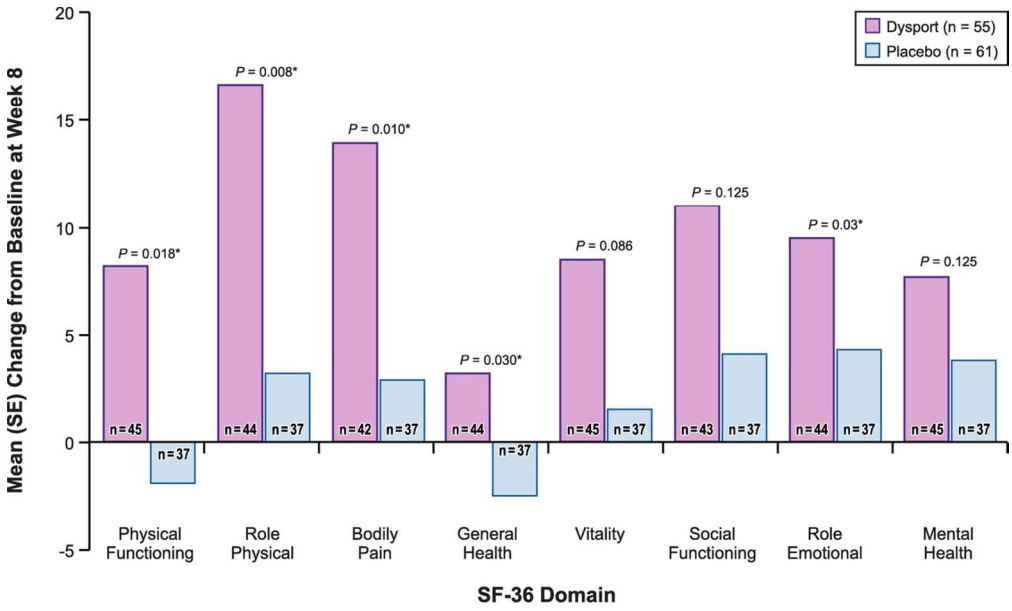
* $P < 0.05$.

Note: Positive changes in score indicate improvement.

SE, standard error; SF-36, SF-36 Health Survey.

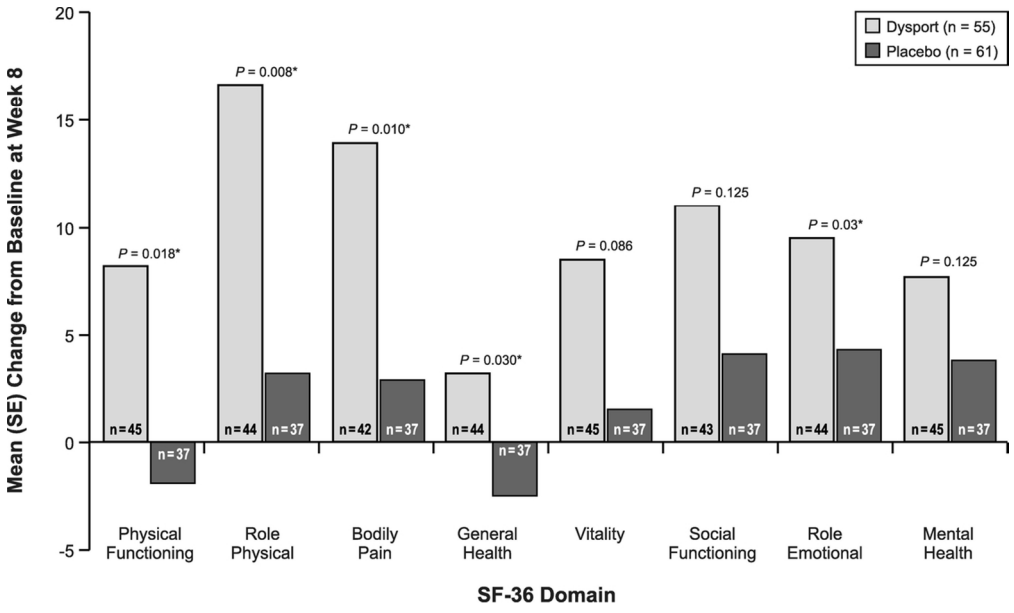
For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml



111x66mm (300 x 300 DPI)

review only



111x66mm (300 x 300 DPI)

review only

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2014-005150.R1
Article Type:	Research
Date Submitted by the Author:	20-Aug-2014
Complete List of Authors:	Mordin, Margaret; RTI Health Solutions, Market Access & Outcomes Strategy Masaquel, Catherine; RTI Health Solutions, Market Access & Outcomes Strategy Coleman Abbott, Chandra; Ipsen Biopharmaceuticals, Neurology Medical Affairs Copley-Merriman, Catherine; RTI Health Solutions, Market Access & Outomes Strategy
Primary Subject Heading:	Neurology
Secondary Subject Heading:	Qualitative research
Keywords:	Adult neurology < NEUROLOGY, QUALITATIVE RESEARCH, Motor neurone disease < NEUROLOGY

For peer review only

SCHOLARONE™
Manuscripts

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

Margaret Mordin, MS, Market Access and Outcomes Strategy, RTI Health Solutions, Ann Arbor, MI, United States

Catherine Masaquel, MPH, Market Access and Outcomes Strategy, RTI Health Solutions, Ann Arbor, MI, United States

Chandra Abbott, PhD,* Neurology Medical Affairs, Ipsen Biopharmaceuticals, Inc, Basking Ridge, NJ, United States

Catherine Copley-Merriman, MBA, MS, Market Access and Outcomes Strategy, RTI Health Solutions, Ann Arbor, MI, United States

Corresponding Author:

Margaret Mordin

RTI Health Solutions

3005 Boardwalk St., Suite 105

* Former employee of Ipsen Biopharmaceuticals, Inc.

For peer review only

Ann Arbor, MI 48108

Telephone: +1.703.483.9009

Fax: +1.734.213.6169

E-mail: mmordin@rti.org

Key words: cervical dystonia, botulinum toxin type A, Dysport, spasmodic torticollis, health-related quality of life

Word Count (excluding title page, abstract, references, tables, and figure legends): ~3,138

For peer review only

ABSTRACT

Objective: To describe the health-related quality of life (HRQOL) burden of cervical dystonia (CD) and report on the HRQOL and patient perception of treatment benefits of abobotulinumtoxinA (Dysport®).

Design: The safety and efficacy of a single injection of abobotulinumtoxinA for CD treatment were evaluated in a previously reported international, multicenter, double-blind, randomized trial. HRQOL measures were assessed in the trial and have not been previously reported.

Setting: Movement disorder clinics in the United States (US) and Russia.

Participants: Patients had to have a diagnosis of CD with symptoms for at least 18 months, as well as a total Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) score of at least 30; a Severity domain score of at least 15; and a Disability domain score of at least 3. Key exclusion criteria included treatment with botulinum toxin type A (BoNT-A) or botulinum toxin type B (BoNT-B) within 16 weeks of enrollment.

Interventions: Patients were randomized to receive either 500 U abobotulinumtoxinA (n = 55) or placebo (n = 61).

Primary and secondary outcome measures: Efficacy assessments included TWSTRS total (primary endpoint) and subscale scores, a pain visual analog scale, and HRQOL assessed by the SF-36 Health Survey (SF-36) (secondary endpoint).

Results: Patients with CD reported significantly greater impairment for all SF-36 domains relative to US norms. Patients treated with abobotulinumtoxinA reported significantly greater improvements in Physical Functioning, Role Physical, Bodily Pain,

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

General Health, and Role Emotional domains than placebo patients ($P \leq 0.03$ for all). The TWSTRS was significantly correlated with Physical Functioning, Role Physical, and Bodily Pain scores, for those on active treatment.

Conclusions: CD has a marked impact on HRQOL. Treatment with a single abobotulinumtoxinA injection results in significant improvement in patients' HRQOL.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

ARTICLE SUMMARY

Strengths and limitations of this study

- The efficacy and safety of a single injection of abobotulinumtoxinA for CD treatment were evaluated in an international, multicenter, randomized double-blind trial.
- This paper presents previously unreported findings of health-related quality of life assessed during the international, multicenter, randomized double-blind trial of abobotulinumtoxinA.
- The size of this study was small; therefore, 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.

For peer review only

INTRODUCTION

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] Cervical dystonia (CD), the most common form of focal dystonia, is characterized by sustained involuntary muscle contraction and/or twitching of cervical musculature resulting in abnormal postures and repetitive movements of the head.[2] Depending on the muscles involved, the following head positions, or combination of head positions, may occur: torticollis (rotation), laterocollis (tilting), anterocollis (flexion), and retrocollis (extension).[3] CD may be accompanied by pulling or stiffness, pain, and sensory symptoms in the affected area.[4] The diagnosis of CD is based on clinical signs and symptoms: deviation in head/neck posture; involuntary neck movements resulting in turn, tilt, and/or shoulder elevation; and neck pain.[3, 5]

Besides the clinical problems of involuntary abnormal postures and repetitive movements frequently associated with pain, patients with CD present with a wide range of social disabilities and impairments in health-related quality of life (HRQOL).[6] HRQOL is defined as the subjective perception of the impact of health status, including

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

disease and treatment, on physical, psychological, and social functioning and well-being.

Recognizing the critical link between physical and psychological health allows a more holistic approach to patient care. By measuring HRQOL, we can ascertain the effects of a disease on individuals from the patient perspective and, thereafter, to some extent, be able to judge the benefit of therapeutic interventions. With CD, several physical and emotional factors such as reduced mobility, pain, low self-esteem, embarrassment, depression, anxiety, and limited social interaction may be present. Pain is a predominant feature of CD and is reported in up to 75% of patients [7] and is associated with reduced HRQOL. A study conducted by Degirmenci *et al*[8] evaluated anxiety and depression in dystonia patients using the Hospital Anxiety Depression (HAD) scale and assessed quality of life using the SF-36 Health Survey (SF-36), a general measure widely used to assess HRQOL. Mean Anxiety and Depression subscale scores were higher in patients with dystonia when compared with the control group. Moreover, patients with dystonia had worse (lower) SF-36 scores for all domains when compared with controls.

AbobotulinumtoxinA (Dysport) 500 U was compared with placebo in two multicenter, double-blinded, randomized trials: one international[9] and one in the United States (US).[10] The international study included the SF-36 to evaluate treatment benefit with 500 U abobotulinumtoxinA compared with placebo as a secondary endpoint. As a result of the tremendous amount of research conducted using the SF-36 over the past two decades, population norms are available that can facilitate the interpretation of research results across a wide variety of patient populations, putting

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

specific study data into “larger context.”[11] In order to understand the HRQOL impairment unique to CD, SF-36 scores for the study sample were compared with other published scores for populations with various neurological conditions, in particular Parkinson’s disease and multiple sclerosis; like CD, these conditions are generally progressive and affect motor and non-motor function. Specifically, because the HRQOL impairment of Parkinson’s disease and that of multiple sclerosis have been well established,[12] these conditions were deemed appropriate comparisons in evaluating the unique nature of HRQOL impairment due to CD.

Botulinum toxin (BoNT), a treatment with established safety and efficacy, has been recommended as first-line treatment for symptoms of CD.[13, 14] No botulinum toxin is indicated for improving HRQOL in CD. The reported benefits from BoNT are relief from pain, increased range of free movement, and improved resting posture.[15, 16] BoNT injections typically offer temporary relief, and the symptoms gradually return. For CD, as for most other neurological disorders, more data exist regarding the efficacy of the Botulinum toxin type A (BoNT-A) compared with type B. BoNT-A and BoNT-B have been shown to reduce both symptom severity and pain.[15] Currently, there are three major commercially available preparations of type A toxins: abobotulinumtoxinA (Dysport® [Ipsen Biopharm Ltd, Wrexham, UK]), onabotulinumtoxinA (Botox® [Allergan, Inc.; Irvine, CA]), and incobotulinumtoxinA (Xeomin® [Merz Pharmaceuticals GmbH; Frankfurt am Main, Germany). The potency units of abobotulinumtoxinA are specific to the preparation and assay method utilized. They are not interchangeable with other preparations of botulinum toxin products and, therefore, units of biological activity of one BoNT product cannot be compared to or converted into units of any other botulinum

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

toxin products. Accordingly, information regarding the specific benefits of a particular BoNT-A preparation and the impact on HRQOL would be valuable.

The objectives of this article are to describe the HRQOL burden of CD, as measured at baseline in a previously reported randomized, double-blind, placebo-controlled, pivotal clinical study,[9] as well as report on the HRQOL and treatment benefits of abobotulinumtoxinA.

MATERIALS AND METHODS

Study design

The study design has been reported previously.[9] An international, multicenter (movement disorder clinics in the US [n = 16] and Russia [n = 4]), double-blind, randomized, placebo-controlled trial was conducted to evaluate the safety and efficacy of a single injection of abobotulinumtoxinA for the treatment of CD. To be eligible for study entry, patients had to have a diagnosis of CD with symptoms for at least 18 months, as well as the following baseline Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) scores: a total score of at least 30; a Severity domain score of at least 15; and a Disability domain score of at least 3. The TWSTRS is an assessment of CD that includes a total CD rating score and three domain scores (Torticollis Severity, Disability, and Pain).

Key exclusion criteria were standard for efficacy trials of BoNT and included treatment with BoNT-A or BoNT-B within 16 weeks of enrollment, any disease of the neuromuscular junction, previous phenol injection to the neck muscles, myotomy or denervation surgery in the neck/shoulder region, cervical contracture, suspected

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

secondary non-responsiveness or a history of poor response to BoNT-A, pure anterocollis or retrocollis, symptom remission at screening, symptoms that could interfere with TWSTRS scoring, or BoNT-A neutralizing antibodies.

A total of 120 patients were to be recruited in the study to allow for 47 patients per treatment group to be evaluable on the primary efficacy endpoint (TWSTRS).[9] Patients were randomized using a pregenerated randomization code in a 1:1 ratio to receive an intramuscular injection of either 500 U abobotulinumtoxinA or placebo. Study medication was administered in a double-blind manner by intramuscular injection into two, three, or four clinically indicated neck muscles during a single dosing session at baseline. 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.

Assessments

Assessments have been described previously.[9] The TWSTRS was determined at week 0 (baseline), at week 4 (primary), and at weeks 8 and 12 (posttreatment) by investigators trained in TWSTRS scoring. Pain was evaluated with the Pain domain of the TWSTRS and a self-reported visual analog scale (VAS) assessing pain in the past 24 hours. Participants completed the pain VAS at baseline and week 4.

HRQOL was assessed using the SF-36, version 1.0. The SF-36 is a commonly used health profile that contains 36 items and includes multi-item domains to measure health status across eight dimensions: Physical Functioning, Role Limitations due to Physical Health Problems (Role Physical), Bodily Pain, Social Functioning, General Mental Health, Role Limitations due to Emotional Problems (Role Emotional), Vitality,

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

and General Health Perceptions. Responses to questions within each domain are summed and transformed to a scale ranging from 0 to 100, with higher scores suggesting better functioning. Participants completed the SF-36 at week 0 (baseline; prior to dosing) and at week 8 (posttreatment). SF-36 scores were generated according to published algorithms.[11]

Safety assessments included incidence of treatment-emergent adverse events, electrocardiogram, neurological and physical examinations, and vital signs.

Statistical analyses

Burden of cervical dystonia

Population norms are available for the SF-36 that can facilitate the interpretation of research results across a wide variety of patient populations.[11] The unique burden of illness associated with CD was assessed by comparing patients' baseline domain scores to age- and gender-adjusted SF-36 domain scores for the US population norms.[11] The 95% confidence interval was computed for the baseline SF-36 scores relative to the age- and gender-adjusted US population norms.

For comparisons relative to other neurologic conditions, baseline SF-36 scores for the study sample were compared with other published scores for populations with Parkinson's disease and multiple sclerosis. The patients with Parkinson's disease were patients attending six neurology centers in the US, with a mix of Hoehn and Yahr scores representing early-, middle-, and late-stage disease.[17] The patients with multiple sclerosis were part of a longitudinal study in Ontario, Canada.[18]

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Treatment effect analysis

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.

Continuous primary (TWSTRS) and secondary variables (SF-36 domains) were analyzed using analysis of covariance (ANCOVA), controlling for treatment group, baseline score (where appropriate), treatment history (i.e., previous treatment with BoNT), and center.

Pearson correlation coefficients were calculated among the eight week 8 SF-36 domain scores and the week 4 and week 8 TWSTRS domain scores and total score by treatment group.

A responder was defined, a priori, as a patient with a decrease in TWSTRS total score of at least 30% (at week 4) compared with baseline.[9] Mean SF-36 scores by TWSTRS responder status were evaluated using a *t* test. Safety assessments were based on the safety population, which included all patients who received at least one dose of study medication. Safety variables were summarised by descriptive statistics. Safety results have been reported previously.[9]

RESULTS

Patient disposition and demographics

All 116 randomized patients (abobotulinumtoxinA n = 55; placebo n = 61) received at least one dose of study medication and were included in the intent-to-treat population. The mean (standard deviation [SD]) age was similar across treatment

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

groups: 51.9 (13.4) years for the abobotulinumtoxinA group and 53.9 (12.5) years for placebo group. Similarly, both treatment groups were predominantly female (67.0% in the abobotulinumtoxinA group and 62.0% in the placebo group). All other patient demographics and baseline characteristics were similar between treatment groups.[9] A total of 33 patients discontinued the study because of insufficient response, withdrawal of consent, loss to follow-up, or other reasons (Figure 1).

Comparison with US population and other neurological conditions

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). For example, upon study entry, patients with CD reported Role Physical impairments that were approximately 32% lower (worse) than the age- and gender-adjusted US norm (domain score of 52.4 among patients with CD vs. 76.6 for the US norm, $P < 0.05$). Similarly, patients with CD reported experiencing significantly more pain than the age- and gender-adjusted US norm upon study entry, with Bodily Pain scores that were 23 percentage points lower (worse) for patients with CD than the US norms (47.7 vs. 71.3, $P < 0.05$).

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table 1. Mean SF-36 scores for the normative US population and patients with cervical dystonia, Parkinson's disease, or multiple sclerosis

SF-36 Domain	Cervical dystonia study sample (n = 116) Mean (SD)*	US normative sample† Mean	Parkinson's disease‡ (n = 150) Mean	Multiple sclerosis§ (n = 300) Mean (SD)
Physical Functioning	67.2 (22.2)	79.7	50.4	40.5 (30.2)
Role Physical	52.4 (29.5)	76.6	31.4	24.0 (36.8)
Bodily Pain	47.7 (21.6)	71.3	59.9	59.5 (27.2)
General Health	61.4 (19.7)	68.6	51.5	51.7 (24.1)
Vitality	50.6 (18.1)	60.1	46.1	35.1 (21.7)
Social Functioning	64.8 (24.6)	82.0	62.6	57.3 (27.6)
Role Emotional	68.8 (27.1)	80.6	49.0	56.1 (44.9)
Mental Health	64.1 (18.4)	74.8	67.1	67.1 (20.8)

* Baseline domain scores significantly lower than age- and gender-adjusted general US population norm for all domains ($P < 0.05$).

† Age- and gender-adjusted US norms.[11]

‡ Damiano *et al.*[17]

§ Hopman *et al.*[18]

SD, standard deviation; SF-36, SF-36 Health Survey; US, United States.

For peer review only

Like individuals with CD, patients with Parkinson's disease and multiple sclerosis report substantial impairments in HRQOL relative to US norms (Table 1). However, each of these neurologic conditions presents with a unique profile of HRQOL impairment. Patients with CD report the greatest limitation in the Bodily Pain domain, whereas patients with Parkinson's disease report the greatest impairments in the Role Physical domain, and patients with multiple sclerosis report the greatest impairments in the Vitality domain. Each of these neurological conditions impairs patients physically, yet the presentation of the disease manifests itself differently in terms of HRQOL impairment.

Treatment effect

Improvements from baseline to week 8 were observed for all eight SF-36 domains in the abobotulinumtoxinA group, whereas the placebo group showed some decline in Physical Functioning and little to no change in other SF-36 domains (Table 2; Figure 2). The largest improvements occurred in the Role Physical and Bodily Pain domains.

Patients treated with abobotulinumtoxinA reported significantly greater improvements than placebo patients from baseline to week 8 in five of the eight SF-36 domains (Table 2; Figure 2). Specifically, patients treated with abobotulinumtoxinA reported significantly greater improvements in the Physical Functioning, Role Physical, Bodily Pain, General Health, and Role Emotional domains ($P \leq 0.03$ for all) than patients treated with placebo.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table 2. Mean (SE) SF-36 scores by treatment group: baseline and week 8

	AbobotulinumtoxinA				Placebo			
SF-36 Domain	N	Baseline mean (SD)	Week 8 mean (SD)	Change mean (SD)	N	Baseline mean (SD)	Week 8 mean (SD)	Change mean (SD)	*P* value
Physical Functioning	45	61.9 (20.0)	70.1 (20.1)	8.2 (16.0)	37	68.2 (21.7)	66.4 (23.4)	–1.9 (16.8)	0.018
Role Physical	44	46.3 (28.5)	62.9 (25.1)	16.6 (21.1)	37	50.5 (29.9)	53.7 (25.6)	3.2 (24.0)	0.008
Bodily Pain	42	47.9 (23.0)	61.8 (20.4)	13.9 (19.7)	37	49.0 (19.7)	51.9 (22.0)	2.9 (20.3)	0.010
General Health	44	58.9 (19.4)	62.1 (18.4)	3.2 (11.1)	37	62.2 (19.6)	59.7 (21.1)	-2.5 (10.6)	0.030
Vitality	45	47.5 (15.6)	56.0 (16.8)	8.5 (15.0)	37	50.5 (19.5)	52.0 (19.2)	1.5 (17.8)	0.086
Social Functioning	43	62.2 (26.8)	73.3 (22.9)	11.0 (25.8)	37	63.2 (25.0)	67.2 (25.6)	4.1 (15.6)	0.125
Role Emotional	44	71.0 (25.4)	80.5 (21.5)	9.5 (20.9)	37	62.2 (28.0)	66.4 (25.3)	4.3 (26.8)	0.030
Mental Health	45	62.6 (16.3)	70.2 (15.8)	7.7 (14.5)	37	60.1 (20.9)	63.9 (21.0)	3.8 (15.2)	0.125

Note: Comparison between AbobotulinumtoxinA and placebo for change from baseline to week 8 using an ANCOVA model with baseline value as covariate.

ANCOVA, analysis of covariance; SD, standard deviation; SE, standard error; SF-36, SF-36 Health Survey.

For Peer review only

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).

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table 3. Correlations between the week 8 SF-36 scores with the TWSTRS at week 4 by treatment group

	Week 4: correlation; *P* value; n							
	Total		Disability		Severity		Pain	
	Abobotulinum-toxinA	Placebo	Abobotulinum-toxinA	Placebo	Abobotulinum-toxinA	Placebo	Abobotulinum-toxinA	Placebo
Physical Functioning	–0.34; 0.0278; 43	–0.19; 0.2801; 36	–0.34; 0.0257; 44	–0.03; 0.8978; 36	–0.35; 0.0223; 43	–0.31; 0.0694; 36	–0.13; 0.3969; 44	–0.10; 0.55; 36
Role Physical	–0.34; 0.0295; 42	–0.34; 0.0422; 36	–0.34; 0.0270; 43	–0.27; 0.1069; 36	–0.35; 0.0229; 42	–0.37; 0.0255; 36	–0.12; 0.4265; 43	–0.18; 0.2811; 36
Bodily Pain	–0.41; 0.00080; 40	–0.35; 0.0345; 36	–0.31; 0.0523; 41	–0.29; 0.0871; 36	–0.20; 0.2133; 40	–0.44; 0.0076; 36	–0.53; 0.0003; 41	–0.14; 0.4296; 36
General Health	–0.31; 0.0422 42	0.08 0.6521 36	–0.26 0.1459 43	0.16 0.3639 36	–0.43 0.0045 42	0.06 0.7217 36	–0.09 0.5785 43	–0.02 0.9235 36

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

	Week 4: correlation; *P* value; n							
	Total		**Disability**		**Severity**		**Pain**	
	Abobotulinum-toxinA	**Placebo**	**Abobotulinum-toxinA**	**Placebo**	**Abobotulinum-toxinA**	**Placebo**	**Abobotulinum-toxinA**	**Placebo**
Vitality	–0.26	–0.20	–0.25	–0.06	–0.38	–0.14	0.04	–0.27
	0.0983	0.2517	0.0963	0.7272	0.0123	0.4201	0.7860	0.1172
	43	36	44	36	43	36	44	36
Social	–0.25	–0.11	–0.32	0.15	–0.32	–0.08	0.06	–0.31
Functioning	0.1217	0.5206	0.0394	0.3909	0.0437	0.6437	0.7280	0.0683
	41	36	42	36	41	36	42	36
Role	–0.18	–0.14	–0.29	0.01	–0.14	–0.15	–0.01	–0.19
Emotional	0.2877	0.4150	0.0612	0.9460	0.3874	0.3947	0.9383	0.2634
	42	36	43	36	42	36	43	36
Mental	–0.17	0.05	–0.13	0.22	–0.38	0.16	0.14	–0.24
Health	0.2668	0.7815	0.3990	0.1949	0.0128	0.3365	0.3786	0.1502
	43	36	44	36	43	36	44	36

Note: Correlations are negative as the TWSTRS and SF-36 are scored in opposite directions.

SF-36, SF-36 Health Survey; TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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). The largest improvements occurred in the Role Physical and Bodily Pain domains. 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 4). Specifically, responders reported significantly greater improvements in Physical Functioning, Role Physical, Bodily Pain, Vitality, and Social Functioning ($P \leq 0.03$ for all) than patients considered non-responsive to treatment.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table 4. Mean change in SF-36 scores by TWSTRS response status

	TWSTRS Responder Status			
	Mean Change in SF-36			
SF-36 Domain	TWSTRS non-responder (n = 47)	TWSTRS responder (n = 36)	Difference (responder – non-responder)	*P* value
Physical Functioning	–0.6	9.1	9.7	0.0091
Role Physical	3.5	19.3	15.8	0.0020
Bodily Pain	1.8	17.6	15.8	0.0005
General Health	–1.5	3.3	4.8	0.0552
Vitality	0.8	11.1	10.3	0.0067
Social Functioning	2.8	14.3	11.5	0.0251
Role Emotional	2.8	12.5	9.7	0.0665
Mental Health	3.9	8.5	4.6	0.1691

SF-36, SF-36 Health Survey; TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale.

For peer review only

DISCUSSION

Although CD is usually non-progressive and limited to involuntary muscle spasms of the neck, its detrimental effect on health status is comparable to progressive and generalized conditions clinically perceived to be of greater severity (such as multiple sclerosis and Parkinson's disease). Camfield[19] conducted a survey of 150 patients with CD that included the SF-36 and the Beck anxiety and depression indexes.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Patients with CD had lower scores in all eight SF-36 domains compared with controls in the United Kingdom (UK), particularly in the Role Physical (41.6 vs. 85.8), Bodily Pain (54.6 vs. 81.5), and General Health (46.2 vs. 73.5) domains. Domain scores were comparable to data from patients with mild to moderate multiple sclerosis and moderate epilepsy. Our results are similar to those of Camfield[19], in that baseline scores for patients with CD were lower (worse) than for US normative data, particularly for the Role Physical (52.4 vs. 76.6), and Bodily Pain (47.7 vs. 71.3) domains. Our findings support the implication that CD has a significant impact on health status that is comparable with other neurological disorders of high morbidity. CD appears to have a disproportionate negative impact on patients' physical role limitation, despite their good physical functioning. One possible explanation is that pain limits such activities. Another possibility is that patients with CD consciously limit activities that make their dystonia visible to others to avoid mockery.[20]

A few studies have investigated the impact of CD on HRQOL and factors modifying a patient's ability to cope with this disease. Slawek *et al*[21] conducted an HRQOL survey study in 101 patients previously treated with BoNT-A using the TWSTRS, a pain VAS (0-100%), the SF-36, and the Montgomery-Åsberg Depression Rating Scale (MADRS). Patients' baseline SF-36 scores were worse than those of healthy controls in all eight SF-36 domains. Improvements were observed 4 weeks after the single BoNT-A injections in all SF-36 domains, and in the VAS, TWSTRS, and MADRS scores. The TWSTRS results did not correlate with any of the SF-36 domains. Longer treatment with BoNT-A was associated with better scores. Hefter *et al*[22, 23] conducted a prospective, open-label study of abobotulinumtoxinA in 516 de novo CD

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

patients using the TWSTRS, the Craniocervical Dystonia Questionnaire (CDQ-24), patient diaries, and a global assessment of pain. In contrast with the SF-36, which is a general measure of HRQOL, the CDQ-24 is a disease-specific questionnaire that evaluates HRQOL in patients with CD.[24] The CDQ-24 has five subscales: Stigma, Emotional Wellbeing, Pain, Activities of Daily Living, and Social/Family Life. At week 4, significant improvements were observed in CDQ-24 total and subscale scores that were sustained up to week 12. Significant reductions in patient diary item scores for activities of daily living, pain, and pain duration at week 4 and 12 were observed. Sixty-six percent of patients reported pain relief (less or no pain) at week 4 and 74% at week 12. Improvements in quality of life and pain intensity for up to 12 weeks in patients with CD were observed after treatment with abobotulinumtoxinA.

Likewise, in our findings, patients treated with abobotulinumtoxinA reported significantly greater improvements in TWSTRS total mean scores at weeks 4, 8, and 12 ($P \leq 0.019$) compared with placebo.[9] Improvements from baseline to week 8 were observed for all eight SF-36 domains in the abobotulinumtoxinA group, whereas the placebo group either stayed the same or became worse (with a decline in physical functioning). In this study, the SF-36 results did correlate with the TWSTRS for the Role Physical and Bodily Pain domains across treatment groups and time periods. AbobotulinumtoxinA was well tolerated in this study, as previously published.[9]

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 HRQOL. Secondly, the size of this study was small. Studies with a larger sample size

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

are required to demonstrate the outcomes of abobotulinumtoxinA treatment in a study population that is more representative of the general population.

CONCLUSION

CD has a marked impact on HRQOL for patients. Patients with CD report significantly worse functioning than that of their peers (age- and gender-adjusted US normative values). Results from this prospective, randomized controlled trial support the ability of abobotulinumtoxinA 500 U to provide efficacy in reducing motor symptoms in conjunction with significant improvements in HRQOL for patients.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

ACKNOWLEDGMENTS

The authors wish to acknowledge Jean Hubble, MD, formerly of Ipsen Biopharmaceuticals, Inc., for her clinical contributions to this paper; and Stephen Chang, PhD, formerly of Ipsen Biopharmaceuticals, Inc., for conduct of the statistical analyses of the trial data reported in this manuscript. Rosemarie Kelly, PhD, consultant to Ipsen, provided critical review of the manuscript.

FUNDING

This work was supported by Ipsen Biopharmaceuticals, Inc.

AUTHOR CONTRIBUTIONS

All authors were involved in the analysis and interpretation of the data, manuscript writing, review and critique. All authors approved the final manuscript.

COMPETING INTERESTS

Chandra Abbott is a former employee of Ipsen Biopharmaceuticals, Inc. Margaret Mordin, Catherine Masaquel, and Catherine Copley-Merriman, employees of RTI Health Solutions, were contracted by Ipsen Biopharmaceuticals, Inc. to perform and report on the research described here.

DATA SHARING STATEMENT

No additional data available

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

REGISTRATION

The trial is registered at ClinicalTrials.gov, numbers NCT00257660 and NCT00288509.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

FIGURE LEGENDS

Figure 1. Study Flow Diagram

Figure 2. Mean (SE) change in SF-36 scores at week 8

* $P < 0.05$.

Note: Positive changes in score indicate improvement.

SE, standard error; SF-36, SF-36 Health Survey.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

REFERENCES

1. Albanese A, Del Sorbo F, Comella C, *et al*. Dystonia rating scales: Critique and recommendations. *Mov Disord* 2013;**28**:874–83.
2. Van Zandijcke M. Cervical dystonia (spasmodic torticollis). Some aspects of the natural history. *Acta Neurol Belg* 1995;**95**:210–15.
3. Geyer HL, Bressman SB. The diagnosis of dystonia. *Lancet Neurol* 2006;5:780–90.
4. Kutvonen O, Dastidar P, Nurmikko T. Pain in spasmodic torticollis. *Pain* 1997;**69**:279–86.
5. Chan J, Brin MF, Fahn S. Idiopathic cervical dystonia: clinical characteristics. *Mov Disord* 1991;**6**:119–26.
6. Pekmezovic T, Svetel M, Ivanovic N, *et al*. Quality of life in patients with focal dystonia. *Clin Neurol Neurosurg* 2009;**111**:161–64.
7. Ben-Shlomo Y, Camfield L, Warner T. What are the determinants of quality of life in people with cervical dystonia? *J Neurol Neurosurg Psychiatry* 2002;**72**:608–14.
8. Degirmenci Y, Oyekcin DG, Bakar C, *et al*. Anxiety and depression in primary and secondary dystonia: A burden on health related quality of life. *Neurology, Psychiatry, and Brain Research* 2013;**19**:80-5.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

9. Truong D, Brodsky, Lew M, *et al*. Long-term efficacy and safety of botulinum toxin type A (Dysport) in cervical dystonia. *Parkinsonism Relat Disord* 2010;**16**:316–23.

10. Truong D, Duane DD, Jankovic J, *et al*. Efficacy and safety of botulinum type A toxin (Dysport) in cervical dystonia: Results of the first US randomized, double-blind, placeo-controlled study. *Movement Disorders* 2005;**20**(7):783-791. 4.

11. Ware JE, Snow KK, Kosinski M, *et al*. SF-36 Health Survey: manual and interpretation guide. Boston: The Health Institute, New England Medical Center, 1993.

12. Welsh M. Parkinson's disease and quality of life: issues and challenges beyond motor symptoms. *Neurol Clin* 2004;**22**:S141–8.

13. Simpson DM, Blitzer A, Brashear A, *et al*. Assessment: botulinum neurotoxin for the treatment of movement disorders (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2008;**70**:1699–706.

14. Hallett M, Albanese A, Dressler D, et al. Evidence-based review and assessment of botulinum neurotoxin for the treatment of movement disorders. Toxicon 2013;**67**:94–114.

15. Costa J, Espirito-Santo C, Borges A, *et al*. Botulinum toxin type A therapy for cervical dystonia. *Cochrane Database Syst Rev* 2005;CD003633.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

16. Jankovic J, Brin MF. Therapeutic uses of botulinum toxin. *N Engl J Med* 1991;**324**:1186–94.

17. Damiano AM, McGrath MM, Willian MK, *et al*. Evaluation of a measurement strategy for Parkinson's disease: assessing patient health-related quality of life. *Qual Life Res* 2000;**9**:87–100.

18. Hopman W, Coo H, Edgar C, *et al*., Factors Associated with Health-Related Quality of Life in Multiple Sclerosis. *Can J Neurol Sci* 2007;**34**:160–6.

19. Camfield L. Quality of life in cervical dystonia. *Mov Disord* 2000;**15**(suppl).

20. Camfield L, Ben-Shlomo Y, Warner TT; Epidemiological Study of Dystonia in Europe Collaborative Group. Impact of cervical dystonia on quality of life. *Mov Disord* 2002;**17**:838–45.

21. Slawek J, Friedman A, Potulska A, *et al*. Factors affecting the health-related quality of life of patients with cervical dystonia and the impact of botulinum toxin type A injections. *Funct Neurol* 2007;**22**:95–100.

22. Hefter H, Benecke R, Erbguth F, *et al*. An open-label cohort study of the improvement of quality of life and pain in de novo cervical dystonia patients after injections with 500 U botulinum toxin A (Dysport). *BMJ Open* 2013;**3**:e001853.doi:10.1136/bmjopen-2012-001853.

23. Hefter H, Kupsch A, Mungersdorf M, *et al*; on behalf of the Dysport Cervical Dystonia Study Group. A botulinum toxin A treatment algorithm for de novo

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

management of torticollis and laterocollis. *BMJ Open* 2011;**2**:e000196.doi:10.1136/bmjopen-2011-000196.

24. Müller J, Wissel J, Kemmler G, *et al*. Craniocervical dystonia questionnaire (CDQ-24): development and validation of a disease-specific quality of life instrument. *J Neurol Neurosurg Psychiatry* 2004;**75**:749–53.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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

Margaret Mordin, MS, Market Access and Outcomes Strategy, RTI Health Solutions, Ann Arbor, MI, United States

Catherine Masaquel, MPH, Market Access and Outcomes Strategy, RTI Health Solutions, Ann Arbor, MI, United States

Chandra Abbott, PhD,* Neurology Medical Affairs, Ipsen Biopharmaceuticals, Inc, Basking Ridge, NJ, United States

Catherine Copley-Merriman, MBA, MS, Market Access and Outcomes Strategy, RTI Health Solutions, Ann Arbor, MI, United States

Corresponding Author:

Margaret Mordin

RTI Health Solutions

3005 Boardwalk St., Suite 105

* Former employee of Ipsen Biopharmaceuticals, Inc.

For peer review only

Ann Arbor, MI 48108

Telephone: +1.703.483.9009

Fax: +1.734.213.6169

E-mail: mmordin@rti.org

Key words: cervical dystonia, botulinum toxin type A, Dysport, spasmodic torticollis, health-related quality of life

Word Count (excluding title page, abstract, references, tables, and figure legends): ~3,138

For peer review only

ABSTRACT

Objective: To describe the health-related quality of life (HRQOL) burden of cervical dystonia (CD) and report on the HRQOL and patient perception of treatment benefits of abobotulinumtoxinA (Dysport®).

Design: The safety and efficacy of a single injection of abobotulinumtoxinA for CD treatment were evaluated in a previously reported international, multicenter, double-blind, randomized trial. HRQOL measures were assessed in the trial and have not been previously reported.

Setting: Movement disorder clinics in the United States (US) and Russia.

Participants: Patients had to have a diagnosis of CD with symptoms for at least 18 months, as well as a total Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) score of at least 30; a Severity domain score of at least 15; and a Disability domain score of at least 3. Key exclusion criteria included treatment with botulinum toxin type A (BoNT-A) or botulinum toxin type B (BoNT-B) within 16 weeks of enrollment.

Interventions: Patients were randomized to receive either 500 U abobotulinumtoxinA (n = 55) or placebo (n = 61).

Primary and secondary outcome measures: Efficacy assessments included TWSTRS total (primary endpoint) and subscale scores, a pain visual analog scale, and HRQOL assessed by the SF-36 Health Survey (SF-36) (secondary endpoint).

Results: Patients with CD reported significantly greater impairment for all SF-36 domains relative to US norms. Patients treated with abobotulinumtoxinA reported significantly greater improvements in Physical Functioning, Role Physical, Bodily Pain, General Health, and Role Emotional domains than placebo patients ($P \leq 0.03$ for all). The TWSTRS was significantly

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

correlated with Physical ~~Function~~Functioning, Role Physical, and Bodily Pain scores, for those on active treatment.

Conclusions: CD has a marked impact on HRQOL. Treatment with a single abobotulinumtoxinA injection results in significant improvement in patients' HRQOL.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

ARTICLE SUMMARY

Strengths and limitations of this study

- ~~This clinical study has been classified as class I study according to the American Academy of Neurology (AAN) Classification of Quality of Evidence for Clinical Trials.[1]~~
- The efficacy and safety of a single injection of abobotulinumtoxinA for CD treatment were evaluated in an international, multi-center, randomized double-blind trial ~~[9]~~.
- This paper presents previously unreported findings of health-related quality of life assessed during the international, multi-center, randomized double-blind trial of abobotulinumtoxinA.
- The size of this study was small; therefore, 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.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

INTRODUCTION

Dystonia ~~is a~~ , one of the most common movement ~~disorder~~ 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 ~~patterned, directional, and often~~ motor manifestations, primarily sustained or intermittent muscle contractions ~~that produce~~causing abnormal ~~postures or~~, often repetitive, movements~~.[2] When classified by distribution, patients are categorized as having hemidystonia or focal, segmental, multifocal, or generalized dystonia.[3] With cervical~~, postures, or both.[1] Cervical dystonia (CD), the most common form of focal dystonia, ~~abnormal movements affect a single body region. CD~~ is characterized by sustained involuntary muscle contraction and/or twitching of cervical musculature resulting in abnormal postures and repetitive movements of the head.[4~~2] Depending on the ~~particular combination of~~ muscles involved, the following head positions ~~can~~ , or combination of head positions, may occur: torticollis (~~horizontal turning~~rotation), laterocollis (tilting), anterocollis (flexion), and retrocollis (extension).[~~2~~3] CD may be accompanied by pulling or stiffness, pain, and sensory symptoms in the affected area.[~~5~~4] The diagnosis of CD is based on clinical signs and symptoms: deviation in head/neck posture; involuntary neck movements resulting in turn, tilt, and/or shoulder elevation; and neck pain.[~~2, 6~~3, 5]

Besides the clinical problems of involuntary abnormal postures and repetitive movements frequently associated with pain, patients with CD present with a wide range of social disabilities and impairments in health-related quality of life (HRQOL).[~~3~~6] HRQOL is defined as the

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

subjective perception of the impact of health status, including disease and treatment, on physical, psychological, and social functioning and well-being.

Recognizing the critical link between physical and psychological health allows a more holistic approach to patient care. By measuring HRQOL, we can ascertain the effects of a disease on individuals from the patient perspective and, thereafter, to some extent, be able to judge the benefit of therapeutic interventions. With CD, several physical and emotional factors such as reduced mobility, pain, low self-esteem, embarrassment, depression, anxiety, and limited social interaction may be present. ~~Unlike other forms of focal dystonia, pain~~Pain is a predominant feature of CD and is reported in up to 75% of patients~~.~~ [7] and is associated with reduced HRQOL. A study conducted by Degirmenci *et al*[8] evaluated anxiety and depression in dystonia patients using the Hospital Anxiety Depression (HAD) scale and assessed quality of life using the SF-36 Health Survey (SF-36), a ~~generic~~general ~~HRQOL~~ measure~~.~~ widely used to assess HRQOL. Mean Anxiety and Depression ~~subscales~~subscale scores were higher in patients with dystonia when compared with the control group. Moreover, patients with dystonia had worse (lower) SF-~~-~~36 scores for all domains when compared with controls.

AbobotulinumtoxinA (Dysport) 500 U was compared with placebo in ~~an international,~~two multicenter, double-blinded, randomized ~~trial.~~[trials:— one international[9] and one in the United States (US).[10]. The international study ~~was classified as class I study according to the American Academy of Neurology (AAN) Classification of Quality of Evidence for Clinical Trials.[1] This study used~~included the SF-36~~,~~ to evaluate treatment benefit with 500 U abobotulinumtoxinA compared with placebo as a secondary endpoint. As a result of the tremendous amount of research conducted using the SF-36 over the past two decades, population

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

norms are available that can facilitate the interpretation of research results across a wide variety of patient populations, putting specific study data into "larger context."[~~10~~11] In order to understand the HRQOL impairment unique to CD, SF-36 scores for the study sample were compared with other published scores for populations with various neurological conditions~~.~~, in particular Parkinson's disease and multiple sclerosis; like CD, these conditions are generally progressive and affect motor and non-motor function. Specifically, because the HRQOL impairment of Parkinson's disease and that of multiple sclerosis have been well established,[~~11~~12] these conditions were deemed appropriate comparisons in evaluating the unique nature of HRQOL impairment due to CD.

Botulinum toxin (BoNT), a treatment with established safety and efficacy, has been recommended as first-line treatment for symptoms of CD.[13, 14]~~[1, 12]14 ,13]~~ No botulinum toxin is indicated for improving HRQOL in CD. The reported benefits from BoNT are relief from pain, increased range of free movement, and improved resting posture.[~~13, 14~~15, 16] BoNT injections typically offer temporary relief, and the symptoms gradually return. For CD, as for most other neurological disorders, more data exist regarding the efficacy of the Botulinum toxin type A (BoNT-A) compared with type B. BoNT-A ~~has~~and BoNT-B have been shown to reduce both symptom severity and pain.[~~13~~15] Currently, there are three major commercially available preparations of type A toxins: abobotulinumtoxinA (Dysport® [Ipsen Biopharm Ltd, Wrexham, UK]), onabotulinumtoxinA (Botox® [Allergan, Inc.; Irvine, CA]), and incobotulinumtoxinA (Xeomin® [Merz Pharmaceuticals GmbH; Frankfurt am Main, Germany). The potency ~~Units~~units of abobotulinumtoxinA are specific to the preparation and assay method utilized. They are not interchangeable with other preparations of botulinum toxin products and, therefore, units of biological activity of one BoNT product cannot be compared to or converted into units

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

of any other botulinum toxin products ~~assessed with any other specific assay method. Due to this~~. Accordingly, information regarding the specific benefits of a particular BoNT-A preparation and the impact on HRQOL would be valuable.

The objectives of this article are to describe the HRQOL burden of CD, as measured at baseline in a previously reported randomized, double-blind, placebo-controlled, pivotal clinical study,[9] as well as report on the HRQOL and treatment benefits of abobotulinumtoxinA.

MATERIALS AND METHODS

Study design

The study design has been reported previously.[9] ~~Briefly, an~~An international, multicenter~~,~~ (movement disorder clinics in the ~~United States [~~US~~]~~ [n = 16] and Russia [n = 4]), double-blind, randomized, placebo-controlled trial was conducted to evaluate the safety and efficacy of a single injection of abobotulinumtoxinA for the treatment of CD. To be eligible for study entry, patients had to have a diagnosis of CD with symptoms for at least 18 months, as well as the following baseline Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) scores: a total score of at least 30; a Severity domain score of at least 15; and a Disability domain score of at least 3. The TWSTRS is an assessment of CD that includes a total CD rating score and three domain scores (Torticollis Severity, Disability, and Pain).

Key exclusion criteria were standard for efficacy trials of BoNT and included treatment with BoNT-A or BoNT-B within 16 weeks of enrollment, any disease of the neuromuscular junction, previous phenol injection to the neck muscles, myotomy or denervation surgery in the neck/shoulder region, cervical contracture, suspected secondary non-responsiveness or a history

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

of poor response to BoNT-A, pure anterocollis or retrocollis, symptom remission at screening, symptoms that could interfere with TWSTRS scoring, or BoNT-A neutralizing antibodies.

A total of 120 patients were to be recruited in the study to allow for 47 patients per treatment group to be evaluable on the primary efficacy endpoint (TWSTRS).[9] Patients ~~received~~were randomized using a pregenerated randomization code in a 1:1 ratio to receive an intramuscular injection of either 500 U abobotulinumtoxinA or placebo ~~in a 1:1 ratio.~~. Study medication was administered in a double-blind manner by intramuscular injection into two, three, or four clinically indicated neck muscles during a single dosing session at baseline. 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.

Assessments

Assessments have been described previously.[9] The TWSTRS was determined at week 0 (baseline), at week 4 (primary), and at weeks 8 and 12 (posttreatment) by investigators trained in TWSTRS scoring. Pain was evaluated with the Pain domain of the TWSTRS and a self-reported visual analog scale (VAS) assessing pain in the past 24 hours. Participants completed the pain VAS at baseline and week 4.

HRQOL was assessed using the SF-36, version 1.0. The SF-36 is a commonly used health profile that contains 36 items and includes multi-item domains to measure health status across eight dimensions: Physical Functioning, Role Limitations due to Physical Health Problems (Role Physical), Bodily Pain, Social Functioning, General Mental Health, Role Limitations due to Emotional Problems (Role Emotional), Vitality, and General Health Perceptions. Responses to questions within each domain are summed and transformed to a scale

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

ranging from 0 to 100, with higher scores suggesting better functioning. Participants completed the SF-36 at week 0 (baseline; prior to dosing) and at week 8 (posttreatment). SF-36 scores were generated according to published algorithms.[~~10~~11]

Safety assessments included incidence of treatment-emergent adverse events ~~(TEAEs),~~ electrocardiogram ~~(ECG),~~ neurological and physical examinations, and vital signs.

Statistical analyses

Burden of cervical dystonia

Population norms are available for the SF-36 that can facilitate the interpretation of research results across a wide variety of patient populations.[~~10~~11] The unique burden of illness associated with CD was assessed by comparing patients' baseline domain scores to age- and gender-adjusted SF-36 domain scores for the US population norms.[~~10~~11] The 95% confidence interval was computed for the baseline SF-36 scores relative to the age- and gender-adjusted US population norms.

~~Baseline~~For comparisons relative to other neurologic conditions, baseline SF-36 scores for the study sample were compared with other published scores for populations with Parkinson's disease and multiple sclerosis. The patients with Parkinson's disease were patients attending six neurology centers in the US, with a mix of Hoehn and Yahr scores representing early-, middle-, and late-stage disease.[~~15~~17] The patients with multiple sclerosis were part of a longitudinal study in Ontario, Canada.[~~16~~18]

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Treatment effect analysis

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.

Continuous primary (TWSTRS) and secondary variables (SF-36 domains) were analyzed using analysis of covariance (ANCOVA), controlling for treatment group, baseline score (where appropriate), treatment history (i.e., previous treatment with BoNT), and center.

Pearson correlation coefficients were calculated among the eight week 8 SF-36 domain scores and the week 4 and week 8 TWSTRS domain scores and total score by treatment group.

A responder was defined, a priori, as a patient with a decrease in TWSTRS total score of at least 30% (at week 4) compared with baseline.[9] Mean SF-36 scores by TWSTRS responder status were evaluated using a *t* test. Safety assessments were based on the safety population, which included all patients who received at least one dose of study medication. Safety variables were summarised by descriptive statistics. Safety results have been reported previously.[9]

RESULTS

Patient disposition and demographics

All 116 randomized patients (abobotulinumtoxinA n = 55; placebo n = 61) received at least one dose of study medication and were included in the intent-to-treat ~~(ITT)~~ population. The mean (standard deviation [SD]) age was similar across treatment groups: 51.9 (13.4) years for the abobotulinumtoxinA group and 53.9 (12.5) years for placebo group. Similarly, both treatment groups were predominantly female (67.0% in the abobotulinumtoxinA group and 62.0% in the placebo group). All other patient demographics and baseline characteristics were similar between

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

treatment groups.[9] A total of 33 patients discontinued the study ~~due to~~because of insufficient response, withdrawal of consent ~~withdrawn, lost~~, loss to follow-up, or other reasons. (Figure 1).

Comparison with US population and other neurological conditions

Baseline SF-36 scores for the patients with CD were lower (worse) than US population normative values[~~10~~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). For example, upon study entry, patients with CD reported Role Physical impairments that were approximately 32% lower (worse) than the age- and gender-adjusted US norm (domain score of 52.4 among patients with CD vs. 76.6 for the US norm, $P < 0.05$). Similarly, patients with CD reported experiencing significantly more pain than the age- and gender-adjusted US norm upon study entry, with Bodily Pain scores that were ~~33%~~23 percentage points lower (worse) for patients with CD than the US norms (47.7 vs. 71.3, $P < 0.05$).

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table 1. Mean SF-36 scores for the normative US population and patients with cervical dystonia, Parkinson's disease, or multiple sclerosis

SF-36 Domain	Cervical dystonia study sample (n = 116) Mean (SD)*	US normative sample† Mean	Parkinson's disease‡ (n = 150) Mean	Multiple sclerosis§ (n = 300) Mean (SD)
Physical Functioning	67.2 (22.2)	79.7	50.4	40.5 (30.2)
Role Physical	52.4 (29.5)	76.6	31.4	24.0 (36.8)
Bodily Pain	47.7 (21.6)	71.3	59.9	59.5 (27.2)
General Health	61.4 (19.7)	68.6	51.5	51.7 (24.1)
Vitality	50.6 (18.1)	60.1	46.1	35.1 (21.7)
Social Functioning	64.8 (24.6)	82.0	62.6	57.3 (27.6)
Role Emotional	68.8 (27.1)	80.6	49.0	56.1 (44.9)
Mental Health	64.1 (18.4)	74.8	67.1	67.1 (20.8)

* Baseline domain scores significantly lower than age- and gender-adjusted general US population norm for all domains ($P < 0.05$).

† Age- and gender-adjusted US norms.[~~10~~11]

‡ Damiano *et al.*[~~15~~17]

§ Hopman *et al.*[~~16~~18]

SD, standard deviation; SF-36, SF-36 Health Survey; US, United States.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Like individuals with CD, patients with Parkinson's disease and multiple sclerosis report substantial impairments in HRQOL relative to US norms (Table 1). However, each of these neurologic conditions presents with a unique profile of HRQOL impairment. Patients with CD report the greatest limitation in the Bodily Pain domain, whereas patients with Parkinson's disease report the greatest impairments in the Role Physical domain, and patients with multiple sclerosis report the greatest impairments in the Vitality domain (Table 2). Each of these neurological conditions impairs patients physically, yet the presentation of the disease manifests itself differently in terms of HRQOL impairment.

Table 2. Three most impaired SF-36 domains for patients with cervical dystonia, Parkinson's disease, or multiple sclerosis

Cervical dystonia	Parkinson's disease	Multiple sclerosis
Bodily Pain	Role Physical	Vitality
Vitality	Vitality	Physical Functioning
Role Physical	Physical Functioning	General Health

Treatment effect

Improvements from baseline to week 8 were observed for all eight SF-36 domains in the abobotulinumtoxinA group, whereas the placebo group showed some decline in Physical Functioning and little to no change in other SF-36 domains (Table 2; Figure 12). The largest improvements occurred in the Role Physical and Bodily Pain domains.

Patients treated with abobotulinumtoxinA reported significantly greater improvements than placebo patients from baseline to week 8 in five of the eight SF-36 domains (Table 2; Figure 12). Specifically, patients treated with abobotulinumtoxinA reported significantly greater

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

improvements in the Physical Functioning, Role Physical, Bodily Pain, General Health, and Role Emotional domains ($P \leq 0.03$ for all) than patients treated with placebo.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table 2. Mean (SE) SF-36 scores by treatment group: baseline and week 8

	AbobotulinumtoxinA				Placebo				
SF-36 Domain	N	Baseline mean (SD)	Week 8 mean (SD)	Change mean (SD)	N	Baseline mean (SD)	Week 8 mean (SD)	Change mean (SD)	*P* value
Physical Functioning	45	61.9 (20.0)	70.1 (20.1)	8.2 (16.0)	37	68.2 (21.7)	66.4 (23.4)	–1.9 (16.8)	0.018
Role Physical	44	46.3 (28.5)	62.9 (25.1)	16.6 (21.1)	37	50.5 (29.9)	53.7 (25.6)	3.2 (24.0)	0.008
Bodily Pain	42	47.9 (23.0)	61.8 (20.4)	13.9 (19.7)	37	49.0 (19.7)	51.9 (22.0)	2.9 (20.3)	0.010
General Health	44	58.9 (19.4)	62.1 (18.4)	3.2 (11.1)	37	62.2 (19.6)	59.7 (21.1)	-2.5 (10.6)	0.030
Vitality	45	47.5 (15.6)	56.0 (16.8)	8.5 (15.0)	37	50.5 (19.5)	52.0 (19.2)	1.5 (17.8)	0.086
Social Functioning	43	62.2 (26.8)	73.3 (22.9)	11.0 (25.8)	37	63.2 (25.0)	67.2 (25.6)	4.1 (15.6)	0.125
Role Emotional	44	71.0 (25.4)	80.5 (21.5)	9.5 (20.9)	37	62.2 (28.0)	66.4 (25.3)	4.3 (26.8)	0.030
Mental Health	45	62.6 (16.3)	70.2 (15.8)	7.7 (14.5)	37	60.1 (20.9)	63.9 (21.0)	3.8 (15.2)	0.125

Note: Comparison between AbobotulinumtoxinA and placebo for change from baseline to week 8 using an ANCOVA model with baseline value as covariate.

ANCOVA, analysis of covariance; SD, standard deviation; SE, standard error; SF-36, SF-36 Health Survey.

For peer review only

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 ~~Function~~Functioning, Role Physical, and Bodily Pain domain scores. ~~Across treatment groups and time periods, the~~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. ~~Week 8 correlations~~ 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).

For peer review only

Table 3. Correlations between the week 8 SF-36 ~~Physical Function, Role Physical, and Bodily Pain domain~~ scores with the TWSTRS at week 4 by treatment group

	Week 4: correlation; *P*- value; n							
	Total		Disability		Severity		Pain	
	~~Dysport~~Abobotulinum-toxinA	Placebo	~~Dysport~~Abobotulinum-toxinA	Placebo	~~Dysport~~Abobotulinum-toxinA	Placebo	~~Dysport~~Abobotulinum-toxinA	Placebo
Physical ~~Function~~Functioning	–0.34; 0.0278; 43	–0.19; 0.2801; 36	–0.34; 0.0257; 44	–0.03; 0.8978; 36	–0.35; 0.0223; 43	–0.31; 0.0694; 36	–0.13; 0.3969; 44	–0.10; 0.55; 36
Role Physical	–0.34; 0.0295; 42	–0.34; 0.0422; 36	–0.34; 0.0270; 43	–0.27; 0.1069; 36	–0.35; 0.0229; 42	–0.37; 0.0255; 36	–0.12; 0.4265; 43	–0.18; 0.2811; 36
Bodily Pain	–0.41; 0.00080; 40	–0.35; 0.0345; 36	–0.31; 0.0523; 41	–0.29; 0.0871; 36	–0.20; 0.2133; 40	–0.44; 0.0076; 36	–0.53; 0.0003; 41	–0.14; 0.4296; 36
General Health	–0.31; 0.0422	0.08 0.6521	–0.26 0.1459	0.16 0.3639	–0.43 0.0045	0.06 0.7217	–0.09 0.5785	–0.02 0.9235

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

	Week 4: correlation; *P*-value; n							
	Total		Disability		Severity		Pain	
	~~Dysport~~Abobotulinum-toxinA	Placebo	~~Dysport~~Abobotulinum-toxinA	Placebo	~~Dysport~~Abobotulinum-toxinA	Placebo	~~Dysport~~Abobotulinum-toxinA	Placebo
	42	36	43	36	42	36	43	36
Vitality	–0.26	–0.20	–0.25	–0.06	–0.38	–0.14	0.04	–0.27
	0.0983	0.2517	0.0963	0.7272	0.0123	0.4201	0.7860	0.1172
	43	36	44	36	43	36	44	36
Social Functioning	–0.25	–0.11	–0.32	0.15	–0.32	–0.08	0.06	–0.31
	0.1217	0.5206	0.0394	0.3909	0.0437	0.6437	0.7280	0.0683
	41	36	42	36	41	36	42	36
Role Emotional	–0.18	–0.14	–0.29	0.01	–0.14	–0.15	–0.01	–0.19
	0.2877	0.4150	0.0612	0.9460	0.3874	0.3947	0.9383	0.2634
	42	36	43	36	42	36	43	36
Mental Health	–0.17	0.05	–0.13	0.22	–0.38	0.16	0.14	–0.24
	0.2668	0.7815	0.3990	0.1949	0.0128	0.3365	0.3786	0.1502
	43	36	44	36	43	36	44	36

Note: Correlations are negative as the TWSTRS and SF-36 are scored in opposite directions.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

SF-36, SF-36 Health Survey; TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

~~Improvements~~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 ~~in the TWSTRS responder group~~, whereas the non-responder group showed little to no change in SF-36 domains (Table 4). The largest improvements occurred in the Role Physical and Bodily Pain domains. 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 4). Specifically, responders reported significantly greater improvements in Physical Functioning, Role Physical, Bodily Pain, Vitality, and Social Functioning ($P \leq 0.03$ for all) than patients considered non-responsive to treatment.

For peer review only

Table 4. Mean change in SF-36 scores by TWSTRS response status

	TWSTRS Responder Status			
	Mean Change in SF-36			
SF-36 Domain	TWSTRS ~~Non~~ non-responder (n = 47)	TWSTRS responder (n = 36)	Difference (responder – non-responder)	*P*- value
Physical Functioning	–0.6	9.1	9.7	0.0091
Role Physical	3.5	19.3	15.8	0.0020
Bodily Pain	1.8	17.6	15.8	0.0005
General Health	–1.5	3.3	4.8	0.0552
Vitality	0.8	11.1	10.3	0.0067
Social Functioning	2.8	14.3	11.5	0.0251
Role Emotional	2.8	12.5	9.7	0.0665
Mental Health	3.9	8.5	4.6	0.1691

SF-36, SF-36 Health Survey; TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale.

For peer review only

DISCUSSION

Although CD is usually non-progressive and limited to involuntary muscle spasms of the neck, its detrimental effect on health status is comparable to progressive and generalized conditions clinically perceived to be of greater severity (such as multiple sclerosis and

Parkinson's disease). Camfield[~~17~~19] conducted a survey of 150 patients with CD that included the SF-36 and the Beck anxiety and depression indexes. Patients with CD had lower scores in all eight SF-36 domains compared with controls in the United Kingdom (UK), particularly in the Role Physical (41.6 vs. 85.8), Bodily Pain (54.6 vs. 81.5), and General Health (46.2 vs. 73.5) domains. Domain scores were comparable to data from patients with mild to moderate multiple sclerosis and moderate epilepsy. Our results are similar to those of Camfield[~~17], and~~19], in that baseline scores for patients with CD were lower (worse) than for US normative data, particularly for the Role Physical (52.4 vs. 76.6), and Bodily Pain (47.7 vs. 71.3) domains. Our findings support the implication that CD has a significant impact on health status that is comparable with other neurological disorders of high morbidity. CD appears to have a disproportionate negative impact on patients' physical role limitation, despite their good physical functioning. One possible explanation is that pain limits such activities. Another possibility is that patients with CD consciously limit activities that make their dystonia visible to others to avoid mockery.[~~18~~20]

A few studies have investigated the impact of CD on HRQOL and factors modifying a patient's ability to cope with this disease. Slawek *et al*[~~19~~21] conducted an HRQOL survey study in 101 patients previously treated with BoNT-A using the TWSTRS, a pain VAS (0-100%), the SF-~~-~~36, and the Montgomery-Åsberg Depression Rating Scale (MADRS). ~~The patients'~~Patients' baseline SF-~~-~~36 scores were worse than those of healthy controls in all eight SF-36 domains. Improvements were observed 4 weeks after the single BoNT-A injections in all SF-36 domains, and in the VAS, TWSTRS, and MADRS scores. The TWSTRS results did not correlate with any of the SF-36 domains. Longer treatment with BoNT-A was associated with better scores. Hefter *et al*[~~20, 21~~[~~,~~22, 23] conducted a prospective, open-label study of abobotulinumtoxinA in 516 de novo CD patients using the TWSTRS, the Craniocervical Dystonia Questionnaire (CDQ-24),

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

patient diaries, and a global assessment of pain. In contrast with the SF-36, which is a general measure of HRQOL, the CDQ-24 is a disease-specific questionnaire that evaluates HRQOL in patients with CD.[~~22~~24] The CDQ-24 has five subscales: Stigma, Emotional Wellbeing, Pain, Activities of Daily Living, and Social/Family Life. At week 4, significant improvements were observed in CDQ-24 total and subscale scores that were sustained up to week 12. Significant reductions in patient diary item scores for activities of daily living, pain, and pain duration at week 4 and 12 were observed. Sixty-six percent of patients reported pain relief (less or no pain) at week 4 and 74% at week 12. Improvements in quality of life and pain intensity for up to 12 weeks in patients with CD were observed after treatment with abobotulinumtoxinA.

Likewise, in our findings, patients treated with abobotulinumtoxinA reported significantly greater improvements in TWSTRS total mean scores at weeks 4, 8, and 12 ($P \leq 0.019$) compared with placebo.[9] Improvements from baseline to week 8 were observed for all eight SF-36 domains in the abobotulinumtoxinA group, whereas the placebo group either stayed the same or became worse (with a decline in physical functioning). In this study, the SF--36 results did correlate with the TWSTRS for the Role Physical and Bodily Pain domains across treatment groups and time periods. AbobotulinumtoxinA was well tolerated in this study, as previously published.[9]

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~~HRQOL. 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.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

CONCLUSION

CD has a marked impact on HRQOL for patients. Patients with CD report significantly worse functioning than that of their peers (age- and gender-adjusted US normative values). Results from this prospective, randomized controlled trial support the ability of abobotulinumtoxinA 500 U to provide efficacy in reducing motor symptoms in conjunction with significant improvements in HRQOL for patients.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

~~acknowledgments~~

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

REGISTRATION

The trial is registered at ClinicalTrials.gov, numbers NCT00257660 and NCT00288509.

FUNDING

This work was supported by Ipsen Biopharmaceuticals, Inc.

COMPETING INTERESTS

Chandra Abbott is a former employee of Ipsen Biopharmaceuticals, Inc. Margaret Mordin, Catherine Masaquel, and Catherine Copley-Merriman, employees of RTI Health Solutions, were contracted by Ipsen Biopharmaceuticals, Inc. to perform and report on the research described here.

AUTHOR CONTRIBUTIONS

All authors were involved in the analysis and interpretation of the data, manuscript writing, review and critique. All authors approved the final manuscript.

ACKNOWLEDGMENTS

The authors wish to acknowledge Jean Hubble, MD, formerly of Ipsen Biopharmaceuticals, Inc., for her clinical contributions to this paper; and Stephen Chang, PhD, formerly of Ipsen Biopharmaceuticals, Inc., for conduct of the statistical analyses of the trial data reported in this

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

manuscript. Rosemarie Kelly, PhD, consultant to Ipsen, provided critical review of the manuscript.

COMPETING INTERESTS

Chandra Abbott is an employee of Ipsen Biopharmaceuticals, Inc. Margaret Mordin, Catherine Masaquel, and Catherine Copley-Merriman, employees of RTI Health Solutions, were contracted by Ipsen Biopharmaceuticals, Inc. to perform and report on the research described here.

FUNDING

This work was supported by Ipsen Biopharmaceuticals, Inc.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

FIGURE LEGENDS

Figure 1. Study Flow Diagram

Figure 2. Mean (SE) change in SF-36 scores at week 8

* $P < 0.05$.

Note: Positive changes in score indicate improvement.

SE, standard error; SF-36, SF-36 Health Survey.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

REFERENCES

1. Albanese A, Del Sorbo F, Comella C, *et al*. Dystonia rating scales: Critique and recommendations. *Mov Disord* 2013;**28**:874–83.

2. Van Zandijcke M. Cervical dystonia (spasmodic torticollis). Some aspects of the natural history. *Acta Neurol Belg* 1995;**95**:210–15.

~~1. Hallett M, Albanese A, Dressler D, et al. Evidence-based review and assessment of botulinum neurotoxin for the treatment of movement disorders. Toxicon 2013;67:94–114.~~

~~2~~3. Geyer HL, Bressman SB. The diagnosis of dystonia. *Lancet Neurol* 2006;5:780–90.

4. Kutvonen O, Dastidar P, Nurmikko T. Pain in spasmodic torticollis. *Pain* 1997;**69**:279–86.

5. Chan J, Brin MF, Fahn S. Idiopathic cervical dystonia: clinical characteristics. *Mov Disord* 1991;**6**:119–26.

~~3~~6. Pekmezovic T, Svetel M, Ivanovic N, *et al*. Quality of life in patients with focal dystonia. *Clin Neurol Neurosurg* 2009;**111**:161–64.

~~4. Van Zandijcke M. Cervical dystonia (spasmodic torticollis). Some aspects of the natural history. *Acta Neurol Belg* 1995;95:210–15.~~

~~5. Kutvonen O, Dastidar P, Nurmikko T. Pain in spasmodic torticollis. *Pain* 1997;69:279–86.~~

~~6. Chan J, Brin MF, Fahn S. Idiopathic cervical dystonia: clinical characteristics. *Mov Disord* 1991;6:119–26.~~

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

7. Ben-Shlomo Y, Camfield L, Warner T. What are the determinants of quality of life in people with cervical dystonia? *J Neurol Neurosurg Psychiatry* 2002;**72**:608–14.

8. Degirmenci Y, Oyekcin DG, Bakar C, *et al*. Anxiety and depression in primary and secondary dystonia: A burden on health related quality of life. *Neurology, Psychiatry, and Brain Research* 2013;**19**:80-5.

9. Truong D, Brodsky, Lew M, *et al*. Long-term efficacy and safety of botulinum toxin type A (Dysport) in cervical dystonia. *Parkinsonism Relat Disord* 2010;**16**:316–23.

~~10~~10. Truong D, Duane DD, Jankovic J, *et al*. Efficacy and safety of botulinum type A toxin (Dysport) in cervical dystonia: Results of the first US randomized, double-blind, placeo-controlled study. *Movement Disorders* 2005;**20**(7):783-791. 4.

11. Ware JE, Snow KK, Kosinski M, *et al*. SF-36 Health Survey: manual and interpretation guide. Boston: The Health Institute, New England Medical Center, 1993.

~~11~~12. Welsh M. Parkinson's disease and quality of life: issues and challenges beyond motor symptoms. *Neurol Clin* 2004;**22**:S141–8.

~~12~~13. Simpson DM, Blitzer A, Brashear A, *et al*. Assessment: botulinum neurotoxin for the treatment of movement disorders (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2008;**70**:1699–706.

~~13~~14. Hallett M, Albanese A, Dressler D, et al. Evidence-based review and assessment of botulinum neurotoxin for the treatment of movement disorders. Toxicon 2013;**67**:94–114.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

15. Costa J, Espirito-Santo C, Borges A, *et al*. Botulinum toxin type A therapy for cervical dystonia. *Cochrane Database Syst Rev* 2005;CD003633.

~~14~~16. Jankovic J, Brin MF. Therapeutic uses of botulinum toxin. *N Engl J Med* 1991;**324**:1186–94.

~~15~~17. Damiano AM, McGrath MM, Willian MK, *et al*. Evaluation of a measurement strategy for Parkinson's disease: assessing patient health-related quality of life. *Qual Life Res* 2000;**9**:87–100.

~~16~~18. Hopman W, Coo H, Edgar C, *et al*., Factors Associated with Health-Related Quality of Life in Multiple Sclerosis. *Can J Neurol Sci* 2007;**34**:160–6.

~~17~~19. Camfield L. Quality of life in cervical dystonia. *Mov Disord* 2000;**15**(suppl).

~~18~~20. Camfield L, Ben-Shlomo Y, Warner TT; Epidemiological Study of Dystonia in Europe Collaborative Group. Impact of cervical dystonia on quality of life. *Mov Disord* 2002;**17**:838–45.

~~19~~21. Slawek J, Friedman A, Potulska A, *et al*. Factors affecting the health-related quality of life of patients with cervical dystonia and the impact of botulinum toxin type A injections. *Funct Neurol* 2007;**22**:95–100.

~~20~~22. Hefter H, Benecke R, Erbguth F, *et al*. An open-label cohort study of the improvement of quality of life and pain in de novo cervical dystonia patients after injections with 500 U botulinum toxin A (Dysport). *BMJ Open* 2013;**3**:e001853.doi:10.1136/bmjopen-2012-001853.

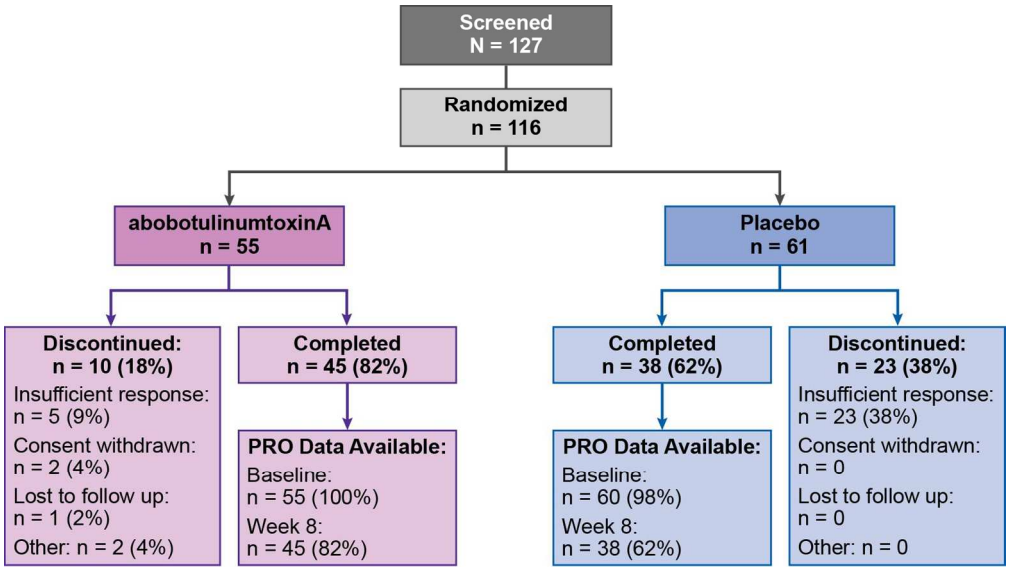
For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

~~21~~23. Hefter H, Kupsch A, Mungersdorf M, *et al*; on behalf of the Dysport Cervical Dystonia Study Group. A botulinum toxin A treatment algorithm for de novo management of torticollis and laterocollis. *BMJ Open* 2011;**2**:e000196.doi:10.1136/bmjopen-2011-000196.

~~22~~24. Müller J, Wissel J, Kemmler G, *et al*. Craniocervical dystonia questionnaire (CDQ-24): development and validation of a disease-specific quality of life instrument. *J Neurol Neurosurg Psychiatry* 2004;**75**:749–53.

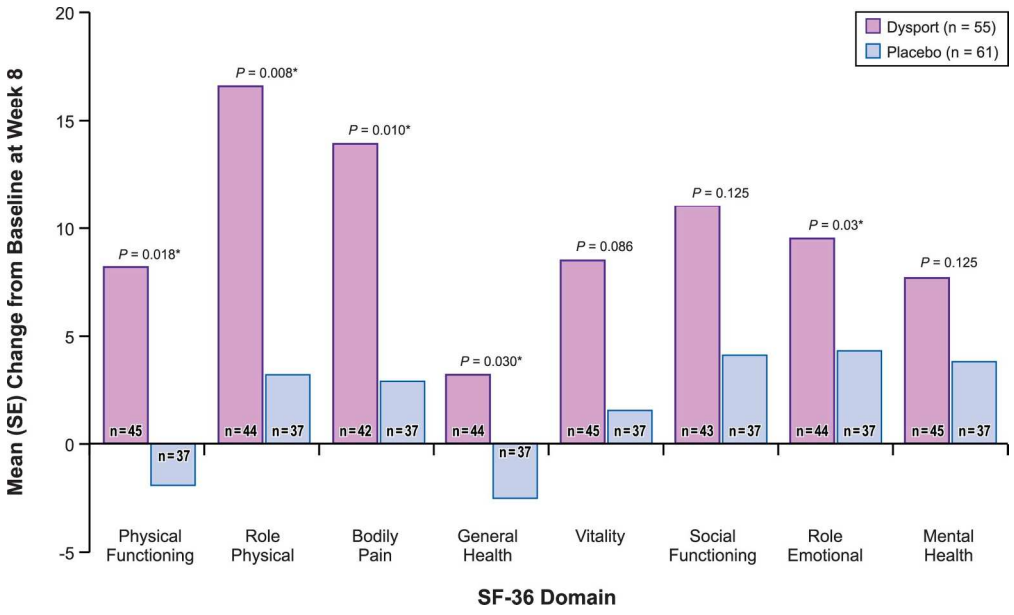
For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml



152x85mm (300 x 300 DPI)

review only



186x111mm (300 x 300 DPI)

review only

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	6
	2b	Specific objectives or hypotheses	7
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	9
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	Not Applicable
Participants	4a	Eligibility criteria for participants	9
	4b	Settings and locations where the data were collected	9
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	9
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	9
	6b	Any changes to trial outcomes after the trial commenced, with reasons	Not Applicable
Sample size	7a	How sample size was determined	9
	7b	When applicable, explanation of any interim analyses and stopping guidelines	Not Applicable
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	9
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Not Applicable
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	9
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Not available at this time (study completed in 2006)

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	9
	11b	If relevant, description of the similarity of interventions	Not Applicable
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	11
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	11
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	12
	13b	For each group, losses and exclusions after randomisation, together with reasons	12
Recruitment	14a	Dates defining the periods of recruitment and follow-up	10
	14b	Why the trial ended or was stopped	Not Applicable
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Reported in Truong, 2010
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Figure 1 in separate file
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Figure 1 in separate file
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Not Applicable
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	17-19
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	Reported in Truong, 2010
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	23
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	21-22
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	22-23
Other information			
Registration	23	Registration number and name of trial registry	25
Protocol	24	Where the full trial protocol can be accessed, if available	Not available
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	25

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2014-005150.R2
Article Type:	Research
Date Submitted by the Author:	24-Sep-2014
Complete List of Authors:	Mordin, Margaret; RTI Health Solutions, Market Access & Outcomes Strategy Masaquel, Catherine; RTI Health Solutions, Market Access & Outcomes Strategy Coleman Abbott, Chandra; Ipsen Biopharmaceuticals, Neurology Medical Affairs Copley-Merriman, Catherine; RTI Health Solutions, Market Access & Outomes Strategy
Primary Subject Heading:	Neurology
Secondary Subject Heading:	Qualitative research
Keywords:	Adult neurology < NEUROLOGY, QUALITATIVE RESEARCH, Motor neurone disease < NEUROLOGY

For peer review only

SCHOLARONE™
Manuscripts

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

Margaret Mordin, MS, Market Access and Outcomes Strategy, RTI Health Solutions, Ann Arbor, MI, United States

Catherine Masaquel, MPH, Market Access and Outcomes Strategy, RTI Health Solutions, Ann Arbor, MI, United States

Chandra Abbott, PhD,* Neurology Medical Affairs, Ipsen Biopharmaceuticals, Inc, Basking Ridge, NJ, United States

Catherine Copley-Merriman, MBA, MS, Market Access and Outcomes Strategy, RTI Health Solutions, Ann Arbor, MI, United States

Corresponding Author:

Margaret Mordin

RTI Health Solutions

3005 Boardwalk St., Suite 105

* Former employee of Ipsen Biopharmaceuticals, Inc.

For peer review only

Ann Arbor, MI 48108

Telephone: +1.703.483.9009

Fax: +1.734.213.6169

E-mail: mmordin@rti.org

Key words: cervical dystonia, botulinum toxin type A, Dysport, spasmodic torticollis, health-related quality of life

Word Count (excluding title page, abstract, references, tables, and figure legends): ~3,165

For peer review only

ABSTRACT

Objective: To describe the health-related quality of life (HRQOL) burden of cervical dystonia (CD) and report on the HRQOL and patient perception of treatment benefits of abobotulinumtoxinA (Dysport®).

Design: The safety and efficacy of a single injection of abobotulinumtoxinA for CD treatment were evaluated in a previously reported international, multicenter, double-blind, randomized trial. HRQOL measures were assessed in the trial and have not been previously reported.

Setting: Movement disorder clinics in the United States (US) and Russia.

Participants: Patients had to have a diagnosis of CD with symptoms for at least 18 months, as well as a total Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) score of at least 30; a Severity domain score of at least 15; and a Disability domain score of at least 3. Key exclusion criteria included treatment with botulinum toxin type A (BoNT-A) or botulinum toxin type B (BoNT-B) within 16 weeks of enrollment.

Interventions: Patients were randomized to receive either 500 U abobotulinumtoxinA (n = 55) or placebo (n = 61).

Primary and secondary outcome measures: Efficacy assessments included TWSTRS total (primary endpoint) and subscale scores at weeks 0, 4, 8, 12 ; a pain visual analog scale at weeks 0 and 4; and HRQOL assessed by the SF-36 Health Survey (SF-36) (secondary endpoint) at weeks 0 and 8.

Results: Patients with CD reported significantly greater impairment for all SF-36 domains relative to US norms. Patients treated with abobotulinumtoxinA reported significantly greater improvements in Physical Functioning, Role Physical, Bodily Pain, General Health, and Role Emotional domains than placebo patients ($P \leq 0.03$ for all). The TWSTRS was significantly

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

correlated with Physical Functioning, Role Physical, and Bodily Pain scores, for those on active treatment.

Conclusions: CD has a marked impact on HRQOL. Treatment with a single abobotulinumtoxinA injection results in significant improvement in patients' HRQOL.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

ARTICLE SUMMARY

Strengths and limitations of this study

- The efficacy and safety of a single injection of abobotulinumtoxinA for CD treatment were evaluated in an international, multicenter, randomized double-blind trial.
- This paper presents previously unreported findings of health-related quality of life assessed during the international, multicenter, randomized double-blind trial of abobotulinumtoxinA.
- The size of this study was small; therefore, 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.

For peer review only

INTRODUCTION

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] Cervical dystonia (CD), the most common form of focal dystonia, is characterized by sustained involuntary muscle contraction and/or twitching of cervical musculature resulting in abnormal postures and repetitive movements of the head.[2] Depending on the muscles involved, the following head positions, or combination of head positions, may occur: torticollis (rotation), laterocollis (tilting), anterocollis (flexion), and retrocollis (extension).[3] CD may be accompanied by pulling or stiffness, pain, and sensory symptoms in the affected area.[4] The diagnosis of CD is based on clinical signs and symptoms: deviation in head/neck posture; involuntary neck movements resulting in turn, tilt, and/or shoulder elevation; and neck pain.[3, 5]

Besides the clinical problems of involuntary abnormal postures and repetitive movements frequently associated with pain, patients with CD present with a wide range of social disabilities and impairments in health-related quality of life (HRQOL).[6] HRQOL is defined as the subjective perception of the impact of health status, including disease and treatment, on physical, psychological, and social functioning and well-being.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Recognizing the critical link between physical and psychological health allows a more holistic approach to patient care. By measuring HRQOL, we can ascertain the effects of a disease on individuals from the patient perspective and, thereafter, to some extent, be able to judge the benefit of therapeutic interventions. With CD, several physical and emotional factors such as reduced mobility, pain, low self-esteem, embarrassment, depression, anxiety, and limited social interaction may be present. Pain is a predominant feature of CD and is reported in up to 75% of patients [7] and is associated with reduced HRQOL. A study conducted by Degirmenci *et al*[8] evaluated anxiety and depression in dystonia patients using the Hospital Anxiety Depression (HAD) scale and assessed quality of life using the SF-36 Health Survey (SF-36), a general measure widely used to assess HRQOL. Mean Anxiety and Depression subscale scores were higher in patients with dystonia when compared with the control group. Moreover, patients with dystonia had worse (lower) SF-36 scores for all domains when compared with controls.

AbobotulinumtoxinA (Dysport) 500 U was compared with placebo in two multicenter, double-blinded, randomized trials: one international[9] and one in the United States (US).[10] The international study included the SF-36 to evaluate treatment benefit with 500 U abobotulinumtoxinA compared with placebo as a secondary endpoint. As a result of the tremendous amount of research conducted using the SF-36 over the past two decades, population norms are available that can facilitate the interpretation of research results across a wide variety of patient populations, putting specific study data into “larger context.”[11] In order to understand the HRQOL impairment unique to CD, SF-36 scores for the study sample were compared with other published scores for populations with various neurological conditions, in particular Parkinson’s disease and multiple sclerosis; like CD, these conditions are generally progressive and affect motor and non-motor function. Specifically, because the HRQOL

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

impairment of Parkinson's disease and that of multiple sclerosis have been well established,[12] these conditions were deemed appropriate comparisons in evaluating the unique nature of HRQOL impairment due to CD.

Botulinum toxin (BoNT), a treatment with established safety and efficacy, has been recommended as first-line treatment for symptoms of CD.[13, 14] No botulinum toxin is indicated for improving HRQOL in CD. The reported benefits from BoNT are relief from pain, increased range of free movement, and improved resting posture.[15, 16] BoNT injections typically offer temporary relief, and the symptoms gradually return. For CD, as for most other neurological disorders, more data exist regarding the efficacy of the Botulinum toxin type A (BoNT-A) compared with type B. BoNT-A and BoNT-B have been shown to reduce both symptom severity and pain.[15] Currently, there are three major commercially available preparations of type A toxins: abobotulinumtoxinA (Dysport® [Ipsen Biopharm Ltd, Wrexham, UK]), onabotulinumtoxinA (Botox® [Allergan, Inc.; Irvine, CA]), and incobotulinumtoxinA (Xeomin® [Merz Pharmaceuticals GmbH; Frankfurt am Main, Germany). The potency units of abobotulinumtoxinA are specific to the preparation and assay method utilized. They are not interchangeable with other preparations of botulinum toxin products and, therefore, units of biological activity of one BoNT product cannot be compared to or converted into units of any other botulinum toxin products. Accordingly, information regarding the specific benefits of a particular BoNT-A preparation and the impact on HRQOL would be valuable.

The objectives of this article are to describe the HRQOL burden of CD, as measured at baseline in a previously reported randomized, double-blind, placebo-controlled, pivotal clinical study,[9] as well as report on the HRQOL and treatment benefits of abobotulinumtoxinA.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

MATERIALS AND METHODS

Study design

The study design has been reported previously.[9] An international, multicenter (movement disorder clinics in the US [n = 16] and Russia [n = 4]), double-blind, randomized, placebo-controlled trial was conducted between October 10, 2005 and September 7, 2006 to evaluate the safety and efficacy of a single injection of abobotulinumtoxinA for the treatment of CD. To be eligible for study entry, patients had to have a diagnosis of CD with symptoms for at least 18 months, as well as the following baseline Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) scores: a total score of at least 30; a Severity domain score of at least 15; and a Disability domain score of at least 3. The TWSTRS is an assessment of CD that includes a total CD rating score and three domain scores (Torticollis Severity, Disability, and Pain).

Key exclusion criteria were standard for efficacy trials of BoNT and included treatment with BoNT-A or BoNT-B within 16 weeks of enrollment, any disease of the neuromuscular junction, previous phenol injection to the neck muscles, myotomy or denervation surgery in the neck/shoulder region, cervical contracture, suspected secondary non-responsiveness or a history of poor response to BoNT-A, pure anterocollis or retrocollis, symptom remission at screening, symptoms that could interfere with TWSTRS scoring, or BoNT-A neutralizing antibodies.

A total of 120 patients were to be recruited in the study to allow for 47 patients per treatment group to be evaluable on the primary efficacy endpoint (TWSTRS).[9] Patients were randomized using a pregenerated randomization code in a 1:1 ratio to receive an intramuscular injection of either 500 U abobotulinumtoxinA or placebo. Study medication was administered in a double-blind manner by intramuscular injection into two, three, or four clinically indicated neck muscles during a single dosing session at baseline. The study was conducted in accordance

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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.

Assessments

Assessments have been described previously.[9] The TWSTRS was determined at week 0 (baseline), at week 4 (primary), and at weeks 8 and 12 (posttreatment) by investigators trained in TWSTRS scoring. Pain was evaluated with the Pain domain of the TWSTRS and a self-reported visual analog scale (VAS) assessing pain in the past 24 hours. Participants completed the pain VAS at baseline and week 4.

HRQOL was assessed using the SF-36, version 1.0. The SF-36 is a commonly used health profile that contains 36 items and includes multi-item domains to measure health status across eight dimensions: Physical Functioning, Role Limitations due to Physical Health Problems (Role Physical), Bodily Pain, Social Functioning, General Mental Health, Role Limitations due to Emotional Problems (Role Emotional), Vitality, and General Health Perceptions. Responses to questions within each domain are summed and transformed to a scale ranging from 0 to 100, with higher scores suggesting better functioning. Participants completed the SF-36 at week 0 (baseline; prior to dosing) and at week 8 (posttreatment). SF-36 scores were generated according to published algorithms.[11]

Safety assessments included incidence of treatment-emergent adverse events, electrocardiogram, neurological and physical examinations, and vital signs.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Statistical analyses

Burden of cervical dystonia

Population norms are available for the SF-36 that can facilitate the interpretation of research results across a wide variety of patient populations.[11] The unique burden of illness associated with CD was assessed by comparing patients' baseline domain scores (regardless of enrollment location) to age- and gender-adjusted SF-36 domain scores for the US population norms.[11] The 95% confidence interval was computed for the baseline SF-36 scores relative to the age- and gender-adjusted US population norms.

For comparisons relative to other neurologic conditions, baseline SF-36 scores for the study sample were compared with other published scores for populations with Parkinson's disease and multiple sclerosis. The patients with Parkinson's disease were patients attending six neurology centers in the US, with a mix of Hoehn and Yahr scores representing early-, middle-, and late-stage disease.[17] The patients with multiple sclerosis were part of a longitudinal study in Ontario, Canada.[18]

Treatment effect analysis

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.

Continuous primary (TWSTRS) and secondary variables (SF-36 domains) were analyzed using analysis of covariance (ANCOVA), controlling for treatment group, baseline score (where appropriate), treatment history (i.e., previous treatment with BoNT), and center.

Pearson correlation coefficients were calculated among the eight week 8 SF-36 domain scores and the week 4 and week 8 TWSTRS domain scores and total score by treatment group.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

A responder was defined, a priori, as a patient with a decrease in TWSTRS total score of at least 30% (at week 4) compared with baseline.[9] Mean SF-36 scores by TWSTRS responder status were evaluated using a *t* test. Safety assessments were based on the safety population, which included all patients who received at least one dose of study medication. Safety variables were summarized by descriptive statistics. Safety results have been reported previously.[9]

RESULTS

Patient disposition and demographics

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 intent-to-treat and safety populations. Of these, 83 patients (abobotulinumtoxinA n = 45; placebo n = 38) were analyzed in the HRQOL assessment. The mean (standard deviation [SD]) age was similar across treatment groups: 51.9 (13.4) years for the abobotulinumtoxinA group and 53.9 (12.5) years for placebo group. Similarly, both treatment groups were predominantly female (67.0% in the abobotulinumtoxinA group and 62.0% in the placebo group). All other patient demographics and baseline characteristics were similar between treatment groups (Table 1).[9] A total of 33 patients discontinued the study because of insufficient response, withdrawal of consent, loss to follow-up, or other reasons (Figure 1).

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table 1. Patient demographics and baseline characteristics (intent-to-treat population)

Characteristic	AbobotulinumtoxinA (n = 55)	Placebo (n = 61)
Age, years		
Mean (SD)	51.9 (13.4)	53.9 (12.5)
Median (range)	53.0 (20-79)	56.0 (28-78)
Sex, n (%) male	18 (33)	23 (38)
Race, n (%) Caucasian	55 (100)	61 (100)
Ethnicity, n (%)		
Hispanic/Latino	3 (5)	4 (7)
Not Hispanic/Latino	52 (95)	57 (93)
Height, cm		
Mean (SD)	167 (10.3)	170 (8.5)
Median (range)	167 (147-196)	168 (154-193)
Weight, kg		
Mean (SD)	73.4 (13.8)	77.4 (15.0)
Median (range)	73.0 (46.4-108.0)	75.5 (48.2-118.0)
Time since onset of cervical dystonia, years	12.0 (8.8)	11.8 (8.8)
Patients previously treated with botulinum toxin, n (%)	45 (82)	51 (84)
TWSTRS total score—mean (SD)	43.8 (8.0)	45.8 (8.8)
Subject's VAS for symptom severity, mm—mean	67.7 (19.7)	63.6 (18.9)
Investigator's VAS for symptom severity, mm—mean (SD)	62.3 (15.8)	65.3 (18.0)
SF-36 mental health summary score—mean (SD)	44.5 (10.4)	43.3 (11.1)

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Characteristic	AbobotulinumtoxinA (n = 55)	Placebo (n = 61)
SF-36 physical health summary score—mean (SD)	39.4 (8.8)	43.2 (7.9)
Subject's VAS for pain severity, mm—mean (SD)	47.4 (25.0)	49.6 (24.5)
TWSTRS severity subscale score—mean (SD)	20.4 (3.0)	21.2 (2.8)
TWSTRS disability subscale score—mean (SD)	12.9 (3.8)	13.8 (4.5)
TWSTRS pain subscale score—mean (SD)	10.6 (4.2)	10.9 (4.6)

SD, standard deviation; SF-36, SF-36 Health Survey; TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale; VAS, visual analog scale.

Comparison with US population and other neurological conditions

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 2). For example, upon study entry, patients with CD reported Role Physical impairments that were approximately 32% lower (worse) than the age- and gender-adjusted US norm (domain score of 52.4 among patients with CD vs. 76.6 for the US norm, $P < 0.05$). Similarly, patients with CD reported experiencing significantly more pain than the age- and gender-adjusted US norm upon study entry, with Bodily Pain scores that were 23 percentage points lower (worse) for patients with CD than the US norms (47.7 vs. 71.3, $P < 0.05$).

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table 2. Mean SF-36 scores for the normative US population and patients with cervical dystonia, Parkinson's disease, or multiple sclerosis

SF-36 Domain	Cervical dystonia study sample (n = 116) Mean (SD)*	US normative sample† Mean	Parkinson's disease‡ (n = 150) Mean	Multiple sclerosis§ (n = 300) Mean (SD)
Physical Functioning	67.2 (22.2)	79.7	50.4	40.5 (30.2)
Role Physical	52.4 (29.5)	76.6	31.4	24.0 (36.8)
Bodily Pain	47.7 (21.6)	71.3	59.9	59.5 (27.2)
General Health	61.4 (19.7)	68.6	51.5	51.7 (24.1)
Vitality	50.6 (18.1)	60.1	46.1	35.1 (21.7)
Social Functioning	64.8 (24.6)	82.0	62.6	57.3 (27.6)
Role Emotional	68.8 (27.1)	80.6	49.0	56.1 (44.9)
Mental Health	64.1 (18.4)	74.8	67.1	67.1 (20.8)

* Baseline domain scores significantly lower than age- and gender-adjusted general US population norm for all domains ($P < 0.05$).

† Age- and gender-adjusted US norms.[11]

‡ Damiano *et al.*[17]

§ Hopman *et al.*[18]

SD, standard deviation; SF-36, SF-36 Health Survey; US, United States.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Like individuals with CD, patients with Parkinson's disease and multiple sclerosis report substantial impairments in HRQOL relative to US norms (Table 2). However, each of these neurologic conditions presents with a unique profile of HRQOL impairment. Patients with CD report the greatest limitation in the Bodily Pain domain, whereas patients with Parkinson's disease report the greatest impairments in the Role Physical domain, and patients with multiple sclerosis report the greatest impairments in the Vitality domain. Each of these neurological conditions impairs patients physically, yet the presentation of the disease manifests itself differently in terms of HRQOL impairment.

Treatment effect

Improvements from baseline to week 8 were observed for all eight SF-36 domains in the abobotulinumtoxinA group, whereas the placebo group showed some decline in Physical Functioning and little to no change in other SF-36 domains (Table 3; Figure 2). The largest improvements occurred in the Role Physical and Bodily Pain domains.

Patients treated with abobotulinumtoxinA reported significantly greater improvements than placebo patients from baseline to week 8 in five of the eight SF-36 domains (Table 3; Figure 2). Specifically, patients treated with abobotulinumtoxinA reported significantly greater improvements in the Physical Functioning, Role Physical, Bodily Pain, General Health, and Role Emotional domains ($P \leq 0.03$ for all) than patients treated with placebo.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table 3. Mean (SE) SF-36 scores by treatment group: baseline and week 8

	AbobotulinumtoxinA				Placebo			
SF-36 Domain	N	Baseline mean (SD)	Week 8 mean (SD)	Change mean (SD)	N	Baseline mean (SD)	Week 8 mean (SD)	Change mean (SD)	*P* value
Physical Functioning*	45	61.9 (20.0)	70.1 (20.1)	8.2 (16.0)	37	68.2 (21.7)	66.4 (23.4)	–1.9 (16.8)	0.018
Role Physical*	44	46.3 (28.5)	62.9 (25.1)	16.6 (21.1)	37	50.5 (29.9)	53.7 (25.6)	3.2 (24.0)	0.008
Bodily Pain*	42	47.9 (23.0)	61.8 (20.4)	13.9 (19.7)	37	49.0 (19.7)	51.9 (22.0)	2.9 (20.3)	0.010
General Health*	44	58.9 (19.4)	62.1 (18.4)	3.2 (11.1)	37	62.2 (19.6)	59.7 (21.1)	-2.5 (10.6)	0.030
Vitality	45	47.5 (15.6)	56.0 (16.8)	8.5 (15.0)	37	50.5 (19.5)	52.0 (19.2)	1.5 (17.8)	0.086
Social Functioning	43	62.2 (26.8)	73.3 (22.9)	11.0 (25.8)	37	63.2 (25.0)	67.2 (25.6)	4.1 (15.6)	0.125
Role Emotional *	44	71.0 (25.4)	80.5 (21.5)	9.5 (20.9)	37	62.2 (28.0)	66.4 (25.3)	4.3 (26.8)	0.030
Mental Health	45	62.6 (16.3)	70.2 (15.8)	7.7 (14.5)	37	60.1 (20.9)	63.9 (21.0)	3.8 (15.2)	0.125

Note: Comparison between AbobotulinumtoxinA and placebo for change from baseline to week 8 using an ANCOVA model with baseline value as covariate.

* SF-36 domains that differed significantly ($P < 0.05$) between abobotulinumtoxinA and placebo.

ANCOVA, analysis of covariance; SD, standard deviation; SE, standard error; SF-36, SF-36 Health Survey.

For Peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table 4 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).

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table 4. Correlations between the week 8 SF-36 scores with the TWSTRS at week 4 by treatment group

	Week 4: correlation; *P* value; n							
	Total		Disability		Severity		Pain	
	Abobotulinum-toxinA	Placebo	Abobotulinum-toxinA	Placebo	Abobotulinum-toxinA	Placebo	Abobotulinum-toxinA	Placebo
Physical Functioning	–0.34; 0.0278; 43	–0.19; 0.2801; 36	–0.34; 0.0257; 44	–0.03; 0.8978; 36	–0.35; 0.0223; 43	–0.31; 0.0694; 36	–0.13; 0.3969; 44	–0.10; 0.55; 36
Role Physical	–0.34; 0.0295; 42	–0.34; 0.0422; 36	–0.34; 0.0270; 43	–0.27; 0.1069; 36	–0.35; 0.0229; 42	–0.37; 0.0255; 36	–0.12; 0.4265; 43	–0.18; 0.2811; 36
Bodily Pain	–0.41; 0.00080; 40	–0.35; 0.0345; 36	–0.31; 0.0523; 41	–0.29; 0.0871; 36	–0.20; 0.2133; 40	–0.44; 0.0076; 36	–0.53; 0.0003; 41	–0.14; 0.4296; 36
General Health	–0.31; 0.0422 42	0.08 0.6521 36	–0.26 0.1459 43	0.16 0.3639 36	–0.43 0.0045 42	0.06 0.7217 36	–0.09 0.5785 43	–0.02 0.9235 36

For peer review only

	Week 4: correlation; *P* value; n							
	Total		**Disability**		**Severity**		**Pain**	
	Abobotulinum-toxinA	**Placebo**	**Abobotulinum-toxinA**	**Placebo**	**Abobotulinum-toxinA**	**Placebo**	**Abobotulinum-toxinA**	**Placebo**
Vitality	–0.26	–0.20	–0.25	–0.06	–0.38	–0.14	0.04	–0.27
	0.0983	0.2517	0.0963	0.7272	0.0123	0.4201	0.7860	0.1172
	43	36	44	36	43	36	44	36
Social	–0.25	–0.11	–0.32	0.15	–0.32	–0.08	0.06	–0.31
Functioning	0.1217	0.5206	0.0394	0.3909	0.0437	0.6437	0.7280	0.0683
	41	36	42	36	41	36	42	36
Role	–0.18	–0.14	–0.29	0.01	–0.14	–0.15	–0.01	–0.19
Emotional	0.2877	0.4150	0.0612	0.9460	0.3874	0.3947	0.9383	0.2634
	42	36	43	36	42	36	43	36
Mental	–0.17	0.05	–0.13	0.22	–0.38	0.16	0.14	–0.24
Health	0.2668	0.7815	0.3990	0.1949	0.0128	0.3365	0.3786	0.1502
	43	36	44	36	43	36	44	36

Note: Correlations are negative as the TWSTRS and SF-36 are scored in opposite directions.

SF-36, SF-36 Health Survey; TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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. 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, the largest improvements occurred in Physical Functioning, Role Physical, Bodily Pain, Vitality, and Social Functioning ($P \leq 0.03$ for all).

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table 5. Mean change in SF-36 scores by TWSTRS response status

	TWSTRS Responder Status			
	Mean Change in SF-36			
SF-36 Domain	TWSTRS non-responder (n = 47)	TWSTRS responder (n = 36)	Difference (responder – non-responder)	*P* value
Physical Functioning	–0.6	9.1	9.7	0.0091
Role Physical	3.5	19.3	15.8	0.0020
Bodily Pain	1.8	17.6	15.8	0.0005
General Health	–1.5	3.3	4.8	0.0552
Vitality	0.8	11.1	10.3	0.0067
Social Functioning	2.8	14.3	11.5	0.0251
Role Emotional	2.8	12.5	9.7	0.0665
Mental Health	3.9	8.5	4.6	0.1691

SF-36, SF-36 Health Survey; TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale.

For peer review only

DISCUSSION

Although CD is limited to involuntary muscle spasms of the neck, its detrimental effect on health status is comparable to progressive and generalized conditions clinically perceived to be of greater severity (such as multiple sclerosis and Parkinson's disease). Camfield[19] conducted a survey of 150 patients with CD that included the SF-36 and the Beck anxiety and depression indexes. Patients with CD had lower scores in all eight SF-36 domains compared with

controls in the United Kingdom (UK), particularly in the Role Physical (41.6 vs. 85.8), Bodily Pain (54.6 vs. 81.5), and General Health (46.2 vs. 73.5) domains. Domain scores were comparable to data from patients with mild to moderate multiple sclerosis and moderate epilepsy. Our results are similar to those of Camfield[19], in that baseline scores for patients with CD were lower (worse) than for US normative data, particularly for the Role Physical (52.4 vs. 76.6), and Bodily Pain (47.7 vs. 71.3) domains. Our findings support the implication that CD has a significant impact on health status that is comparable with other neurological disorders of high morbidity. CD appears to have a disproportionate negative impact on patients' physical role limitation, despite their good physical functioning. One possible explanation is that pain limits such activities. Another possibility is that patients with CD consciously limit activities that make their dystonia visible to others to avoid mockery.[20]

A few studies have investigated the impact of CD on HRQOL and factors modifying a patient's ability to cope with this disease. Slawek *et al*[21] conducted an HRQOL survey study in 101 patients previously treated with BoNT-A using the TWSTRS, a pain VAS (0-100%), the SF-36, and the Montgomery-Åsberg Depression Rating Scale (MADRS). Patients' baseline SF-36 scores were worse than those of healthy controls in all eight SF-36 domains. Improvements were observed 4 weeks after the single BoNT-A injections in all SF-36 domains, and in the VAS, TWSTRS, and MADRS scores. The TWSTRS results did not correlate with any of the SF-36 domains. Longer treatment with BoNT-A was associated with better scores. Hefter *et al*[22, 23] conducted a prospective, open-label study of abobotulinumtoxinA in 516 de novo CD patients using the TWSTRS, the Craniocervical Dystonia Questionnaire (CDQ-24), patient diaries, and a global assessment of pain. In contrast with the SF-36, which is a general measure of HRQOL, the CDQ-24 is a disease-specific questionnaire that evaluates HRQOL in patients

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

with CD.[24] The CDQ-24 has five subscales: Stigma, Emotional Wellbeing, Pain, Activities of Daily Living, and Social/Family Life. At week 4, significant improvements were observed in CDQ-24 total and subscale scores that were sustained up to week 12. Significant reductions in patient diary item scores for activities of daily living, pain, and pain duration at week 4 and 12 were observed. Sixty-six percent of patients reported pain relief (less or no pain) at week 4 and 74% at week 12. Improvements in quality of life and pain intensity for up to 12 weeks in patients with CD were observed after treatment with abobotulinumtoxinA.

Likewise, in our findings, patients treated with abobotulinumtoxinA reported significantly greater improvements in TWSTRS total mean scores at weeks 4, 8, and 12 ($P \leq 0.019$) compared with placebo.[9] Improvements from baseline to week 8 were observed for all eight SF-36 domains in the abobotulinumtoxinA group, whereas the placebo group either stayed the same or became worse (with a decline in physical functioning). In this study, the SF-36 results did correlate with the TWSTRS for the Role Physical and Bodily Pain domains across treatment groups and time periods. AbobotulinumtoxinA was well tolerated in this study, as previously published.[9]

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 HRQOL. 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. Lastly, there were quite a few withdrawals from the study, which could affect overall findings. There were a total of 33 patients

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

(abobotulinumtoxinA n = 10; placebo n = 23) who discontinued the study, two-thirds of whom were in the placebo group.

CONCLUSION

CD has a marked impact on HRQOL for patients. Patients with CD report significantly worse functioning than that of their peers (age- and gender-adjusted US normative values). Results from this prospective, randomized controlled trial support the ability of abobotulinumtoxinA 500 U to provide efficacy in reducing motor symptoms in conjunction with significant improvements in HRQOL for patients.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

REGISTRATION

The trial is registered at ClinicalTrials.gov, numbers NCT00257660 and NCT00288509.

FUNDING

This work was supported by Ipsen Biopharmaceuticals, Inc.

COMPETING INTERESTS

Chandra Abbott is a former employee of Ipsen Biopharmaceuticals, Inc. Margaret Mordin, Catherine Masaquel, and Catherine Copley-Merriman, employees of RTI Health Solutions, were contracted by Ipsen Biopharmaceuticals, Inc. to perform and report on the research described here.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

AUTHOR CONTRIBUTIONS

ALL AUTHORS FULFILL ALL THREE OF THE ICMJE GUIDELINES FOR AUTHORSHIP.

MARGARET MORDIN, CATHERINE MASAQUEL, CHANDRA ABBOTT, AND KATI COPLEY-MERRIMAN CONTRIBUTED SUBSTANTIALLY TO THE CONCEPTION AND DESIGN, ACQUISITION OF DATA, AND ANALYSIS AND INTERPRETATION OF DATA

MARGARET MORDIN AND CATHERINE MASAQUEL DRAFTED THE ARTICLE.
MARGARET MORDIN, CATHERINE MASAQUEL, CHANDRA ABBOTT, AND KATI COPLEY-MERRIMAN REVISED IT CRITICALLY FOR IMPORTANT INTELLECTUAL CONTENT; AND

MARGARET MORDIN, CATHERINE MASAQUEL, CHANDRA ABBOTT, AND KATI COPLEY-MERRIMAN APPROVED THE FINAL VERSION TO BE PUBLISHED.

ACKNOWLEDGMENTS

The authors wish to acknowledge Jean Hubble, MD, formerly of Ipsen Biopharmaceuticals, Inc., for her clinical contributions to this paper; and Stephen Chang, PhD, formerly of Ipsen Biopharmaceuticals, Inc., for conduct of the statistical analyses of the trial data reported in this manuscript. Rosemarie Kelly, PhD, consultant to Ipsen, provided critical review of the manuscript.

For peer review only

FIGURE LEGENDS

Figure 1. Study Flow Diagram

Figure 2. Mean (SE) change in SF-36 scores at week 8

* $P < 0.05$.

Note: Positive changes in score indicate improvement.

SE, standard error; SF-36, SF-36 Health Survey.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

REFERENCES

1. Albanese A, Del Sorbo F, Comella C, *et al*. Dystonia rating scales: Critique and recommendations. *Mov Disord* 2013;**28**:874–83.
2. Van Zandijcke M. Cervical dystonia (spasmodic torticollis). Some aspects of the natural history. *Acta Neurol Belg* 1995;**95**:210–15.
3. Geyer HL, Bressman SB. The diagnosis of dystonia. *Lancet Neurol* 2006;5:780–90.
4. Kutvonen O, Dastidar P, Nurmikko T. Pain in spasmodic torticollis. *Pain* 1997;**69**:279–86.
5. Chan J, Brin MF, Fahn S. Idiopathic cervical dystonia: clinical characteristics. *Mov Disord* 1991;**6**:119–26.
6. Pekmezovic T, Svetel M, Ivanovic N, *et al*. Quality of life in patients with focal dystonia. *Clin Neurol Neurosurg* 2009;**111**:161–64.
7. Ben-Shlomo Y, Camfield L, Warner T. What are the determinants of quality of life in people with cervical dystonia? *J Neurol Neurosurg Psychiatry* 2002;**72**:608–14.
8. Degirmenci Y, Oyekcin DG, Bakar C, *et al*. Anxiety and depression in primary and secondary dystonia: A burden on health related quality of life. *Neurology, Psychiatry, and Brain Research* 2013;**19**:80-5.
9. Truong D, Brodsky, Lew M, *et al*. Long-term efficacy and safety of botulinum toxin type A (Dysport) in cervical dystonia. *Parkinsonism Relat Disord* 2010;**16**:316–23.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

10. Truong D, Duane DD, Jankovic J, *et al*. Efficacy and safety of botulinum type A toxin (Dysport) in cervical dystonia: Results of the first US randomized, double-blind, placeo-controlled study. *Movement Disorders* 2005;**20**(7):783-791. 4.

11. Ware JE, Snow KK, Kosinski M, *et al*. SF-36 Health Survey: manual and interpretation guide. Boston: The Health Institute, New England Medical Center, 1993.

12. Welsh M. Parkinson's disease and quality of life: issues and challenges beyond motor symptoms. *Neurol Clin* 2004;**22**:S141–8.

13. Simpson DM, Blitzer A, Brashear A, *et al*. Assessment: botulinum neurotoxin for the treatment of movement disorders (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2008;**70**:1699–706.

14. Hallett M, Albanese A, Dressler D, et al. Evidence-based review and assessment of botulinum neurotoxin for the treatment of movement disorders. Toxicon 2013;**67**:94–114.

15. Costa J, Espirito-Santo C, Borges A, *et al*. Botulinum toxin type A therapy for cervical dystonia. *Cochrane Database Syst Rev* 2005;CD003633.

16. Jankovic J, Brin MF. Therapeutic uses of botulinum toxin. *N Engl J Med* 1991;**324**:1186–94.

17. Damiano AM, McGrath MM, Willian MK, *et al*. Evaluation of a measurement strategy for Parkinson's disease: assessing patient health-related quality of life. *Qual Life Res* 2000;**9**:87–100.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

18. Hopman W, Coo H, Edgar C, *et al*., Factors Associated with Health-Related Quality of Life in Multiple Sclerosis. *Can J Neurol Sci* 2007;**34**:160–6.

19. Camfield L. Quality of life in cervical dystonia. *Mov Disord* 2000;**15**(suppl).

20. Camfield L, Ben-Shlomo Y, Warner TT; Epidemiological Study of Dystonia in Europe Collaborative Group. Impact of cervical dystonia on quality of life. *Mov Disord* 2002;**17**:838–45.

21. Slawek J, Friedman A, Potulska A, *et al*. Factors affecting the health-related quality of life of patients with cervical dystonia and the impact of botulinum toxin type A injections. *Funct Neurol* 2007;**22**:95–100.

22. Hefter H, Benecke R, Erbguth F, *et al*. An open-label cohort study of the improvement of quality of life and pain in de novo cervical dystonia patients after injections with 500 U botulinum toxin A (Dysport). *BMJ Open* 2013;**3**:e001853.doi:10.1136/bmjopen-2012-001853.

23. Hefter H, Kupsch A, Mungersdorf M, *et al*; on behalf of the Dysport Cervical Dystonia Study Group. A botulinum toxin A treatment algorithm for de novo management of torticollis and laterocollis. *BMJ Open* 2011;**2**:e000196.doi:10.1136/bmjopen-2011-000196.

24. Müller J, Wissel J, Kemmler G, *et al*. Craniocervical dystonia questionnaire (CDQ-24): development and validation of a disease-specific quality of life instrument. *J Neurol Neurosurg Psychiatry* 2004;**75**:749–53.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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

Margaret Mordin, MS, Market Access and Outcomes Strategy, RTI Health Solutions, Ann Arbor, MI, United States

Catherine Masaquel, MPH, Market Access and Outcomes Strategy, RTI Health Solutions, Ann Arbor, MI, United States

Chandra Abbott, PhD,* Neurology Medical Affairs, Ipsen Biopharmaceuticals, Inc, Basking Ridge, NJ, United States

Catherine Copley-Merriman, MBA, MS, Market Access and Outcomes Strategy, RTI Health Solutions, Ann Arbor, MI, United States

Corresponding Author:

Margaret Mordin

RTI Health Solutions

3005 Boardwalk St., Suite 105

* Former employee of Ipsen Biopharmaceuticals, Inc.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Ann Arbor, MI 48108

Telephone: +1.703.483.9009

Fax: +1.734.213.6169

E-mail: mmordin@rti.org

Key words: cervical dystonia, botulinum toxin type A, Dysport, spasmodic torticollis, health-related quality of life

Word Count (excluding title page, abstract, references, tables, and figure legends): ~3,165

For peer review only

ABSTRACT

Objective: To describe the health-related quality of life (HRQOL) burden of cervical dystonia (CD) and report on the HRQOL and patient perception of treatment benefits of abobotulinumtoxinA (Dysport®).

Design: The safety and efficacy of a single injection of abobotulinumtoxinA for CD treatment were evaluated in a previously reported international, multicenter, double-blind, randomized trial. HRQOL measures were assessed in the trial and have not been previously reported.

Setting: Movement disorder clinics in the United States (US) and Russia.

Participants: Patients had to have a diagnosis of CD with symptoms for at least 18 months, as well as a total Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) score of at least 30; a Severity domain score of at least 15; and a Disability domain score of at least 3. Key exclusion criteria included treatment with botulinum toxin type A (BoNT-A) or botulinum toxin type B (BoNT-B) within 16 weeks of enrollment.

Interventions: Patients were randomized to receive either 500 U abobotulinumtoxinA (n = 55) or placebo (n = 61).

Primary and secondary outcome measures: Efficacy assessments included TWSTRS total (primary endpoint) and subscale scores at weeks 0, 4, 8, 12 ; a pain visual analog scale at weeks 0 and 4; and HRQOL assessed by the SF-36 Health Survey (SF-36) (secondary endpoint) at weeks 0 and 8.

Results: Patients with CD reported significantly greater impairment for all SF-36 domains relative to US norms. Patients treated with abobotulinumtoxinA reported significantly greater improvements in Physical Functioning, Role Physical, Bodily Pain, General Health, and Role Emotional domains than placebo patients ($P \leq 0.03$ for all). The TWSTRS was significantly

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

correlated with Physical Functioning, Role Physical, and Bodily Pain scores, for those on active treatment.

Conclusions: CD has a marked impact on HRQOL. Treatment with a single abobotulinumtoxinA injection results in significant improvement in patients' HRQOL.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

ARTICLE SUMMARY

Strengths and limitations of this study

- The efficacy and safety of a single injection of abobotulinumtoxinA for CD treatment were evaluated in an international, multicenter, randomized double-blind trial.
- This paper presents previously unreported findings of health-related quality of life assessed during the international, multicenter, randomized double-blind trial of abobotulinumtoxinA.
- The size of this study was small; therefore, 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.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

INTRODUCTION

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] Cervical dystonia (CD), the most common form of focal dystonia, is characterized by sustained involuntary muscle contraction and/or twitching of cervical musculature resulting in abnormal postures and repetitive movements of the head.[2] Depending on the muscles involved, the following head positions, or combination of head positions, may occur: torticollis (rotation), laterocollis (tilting), anterocollis (flexion), and retrocollis (extension).[3] CD may be accompanied by pulling or stiffness, pain, and sensory symptoms in the affected area.[4] The diagnosis of CD is based on clinical signs and symptoms: deviation in head/neck posture; involuntary neck movements resulting in turn, tilt, and/or shoulder elevation; and neck pain.[3, 5]

Besides the clinical problems of involuntary abnormal postures and repetitive movements frequently associated with pain, patients with CD present with a wide range of social disabilities and impairments in health-related quality of life (HRQOL).[6] HRQOL is defined as the subjective perception of the impact of health status, including disease and treatment, on physical, psychological, and social functioning and well-being.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Recognizing the critical link between physical and psychological health allows a more holistic approach to patient care. By measuring HRQOL, we can ascertain the effects of a disease on individuals from the patient perspective and, thereafter, to some extent, be able to judge the benefit of therapeutic interventions. With CD, several physical and emotional factors such as reduced mobility, pain, low self-esteem, embarrassment, depression, anxiety, and limited social interaction may be present. Pain is a predominant feature of CD and is reported in up to 75% of patients [7] and is associated with reduced HRQOL. A study conducted by Degirmenci *et al*[8] evaluated anxiety and depression in dystonia patients using the Hospital Anxiety Depression (HAD) scale and assessed quality of life using the SF-36 Health Survey (SF-36), a general measure widely used to assess HRQOL. Mean Anxiety and Depression subscale scores were higher in patients with dystonia when compared with the control group. Moreover, patients with dystonia had worse (lower) SF-36 scores for all domains when compared with controls.

AbobotulinumtoxinA (Dysport) 500 U was compared with placebo in two multicenter, double-blinded, randomized trials: one international[9] and one in the United States (US).[10] The international study included the SF-36 to evaluate treatment benefit with 500 U abobotulinumtoxinA compared with placebo as a secondary endpoint. As a result of the tremendous amount of research conducted using the SF-36 over the past two decades, population norms are available that can facilitate the interpretation of research results across a wide variety of patient populations, putting specific study data into "larger context."[11] In order to understand the HRQOL impairment unique to CD, SF-36 scores for the study sample were compared with other published scores for populations with various neurological conditions, in particular Parkinson's disease and multiple sclerosis; like CD, these conditions are generally progressive and affect motor and non-motor function. Specifically, because the HRQOL

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

impairment of Parkinson's disease and that of multiple sclerosis have been well established,[12] these conditions were deemed appropriate comparisons in evaluating the unique nature of HRQOL impairment due to CD.

Botulinum toxin (BoNT), a treatment with established safety and efficacy, has been recommended as first-line treatment for symptoms of CD.[13, 14] No botulinum toxin is indicated for improving HRQOL in CD. The reported benefits from BoNT are relief from pain, increased range of free movement, and improved resting posture.[15, 16] BoNT injections typically offer temporary relief, and the symptoms gradually return. For CD, as for most other neurological disorders, more data exist regarding the efficacy of the Botulinum toxin type A (BoNT-A) compared with type B. BoNT-A and BoNT-B have been shown to reduce both symptom severity and pain.[15] Currently, there are three major commercially available preparations of type A toxins: abobotulinumtoxinA (Dysport® [Ipsen Biopharm Ltd, Wrexham, UK]), onabotulinumtoxinA (Botox® [Allergan, Inc.; Irvine, CA]), and incobotulinumtoxinA (Xeomin® [Merz Pharmaceuticals GmbH; Frankfurt am Main, Germany). The potency units of abobotulinumtoxinA are specific to the preparation and assay method utilized. They are not interchangeable with other preparations of botulinum toxin products and, therefore, units of biological activity of one BoNT product cannot be compared to or converted into units of any other botulinum toxin products. Accordingly, information regarding the specific benefits of a particular BoNT-A preparation and the impact on HRQOL would be valuable.

The objectives of this article are to describe the HRQOL burden of CD, as measured at baseline in a previously reported randomized, double-blind, placebo-controlled, pivotal clinical study,[9] as well as report on the HRQOL and treatment benefits of abobotulinumtoxinA.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

MATERIALS AND METHODS

Study design

The study design has been reported previously.[9] An international, multicenter (movement disorder clinics in the US [n = 16] and Russia [n = 4]), double-blind, randomized, placebo-controlled trial was conducted between October 10, 2005 and September 7, 2006 to evaluate the safety and efficacy of a single injection of abobotulinumtoxinA for the treatment of CD. To be eligible for study entry, patients had to have a diagnosis of CD with symptoms for at least 18 months, as well as the following baseline Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) scores: a total score of at least 30; a Severity domain score of at least 15; and a Disability domain score of at least 3. The TWSTRS is an assessment of CD that includes a total CD rating score and three domain scores (Torticollis Severity, Disability, and Pain).

Key exclusion criteria were standard for efficacy trials of BoNT and included treatment with BoNT-A or BoNT-B within 16 weeks of enrollment, any disease of the neuromuscular junction, previous phenol injection to the neck muscles, myotomy or denervation surgery in the neck/shoulder region, cervical contracture, suspected secondary non-responsiveness or a history of poor response to BoNT-A, pure anterocollis or retrocollis, symptom remission at screening, symptoms that could interfere with TWSTRS scoring, or BoNT-A neutralizing antibodies.

A total of 120 patients were to be recruited in the study to allow for 47 patients per treatment group to be evaluable on the primary efficacy endpoint (TWSTRS).[9] Patients were randomized using a pregenerated randomization code in a 1:1 ratio to receive an intramuscular injection of either 500 U abobotulinumtoxinA or placebo. Study medication was administered in a double-blind manner by intramuscular injection into two, three, or four clinically indicated neck muscles during a single dosing session at baseline. The study was conducted in accordance

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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.

Assessments

Assessments have been described previously.[9] The TWSTRS was determined at week 0 (baseline), at week 4 (primary), and at weeks 8 and 12 (posttreatment) by investigators trained in TWSTRS scoring. Pain was evaluated with the Pain domain of the TWSTRS and a self-reported visual analog scale (VAS) assessing pain in the past 24 hours. Participants completed the pain VAS at baseline and week 4.

HRQOL was assessed using the SF-36, version 1.0. The SF-36 is a commonly used health profile that contains 36 items and includes multi-item domains to measure health status across eight dimensions: Physical Functioning, Role Limitations due to Physical Health Problems (Role Physical), Bodily Pain, Social Functioning, General Mental Health, Role Limitations due to Emotional Problems (Role Emotional), Vitality, and General Health Perceptions. Responses to questions within each domain are summed and transformed to a scale ranging from 0 to 100, with higher scores suggesting better functioning. Participants completed the SF-36 at week 0 (baseline; prior to dosing) and at week 8 (posttreatment). SF-36 scores were generated according to published algorithms.[11]

Safety assessments included incidence of treatment-emergent adverse events, electrocardiogram, neurological and physical examinations, and vital signs.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Statistical analyses

Burden of cervical dystonia

Population norms are available for the SF-36 that can facilitate the interpretation of research results across a wide variety of patient populations.[11] The unique burden of illness associated with CD was assessed by comparing -patients' baseline domain scores (regardless of enrollment location) to age- and gender-adjusted SF-36 domain scores for the US population norms.[11] The 95% confidence interval was computed for the baseline SF-36 scores relative to the age- and gender-adjusted US population norms.

For comparisons relative to other neurologic conditions, baseline SF-36 scores for the study sample were compared with other published scores for populations with Parkinson's disease and multiple sclerosis. The patients with Parkinson's disease were patients attending six neurology centers in the US, with a mix of Hoehn and Yahr scores representing early-, middle-, and late-stage disease.[17] The patients with multiple sclerosis were part of a longitudinal study in Ontario, Canada.[18]

Treatment effect analysis

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.

Continuous primary (TWSTRS) and secondary variables (SF-36 domains) were analyzed using analysis of covariance (ANCOVA), controlling for treatment group, baseline score (where appropriate), treatment history (i.e., previous treatment with BoNT), and center.

Pearson correlation coefficients were calculated among the eight week 8 SF-36 domain scores and the week 4 and week 8 TWSTRS domain scores and total score by treatment group.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

A responder was defined, a priori, as a patient with a decrease in TWSTRS total score of at least 30% (at week 4) compared with baseline.[9] Mean SF-36 scores by TWSTRS responder status were evaluated using a *t* test. Safety assessments were based on the safety population, which included all patients who received at least one dose of study medication. Safety variables were summarizsed by descriptive statistics. Safety results have been reported previously.[9]

RESULTS

Patient disposition and demographics

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 intent-to-treat and safety populations. Of these, 83 patients (abobotulinumtoxinA n = 45; placebo n = 38) were analyzed in the HRQOL assessment. The mean (standard deviation [SD]) age was similar across treatment groups: 51.9 (13.4) years for the abobotulinumtoxinA group and 53.9 (12.5) years for placebo group. Similarly, both treatment groups were predominantly female (67.0% in the abobotulinumtoxinA group and 62.0% in the placebo group). All other patient demographics and baseline characteristics were similar between treatment groups (Table 1).[9] A total of 33 patients discontinued the study because of insufficient response, withdrawal of consent, loss to follow-up, or other reasons (Figure 1).

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table 1. Patient demographics and baseline characteristics (intent-to-treat population)

Characteristic	AbobotulinumtoxinA (n = 55)	Placebo (n = 61)
Age, years		
Mean (SD)	51.9 (13.4)	53.9 (12.5)
Median (range)	53.0 (20-79)	56.0 (28-78)
Sex, n (%) male	18 (33)	23 (38)
Race, n (%) Caucasian	55 (100)	61 (100)
Ethnicity, n (%)		
Hispanic/Latino	3 (5)	4 (7)
Not Hispanic/Latino	52 (95)	57 (93)
Height, cm		
Mean (SD)	167 (10.3)	170 (8.5)
Median (range)	167 (147-196)	168 (154-193)
Weight, kg		
Mean (SD)	73.4 (13.8)	77.4 (15.0)
Median (range)	73.0 (46.4-108.0)	75.5 (48.2-118.0)
Time since onset of cervical dystonia, years	12.0 (8.8)	11.8 (8.8)
Patients previously treated with botulinum toxin, n (%)	45 (82)	51 (84)
TWSTRS total score—mean (SD)	43.8 (8.0)	45.8 (8.8)
Subject's VAS for symptom severity, mm—mean	67.7 (19.7)	63.6 (18.9)
Investigator's VAS for symptom severity, mm—mean (SD)	62.3 (15.8)	65.3 (18.0)
SF-36 mental health summary score—mean (SD)	44.5 (10.4)	43.3 (11.1)

For peer review only

Characteristic	AbobotulinumtoxinA (n = 55)	Placebo (n = 61)
SF-36 physical health summary score—mean (SD)	39.4 (8.8)	43.2 (7.9)
Subject's VAS for pain severity, mm—mean (SD)	47.4 (25.0)	49.6 (24.5)
TWSTRS severity subscale score—mean (SD)	20.4 (3.0)	21.2 (2.8)
TWSTRS disability subscale score—mean (SD)	12.9 (3.8)	13.8 (4.5)
TWSTRS pain subscale score—mean (SD)	10.6 (4.2)	10.9 (4.6)

SD, standard deviation; SF-36, SF-36 Health Survey; TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale; VAS, visual analog scale.

Comparison with US population and other neurological conditions

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~~2). For example, upon study entry, patients with CD reported Role Physical impairments that were approximately 32% lower (worse) than the age- and gender-adjusted US norm (domain score of 52.4 among patients with CD vs. 76.6 for the US norm, $P < 0.05$). Similarly, patients with CD reported experiencing significantly more pain than the age- and gender-adjusted US norm upon study entry, with Bodily Pain scores that were 23 percentage points lower (worse) for patients with CD than the US norms (47.7 vs. 71.3, $P < 0.05$).

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table ~~1~~2. Mean SF-36 scores for the normative US population and patients with cervical dystonia, Parkinson's disease, or multiple sclerosis

SF-36 Domain	Cervical dystonia study sample (n = 116) Mean (SD)*	US normative sample† Mean	Parkinson's disease‡ (n = 150) Mean	Multiple sclerosis§ (n = 300) Mean (SD)
Physical Functioning	67.2 (22.2)	79.7	50.4	40.5 (30.2)
Role Physical	52.4 (29.5)	76.6	31.4	24.0 (36.8)
Bodily Pain	47.7 (21.6)	71.3	59.9	59.5 (27.2)
General Health	61.4 (19.7)	68.6	51.5	51.7 (24.1)
Vitality	50.6 (18.1)	60.1	46.1	35.1 (21.7)
Social Functioning	64.8 (24.6)	82.0	62.6	57.3 (27.6)
Role Emotional	68.8 (27.1)	80.6	49.0	56.1 (44.9)
Mental Health	64.1 (18.4)	74.8	67.1	67.1 (20.8)

* Baseline domain scores significantly lower than age- and gender-adjusted general US population norm for all domains ($P < 0.05$).

† Age- and gender-adjusted US norms.[11]

‡ Damiano *et al.*[17]

§ Hopman *et al.*[18]

SD, standard deviation; SF-36, SF-36 Health Survey; US, United States.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Like individuals with CD, patients with Parkinson's disease and multiple sclerosis report substantial impairments in HRQOL relative to US norms (Table 2~~1~~). However, each of these neurologic conditions presents with a unique profile of HRQOL impairment. Patients with CD report the greatest limitation in the Bodily Pain domain, whereas patients with Parkinson's disease report the greatest impairments in the Role Physical domain, and patients with multiple sclerosis report the greatest impairments in the Vitality domain. Each of these neurological conditions impairs patients physically, yet the presentation of the disease manifests itself differently in terms of HRQOL impairment.

Treatment effect

Improvements from baseline to week 8 were observed for all eight SF-36 domains in the abobotulinumtoxinA group, whereas the placebo group showed some decline in Physical Functioning and little to no change in other SF-36 domains (Table ~~2~~3; Figure 2). The largest improvements occurred in the Role Physical and Bodily Pain domains.

Patients treated with abobotulinumtoxinA reported significantly greater improvements than placebo patients from baseline to week 8 in five of the eight SF-36 domains (Table ~~2~~3; Figure 2). Specifically, patients treated with abobotulinumtoxinA reported significantly greater improvements in the Physical Functioning, Role Physical, Bodily Pain, General Health, and Role Emotional domains ($P \leq 0.03$ for all) than patients treated with placebo.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table ~~2~~3. Mean (SE) SF-36 scores by treatment group: baseline and week 8

	AbobotulinumtoxinA				Placebo			
SF-36 Domain	N	Baseline mean (SD)	Week 8 mean (SD)	Change mean (SD)	N	Baseline mean (SD)	Week 8 mean (SD)	Change mean (SD)	*P* value
Physical Functioning*	45	61.9 (20.0)	70.1 (20.1)	8.2 (16.0)	37	68.2 (21.7)	66.4 (23.4)	–1.9 (16.8)	0.018
Role Physical*	44	46.3 (28.5)	62.9 (25.1)	16.6 (21.1)	37	50.5 (29.9)	53.7 (25.6)	3.2 (24.0)	0.008
Bodily Pain*	42	47.9 (23.0)	61.8 (20.4)	13.9 (19.7)	37	49.0 (19.7)	51.9 (22.0)	2.9 (20.3)	0.010
General Health*	44	58.9 (19.4)	62.1 (18.4)	3.2 (11.1)	37	62.2 (19.6)	59.7 (21.1)	-2.5 (10.6)	0.030
Vitality	45	47.5 (15.6)	56.0 (16.8)	8.5 (15.0)	37	50.5 (19.5)	52.0 (19.2)	1.5 (17.8)	0.086
Social Functioning	43	62.2 (26.8)	73.3 (22.9)	11.0 (25.8)	37	63.2 (25.0)	67.2 (25.6)	4.1 (15.6)	0.125
Role Emotional *	44	71.0 (25.4)	80.5 (21.5)	9.5 (20.9)	37	62.2 (28.0)	66.4 (25.3)	4.3 (26.8)	0.030
Mental Health	45	62.6 (16.3)	70.2 (15.8)	7.7 (14.5)	37	60.1 (20.9)	63.9 (21.0)	3.8 (15.2)	0.125

Note: Comparison between AbobotulinumtoxinA and placebo for change from baseline to week 8 using an ANCOVA model with baseline value as covariate.

* SF-36 domains that differed significantly ($P < 0.05$) between abobotulinumtoxinA and placebo.

ANCOVA, analysis of covariance; SD, standard deviation; SE, standard error; SF-36, SF-36 Health Survey.

For Peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table ~~3~~4 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).

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table ~~34~~. Correlations between the week 8 SF-36 scores with the TWSTRS at week 4 by treatment group

	Week 4: correlation; *P* value; n							
	Total		**Disability**		**Severity**		**Pain**	
	Abobotulinum-toxinA	**Placebo**	**Abobotulinum-toxinA**	**Placebo**	**Abobotulinum-toxinA**	**Placebo**	**Abobotulinum-toxinA**	**Placebo**
Physical Functioning	–0.34; 0.0278; 43	–0.19; 0.2801; 36	–0.34; 0.0257; 44	–0.03; 0.8978; 36	–0.35; 0.0223; 43	–0.31; 0.0694; 36	–0.13; 0.3969; 44	–0.10; 0.55; 36
Role Physical	–0.34; 0.0295; 42	–0.34; 0.0422; 36	–0.34; 0.0270; 43	–0.27; 0.1069; 36	–0.35; 0.0229; 42	–0.37; 0.0255; 36	–0.12; 0.4265; 43	–0.18; 0.2811; 36
Bodily Pain	–0.41; 0.00080; 40	–0.35; 0.0345; 36	–0.31; 0.0523; 41	–0.29; 0.0871; 36	–0.20; 0.2133; 40	–0.44; 0.0076; 36	–0.53; 0.0003; 41	–0.14; 0.4296; 36
General Health	–0.31; 0.0422 42	0.08 0.6521 36	–0.26 0.1459 43	0.16 0.3639 36	–0.43 0.0045 42	0.06 0.7217 36	–0.09 0.5785 43	–0.02 0.9235 36

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

	Week 4: correlation; *P* value; n							
	Total		Disability		Severity		Pain	
	Abobotulinum-toxinA	Placebo	Abobotulinum-toxinA	Placebo	Abobotulinum-toxinA	Placebo	Abobotulinum-toxinA	Placebo
Vitality	–0.26	–0.20	–0.25	–0.06	–0.38	–0.14	0.04	–0.27
	0.0983	0.2517	0.0963	0.7272	0.0123	0.4201	0.7860	0.1172
	43	36	44	36	43	36	44	36
Social	–0.25	–0.11	–0.32	0.15	–0.32	–0.08	0.06	–0.31
Functioning	0.1217	0.5206	0.0394	0.3909	0.0437	0.6437	0.7280	0.0683
	41	36	42	36	41	36	42	36
Role	–0.18	–0.14	–0.29	0.01	–0.14	–0.15	–0.01	–0.19
Emotional	0.2877	0.4150	0.0612	0.9460	0.3874	0.3947	0.9383	0.2634
	42	36	43	36	42	36	43	36
Mental	–0.17	0.05	–0.13	0.22	–0.38	0.16	0.14	–0.24
Health	0.2668	0.7815	0.3990	0.1949	0.0128	0.3365	0.3786	0.1502
	43	36	44	36	43	36	44	36

Note: Correlations are negative as the TWSTRS and SF-36 are scored in opposite directions.

SF-36, SF-36 Health Survey; TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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). The largest improvements occurred in the Role Physical and Bodily Pain domains.~~ 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 45). Specifically, the largest improvements occurred ~~responders reported significantly greater improvements~~ in Physical Functioning, Role Physical, Bodily Pain, Vitality, and Social Functioning ($P \leq 0.03$ for all) ~~than patients considered non-responsive to treatment~~.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table 45. Mean change in SF-36 scores by TWSTRS response status

	TWSTRS Responder Status			
	Mean Change in SF-36			
SF-36 Domain	TWSTRS non-responder (n = 47)	TWSTRS responder (n = 36)	Difference (responder – non-responder)	*P* value
Physical Functioning	–0.6	9.1	9.7	0.0091
Role Physical	3.5	19.3	15.8	0.0020
Bodily Pain	1.8	17.6	15.8	0.0005
General Health	–1.5	3.3	4.8	0.0552
Vitality	0.8	11.1	10.3	0.0067
Social Functioning	2.8	14.3	11.5	0.0251
Role Emotional	2.8	12.5	9.7	0.0665
Mental Health	3.9	8.5	4.6	0.1691

SF-36, SF-36 Health Survey; TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale.

For peer review only

DISCUSSION

Although CD is ~~usually non-progressive and~~ limited to involuntary muscle spasms of the neck, its detrimental effect on health status is comparable to progressive and generalized conditions clinically perceived to be of greater severity (such as multiple sclerosis and Parkinson's disease). Camfield[19] conducted a survey of 150 patients with CD that included the SF-36 and the Beck anxiety and depression indexes. Patients with CD had lower scores in all

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

eight SF-36 domains compared with controls in the United Kingdom (UK), particularly in the Role Physical (41.6 vs. 85.8), Bodily Pain (54.6 vs. 81.5), and General Health (46.2 vs. 73.5) domains. Domain scores were comparable to data from patients with mild to moderate multiple sclerosis and moderate epilepsy. Our results are similar to those of Camfield[19], in that baseline scores for patients with CD were lower (worse) than for US normative data, particularly for the Role Physical (52.4 vs. 76.6), and Bodily Pain (47.7 vs. 71.3) domains. Our findings support the implication that CD has a significant impact on health status that is comparable with other neurological disorders of high morbidity. CD appears to have a disproportionate negative impact on patients' physical role limitation, despite their good physical functioning. One possible explanation is that pain limits such activities. Another possibility is that patients with CD consciously limit activities that make their dystonia visible to others to avoid mockery.[20]

A few studies have investigated the impact of CD on HRQOL and factors modifying a patient's ability to cope with this disease. Slawek *et al*[21] conducted an HRQOL survey study in 101 patients previously treated with BoNT-A using the TWSTRS, a pain VAS (0-100%), the SF-36, and the Montgomery-Åsberg Depression Rating Scale (MADRS). Patients' baseline SF-36 scores were worse than those of healthy controls in all eight SF-36 domains. Improvements were observed 4 weeks after the single BoNT-A injections in all SF-36 domains, and in the VAS, TWSTRS, and MADRS scores. The TWSTRS results did not correlate with any of the SF-36 domains. Longer treatment with BoNT-A was associated with better scores. Hefter *et al*[22, 23] conducted a prospective, open-label study of abobotulinumtoxinA in 516 de novo CD patients using the TWSTRS, the Craniocervical Dystonia Questionnaire (CDQ-24), patient diaries, and a global assessment of pain. In contrast with the SF-36, which is a general measure of HRQOL, the CDQ-24 is a disease-specific questionnaire that evaluates HRQOL in patients

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

with CD.[24] The CDQ-24 has five subscales: Stigma, Emotional Wellbeing, Pain, Activities of Daily Living, and Social/Family Life. At week 4, significant improvements were observed in CDQ-24 total and subscale scores that were sustained up to week 12. Significant reductions in patient diary item scores for activities of daily living, pain, and pain duration at week 4 and 12 were observed. Sixty-six percent of patients reported pain relief (less or no pain) at week 4 and 74% at week 12. Improvements in quality of life and pain intensity for up to 12 weeks in patients with CD were observed after treatment with abobotulinumtoxinA.

Likewise, in our findings, patients treated with abobotulinumtoxinA reported significantly greater improvements in TWSTRS total mean scores at weeks 4, 8, and 12 ($P \leq 0.019$) compared with placebo.[9] Improvements from baseline to week 8 were observed for all eight SF-36 domains in the abobotulinumtoxinA group, whereas the placebo group either stayed the same or became worse (with a decline in physical functioning). In this study, the SF-36 results did correlate with the TWSTRS for the Role Physical and Bodily Pain domains across treatment groups and time periods. AbobotulinumtoxinA was well tolerated in this study, as previously published.[9]

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 HRQOL. 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. Lastly, there were quite a few withdrawals from the study, which could affect overall findings. There were a total of 33 patients

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

(abobotulinumtoxinA n = 10; placebo n = 23) who discontinued the study, two-thirds of whom were in the placebo group.

CONCLUSION

CD has a marked impact on HRQOL for patients. Patients with CD report significantly worse functioning than that of their peers (age- and gender-adjusted US normative values). Results from this prospective, randomized controlled trial support the ability of abobotulinumtoxinA 500 U to provide efficacy in reducing motor symptoms in conjunction with significant improvements in HRQOL for patients.

For peer review only

REGISTRATION

The trial is registered at ClinicalTrials.gov, numbers NCT00257660 and NCT00288509.

FUNDING

This work was supported by Ipsen Biopharmaceuticals, Inc.

COMPETING INTERESTS

Chandra Abbott is a former employee of Ipsen Biopharmaceuticals, Inc. Margaret Mordin, Catherine Masaquel, and Catherine Copley-Merriman, employees of RTI Health Solutions, were contracted by Ipsen Biopharmaceuticals, Inc. to perform and report on the research described here.

AUTHOR CONTRIBUTIONS

All authors were involved in the analysis and interpretation of the data, manuscript writing, review and critique. All authors approved the final manuscript.

ACKNOWLEDGMENTS

The authors wish to acknowledge Jean Hubble, MD, formerly of Ipsen Biopharmaceuticals, Inc., for her clinical contributions to this paper; and Stephen Chang, PhD, formerly of Ipsen Biopharmaceuticals, Inc., for conduct of the statistical analyses of the trial data reported in this

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

manuscript. Rosemarie Kelly, PhD, consultant to Ipsen, provided critical review of the manuscript.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

FIGURE LEGENDS

Figure 1. Study Flow Diagram

Figure 2. Mean (SE) change in SF-36 scores at week 8

* $P < 0.05$.

Note: Positive changes in score indicate improvement.

SE, standard error; SF-36, SF-36 Health Survey.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

REFERENCES

1. Albanese A, Del Sorbo F, Comella C, *et al*. Dystonia rating scales: Critique and recommendations. *Mov Disord* 2013;**28**:874–83.

2. Van Zandijcke M. Cervical dystonia (spasmodic torticollis). Some aspects of the natural history. *Acta Neurol Belg* 1995;**95**:210–15.

3. Geyer HL, Bressman SB. The diagnosis of dystonia. *Lancet Neurol* 2006;5:780–90.

4. Kutvonen O, Dastidar P, Nurmikko T. Pain in spasmodic torticollis. *Pain* 1997;**69**:279–86.

5. Chan J, Brin MF, Fahn S. Idiopathic cervical dystonia: clinical characteristics. *Mov Disord* 1991;**6**:119–26.

6. Pekmezovic T, Svetel M, Ivanovic N, *et al*. Quality of life in patients with focal dystonia. *Clin Neurol Neurosurg* 2009;**111**:161–64.

7. Ben-Shlomo Y, Camfield L, Warner T. What are the determinants of quality of life in people with cervical dystonia? *J Neurol Neurosurg Psychiatry* 2002;**72**:608–14.

8. Degirmenci Y, Oyekcin DG, Bakar C, *et al*. Anxiety and depression in primary and secondary dystonia: A burden on health related quality of life. *Neurology, Psychiatry, and Brain Research* 2013;**19**:80-5.

9. Truong D, Brodsky, Lew M, *et al*. Long-term efficacy and safety of botulinum toxin type A (Dysport) in cervical dystonia. *Parkinsonism Relat Disord* 2010;**16**:316–23.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

10. Truong D, Duane DD, Jankovic J, *et al*. Efficacy and safety of botulinum type A toxin (Dysport) in cervical dystonia: Results of the first US randomized, double-blind, placeo-controlled study. *Movement Disorders* 2005;**20**(7):783-791. 4.

11. Ware JE, Snow KK, Kosinski M, *et al*. SF-36 Health Survey: manual and interpretation guide. Boston: The Health Institute, New England Medical Center, 1993.

12. Welsh M. Parkinson's disease and quality of life: issues and challenges beyond motor symptoms. *Neurol Clin* 2004;**22**:S141–8.

13. Simpson DM, Blitzer A, Brashear A, *et al*. Assessment: botulinum neurotoxin for the treatment of movement disorders (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2008;**70**:1699–706.

14. Hallett M, Albanese A, Dressler D, et al. Evidence-based review and assessment of botulinum neurotoxin for the treatment of movement disorders. Toxicon 2013;**67**:94–114.

15. Costa J, Espirito-Santo C, Borges A, *et al*. Botulinum toxin type A therapy for cervical dystonia. *Cochrane Database Syst Rev* 2005;CD003633.

16. Jankovic J, Brin MF. Therapeutic uses of botulinum toxin. *N Engl J Med* 1991;**324**:1186–94.

17. Damiano AM, McGrath MM, Willian MK, *et al*. Evaluation of a measurement strategy for Parkinson's disease: assessing patient health-related quality of life. *Qual Life Res* 2000;**9**:87–100.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

18. Hopman W, Coo H, Edgar C, *et al*., Factors Associated with Health-Related Quality of Life in Multiple Sclerosis. *Can J Neurol Sci* 2007;**34**:160–6.

19. Camfield L. Quality of life in cervical dystonia. *Mov Disord* 2000;**15**(suppl).

20. Camfield L, Ben-Shlomo Y, Warner TT; Epidemiological Study of Dystonia in Europe Collaborative Group. Impact of cervical dystonia on quality of life. *Mov Disord* 2002;**17**:838–45.

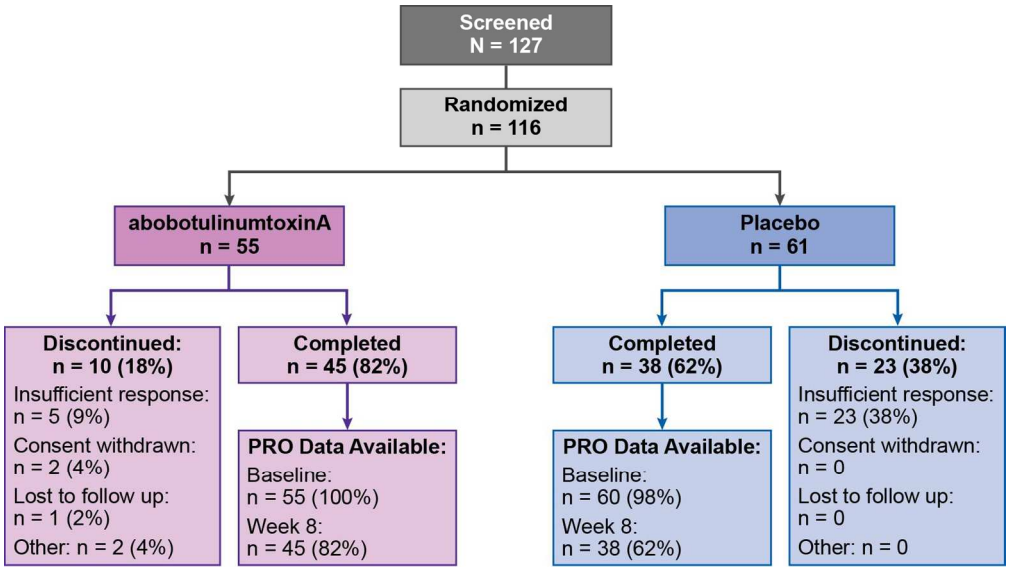
21. Slawek J, Friedman A, Potulska A, *et al*. Factors affecting the health-related quality of life of patients with cervical dystonia and the impact of botulinum toxin type A injections. *Funct Neurol* 2007;**22**:95–100.

22. Hefter H, Benecke R, Erbguth F, *et al*. An open-label cohort study of the improvement of quality of life and pain in de novo cervical dystonia patients after injections with 500 U botulinum toxin A (Dysport). *BMJ Open* 2013;**3**:e001853.doi:10.1136/bmjopen-2012-001853.

23. Hefter H, Kupsch A, Mungersdorf M, *et al*; on behalf of the Dysport Cervical Dystonia Study Group. A botulinum toxin A treatment algorithm for de novo management of torticollis and laterocollis. *BMJ Open* 2011;**2**:e000196.doi:10.1136/bmjopen-2011-000196.

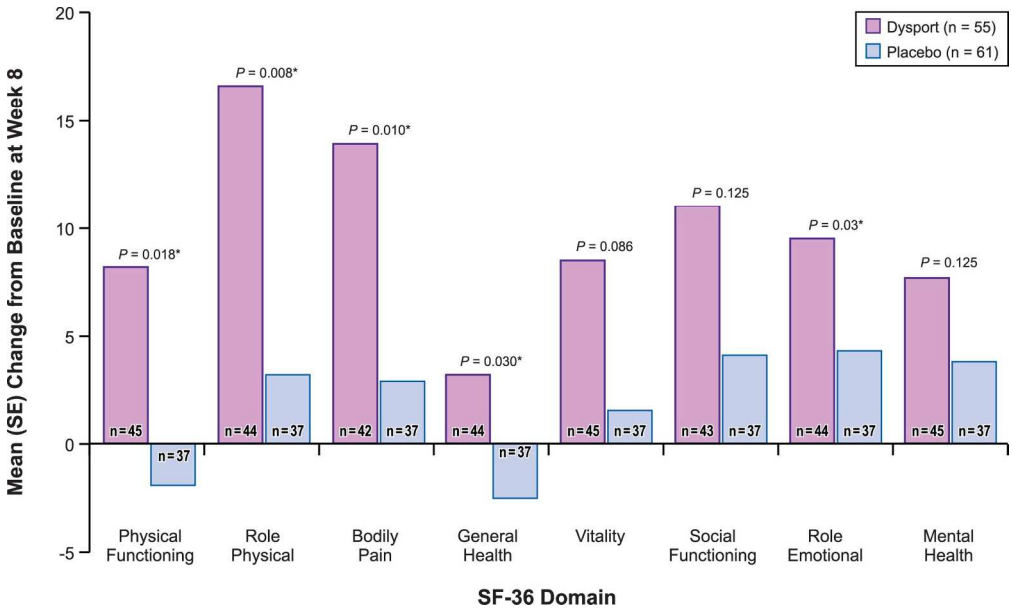
24. Müller J, Wissel J, Kemmler G, *et al*. Craniocervical dystonia questionnaire (CDQ-24): development and validation of a disease-specific quality of life instrument. *J Neurol Neurosurg Psychiatry* 2004;**75**:749–53.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml



152x85mm (300 x 300 DPI)

review only



186x111mm (300 x 300 DPI)

review only

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	6
	2b	Specific objectives or hypotheses	7
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	9
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	Not Applicable
Participants	4a	Eligibility criteria for participants	9
	4b	Settings and locations where the data were collected	9
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	9
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	9
	6b	Any changes to trial outcomes after the trial commenced, with reasons	Not Applicable
Sample size	7a	How sample size was determined	9
	7b	When applicable, explanation of any interim analyses and stopping guidelines	Not Applicable
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	9
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Not Applicable
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	9
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Not available at this time (study completed in 2006)

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	9
	11b	If relevant, description of the similarity of interventions	Not Applicable
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	11
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	11
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	12
	13b	For each group, losses and exclusions after randomisation, together with reasons	12
Recruitment	14a	Dates defining the periods of recruitment and follow-up	10
	14b	Why the trial ended or was stopped	Not Applicable
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Reported in Truong, 2010
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Figure 1 in separate file
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Figure 1 in separate file
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Not Applicable
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	17-19
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	Reported in Truong, 2010
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	23
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	21-22
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	22-23
Other information			
Registration	23	Registration number and name of trial registry	25
Protocol	24	Where the full trial protocol can be accessed, if available	Not available
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	25

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml