



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

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

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## 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.

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

## 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

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3 benefit of therapeutic interventions. With CD, several physical and emotional factors such as  
4 reduced mobility, pain, low self-esteem, embarrassment, depression, anxiety, and limited social  
5 interaction may be present. Unlike other forms of focal dystonia, pain is a predominant feature of  
6 CD and is reported in up to 75% of patients.[7] A study conducted by Degirmenci *et al*[8]  
7 evaluated anxiety and depression in dystonia patients using the Hospital Anxiety Depression  
8 (HAD) scale and assessed quality of life using the SF-36 Health Survey (SF-36), a generic  
9 HRQOL measure. Mean Anxiety and Depression subscales scores were higher in patients with  
10 dystonia when compared with the control group. Moreover, patients with dystonia had lower SF-  
11 36 scores for all domains when compared with controls.

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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.



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3 Botulinum toxin (BoNT), a treatment with established safety and efficacy, has been  
4 recommended as first-line treatment for symptoms of CD.[1, 12] The reported benefits from  
5 BoNT are relief from pain, increased range of free movement, and improved resting posture.[13,  
6 14] BoNT injections typically offer temporary relief and the symptoms gradually return. For CD,  
7 as for most other neurological disorders, more data exist regarding the efficacy of the Botulinum  
8 toxin type A (BoNT-A) compared with type B. BoNT-A has been shown to reduce both  
9 symptom severity and pain.[13] Currently, there are three major commercially available  
10 preparations of type A toxins: abobotulinumtoxinA (Dysport<sup>®</sup> [Ipsen Biopharm Ltd, Wrexham,  
11 UK]), onabotulinumtoxinA (Botox<sup>®</sup> [Allergan, Inc.; Irvine, CA]), and incobotulinumtoxinA  
12 (Xeomin<sup>®</sup> [Merz Pharmaceuticals GmbH; Frankfurt am Main, Germany]). The potency Units of  
13 abobotulinumtoxinA are specific to the preparation and assay method utilized. They are not  
14 interchangeable with other preparations of botulinum toxin products and, therefore, units of  
15 biological activity of one BoNT product cannot be compared to or converted into units of any  
16 other botulinum toxin products assessed with any other specific assay method. Due to this,  
17 information regarding the specific benefits of a particular BoNT-A preparation and the impact on  
18 HRQOL would be valuable.

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

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3 visual analog scale (VAS) assessing pain in the past 24 hours. Participants completed the pain  
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5 VAS at baseline and week 4.  
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8 HRQOL was assessed using the SF-36, version 1.0. The SF-36 is a commonly used  
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10 health profile that contains 36 items and includes multi-item domains to measure health status  
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12 across eight dimensions: Physical Functioning, Role Limitations due to Physical Health  
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14 Problems (Role Physical), Bodily Pain, Social Functioning, General Mental Health, Role  
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16 Limitations due to Emotional Problems (Role Emotional), Vitality, and General Health  
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18 Perceptions. Responses to questions within each domain are summed and transformed to a scale  
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20 ranging from 0 to 100, with higher scores suggesting better functioning. Participants completed  
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22 the SF-36 at week 0 (baseline; prior to dosing) and at week 8 (posttreatment). SF-36 scores were  
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24 generated according to published algorithms.[10]  
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29 Safety assessments included incidence of treatment-emergent adverse events (TEAEs),  
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31 electrocardiogram (ECG), neurological and physical examinations, and vital signs.  
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## 35 **Statistical analyses**

### 36 **Burden of cervical dystonia**

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39 Population norms are available that can facilitate the interpretation of research results  
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41 across a wide variety of patient populations.[10] The unique burden of illness associated with  
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43 CD was assessed by comparing patients' baseline domain scores to age- and gender-adjusted SF-  
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45 36 domain scores for the US population norms.[10] The 95% confidence interval was computed  
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47 for the baseline SF-36 scores relative to the age- and gender-adjusted US population norms.  
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52 Baseline SF-36 scores for the study sample were compared with other published scores  
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54 for populations with Parkinson's disease and multiple sclerosis. The patients with Parkinson's  
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56 disease were patients attending six neurology centers in the US, with a mix of Hoehn and Yahr  
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3 scores representing early-, middle-, and late-stage disease.[15] The patients with multiple  
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5 sclerosis were part of a longitudinal study in Ontario, Canada.[16]  
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## 9 Treatment effect analysis

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11 Continuous primary (TWSTRS) and secondary variables (SF-36 domains) were analyzed  
12 using analysis of covariance (ANCOVA), controlling for treatment group, baseline score (where  
13 appropriate), treatment history (i.e., previous treatment with BoNT), and center.  
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19 Pearson correlation coefficients were calculated among the eight SF-36 domain scores  
20 and the week 4 and week 8 TWSTRS domain scores and total score by treatment group.  
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24 A responder was defined as a patient with a decrease in TWSTRS total score of at least  
25 30% (at week 4) compared with baseline.[9] Mean SF-36 scores by TWSTRS responder status  
26 were evaluated using a *t* test. Safety assessments were based on the safety population, which  
27 included all patients who received at least one dose of study medication. Safety variables were  
28 summarised by descriptive statistics.  
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## 37 RESULTS

### 38 Patient disposition and demographics

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40 All 116 randomized patients (abobotulinumtoxinA n = 55; placebo n = 61) received at  
41 least one dose of study medication and were included in the intent-to-treat (ITT) population. The  
42 mean (standard deviation [SD]) age was similar across treatment groups: 51.9 (13.4) years for  
43 the abobotulinumtoxinA group and 53.9 (12.5) years for placebo group. Similarly, both treatment  
44 groups were predominantly female (67.0% in the abobotulinumtoxinA group and 62.0% in the  
45 placebo group). All other patient demographics and baseline characteristics were similar between  
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3 treatment groups.[9] A total of 33 patients discontinued the study due to insufficient response,  
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5 consent withdrawn, lost to follow up or other reasons.  
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## 8 9 **Comparison with US population and other neurological conditions**

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11 Baseline SF-36 scores for the patients with CD were lower (worse) than US population  
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13 normative values[10] for patients without CD in all domains. Before treatment with either  
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15 abobotulinumtoxinA or placebo, patients with CD in this study reported significantly greater  
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17 impairment for all eight domains of the SF-36 relative to the age- and gender-adjusted US  
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19 population normative values (Table 1). For example, upon study entry, patients with CD reported  
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21 Role Physical impairments that were approximately 32% lower (worse) than the age- and  
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23 gender-adjusted US norm (domain score of 52.4 among patients with CD vs. 76.6 for the US  
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25 norm,  $P < 0.05$ ). Similarly, patients with CD reported experiencing significantly more pain than  
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27 the age- and gender-adjusted US norm upon study entry, with Bodily Pain scores that were 33%  
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29 lower (worse) for patients with CD than the US norms (47.7 vs. 71.3,  $P < 0.05$ ).  
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**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	US	Parkinson's	Multiple
	dystonia study sample (n = 116) Mean (SD)*	normative sample† Mean	disease‡ (n = 150) Mean	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.

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**

<b>Cervical dystonia</b>	<b>Parkinson's disease</b>	<b>Multiple sclerosis</b>
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

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3 improvements in the Physical Functioning, Role Physical, Bodily Pain, General Health, and Role  
4 Emotional domains ( $P \leq 0.03$  for all) than patients treated with placebo.  
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8 Table 3 presents the correlations between the TWSTRS total and domain scores at week  
9 4 with the week 8 SF-36 domain scores. As expected, the TWSTRS was significantly correlated  
10 with the Physical Function, Role Physical, and Bodily Pain domain scores. Across treatment  
11 groups and time periods, the correlations between TWSTRS domain and total scores were  
12 consistently significantly correlated with the Role Physical and Bodily Pain domain scores. The  
13 correlations ranged from  $-0.29$  to  $-0.44$  at week 4. Week 8 correlations were similar:  $-0.33$  to  $-$   
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**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; <i>P</i> -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.

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3 Improvements from baseline to week 8 were observed for most of the SF-36  
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5 domains in the TWSTRS responder group, whereas the non-responder group showed little to no  
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7 change in SF-36 domains (Table 4). The largest improvements occurred in the Role Physical and  
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9 Bodily Pain domains. Patients classified as TWSTRS responders (i.e., those with a  $\geq 30\%$   
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11 improvement in TWSTRS at week 4) reported significantly greater improvements from baseline  
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13 to week 8 in five of the eight SF-36 domains compared with patients who did not respond to  
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15 treatment (Table 4). Specifically, responders reported significantly greater improvements in  
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17 Physical Functioning, Role Physical, Bodily Pain, Vitality, and Social Functioning ( $P \leq 0.03$  for  
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19 all) than patients considered non-responsive to treatment.  
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Table 4. Mean change in SF-36 scores by TWSTRS response status

SF-36 Domain	TWSTRS Responder Status			P-value
	Mean Change in SF-36			
	TWSTRS Non- responder (n = 47)	TWSTRS responder (n = 36)	Difference (responder – non- responder)	
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.

## 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

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3 Parkinson's disease). Camfield[17] conducted a survey of 150 patients with CD that included the  
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5 SF-36 and the Beck anxiety and depression indexes. Patients with CD had lower scores in all  
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7 eight SF-36 domains compared with controls in the United Kingdom (UK), particularly in the  
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9 Role Physical (41.6 vs. 85.8), Bodily Pain (54.6 vs. 81.5), and General Health (46.2 vs. 73.5)  
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11 domains. Domain scores were comparable to data from patients with mild to moderate multiple  
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13 sclerosis and moderate epilepsy. Our results are similar to those of Camfield[17], and support the  
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15 implication that CD has a significant impact on health status that is comparable with other  
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17 neurological disorders of high morbidity. CD appears to have a disproportionate negative impact  
18  
19 on patients' physical role limitation, despite their good physical functioning. One possible  
20  
21 explanation is that pain limits such activities. Another possibility is that patients with CD  
22  
23 consciously limit activities that make their dystonia visible to others to avoid mockery.[18]  
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29 A few studies have investigated the impact of CD on HRQOL and factors modifying a  
30  
31 patient's ability to cope with this disease. Slawek *et al*[19] conducted an HRQOL survey study in  
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33 101 patients previously treated with BoNT-A using the TWSTRS, a pain VAS (0-100%), the SF-  
34  
35 36, and the Montgomery-Åsberg Depression Rating Scale (MADRS). The patients' baseline SF-  
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37 36 scores were worse than those of healthy controls in all eight SF-36 domains. Improvements  
38  
39 were observed 4 weeks after the single BoNT-A injections in all SF-36 domains, and in the VAS,  
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41 TWSTRS, and MADRS scores. The TWSTRS results did not correlate with any of the SF-36  
42  
43 domains. Longer treatment with BoNT-A was associated with better scores. Hefter *et al*[20, 21]  
44  
45 conducted a prospective, open-label study of abobotulinumtoxinA in 516 de novo CD patients  
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47 using the TWSTRS, the Craniocervical Dystonia Questionnaire (CDQ-24), patient diaries, and a  
48  
49 global assessment of pain. In contrast with the SF-36, which is a general measure of HRQOL,  
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51 the CDQ-24 is a disease-specific questionnaire that evaluates HRQOL in patients with CD.[22]  
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3 The CDQ-24 has five subscales: Stigma, Emotional Wellbeing, Pain, Activities of Daily Living,  
4 and Social/Family Life. At week 4, significant improvements were observed in CDQ-24 total  
5 and subscale scores that were sustained up to week 12. Significant reductions in patient diary  
6 and subscale scores that were sustained up to week 12. Significant reductions in patient diary  
7 item scores for activities of daily living, pain, and pain duration at week 4 and 12 were observed.  
8 Sixty-six percent of patients reported pain relief (less or no pain) at week 4 and 74% at week 12.  
9 Improvements in quality of life and pain intensity for up to 12 weeks in patients with CD were  
10 observed after treatment with abobotulinumtoxinA.  
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20 Likewise, in our findings, patients treated with abobotulinumtoxinA reported  
21 significantly greater improvements in TWSTRS total mean scores at weeks 4, 8, and 12  
22 ( $P \leq 0.019$ ) compared with placebo.[9] Improvements from baseline to week 8 were observed for  
23 all eight SF-36 domains in the abobotulinumtoxinA group, whereas the placebo group either  
24 stayed the same or became worse (with a decline in physical functioning). In this study, the SF-  
25 36 results did correlate with the TWSTRS for the Role Physical and Bodily Pain domains across  
26 treatment groups and time periods. AbobotulinumtoxinA was well tolerated in this study, as  
27 previously published.[9]  
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## 40 **CONCLUSION**

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

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## CONTRIBUTORSHIP

All authors meet the ICMJE criteria for authorship.

## DATA SHARING

No additional data are available.

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5 **FIGURE LEGEND**  
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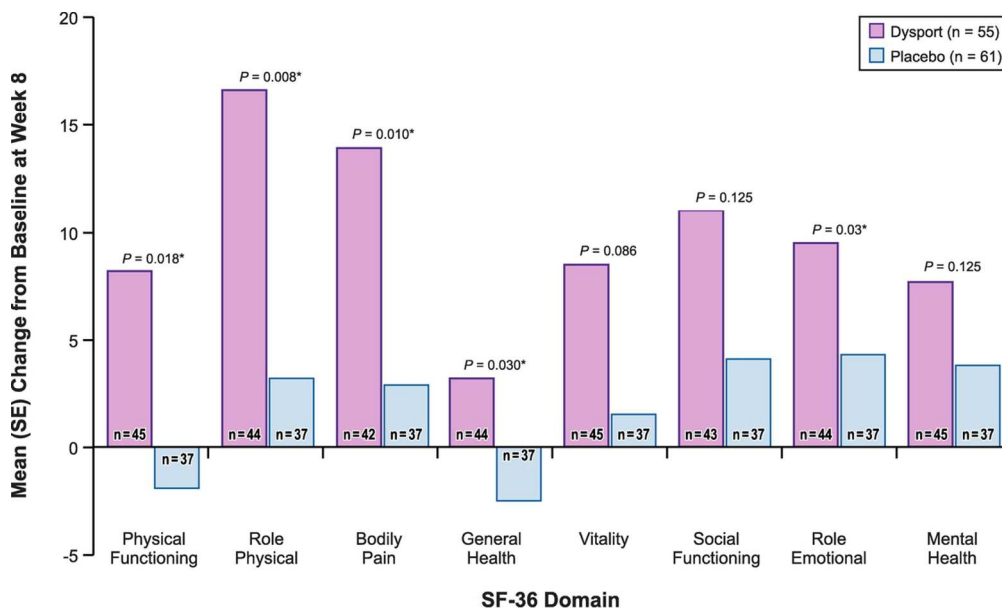
8 **Figure 1. Mean (SE) change in SF-36 scores at week 8**  
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10 \*  $P < 0.05$ .  
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12 Note: Positive changes in score indicate improvement.  
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14 SE, standard error; SF-36, SF-36 Health Survey.  
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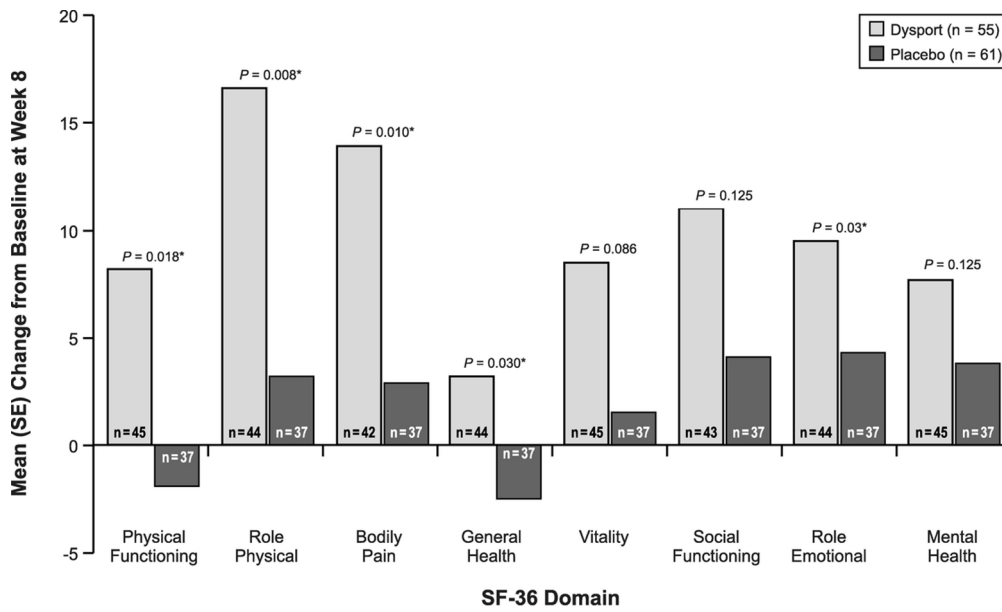
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# BMJ Open

## 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

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<b>Primary Subject Heading</b>:	Neurology
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# 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

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11  
12 **Key words:** cervical dystonia, botulinum toxin type A, Dysport, spasmodic torticollis,  
13 health-related quality of life  
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16  
17 **Word Count (excluding title page, abstract, references, tables, and figure**  
18  
19 **legends):** ~3,138  
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## 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,



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3 General Health, and Role Emotional domains than placebo patients ( $P \leq 0.03$  for all).

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5 The TWSTRS was significantly correlated with Physical Functioning, Role Physical, and  
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8 Bodily Pain scores, for those on active treatment.  
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10 **Conclusions:** CD has a marked impact on HRQOL. Treatment with a single  
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12 abobotulinumtoxinA injection results in significant improvement in patients' HRQOL.  
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## 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.

## 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

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3 disease and treatment, on physical, psychological, and social functioning and well-  
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5 being.  
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8 Recognizing the critical link between physical and psychological health allows a  
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10 more holistic approach to patient care. By measuring HRQOL, we can ascertain the  
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12 effects of a disease on individuals from the patient perspective and, thereafter, to some  
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14 extent, be able to judge the benefit of therapeutic interventions. With CD, several  
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16 physical and emotional factors such as reduced mobility, pain, low self-esteem,  
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18 embarrassment, depression, anxiety, and limited social interaction may be present. Pain  
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20 is a predominant feature of CD and is reported in up to 75% of patients [7] and is  
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22 associated with reduced HRQOL. A study conducted by Degirmenci *et al*[8] evaluated  
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24 anxiety and depression in dystonia patients using the Hospital Anxiety Depression  
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26 (HAD) scale and assessed quality of life using the SF-36 Health Survey (SF-36), a  
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28 general measure widely used to assess HRQOL. Mean Anxiety and Depression  
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30 subscale scores were higher in patients with dystonia when compared with the control  
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32 group. Moreover, patients with dystonia had worse (lower) SF-36 scores for all domains  
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34 when compared with controls.  
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41 AbobotulinumtoxinA (Dysport) 500 U was compared with placebo in two  
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43 multicenter, double-blinded, randomized trials: one international[9] and one in the  
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45 United States (US).[10] The international study included the SF-36 to evaluate  
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47 treatment benefit with 500 U abobotulinumtoxinA compared with placebo as a  
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49 secondary endpoint. As a result of the tremendous amount of research conducted using  
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51 the SF-36 over the past two decades, population norms are available that can facilitate  
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53 the interpretation of research results across a wide variety of patient populations, putting  
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3 specific study data into “larger context.”[11] In order to understand the HRQOL  
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5 impairment unique to CD, SF-36 scores for the study sample were compared with other  
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7 published scores for populations with various neurological conditions, in particular  
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9 Parkinson’s disease and multiple sclerosis; like CD, these conditions are generally  
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11 progressive and affect motor and non-motor function. Specifically, because the HRQOL  
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13 impairment of Parkinson’s disease and that of multiple sclerosis have been well  
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15 established,[12] these conditions were deemed appropriate comparisons in evaluating  
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17 the unique nature of HRQOL impairment due to CD.  
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22 Botulinum toxin (BoNT), a treatment with established safety and efficacy, has  
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24 been recommended as first-line treatment for symptoms of CD.[13, 14] No botulinum  
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26 toxin is indicated for improving HRQOL in CD. The reported benefits from BoNT are  
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28 relief from pain, increased range of free movement, and improved resting posture.[15,  
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30 16] BoNT injections typically offer temporary relief, and the symptoms gradually return.  
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32 For CD, as for most other neurological disorders, more data exist regarding the efficacy  
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34 of the Botulinum toxin type A (BoNT-A) compared with type B. BoNT-A and BoNT-B  
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36 have been shown to reduce both symptom severity and pain.[15] Currently, there are  
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38 three major commercially available preparations of type A toxins: abobotulinumtoxinA  
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40 (Dysport® [Ipsen Biopharm Ltd, Wrexham, UK]), onabotulinumtoxinA (Botox® [Allergan,  
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42 Inc.; Irvine, CA]), and incobotulinumtoxinA (Xeomin® [Merz Pharmaceuticals GmbH;  
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44 Frankfurt am Main, Germany). The potency units of abobotulinumtoxinA are specific to  
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46 the preparation and assay method utilized. They are not interchangeable with other  
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48 preparations of botulinum toxin products and, therefore, units of biological activity of one  
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50 BoNT product cannot be compared to or converted into units of any other botulinum  
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3 toxin products. Accordingly, information regarding the specific benefits of a particular  
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5 BoNT-A preparation and the impact on HRQOL would be valuable.  
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8 The objectives of this article are to describe the HRQOL burden of CD, as  
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10 measured at baseline in a previously reported randomized, double-blind, placebo-  
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12 controlled, pivotal clinical study,[9] as well as report on the HRQOL and treatment  
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14 benefits of abobotulinumtoxinA.  
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## 17 18 19 **MATERIALS AND METHODS**

### 20 21 **Study design**

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23 The study design has been reported previously.[9] An international, multicenter  
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25 (movement disorder clinics in the US [n = 16] and Russia [n = 4]), double-blind,  
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27 randomized, placebo-controlled trial was conducted to evaluate the safety and efficacy  
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29 of a single injection of abobotulinumtoxinA for the treatment of CD. To be eligible for  
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31 study entry, patients had to have a diagnosis of CD with symptoms for at least 18  
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33 months, as well as the following baseline Toronto Western Spasmodic Torticollis Rating  
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35 Scale (TWSTRS) scores: a total score of at least 30; a Severity domain score of at least  
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37 15; and a Disability domain score of at least 3. The TWSTRS is an assessment of CD  
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39 that includes a total CD rating score and three domain scores (Torticollis Severity,  
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41 Disability, and Pain).  
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48 Key exclusion criteria were standard for efficacy trials of BoNT and included  
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50 treatment with BoNT-A or BoNT-B within 16 weeks of enrollment, any disease of the  
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52 neuromuscular junction, previous phenol injection to the neck muscles, myotomy or  
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54 denervation surgery in the neck/shoulder region, cervical contracture, suspected  
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3 secondary non-responsiveness or a history of poor response to BoNT-A, pure  
4 anterocollis or retrocollis, symptom remission at screening, symptoms that could  
5 interfere with TWSTRS scoring, or BoNT-A neutralizing antibodies.  
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10 A total of 120 patients were to be recruited in the study to allow for 47 patients  
11 per treatment group to be evaluable on the primary efficacy endpoint (TWSTRS).[9]  
12 Patients were randomized using a pregenerated randomization code in a 1:1 ratio to  
13 receive an intramuscular injection of either 500 U abobotulinumtoxinA or placebo. Study  
14 medication was administered in a double-blind manner by intramuscular injection into  
15 two, three, or four clinically indicated neck muscles during a single dosing session at  
16 baseline. The study was conducted in accordance with the Declaration of Helsinki and  
17 was reviewed by the ethics committee responsible for each site. All patients provided  
18 written, informed, institutional review board–approved consent before participation.  
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### 33 **Assessments**

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35 Assessments have been described previously.[9] The TWSTRS was determined  
36 at week 0 (baseline), at week 4 (primary), and at weeks 8 and 12 (posttreatment) by  
37 investigators trained in TWSTRS scoring. Pain was evaluated with the Pain domain of  
38 the TWSTRS and a self-reported visual analog scale (VAS) assessing pain in the past  
39 24 hours. Participants completed the pain VAS at baseline and week 4.  
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47 HRQOL was assessed using the SF-36, version 1.0. The SF-36 is a commonly  
48 used health profile that contains 36 items and includes multi-item domains to measure  
49 health status across eight dimensions: Physical Functioning, Role Limitations due to  
50 Physical Health Problems (Role Physical), Bodily Pain, Social Functioning, General  
51 Mental Health, Role Limitations due to Emotional Problems (Role Emotional), Vitality,  
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3 and General Health Perceptions. Responses to questions within each domain are  
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5 summed and transformed to a scale ranging from 0 to 100, with higher scores  
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7 suggesting better functioning. Participants completed the SF-36 at week 0 (baseline;  
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9 prior to dosing) and at week 8 (posttreatment). SF-36 scores were generated according  
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11 to published algorithms.[11]  
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15 Safety assessments included incidence of treatment-emergent adverse events,  
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17 electrocardiogram, neurological and physical examinations, and vital signs.  
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## 20 21 **Statistical analyses**

### 22 23 **Burden of cervical dystonia**

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25 Population norms are available for the SF-36 that can facilitate the interpretation  
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27 of research results across a wide variety of patient populations.[11] The unique burden  
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29 of illness associated with CD was assessed by comparing patients' baseline domain  
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31 scores to age- and gender-adjusted SF-36 domain scores for the US population  
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33 norms.[11] The 95% confidence interval was computed for the baseline SF-36 scores  
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35 relative to the age- and gender-adjusted US population norms.  
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40 For comparisons relative to other neurologic conditions, baseline SF-36 scores  
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42 for the study sample were compared with other published scores for populations with  
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44 Parkinson's disease and multiple sclerosis. The patients with Parkinson's disease were  
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46 patients attending six neurology centers in the US, with a mix of Hoehn and Yahr scores  
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48 representing early-, middle-, and late-stage disease.[17] The patients with multiple  
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50 sclerosis were part of a longitudinal study in Ontario, Canada.[18]  
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## 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

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

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21 Baseline SF-36 scores for the patients with CD were lower (worse) than US  
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23 population normative values[11] for patients without CD in all domains. Before treatment  
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25 with either abobotulinumtoxinA or placebo, patients with CD in this study reported  
26  
27 significantly greater impairment for all eight domains of the SF-36 relative to the age-  
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29 and gender-adjusted US population normative values (Table 1). For example, upon  
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31 study entry, patients with CD reported Role Physical impairments that were  
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33 approximately 32% lower (worse) than the age- and gender-adjusted US norm (domain  
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35 score of 52.4 among patients with CD vs. 76.6 for the US norm,  $P < 0.05$ ). Similarly,  
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37 patients with CD reported experiencing significantly more pain than the age- and  
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39 gender-adjusted US norm upon study entry, with Bodily Pain scores that were 23  
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41 percentage points lower (worse) for patients with CD than the US norms (47.7 vs. 71.3,  
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47  $P < 0.05$ ).  
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**Table 1. Mean SF-36 scores for the normative US population and patients with cervical dystonia, Parkinson's disease, or multiple sclerosis**

<b>SF-36 Domain</b>	<b>Cervical dystonia study sample (n = 116)</b>	<b>US normative sample<sup>†</sup></b>	<b>Parkinson's disease<sup>‡</sup> (n = 150)</b>	<b>Multiple sclerosis<sup>§</sup> (n = 300)</b>
	<b>Mean (SD)<sup>*</sup></b>	<b>Mean</b>	<b>Mean</b>	<b>Mean (SD)</b>
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 ( $P < 0.05$ ).

<sup>†</sup> Age- and gender-adjusted US norms.[11]

<sup>‡</sup> Damiano *et al.*[17]

<sup>§</sup> Hopman *et al.*[18]

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

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3 Like individuals with CD, patients with Parkinson's disease and multiple sclerosis  
4 report substantial impairments in HRQOL relative to US norms (Table 1). However,  
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6 each of these neurologic conditions presents with a unique profile of HRQOL  
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8 impairment. Patients with CD report the greatest limitation in the Bodily Pain domain,  
9  
10 whereas patients with Parkinson's disease report the greatest impairments in the Role  
11  
12 Physical domain, and patients with multiple sclerosis report the greatest impairments in  
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14 the Vitality domain. Each of these neurological conditions impairs patients physically,  
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16 yet the presentation of the disease manifests itself differently in terms of HRQOL  
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18 impairment.  
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### 24 25 26 **Treatment effect**

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28 Improvements from baseline to week 8 were observed for all eight SF-36  
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30 domains in the abobotulinumtoxinA group, whereas the placebo group showed some  
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32 decline in Physical Functioning and little to no change in other SF-36 domains (Table 2;  
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34 Figure 2). The largest improvements occurred in the Role Physical and Bodily Pain  
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36 domains.  
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40 Patients treated with abobotulinumtoxinA reported significantly greater  
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42 improvements than placebo patients from baseline to week 8 in five of the eight SF-36  
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44 domains (Table 2; Figure 2). Specifically, patients treated with abobotulinumtoxinA  
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46 reported significantly greater improvements in the Physical Functioning, Role Physical,  
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48 Bodily Pain, General Health, and Role Emotional domains ( $P \leq 0.03$  for all) than  
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50 patients treated with placebo.  
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**Table 2. Mean (SE) SF-36 scores by treatment group: baseline and week 8**

SF-36 Domain	AbobotulinumtoxinA				Placebo				P value
	N	Baseline mean (SD)	Week 8 mean (SD)	Change mean (SD)	N	Baseline mean (SD)	Week 8 mean (SD)	Change mean (SD)	
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.

1  
2  
3 Table 3 presents the correlations between the TWSTRS total and domain scores  
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5 at week 4 with the week 8 SF-36 domain scores. As expected, the TWSTRS was  
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7 significantly correlated with the Physical Functioning, Role Physical, and Bodily Pain  
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9 domain scores. The correlations between TWSTRS domain and total scores were  
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11 consistently significantly correlated with the Role Physical and Bodily Pain domain  
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13 scores for both treatment groups. The correlations ranged from  $-0.29$  to  $-0.44$  at  
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15 week 4. Correlations were similar when evaluated with week 8 TWSTRS scores and  
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17 week 8 SF-36 scores:  $-0.33$  to  $-0.53$  (week 8 correlations not shown).  
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Table 3. Correlations between the week 8 SF-36 scores with the TWSTRS at week 4 by treatment group

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

Week 4: correlation; <i>P</i> value; n								
	Total		Disability		Severity		Pain	
	Abobotulinum-		Abobotulinum-		Abobotulinum-		Abobotulinum-	
	toxinA	Placebo	toxinA	Placebo	toxinA	Placebo	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.



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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  $\geq 30\%$  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.

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

SF-36 Domain	TWSTRS Responder Status			P value
	Mean Change in SF-36			
	TWSTRS non- responder (n = 47)	TWSTRS responder (n = 36)	Difference (responder – non- responder)	
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.

## 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.

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3 Patients with CD had lower scores in all eight SF-36 domains compared with controls in  
4 the United Kingdom (UK), particularly in the Role Physical (41.6 vs. 85.8), Bodily Pain  
5 (54.6 vs. 81.5), and General Health (46.2 vs. 73.5) domains. Domain scores were  
6 comparable to data from patients with mild to moderate multiple sclerosis and moderate  
7 epilepsy. Our results are similar to those of Camfield[19], in that baseline scores for  
8 patients with CD were lower (worse) than for US normative data, particularly for the  
9 Role Physical (52.4 vs. 76.6), and Bodily Pain (47.7 vs. 71.3) domains. Our findings  
10 support the implication that CD has a significant impact on health status that is  
11 comparable with other neurological disorders of high morbidity. CD appears to have a  
12 disproportionate negative impact on patients' physical role limitation, despite their good  
13 physical functioning. One possible explanation is that pain limits such activities. Another  
14 possibility is that patients with CD consciously limit activities that make their dystonia  
15 visible to others to avoid mockery.[20]

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34 A few studies have investigated the impact of CD on HRQOL and factors  
35 modifying a patient's ability to cope with this disease. Slawek *et al*[21] conducted an  
36 HRQOL survey study in 101 patients previously treated with BoNT-A using the  
37 TWSTRS, a pain VAS (0-100%), the SF-36, and the Montgomery-Åsberg Depression  
38 Rating Scale (MADRS). Patients' baseline SF-36 scores were worse than those of  
39 healthy controls in all eight SF-36 domains. Improvements were observed 4 weeks after  
40 the single BoNT-A injections in all SF-36 domains, and in the VAS, TWSTRS, and  
41 MADRS scores. The TWSTRS results did not correlate with any of the SF-36 domains.  
42 Longer treatment with BoNT-A was associated with better scores. Hefter *et al*[22, 23]  
43 conducted a prospective, open-label study of abobotulinumtoxinA in 516 de novo CD  
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3 patients using the TWSTRS, the Craniocervical Dystonia Questionnaire (CDQ-24),  
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5 patient diaries, and a global assessment of pain. In contrast with the SF-36, which is a  
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7 general measure of HRQOL, the CDQ-24 is a disease-specific questionnaire that  
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9 evaluates HRQOL in patients with CD.[24] The CDQ-24 has five subscales: Stigma,  
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11 Emotional Wellbeing, Pain, Activities of Daily Living, and Social/Family Life. At week 4,  
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13 significant improvements were observed in CDQ-24 total and subscale scores that were  
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15 sustained up to week 12. Significant reductions in patient diary item scores for activities  
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17 of daily living, pain, and pain duration at week 4 and 12 were observed. Sixty-six  
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19 percent of patients reported pain relief (less or no pain) at week 4 and 74% at week 12.  
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21 Improvements in quality of life and pain intensity for up to 12 weeks in patients with CD  
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23 were observed after treatment with abobotulinumtoxinA.  
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30 Likewise, in our findings, patients treated with abobotulinumtoxinA reported  
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32 significantly greater improvements in TWSTRS total mean scores at weeks 4, 8, and 12  
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34 ( $P \leq 0.019$ ) compared with placebo.[9] Improvements from baseline to week 8 were  
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36 observed for all eight SF-36 domains in the abobotulinumtoxinA group, whereas the  
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38 placebo group either stayed the same or became worse (with a decline in physical  
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40 functioning). In this study, the SF-36 results did correlate with the TWSTRS for the Role  
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42 Physical and Bodily Pain domains across treatment groups and time periods.  
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44 AbobotulinumtoxinA was well tolerated in this study, as previously published.[9]  
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49 Our study is not without limitations that should be considered. First, the exclusion  
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51 of those with suspected secondary non-responsiveness or a history of poor response to  
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53 BoNT-A may have excluded those who might not experience a positive change in their  
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55 HRQOL. Secondly, the size of this study was small. Studies with a larger sample size  
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3 are required to demonstrate the outcomes of abobotulinumtoxinA treatment in a study  
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5 population that is more representative of the general population.  
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## 8 9 10 **CONCLUSION**

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

## REGISTRATION

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

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.



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# 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

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## 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<sup>®</sup>).

**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

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3 correlated with Physical ~~Function~~Functioning, Role Physical, and Bodily Pain scores, for those  
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5 on active treatment.  
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8 **Conclusions:** CD has a marked impact on HRQOL. Treatment with a single  
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10 abobotulinumtoxinA injection results in significant improvement in patients' HRQOL.  
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## 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.

## 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.<sup>[1]</sup> 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.<sup>[2]</sup> ~~When classified by distribution, patients are categorized as having hemidystonia or focal, segmental, multifocal, or generalized dystonia.~~<sup>[3]</sup> ~~With cervical, postures, or both.~~<sup>[1]</sup> 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.<sup>[42]</sup> 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).<sup>[23]</sup> CD may be accompanied by pulling or stiffness, pain, and sensory symptoms in the affected area.<sup>[54]</sup> 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.<sup>[2, 63, 5]</sup>

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).<sup>[36]</sup> HRQOL is defined as the

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3 subjective perception of the impact of health status, including disease and treatment, on physical,  
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5 psychological, and social functioning and well-being.  
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8 Recognizing the critical link between physical and psychological health allows a more  
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10 holistic approach to patient care. By measuring HRQOL, we can ascertain the effects of a disease  
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12 on individuals from the patient perspective and, thereafter, to some extent, be able to judge the  
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14 benefit of therapeutic interventions. With CD, several physical and emotional factors such as  
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16 reduced mobility, pain, low self-esteem, embarrassment, depression, anxiety, and limited social  
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18 interaction may be present. ~~Unlike other forms of focal dystonia, pain~~ Pain is a predominant  
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20 feature of CD and is reported in up to 75% of patients. ~~[7]~~ and is associated with reduced  
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22 HRQOL. A study conducted by Degirmenci *et al*[8] evaluated anxiety and depression in dystonia  
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24 patients using the Hospital Anxiety Depression (HAD) scale and assessed quality of life using  
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26 the SF-36 Health Survey (SF-36), a ~~generiegeneral~~ HRQOL-measure. widely used to assess  
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28 HRQOL. Mean Anxiety and Depression ~~subsealssubscale~~ scores were higher in patients with  
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30 dystonia when compared with the control group. Moreover, patients with dystonia had worse  
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32 (lower) SF--36 scores for all domains when compared with controls.  
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41 AbobotulinumtoxinA (Dysport) 500 U was compared with placebo in ~~an~~  
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43 ~~international,two~~ multicenter, ~~\_~~double-blinded, randomized ~~trial.[~~trials:— one international[9] and  
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45 one in the United States (US).[10]- The international study ~~was classified as class I study~~  
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47 ~~according to the American Academy of Neurology (AAN) Classification of Quality of Evidence~~  
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49 ~~for Clinical Trials.[1]~~ This study usedincluded the SF-36; to evaluate treatment benefit with 500  
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51 U abobotulinumtoxinA compared with placebo as a secondary endpoint. As a result of the  
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60 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.”<sup>[1011]</sup> 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,<sup>[1112]</sup> 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.<sup>[13, 14][1, 12][14, 13]</sup> 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.<sup>[13, 14][15, 16]</sup> 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.<sup>[1315]</sup> Currently, there are three major commercially available preparations of type A toxins: abobotulinumtoxinA (Dysport<sup>®</sup> [Ipsen Biopharm Ltd, Wrexham, UK]), onabotulinumtoxinA (Botox<sup>®</sup> [Allergan, Inc.; Irvine, CA]), and incobotulinumtoxinA (Xeomin<sup>®</sup> [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

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3 of any other botulinum toxin products ~~assessed with any other specific assay method. Due to~~  
4 ~~this.~~ Accordingly, information regarding the specific benefits of a particular BoNT-A preparation  
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6 and the impact on HRQOL would be valuable.  
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10 The objectives of this article are to describe the HRQOL burden of CD, as measured at  
11 baseline in a previously reported randomized, double-blind, placebo-controlled, pivotal clinical  
12 study,<sup>[9]</sup> as well as report on the HRQOL and treatment benefits of abobotulinumtoxinA.  
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## 20 MATERIALS AND METHODS

### 21 Study design

22 The study design has been reported previously.<sup>[9]</sup> ~~Briefly, an~~ An international,  
23 multicenter, ~~(movement disorder clinics in the United States [US] [n = 16] and Russia [n = 4]),~~  
24 double-blind, randomized, placebo-controlled trial was conducted to evaluate the safety and  
25 efficacy of a single injection of abobotulinumtoxinA for the treatment of CD. To be eligible for  
26 study entry, patients had to have a diagnosis of CD with symptoms for at least 18 months, as well  
27 as the following baseline Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS)  
28 scores: a total score of at least 30; a Severity domain score of at least 15; and a Disability domain  
29 score of at least 3. The TWSTRS is an assessment of CD that includes a total CD rating score  
30 and three domain scores (Torticollis Severity, Disability, and Pain).  
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46 Key exclusion criteria were standard for efficacy trials of BoNT and included treatment  
47 with BoNT-A or BoNT-B within 16 weeks of enrollment, any disease of the neuromuscular  
48 junction, previous phenol injection to the neck muscles, myotomy or denervation surgery in the  
49 neck/shoulder region, cervical contracture, suspected secondary non-responsiveness or a history  
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3 of poor response to BoNT-A, pure anterocollis or retrocollis, symptom remission at screening,  
4 symptoms that could interfere with TWSTRS scoring, or BoNT-A neutralizing antibodies.  
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8 A total of 120 patients were to be recruited in the study to allow for 47 patients per  
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10 treatment group to be evaluable on the primary efficacy endpoint (TWSTRS).[9] Patients  
11 received were randomized using a pregenerated randomization code in a 1:1 ratio to receive an  
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13 intramuscular injection of either 500 U abobotulinumtoxinA or placebo ~~in a 1:1 ratio.~~ Study  
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15 medication was administered in a double-blind manner by intramuscular injection into two,  
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17 three, or four clinically indicated neck muscles during a single dosing session at baseline. The  
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19 study was conducted in accordance with the Declaration of Helsinki and was reviewed by the  
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21 ethics committee responsible for each site. All patients provided written, informed, institutional  
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23 review board–approved consent before participation.  
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## 30 Assessments

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32 Assessments have been described previously.[9] The TWSTRS was determined at week 0  
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34 (baseline), at week 4 (primary), and at weeks 8 and 12 (posttreatment) by investigators trained in  
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36 TWSTRS scoring. Pain was evaluated with the Pain domain of the TWSTRS and a self-reported  
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38 visual analog scale (VAS) assessing pain in the past 24 hours. Participants completed the pain  
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40 VAS at baseline and week 4.  
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44 HRQOL was assessed using the SF-36, version 1.0. The SF-36 is a commonly used  
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46 health profile that contains 36 items and includes multi-item domains to measure health status  
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48 across eight dimensions: Physical Functioning, Role Limitations due to Physical Health  
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50 Problems (Role Physical), Bodily Pain, Social Functioning, General Mental Health, Role  
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52 Limitations due to Emotional Problems (Role Emotional), Vitality, and General Health  
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54 Perceptions. Responses to questions within each domain are summed and transformed to a scale  
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3 ranging from 0 to 100, with higher scores suggesting better functioning. Participants completed  
4 the SF-36 at week 0 (baseline; prior to dosing) and at week 8 (posttreatment). SF-36 scores were  
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6 generated according to published algorithms.[+011]  
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10 Safety assessments included incidence of treatment-emergent adverse events ~~(TEAEs)~~,  
11 electrocardiogram ~~(ECG)~~,<sup>2</sup> neurological and physical examinations, and vital signs.  
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## 14 15 16 **Statistical analyses**

### 17 18 **Burden of cervical dystonia**

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20 Population norms are available for the SF-36 that can facilitate the interpretation of  
21 research results across a wide variety of patient populations.[+011] The unique burden of illness  
22 associated with CD was assessed by comparing patients' baseline domain scores to age- and  
23 gender-adjusted SF-36 domain scores for the US population norms.[+011] The 95% confidence  
24 interval was computed for the baseline SF-36 scores relative to the age- and gender-adjusted US  
25 population norms.  
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29 ~~Baseline~~For comparisons relative to other neurologic conditions, baseline SF-36 scores  
30 for the study sample were compared with other published scores for populations with  
31 Parkinson's disease and multiple sclerosis. The patients with Parkinson's disease were patients  
32 attending six neurology centers in the US, with a mix of Hoehn and Yahr scores representing  
33 early-, middle-, and late-stage disease.[+517] The patients with multiple sclerosis were part of a  
34 longitudinal study in Ontario, Canada.[+618]  
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## 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



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3 treatment groups.[9] A total of 33 patients discontinued the study ~~due to~~because of insufficient  
4 response, withdrawal of consent~~withdrawn, lost, loss~~ to follow-up, or other reasons. (Figure 1).  
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## 8 9 **Comparison with US population and other neurological conditions**

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11 Baseline SF-36 scores for the patients with CD were lower (worse) than US population  
12 normative values[~~10~~11] for patients without CD in all domains. Before treatment with either  
13 abobotulinumtoxinA or placebo, patients with CD in this study reported significantly greater  
14 impairment for all eight domains of the SF-36 relative to the age- and gender-adjusted US  
15 population normative values (Table 1). For example, upon study entry, patients with CD reported  
16 Role Physical impairments that were approximately 32% lower (worse) than the age- and  
17 gender-adjusted US norm (domain score of 52.4 among patients with CD vs. 76.6 for the US  
18 norm,  $P < 0.05$ ). Similarly, patients with CD reported experiencing significantly more pain than  
19 the age- and gender-adjusted US norm upon study entry, with Bodily Pain scores that were  
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33 33%23 percentage points lower (worse) for patients with CD than the US norms (47.7 vs. 71.3,  
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 $P < 0.05$ ).

**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) <sup>*</sup>	US normative sample <sup>†</sup> Mean	Parkinson's disease <sup>‡</sup> (n = 150) Mean	Multiple sclerosis <sup>§</sup> (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 ( $P < 0.05$ ).

<sup>†</sup> Age- and gender-adjusted US norms.[4011]

<sup>‡</sup> Damiano *et al.*[4517]

<sup>§</sup> Hopman *et al.*[4618]

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

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~~

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

### 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

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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.

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

<b>SF-36 Domain</b>	<b>AbobotulinumtoxinA</b>				<b>Placebo</b>				<b>P value</b>
	<b>N</b>	<b>Baseline mean (SD)</b>	<b>Week 8 mean (SD)</b>	<b>Change mean (SD)</b>	<b>N</b>	<b>Baseline mean (SD)</b>	<b>Week 8 mean (SD)</b>	<b>Change mean (SD)</b>	
<b>Physical Functioning</b>	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
<b>Role Physical</b>	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
<b>Bodily Pain</b>	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
<b>General Health</b>	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
<b>Vitality</b>	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
<b>Social Functioning</b>	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
<b>Role Emotional</b>	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
<b>Mental Health</b>	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.

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3 Table 3 presents the correlations between the TWSTRS total and domain scores at  
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5 week 4 with the week 8 SF-36 domain scores. As expected, the TWSTRS was significantly  
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7 correlated with the Physical ~~Function~~Functioning, Role Physical, and Bodily Pain domain scores.  
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9 ~~Across treatment groups and time periods, the~~The correlations between TWSTRS domain and  
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11 total scores were consistently significantly correlated with the Role Physical and Bodily Pain  
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13 domain scores: for both treatment groups. The correlations ranged from -0.29 to -0.44 at week 4.  
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15 ~~Week 8 correlations~~Correlations were similar when evaluated with week 8 TWSTRS scores and  
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17 week 8 SF-36 scores: -0.33 to -0.53 (week 8 correlations not shown).  
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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; <i>P</i> -value; n							
	Total		Disability		Severity		Pain	
	<del>DyspertAbobot</del>		<del>DyspertAbobotu</del>		<del>DyspertAbobot</del>		<del>DyspertAbobot</del>	
	<u>ulinum-toxinA</u>	Placebo	<u>linum-toxinA</u>	Placebo	<u>ulinum-toxinA</u>	Placebo	<u>ulinum-toxinA</u>	Placebo
Physical	-0.34;	-0.19;	-0.34;	-0.03;	-0.35;	-0.31;	-0.13;	-0.10;
<del>FunctionFu</del>	0.0278;	0.2801;	0.0257;	0.8978;	0.0223;	0.0694;	0.3969;	0.55;
<del>nctioning</del>	43	36	44	36	43	36	44	36
Role	-0.34;	-0.34;	-0.34;	-0.27;	-0.35;	-0.37;	-0.12;	-0.18;
Physical	0.0295;	0.0422;	0.0270;	0.1069;	0.0229;	0.0255;	0.4265;	0.2811;
	42	36	43	36	42	36	43	36
Bodily Pain	-0.41;	-0.35;	-0.31;	-0.29;	-0.20;	-0.44;	-0.53;	-0.14;
	0.00080;	0.0345;	0.0523;	0.0871;	0.2133;	0.0076;	0.0003;	0.4296;
	40	36	41	36	40	36	41	36
<del>General</del>	<u>-0.31;</u>	<u>0.08</u>	<u>-0.26</u>	<u>0.16</u>	<u>-0.43</u>	<u>0.06</u>	<u>-0.09</u>	<u>-0.02</u>
<del>Health</del>	<u>0.0422</u>	<u>0.6521</u>	<u>0.1459</u>	<u>0.3639</u>	<u>0.0045</u>	<u>0.7217</u>	<u>0.5785</u>	<u>0.9235</u>

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

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.

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ImprovementsThe 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  $\geq 30\%$  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.

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

SF-36 Domain	TWSTRS Responder Status			
	Mean Change in SF-36			
	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](#).

## 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

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

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34 A few studies have investigated the impact of CD on HRQOL and factors modifying a  
35 patient's ability to cope with this disease. Slawek *et al*<sup>[19,21]</sup> conducted an HRQOL survey study  
36 in 101 patients previously treated with BoNT-A using the TWSTRS, a pain VAS (0-100%), the  
37 SF-36, and the Montgomery-Åsberg Depression Rating Scale (MADRS). ~~The patients'~~ Patients'  
38 baseline SF-36 scores were worse than those of healthy controls in all eight SF-36 domains.  
39 Improvements were observed 4 weeks after the single BoNT-A injections in all SF-36 domains,  
40 and in the VAS, TWSTRS, and MADRS scores. The TWSTRS results did not correlate with any  
41 of the SF-36 domains. Longer treatment with BoNT-A was associated with better scores. Hefter  
42 *et al*<sup>[20, 21, 22, 23]</sup> conducted a prospective, open-label study of abobotulinumtoxinA in 516 de  
43 novo CD patients using the TWSTRS, the Craniocervical Dystonia Questionnaire (CDQ-24),  
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3 patient diaries, and a global assessment of pain. In contrast with the SF-36, which is a general  
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5 measure of HRQOL, the CDQ-24 is a disease-specific questionnaire that evaluates HRQOL in  
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7 patients with CD.[2224] The CDQ-24 has five subscales: Stigma, Emotional Wellbeing, Pain,  
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10 Activities of Daily Living, and Social/Family Life. At week 4, significant improvements were  
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12 observed in CDQ-24 total and subscale scores that were sustained up to week 12. Significant  
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14 reductions in patient diary item scores for activities of daily living, pain, and pain duration at  
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16 week 4 and 12 were observed. Sixty-six percent of patients reported pain relief (less or no pain)  
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18 at week 4 and 74% at week 12. Improvements in quality of life and pain intensity for up to 12  
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20 weeks in patients with CD were observed after treatment with abobotulinumtoxinA.  
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25 Likewise, in our findings, patients treated with abobotulinumtoxinA reported  
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27 significantly greater improvements in TWSTRS total mean scores at weeks 4, 8, and 12  
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29 ( $P \leq 0.019$ ) compared with placebo.[9] Improvements from baseline to week 8 were observed for  
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31 all eight SF-36 domains in the abobotulinumtoxinA group, whereas the placebo group either  
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33 stayed the same or became worse (with a decline in physical functioning). In this study, the SF-  
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35 -36 results did correlate with the TWSTRS for the Role Physical and Bodily Pain domains across  
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37 treatment groups and time periods. AbobotulinumtoxinA was well tolerated in this study, as  
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39 previously published.[9]  
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44 Our study is not without limitations that should be considered. First, the exclusion of  
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46 those with suspected secondary non-responsiveness or a history of poor response to BoNT-A  
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48 may have excluded those who might not experience a positive change in their health-related  
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50 quality of lifeHRQOL. Secondly, the size of this study was small. -Studies with a larger sample  
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52 size are required to demonstrate the outcomes of abobotulinumtoxinA treatment in a study  
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54 population that is more representative of the general population.  
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## 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.

acknowledgments

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## **REGISTRATION**

The trial is registered at [ClinicalTrials.gov](https://clinicaltrials.gov), numbers NCT00257660 and NCT00288509.

## **FUNDING**

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## **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.

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2  
3 manuscript. Rosemarie Kelly, PhD, consultant to Ipsen, provided critical review of the  
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6 manuscript.  
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## 8 9 10 **COMPETING INTERESTS**

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12 ~~Chandra Abbott is an employee of Ipsen Biopharmaceuticals, Inc. Margaret Mordin, Catherine~~  
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14 ~~Masaquel, and Catherine Copley Merriman, employees of RTI Health Solutions, were contracted~~  
15  
16 ~~by Ipsen Biopharmaceuticals, Inc. to perform and report on the research described here.~~  
17

## 18 19 20 21 **FUNDING**

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25 ~~This work was supported by Ipsen Biopharmaceuticals, Inc.~~  
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6 **FIGURE LEGENDS**  
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8 **Figure 1. Study Flow Diagram**  
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11 **Figure 2. Mean (SE) change in SF-36 scores at week 8**  
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13 \*  $P < 0.05$ .

14 Note: Positive changes in score indicate improvement.

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16 SE, standard error; SF-36, SF-36 Health Survey.  
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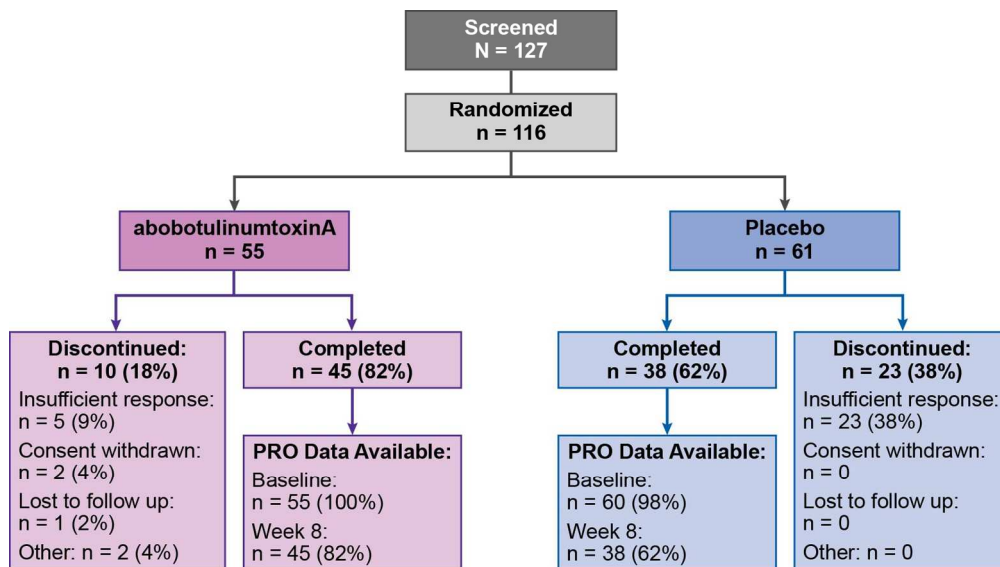
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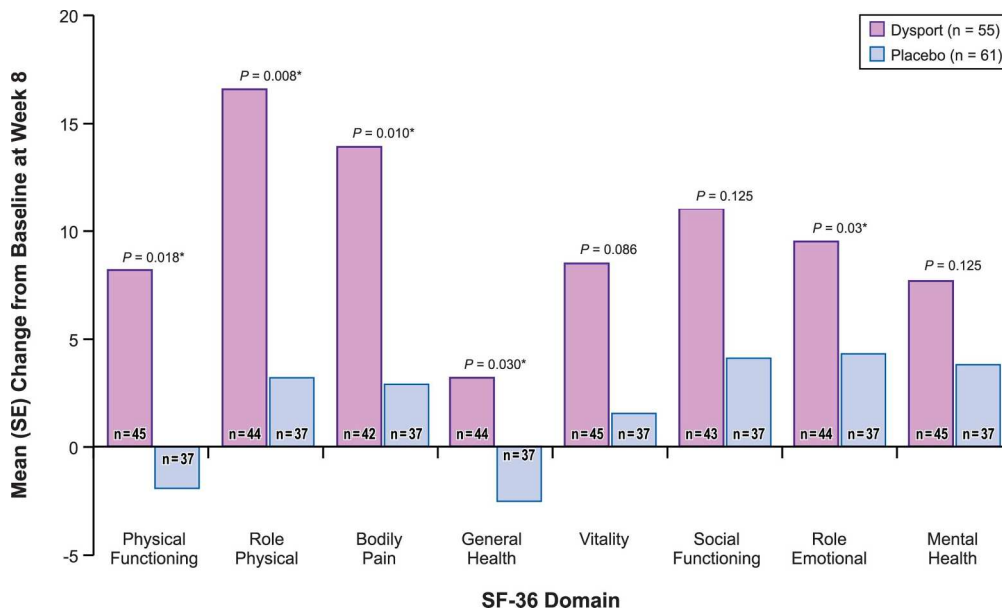
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## CONSORT 2010 checklist of information to include when reporting a randomised trial\*

Section/Topic	Item No	Checklist item	Reported on page No
<b>Title and abstract</b>			
	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
<b>Introduction</b>			
Background and objectives	2a	Scientific background and explanation of rationale	6
	2b	Specific objectives or hypotheses	7
<b>Methods</b>			
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
<b>Randomisation:</b>			
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)

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2	Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how
3			9
4		11b	If relevant, description of the similarity of interventions
5			Not Applicable
6	Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes
7		12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses
8			11
9	<b>Results</b>		
10	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
11			12
12		13b	For each group, losses and exclusions after randomisation, together with reasons
13			12
14	Recruitment	14a	Dates defining the periods of recruitment and follow-up
15		14b	Why the trial ended or was stopped
16			Not Applicable
17	Baseline data	15	A table showing baseline demographic and clinical characteristics for each group
18			Reported in Truong, 2010
19	Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups
20			Figure 1 in separate file
21	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)
22			Figure 1 in separate file
23		17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended
24			Not Applicable
25	Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory
26			17-19
27	Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)
28			Reported in Truong, 2010
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30	<b>Discussion</b>		
31	Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses
32			23
33	Generalisability	21	Generalisability (external validity, applicability) of the trial findings
34			21-22
35	Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence
36			22-23
37	<b>Other information</b>		
38	Registration	23	Registration number and name of trial registry
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40	Protocol	24	Where the full trial protocol can be accessed, if available
41			Not available
42	Funding	25	Sources of funding and other support (such as supply of drugs), role of funders
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2 \*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  
3 recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials.  
4 Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see [www.consort-statement.org](http://www.consort-statement.org).  
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# 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

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<b>Primary Subject Heading</b>:	Neurology
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Keywords:	Adult neurology < NEUROLOGY, QUALITATIVE RESEARCH, Motor neurone disease < NEUROLOGY

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# 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

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12 **Key words:** cervical dystonia, botulinum toxin type A, Dysport, spasmodic torticollis,  
13 health-related quality of life  
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17 **Word Count (excluding title page, abstract, references, tables, and figure**  
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## 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<sup>®</sup>).

**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

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3 correlated with Physical Functioning, Role Physical, and Bodily Pain scores, for those on active  
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5 treatment.  
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8 **Conclusions:** CD has a marked impact on HRQOL. Treatment with a single  
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10 abobotulinumtoxinA injection results in significant improvement in patients' HRQOL.  
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## 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.

## 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.

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4 Recognizing the critical link between physical and psychological health allows a more  
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6 holistic approach to patient care. By measuring HRQOL, we can ascertain the effects of a disease  
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8 on individuals from the patient perspective and, thereafter, to some extent, be able to judge the  
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10 benefit of therapeutic interventions. With CD, several physical and emotional factors such as  
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12 reduced mobility, pain, low self-esteem, embarrassment, depression, anxiety, and limited social  
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14 interaction may be present. Pain is a predominant feature of CD and is reported in up to 75% of  
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16 patients [7] and is associated with reduced HRQOL. A study conducted by Degirmenci *et al*[8]  
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18 evaluated anxiety and depression in dystonia patients using the Hospital Anxiety Depression  
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20 (HAD) scale and assessed quality of life using the SF-36 Health Survey (SF-36), a general  
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22 measure widely used to assess HRQOL. Mean Anxiety and Depression subscale scores were  
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24 higher in patients with dystonia when compared with the control group. Moreover, patients with  
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26 dystonia had worse (lower) SF-36 scores for all domains when compared with controls.  
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32 AbobotulinumtoxinA (Dysport) 500 U was compared with placebo in two multicenter,  
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34 double-blinded, randomized trials: one international[9] and one in the United States (US).[10]  
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36 The international study included the SF-36 to evaluate treatment benefit with 500 U  
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38 abobotulinumtoxinA compared with placebo as a secondary endpoint. As a result of the  
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40 tremendous amount of research conducted using the SF-36 over the past two decades, population  
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42 norms are available that can facilitate the interpretation of research results across a wide variety  
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44 of patient populations, putting specific study data into “larger context.”[11] In order to  
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46 understand the HRQOL impairment unique to CD, SF-36 scores for the study sample were  
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48 compared with other published scores for populations with various neurological conditions, in  
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50 particular Parkinson’s disease and multiple sclerosis; like CD, these conditions are generally  
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52 progressive and affect motor and non-motor function. Specifically, because the HRQOL  
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3 impairment of Parkinson's disease and that of multiple sclerosis have been well established,[12]  
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5 these conditions were deemed appropriate comparisons in evaluating the unique nature of  
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8 HRQOL impairment due to CD.  
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10 Botulinum toxin (BoNT), a treatment with established safety and efficacy, has been  
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12 recommended as first-line treatment for symptoms of CD.[13, 14] No botulinum toxin is  
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14 indicated for improving HRQOL in CD. The reported benefits from BoNT are relief from pain,  
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16 increased range of free movement, and improved resting posture.[15, 16] BoNT injections  
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18 typically offer temporary relief, and the symptoms gradually return. For CD, as for most other  
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20 neurological disorders, more data exist regarding the efficacy of the Botulinum toxin type A  
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22 (BoNT-A) compared with type B. BoNT-A and BoNT-B have been shown to reduce both  
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24 symptom severity and pain.[15] Currently, there are three major commercially available  
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26 preparations of type A toxins: abobotulinumtoxinA (Dysport<sup>®</sup> [Ipsen Biopharm Ltd, Wrexham,  
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28 UK]), onabotulinumtoxinA (Botox<sup>®</sup> [Allergan, Inc.; Irvine, CA]), and incobotulinumtoxinA  
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30 (Xeomin<sup>®</sup> [Merz Pharmaceuticals GmbH; Frankfurt am Main, Germany). The potency units of  
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32 abobotulinumtoxinA are specific to the preparation and assay method utilized. They are not  
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34 interchangeable with other preparations of botulinum toxin products and, therefore, units of  
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36 biological activity of one BoNT product cannot be compared to or converted into units of any  
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38 other botulinum toxin products. Accordingly, information regarding the specific benefits of a  
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40 particular BoNT-A preparation and the impact on HRQOL would be valuable.  
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48 The objectives of this article are to describe the HRQOL burden of CD, as measured at  
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50 baseline in a previously reported randomized, double-blind, placebo-controlled, pivotal clinical  
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52 study,[9] as well as report on the HRQOL and treatment benefits of abobotulinumtoxinA.  
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## 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

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3 with the Declaration of Helsinki and was reviewed by the ethics committee responsible for each  
4 site. All patients provided written, informed, institutional review board–approved consent before  
5 participation.  
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## 10 11 **Assessments**

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13 Assessments have been described previously.[9] The TWSTRS was determined at week 0  
14 (baseline), at week 4 (primary), and at weeks 8 and 12 (posttreatment) by investigators trained in  
15 TWSTRS scoring. Pain was evaluated with the Pain domain of the TWSTRS and a self-reported  
16 visual analog scale (VAS) assessing pain in the past 24 hours. Participants completed the pain  
17 VAS at baseline and week 4.  
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26 HRQOL was assessed using the SF-36, version 1.0. The SF-36 is a commonly used  
27 health profile that contains 36 items and includes multi-item domains to measure health status  
28 across eight dimensions: Physical Functioning, Role Limitations due to Physical Health  
29 Problems (Role Physical), Bodily Pain, Social Functioning, General Mental Health, Role  
30 Limitations due to Emotional Problems (Role Emotional), Vitality, and General Health  
31 Perceptions. Responses to questions within each domain are summed and transformed to a scale  
32 ranging from 0 to 100, with higher scores suggesting better functioning. Participants completed  
33 the SF-36 at week 0 (baseline; prior to dosing) and at week 8 (posttreatment). SF-36 scores were  
34 generated according to published algorithms.[11]  
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47 Safety assessments included incidence of treatment-emergent adverse events,  
48 electrocardiogram, neurological and physical examinations, and vital signs.  
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## 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.

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

### 20 Patient disposition and demographics

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22 All 116 randomized patients (abobotulinumtoxinA n = 55; placebo n = 61) received at  
23 least one dose of study medication in the double-blind phase of the study and were included in  
24 both the intent-to-treat and safety populations. Of these, 83 patients (abobotulinumtoxinA n = 45;  
25 placebo n = 38) were analyzed in the HRQOL assessment. The mean (standard deviation [SD])  
26 age was similar across treatment groups: 51.9 (13.4) years for the abobotulinumtoxinA group  
27 and 53.9 (12.5) years for placebo group. Similarly, both treatment groups were predominantly  
28 female (67.0% in the abobotulinumtoxinA group and 62.0% in the placebo group). All other  
29 patient demographics and baseline characteristics were similar between treatment groups (Table  
30 1).[9] A total of 33 patients discontinued the study because of insufficient response, withdrawal  
31 of consent, loss to follow-up, or other reasons (Figure 1).  
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**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)

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,  $P < 0.05$ ).

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

<b>SF-36 Domain</b>	<b>Cervical dystonia study sample (n = 116)</b>	<b>US normative sample<sup>†</sup></b>	<b>Parkinson's disease<sup>‡</sup> (n = 150)</b>	<b>Multiple sclerosis<sup>§</sup> (n = 300)</b>
	<b>Mean (SD)<sup>*</sup></b>	<b>Mean</b>	<b>Mean</b>	<b>Mean (SD)</b>
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 ( $P < 0.05$ ).

<sup>†</sup> Age- and gender-adjusted US norms.[11]

<sup>‡</sup> Damiano *et al.*[17]

<sup>§</sup> Hopman *et al.*[18]

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

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

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25 Improvements from baseline to week 8 were observed for all eight SF-36  
26 domains in the abobotulinumtoxinA group, whereas the placebo group showed some decline in  
27 Physical Functioning and little to no change in other SF-36 domains (Table 3; Figure 2). The  
28 largest improvements occurred in the Role Physical and Bodily Pain domains.  
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35 Patients treated with abobotulinumtoxinA reported significantly greater improvements  
36 than placebo patients from baseline to week 8 in five of the eight SF-36 domains (Table 3;  
37 Figure 2). Specifically, patients treated with abobotulinumtoxinA reported significantly greater  
38 improvements in the Physical Functioning, Role Physical, Bodily Pain, General Health, and Role  
39 Emotional domains ( $P \leq 0.03$  for all) than patients treated with placebo.  
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Table 3. Mean (SE) SF-36 scores by treatment group: baseline and week 8

SF-36 Domain	AbobotulinumtoxinA				Placebo				P value
	N	Baseline mean (SD)	Week 8 mean (SD)	Change mean (SD)	N	Baseline mean (SD)	Week 8 mean (SD)	Change mean (SD)	
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.

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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).

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

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

Week 4: correlation; <i>P</i> value; n								
	Total		Disability		Severity		Pain	
	Abobotulinum-		Abobotulinum-		Abobotulinum-		Abobotulinum-	
	toxinA	Placebo	toxinA	Placebo	toxinA	Placebo	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.



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3 The proportion of subjects classified as responders (achieving the predetermined 30%  
4 improvement in TWSTRS) was consistently higher for the abobotulinumtoxinA group than for  
5 the placebo group. For the abobotulinumtoxinA treatment group, 49% were classified as  
6 responders at week 4 and 58% were classified as responders at week 8. In contrast, for the  
7 placebo treated group, only 16% were classified as responders at week 4 and 26% at week 8.  
8  
9 Patients classified as TWSTRS responders (i.e., those with a  $\geq 30\%$  improvement in TWSTRS at  
10 week 4) reported significantly greater improvements from baseline to week 8 in five of the eight  
11 SF-36 domains compared with patients who did not respond to treatment (Table 5). Specifically,  
12 the largest improvements occurred in Physical Functioning, Role Physical, Bodily Pain, Vitality,  
13 and Social Functioning ( $P \leq 0.03$  for all).  
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**Table 5. Mean change in SF-36 scores by TWSTRS response status**

SF-36 Domain	TWSTRS Responder Status			P value
	Mean Change in SF-36			
	TWSTRS non- responder (n = 47)	TWSTRS responder (n = 36)	Difference (responder – non- responder)	
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.

## 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

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3 controls in the United Kingdom (UK), particularly in the Role Physical (41.6 vs. 85.8), Bodily  
4 Pain (54.6 vs. 81.5), and General Health (46.2 vs. 73.5) domains. Domain scores were  
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6 comparable to data from patients with mild to moderate multiple sclerosis and moderate  
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8 epilepsy. Our results are similar to those of Camfield[19], in that baseline scores for patients with  
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10 CD were lower (worse) than for US normative data, particularly for the Role Physical (52.4 vs.  
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12 76.6), and Bodily Pain (47.7 vs. 71.3) domains. Our findings support the implication that CD has  
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14 a significant impact on health status that is comparable with other neurological disorders of high  
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16 morbidity. CD appears to have a disproportionate negative impact on patients' physical role  
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18 limitation, despite their good physical functioning. One possible explanation is that pain limits  
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20 such activities. Another possibility is that patients with CD consciously limit activities that make  
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22 their dystonia visible to others to avoid mockery.[20]  
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29 A few studies have investigated the impact of CD on HRQOL and factors modifying a  
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31 patient's ability to cope with this disease. Slawek *et al*[21] conducted an HRQOL survey study in  
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33 101 patients previously treated with BoNT-A using the TWSTRS, a pain VAS (0-100%), the  
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35 SF-36, and the Montgomery-Åsberg Depression Rating Scale (MADRS). Patients' baseline  
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37 SF-36 scores were worse than those of healthy controls in all eight SF-36 domains.  
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39 Improvements were observed 4 weeks after the single BoNT-A injections in all SF-36 domains,  
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41 and in the VAS, TWSTRS, and MADRS scores. The TWSTRS results did not correlate with any  
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43 of the SF-36 domains. Longer treatment with BoNT-A was associated with better scores. Hefter  
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45 *et al*[22, 23] conducted a prospective, open-label study of abobotulinumtoxinA in 516 de novo  
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47 CD patients using the TWSTRS, the Craniocervical Dystonia Questionnaire (CDQ-24), patient  
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49 diaries, and a global assessment of pain. In contrast with the SF-36, which is a general measure  
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51 of HRQOL, the CDQ-24 is a disease-specific questionnaire that evaluates HRQOL in patients  
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3 with CD.[24] The CDQ-24 has five subscales: Stigma, Emotional Wellbeing, Pain, Activities of  
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5 Daily Living, and Social/Family Life. At week 4, significant improvements were observed in  
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7 CDQ-24 total and subscale scores that were sustained up to week 12. Significant reductions in  
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9 patient diary item scores for activities of daily living, pain, and pain duration at week 4 and 12  
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11 were observed. Sixty-six percent of patients reported pain relief (less or no pain) at week 4 and  
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13 74% at week 12. Improvements in quality of life and pain intensity for up to 12 weeks in patients  
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15 with CD were observed after treatment with abobotulinumtoxinA.  
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20 Likewise, in our findings, patients treated with abobotulinumtoxinA reported  
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22 significantly greater improvements in TWSTRS total mean scores at weeks 4, 8, and 12  
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24 ( $P \leq 0.019$ ) compared with placebo.[9] Improvements from baseline to week 8 were observed for  
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26 all eight SF-36 domains in the abobotulinumtoxinA group, whereas the placebo group either  
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28 stayed the same or became worse (with a decline in physical functioning). In this study, the  
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30 SF-36 results did correlate with the TWSTRS for the Role Physical and Bodily Pain domains  
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32 across treatment groups and time periods. AbobotulinumtoxinA was well tolerated in this study,  
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34 as previously published.[9]  
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39 Our study is not without limitations that should be considered. First, the exclusion of  
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41 those with suspected secondary non-responsiveness or a history of poor response to BoNT-A  
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43 may have excluded those who might not experience a positive change in their HRQOL.  
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45 Secondly, the size of this study was small. Studies with a larger sample size are required to  
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47 demonstrate the outcomes of abobotulinumtoxinA treatment in a study population that is more  
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49 representative of the general population. Lastly, there were quite a few withdrawals from the  
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51 study, which could affect overall findings. There were a total of 33 patients  
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3 (abobotulinumtoxinA n = 10; placebo n = 23) who discontinued the study, two-thirds of whom  
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5 were in the placebo group.  
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## 10 **CONCLUSION**

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

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

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## 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 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

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## 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.

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# 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

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

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18 **legends):** ~3,165

## 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<sup>®</sup>).

**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

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3 correlated with Physical Functioning, Role Physical, and Bodily Pain scores, for those on active  
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5 treatment.  
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8 **Conclusions:** CD has a marked impact on HRQOL. Treatment with a single  
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10 abobotulinumtoxinA injection results in significant improvement in patients' HRQOL.  
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## 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.



## 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.

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4 Recognizing the critical link between physical and psychological health allows a more  
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6 holistic approach to patient care. By measuring HRQOL, we can ascertain the effects of a disease  
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8 on individuals from the patient perspective and, thereafter, to some extent, be able to judge the  
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10 benefit of therapeutic interventions. With CD, several physical and emotional factors such as  
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12 reduced mobility, pain, low self-esteem, embarrassment, depression, anxiety, and limited social  
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14 interaction may be present. Pain is a predominant feature of CD and is reported in up to 75% of  
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16 patients [7] and is associated with reduced HRQOL. A study conducted by Degirmenci *et al*[8]  
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18 evaluated anxiety and depression in dystonia patients using the Hospital Anxiety Depression  
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20 (HAD) scale and assessed quality of life using the SF-36 Health Survey (SF-36), a general  
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22 measure widely used to assess HRQOL. Mean Anxiety and Depression subscale scores were  
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24 higher in patients with dystonia when compared with the control group. Moreover, patients with  
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26 dystonia had worse (lower) SF-36 scores for all domains when compared with controls.  
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32 AbobotulinumtoxinA (Dysport) 500 U was compared with placebo in two multicenter,  
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34 double-blinded, randomized trials: one international[9] and one in the United States (US).[10]  
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36 The international study included the SF-36 to evaluate treatment benefit with 500 U  
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38 abobotulinumtoxinA compared with placebo as a secondary endpoint. As a result of the  
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40 tremendous amount of research conducted using the SF-36 over the past two decades, population  
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42 norms are available that can facilitate the interpretation of research results across a wide variety  
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44 of patient populations, putting specific study data into “larger context.”[11] In order to  
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46 understand the HRQOL impairment unique to CD, SF-36 scores for the study sample were  
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48 compared with other published scores for populations with various neurological conditions, in  
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50 particular Parkinson’s disease and multiple sclerosis; like CD, these conditions are generally  
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52 progressive and affect motor and non-motor function. Specifically, because the HRQOL  
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3 impairment of Parkinson's disease and that of multiple sclerosis have been well established,[12]  
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5 these conditions were deemed appropriate comparisons in evaluating the unique nature of  
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8 HRQOL impairment due to CD.  
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10 Botulinum toxin (BoNT), a treatment with established safety and efficacy, has been  
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12 recommended as first-line treatment for symptoms of CD.[13, 14] No botulinum toxin is  
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14 indicated for improving HRQOL in CD. The reported benefits from BoNT are relief from pain,  
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16 increased range of free movement, and improved resting posture.[15, 16] BoNT injections  
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18 typically offer temporary relief, and the symptoms gradually return. For CD, as for most other  
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20 neurological disorders, more data exist regarding the efficacy of the Botulinum toxin type A  
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22 (BoNT-A) compared with type B. BoNT-A and BoNT-B have been shown to reduce both  
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24 symptom severity and pain.[15] Currently, there are three major commercially available  
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26 preparations of type A toxins: abobotulinumtoxinA (Dysport<sup>®</sup> [Ipsen Biopharm Ltd, Wrexham,  
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28 UK]), onabotulinumtoxinA (Botox<sup>®</sup> [Allergan, Inc.; Irvine, CA]), and incobotulinumtoxinA  
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30 (Xeomin<sup>®</sup> [Merz Pharmaceuticals GmbH; Frankfurt am Main, Germany). The potency units of  
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32 abobotulinumtoxinA are specific to the preparation and assay method utilized. They are not  
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34 interchangeable with other preparations of botulinum toxin products and, therefore, units of  
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36 biological activity of one BoNT product cannot be compared to or converted into units of any  
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38 other botulinum toxin products. Accordingly, information regarding the specific benefits of a  
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40 particular BoNT-A preparation and the impact on HRQOL would be valuable.  
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48 The objectives of this article are to describe the HRQOL burden of CD, as measured at  
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50 baseline in a previously reported randomized, double-blind, placebo-controlled, pivotal clinical  
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52 study,[9] as well as report on the HRQOL and treatment benefits of abobotulinumtoxinA.  
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## 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

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3 with the Declaration of Helsinki and was reviewed by the ethics committee responsible for each  
4 site. All patients provided written, informed, institutional review board–approved consent before  
5 participation.  
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## 10 11 **Assessments**

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13 Assessments have been described previously.[9] The TWSTRS was determined at week 0  
14 (baseline), at week 4 (primary), and at weeks 8 and 12 (posttreatment) by investigators trained in  
15 TWSTRS scoring. Pain was evaluated with the Pain domain of the TWSTRS and a self-reported  
16 visual analog scale (VAS) assessing pain in the past 24 hours. Participants completed the pain  
17 VAS at baseline and week 4.  
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26 HRQOL was assessed using the SF-36, version 1.0. The SF-36 is a commonly used  
27 health profile that contains 36 items and includes multi-item domains to measure health status  
28 across eight dimensions: Physical Functioning, Role Limitations due to Physical Health  
29 Problems (Role Physical), Bodily Pain, Social Functioning, General Mental Health, Role  
30 Limitations due to Emotional Problems (Role Emotional), Vitality, and General Health  
31 Perceptions. Responses to questions within each domain are summed and transformed to a scale  
32 ranging from 0 to 100, with higher scores suggesting better functioning. Participants completed  
33 the SF-36 at week 0 (baseline; prior to dosing) and at week 8 (posttreatment). SF-36 scores were  
34 generated according to published algorithms.[11]  
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47 Safety assessments included incidence of treatment-emergent adverse events,  
48 electrocardiogram, neurological and physical examinations, and vital signs.  
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## 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.

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

### 19 Patient disposition and demographics

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21 All 116 randomized patients (abobotulinumtoxinA n = 55; placebo n = 61) received at  
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23 least one dose of study medication in the double-blind phase of the study and were included in  
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25 both the intent-to-treat and safety populations. Of these, 83 patients (abobotulinumtoxinA n = 45;  
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27 placebo n = 38) were analyzed in the HRQOL assessment. The mean (standard deviation [SD])  
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29 age was similar across treatment groups: 51.9 (13.4) years for the abobotulinumtoxinA group  
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31 and 53.9 (12.5) years for placebo group. Similarly, both treatment groups were predominantly  
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33 female (67.0% in the abobotulinumtoxinA group and 62.0% in the placebo group). All other  
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35 patient demographics and baseline characteristics were similar between treatment groups (Table  
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37 1).[9] A total of 33 patients discontinued the study because of insufficient response, withdrawal  
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39 of consent, loss to follow-up, or other reasons (Figure 1).  
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**Table 1. Patient demographics and baseline characteristics (intent-to-treat population)**

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



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

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 12). 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,  $P < 0.05$ ).

**Table 42.** 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) <sup>†</sup>	US normative sample <sup>†</sup> Mean	Parkinson's disease <sup>‡</sup> (n = 150) Mean	Multiple sclerosis <sup>§</sup> (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 ( $P < 0.05$ ).

<sup>†</sup> Age- and gender-adjusted US norms.[11]

<sup>‡</sup> Damiano *et al.*[17]

<sup>§</sup> Hopman *et al.*[18]

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

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2  
3 Like individuals with CD, patients with Parkinson's disease and multiple sclerosis report  
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5 substantial impairments in HRQOL relative to US norms (Table 24). However, each of these  
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7 neurologic conditions presents with a unique profile of HRQOL impairment. Patients with CD  
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9 report the greatest limitation in the Bodily Pain domain, whereas patients with Parkinson's  
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11 disease report the greatest impairments in the Role Physical domain, and patients with multiple  
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13 sclerosis report the greatest impairments in the Vitality domain. Each of these neurological  
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15 conditions impairs patients physically, yet the presentation of the disease manifests itself  
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17 differently in terms of HRQOL impairment.  
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### 23 **Treatment effect**

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25 Improvements from baseline to week 8 were observed for all eight SF-36  
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27 domains in the abobotulinumtoxinA group, whereas the placebo group showed some decline in  
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29 Physical Functioning and little to no change in other SF-36 domains (Table 23; Figure 2). The  
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31 largest improvements occurred in the Role Physical and Bodily Pain domains.  
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35 Patients treated with abobotulinumtoxinA reported significantly greater improvements  
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37 than placebo patients from baseline to week 8 in five of the eight SF-36 domains (Table 23;  
38  
39 Figure 2). Specifically, patients treated with abobotulinumtoxinA reported significantly greater  
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41 improvements in the Physical Functioning, Role Physical, Bodily Pain, General Health, and Role  
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43 Emotional domains ( $P \leq 0.03$  for all) than patients treated with placebo.  
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Table 23. Mean (SE) SF-36 scores by treatment group: baseline and week 8

SF-36 Domain	AbobotulinumtoxinA				Placebo				P value
	N	Baseline mean (SD)	Week 8 mean (SD)	Change mean (SD)	N	Baseline mean (SD)	Week 8 mean (SD)	Change mean (SD)	
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.

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3 Table 34 presents the correlations between the TWSTRS total and domain scores at  
4 week 4 with the week 8 SF-36 domain scores. As expected, the TWSTRS was significantly  
5 correlated with the Physical Functioning, Role Physical, and Bodily Pain domain scores. The  
6 correlations between TWSTRS domain and total scores were consistently significantly correlated  
7 with the Role Physical and Bodily Pain domain scores for both treatment groups. The  
8 correlations ranged from  $-0.29$  to  $-0.44$  at week 4. Correlations were similar when evaluated  
9 with week 8 TWSTRS scores and week 8 SF-36 scores:  $-0.33$  to  $-0.53$  (week 8 correlations not  
10 shown).  
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Table 34. Correlations between the week 8 SF-36 scores with the TWSTRS at week 4 by treatment group

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

Week 4: correlation; <i>P</i> value; n								
	Total		Disability		Severity		Pain	
	Abobotulinum-		Abobotulinum-		Abobotulinum-		Abobotulinum-	
	toxinA	Placebo	toxinA	Placebo	toxinA	Placebo	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.

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3 The proportion of subjects classified as responders (achieving the predetermined 30%  
4 improvement in TWSTRS) was consistently higher for the abobotulinumtoxinA group than for  
5 the placebo group. For the abobotulinumtoxinA treatment group, 49% were classified as  
6 responders at week 4 and 58% were classified as responders at week 8. In contrast, for the  
7 placebo treated group, only 16% were classified as responders at week 4 and 26% at week 8.

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15 ~~Among those classified as TWSTRS responders, improvements from baseline to week 8 were~~  
16 ~~observed for most of the SF-36 domains, whereas the non-responder group showed little to no~~  
17 ~~change in SF-36 domains (Table 4). The largest improvements occurred in the Role Physical and~~  
18 ~~Bodily Pain domains.~~ Patients classified as TWSTRS responders (i.e., those with a  $\geq 30\%$   
19 improvement in TWSTRS at week 4) reported significantly greater improvements from baseline  
20 to week 8 in five of the eight SF-36 domains compared with patients who did not respond to  
21 treatment (Table 4). Specifically, the largest improvements occurred responders reported  
22 significantly greater improvements in Physical Functioning, Role Physical, Bodily Pain, Vitality,  
23 and Social Functioning ( $P \leq 0.03$  for all) ~~than patients considered non-responsive to treatment.~~  
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Table 45. Mean change in SF-36 scores by TWSTRS response status

SF-36 Domain	TWSTRS Responder Status			P value
	Mean Change in SF-36			
	TWSTRS non- responder (n = 47)	TWSTRS responder (n = 36)	Difference (responder – non- responder)	
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.

## 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

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3 eight SF-36 domains compared with controls in the United Kingdom (UK), particularly in the  
4 Role Physical (41.6 vs. 85.8), Bodily Pain (54.6 vs. 81.5), and General Health (46.2 vs. 73.5)  
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6 domains. Domain scores were comparable to data from patients with mild to moderate multiple  
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8 sclerosis and moderate epilepsy. Our results are similar to those of Camfield[19], in that baseline  
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10 scores for patients with CD were lower (worse) than for US normative data, particularly for the  
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12 Role Physical (52.4 vs. 76.6), and Bodily Pain (47.7 vs. 71.3) domains. Our findings support the  
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14 implication that CD has a significant impact on health status that is comparable with other  
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16 neurological disorders of high morbidity. CD appears to have a disproportionate negative impact  
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18 on patients' physical role limitation, despite their good physical functioning. One possible  
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20 explanation is that pain limits such activities. Another possibility is that patients with CD  
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22 consciously limit activities that make their dystonia visible to others to avoid mockery.[20]  
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29 A few studies have investigated the impact of CD on HRQOL and factors modifying a  
30 patient's ability to cope with this disease. Slawek *et al*[21] conducted an HRQOL survey study in  
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32 101 patients previously treated with BoNT-A using the TWSTRS, a pain VAS (0-100%), the  
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34 SF-36, and the Montgomery-Åsberg Depression Rating Scale (MADRS). Patients' baseline  
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36 SF-36 scores were worse than those of healthy controls in all eight SF-36 domains.  
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38 Improvements were observed 4 weeks after the single BoNT-A injections in all SF-36 domains,  
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40 and in the VAS, TWSTRS, and MADRS scores. The TWSTRS results did not correlate with any  
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42 of the SF-36 domains. Longer treatment with BoNT-A was associated with better scores. Hefter  
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44 *et al*[22, 23] conducted a prospective, open-label study of abobotulinumtoxinA in 516 de novo  
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46 CD patients using the TWSTRS, the Craniocervical Dystonia Questionnaire (CDQ-24), patient  
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48 diaries, and a global assessment of pain. In contrast with the SF-36, which is a general measure  
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50 of HRQOL, the CDQ-24 is a disease-specific questionnaire that evaluates HRQOL in patients  
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3 with CD.[24] The CDQ-24 has five subscales: Stigma, Emotional Wellbeing, Pain, Activities of  
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5 Daily Living, and Social/Family Life. At week 4, significant improvements were observed in  
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7 CDQ-24 total and subscale scores that were sustained up to week 12. Significant reductions in  
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9 patient diary item scores for activities of daily living, pain, and pain duration at week 4 and 12  
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11 were observed. Sixty-six percent of patients reported pain relief (less or no pain) at week 4 and  
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13 74% at week 12. Improvements in quality of life and pain intensity for up to 12 weeks in patients  
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15 with CD were observed after treatment with abobotulinumtoxinA.  
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19 Likewise, in our findings, patients treated with abobotulinumtoxinA reported  
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21 significantly greater improvements in TWSTRS total mean scores at weeks 4, 8, and 12  
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23 ( $P \leq 0.019$ ) compared with placebo.[9] Improvements from baseline to week 8 were observed for  
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25 all eight SF-36 domains in the abobotulinumtoxinA group, whereas the placebo group either  
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27 stayed the same or became worse (with a decline in physical functioning). In this study, the  
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29 SF-36 results did correlate with the TWSTRS for the Role Physical and Bodily Pain domains  
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31 across treatment groups and time periods. AbobotulinumtoxinA was well tolerated in this study,  
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33 as previously published.[9]  
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39 Our study is not without limitations that should be considered. First, the exclusion of  
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41 those with suspected secondary non-responsiveness or a history of poor response to BoNT-A  
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43 may have excluded those who might not experience a positive change in their HRQOL.  
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45 Secondly, the size of this study was small. Studies with a larger sample size are required to  
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47 demonstrate the outcomes of abobotulinumtoxinA treatment in a study population that is more  
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49 representative of the general population. Lastly, there were quite a few withdrawals from the  
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51 study, which could affect overall findings. There were a total of 33 patients  
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3 (abobotulinumtoxinA n = 10; placebo n = 23) who discontinued the study, two-thirds of whom  
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6 were in the placebo group.  
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## 10 **CONCLUSION**

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

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

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## 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.

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5 **FIGURE LEGENDS**  
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8 **Figure 1. Study Flow Diagram**  
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11 **Figure 2. Mean (SE) change in SF-36 scores at week 8**  
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13 \*  $P < 0.05$ .  
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15 Note: Positive changes in score indicate improvement.  
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17 SE, standard error; SF-36, SF-36 Health Survey.  
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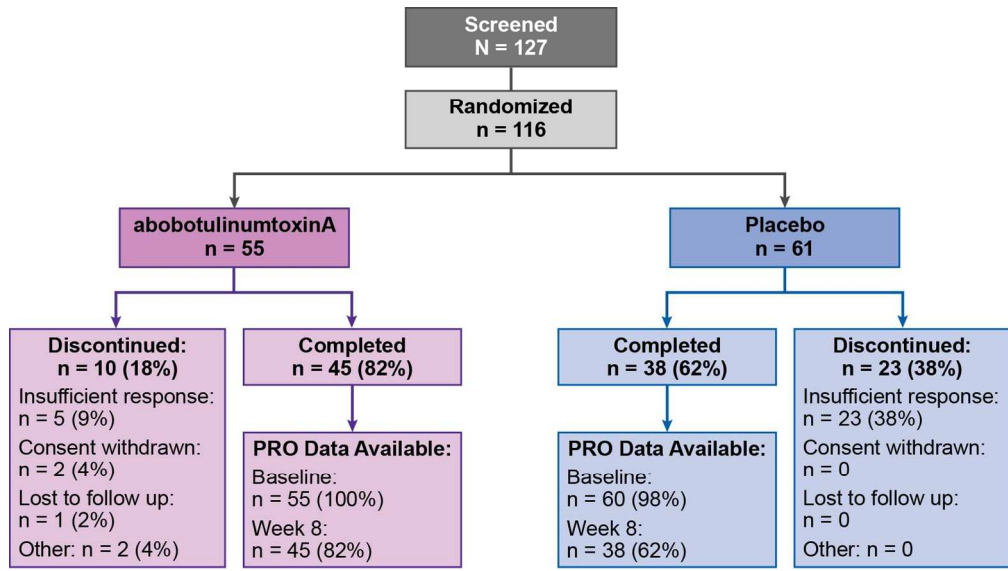
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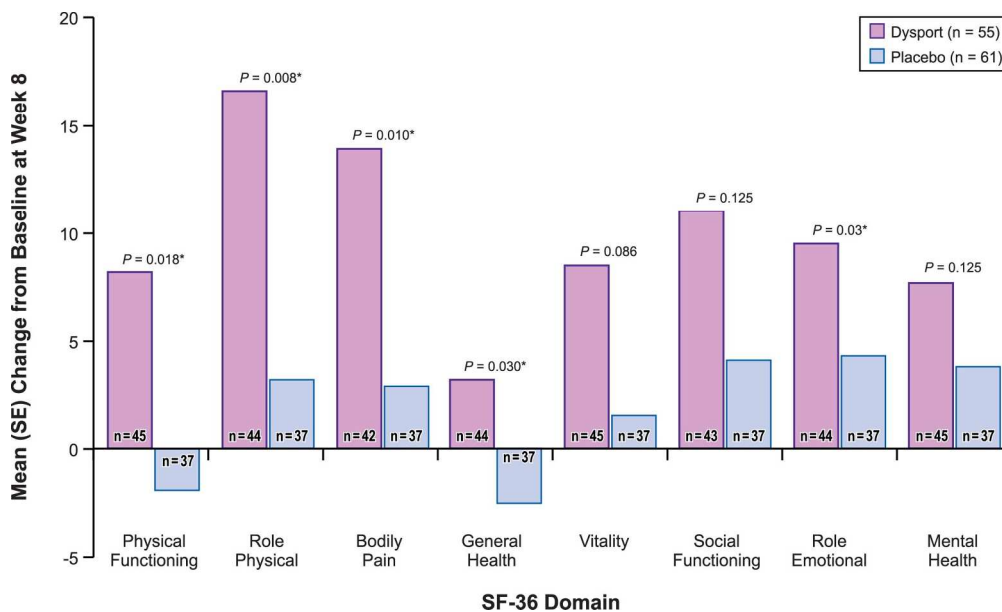
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152x85mm (300 x 300 DPI)

review only



186x111mm (300 x 300 DPI)

review only

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

Section/Topic	Item No	Checklist item	Reported on page No
<b>Title and abstract</b>			
	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
<b>Introduction</b>			
Background and objectives	2a	Scientific background and explanation of rationale	6
	2b	Specific objectives or hypotheses	7
<b>Methods</b>			
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
<b>Randomisation:</b>			
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)

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2	Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how
3			9
4		11b	If relevant, description of the similarity of interventions
5			Not Applicable
6	Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes
7		12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses
8			11
9	<b>Results</b>		
10	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
11			12
12		13b	For each group, losses and exclusions after randomisation, together with reasons
13			12
14	Recruitment	14a	Dates defining the periods of recruitment and follow-up
15		14b	Why the trial ended or was stopped
16			Not Applicable
17	Baseline data	15	A table showing baseline demographic and clinical characteristics for each group
18			Reported in Truong, 2010
19	Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups
20			Figure 1 in separate file
21	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)
22			Figure 1 in separate file
23		17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended
24			Not Applicable
25	Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory
26			17-19
27	Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)
28			Reported in Truong, 2010
29			
30	<b>Discussion</b>		
31	Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses
32			23
33	Generalisability	21	Generalisability (external validity, applicability) of the trial findings
34			21-22
35	Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence
36			22-23
37	<b>Other information</b>		
38	Registration	23	Registration number and name of trial registry
39			25
40	Protocol	24	Where the full trial protocol can be accessed, if available
41			Not available
42	Funding	25	Sources of funding and other support (such as supply of drugs), role of funders
43			25

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\*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](http://www.consort-statement.org).

For peer review only