Title

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Multicenter observational study of abobotulinumtoxinA neurotoxin in cervical dystonia: The ANCHOR-CD registry

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ABSTRACT

Background: The ANCHOR-CD prospective observational registry study evaluated the effectiveness of abobotulinumtoxinA in adult idiopathic cervical dystonia (CD) in clinical practice.
Methods: Adults with CD were eligible. Treating physicians determined abobotulinumtoxinA dose and treatment interval. The primary endpoint was patient response rate (Toronto Western Spasmodic Torticollis Rating Scale [TWSTRS] score reduction ≥ 25% and Patient Global Impression of Change [PGIC] score of +2 or +3 at Week 4 of Cycle 1).
Results: 350 patients enrolled (75% women; mean age 59 ± 13.6 years; 27.4% botulinum neurotoxin-naive) and 347 received at least 1 treatment. The median abobotulinumtoxinA dose for Cycle 1 was 500 Units. At Week 4, the responder rate was 30.6% (n = 304) and the TWSTRS total score decreased 27.4% from baseline. PGIC of at least "Much improved" was documented in 43.6% of patients and maintained in Cycles 2 through 4 (43.3%, 48.9%, and 52.8%, respectively). A total of 39 adverse events (31 study drug-related) were reported in 17 patients (5%); the most common were dysphagia (n = 6), muscle weakness (n = 4), and neck pain (n = 3).
Conclusion: This study confirmed the beneficial effect of abobotulinumtoxinA on CD in routine clinical practice as measured by improvements in TWSTRS and PGIC. No new safety concerns were identified.

1. Introduction

Cervical dystonia (CD) is a chronic movement disorder characterized by abnormal posturing or involuntary movements of the neck, head, and shoulders [1,2]. The movements observed in CD are often complex and can include rotation (rotocollis), flexion (anterocollis), extension (retrocollis), or tilting (laterocollis) [2,3]. In clinical practice, CD is heterogeneous in its presentation, with a wide range of symptom severity and patient comorbidities [3]. The disorder can have a major impact on patient quality of life [2,4].

CD is the most common adult-onset focal dystonia, with an estimated prevalence of 28–183 cases per million people in the general

Abbreviations: BoNT, botulinum neurotoxin; CD, cervical dystonia; CDIP, CD Impact Profile; CGIC, clinical global impression of change; PGIC, Patient Global Impression of Change; PNRS, Pain Numeric Rating Scale; TSQM, Treatment Satisfaction Questionnaire for Medication; TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale.

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population [3]. Geographical and ethnic differences may play a role in the wide range of prevalence estimates. For example, in a study of the multiethnic membership of a health maintenance organization in Northern California, prevalence of CD was higher in white patients of European descent than among Hispanic, Asian, or African-American patients [5].

Botulinum neurotoxin type A (BoNT-A) is established as an effective treatment for CD [6,7]. This neurotoxin inhibits the release of acetylcholine from the presynaptic neuron, inducing a graded muscle weakness. As a result of weakening dystonic muscles, there is a reduction in symptoms with improvement in pain and in control over voluntary head and neck movements. Relief is transient, and the effect wears off over the course of months [8,9].

AbobotulinumtoxinA (Dysport®, Ipsen Biopharmaceuticals, Inc., Basking Ridge, NJ, USA) is a BoNT-A indicated for the treatment of adults with CD [10]. The efficacy and safety of abobotulinumtoxinA for CD has been established in 2 randomized, controlled clinical trials and their open-label safety extensions [10–12]. Controlled studies, however, may not accurately reflect "real life" outcomes. Prospective naturalistic studies are needed to assess the effectiveness of treatment in routine daily practice, particularly in view of the heterogeneity of CD and the diversity in injection techniques by physicians across a variety of clinical practices.

ANCHOR-CD was a prospective, open-label, observational registry designed to evaluate the efficacy and safety of abobotulinumtoxinA for a 1-year period of repeated injections in adults with idiopathic CD treated in routine clinical practice in the United States.

2. Methods

2.1. Study population

Adult patients diagnosed with isolated (idiopathic) CD who gave their informed consent to participate were eligible for enrollment in the study. Patients could be BoNT-naïve or previously treated with BoNT if at least 12 weeks had elapsed since the last BoNT-A or BoNT-B injection. Patients were ineligible to participate if they had secondary CD, if they anticipated concomitant treatment with BoNT for indications other than CD, or if based on investigator opinion, previous BoNT-A or BoNT-B therapy had produced an insufficient response or intolerable adverse event (AE). The decision to prescribe abobotulinumtoxinA was to be made before and independently from the decision to enroll the patient in the registry. This study obtained appropriate institutional review board approval and was conducted under the provisions of the Declaration of Helsinki.

2.2. Treatment and assessments

AbobotulinumtoxinA was administered by intramuscular injection over 4 treatment cycles. The muscles selected for injection, the number of injections into each muscle, doses of BoNT, and method of administration were determined by the investigators in accordance with their standard of practice.

The recommended treatment cycle intervals in the study were consistent with the United States labeling for Dysport® (i.e., every 12 weeks). The treating physician determined the dose and treatment interval, taking into account patient response and label recommendations.

The primary efficacy endpoint was the patient response rate, defined as the percentage of patients with a Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) Severity scale score reduction of ≥25% in combination with a Patient Global Impression of Change (PGIC) score of +2 or +3 (much or very much improved) at Week 4 of Cycle 1.

Secondary endpoints included TWSTRS total and subscale scores, PGIC, Clinical Global Impression of Change scale (CGIC), time to waning effect of treatment, CD Impact Profile (CDIP-58), Pain Numeric Rating Scale (PNRS), and the modified Treatment Satisfaction Questionnaire for Medication (TSQM).

For the first injection (Cycle 1), in-office physician assessments were made at baseline and Week 4 following the injection. These assessments included the TWSTRS total and subscale scores (severity, disability, and pain). The TWSTRS Total score (maximum score of 85) was derived from the sum of the TWSTRS Severity score (0–35), the TWSTRS Disability score (0–30), and the TWSTRS Pain score (0–20). For the first cycle, CGIC was assessed at Week 4 using a 7-point Likert scale, ranging from +3 (very much improved) to −3 (very much worse). Because ANCHOR-CD was designed as a registry intended to capture data in a real-world, pragmatic setting, patients were not asked to come in to the office for physician assessments of efficacy after injection during Cycles 2 through 4. As a result, TWSTRS and CGIC data were only collected for Cycle 1.

Patient assessments of efficacy that were collected through all four cycles of treatment included PGIC, time to waning effect of treatment, PNRS, and the modified TSQM. PGIC was assessed using the same 7-point Likert scale for CGIC ranging from +3 ("very much improved") to −3 ("very much worse"). PGIC was assessed in the office at Week 4 of Cycle 1, during each subsequent treatment visit during Cycles 2 through 4, and at the study termination visit (no sooner than 12 weeks after the fourth treatment). PGIC was also assessed by phone interviews at Week 8 of Cycle 1 and Week 4 and Week 8 of Cycles 2 through 4.

Symptom reemergence was evaluated in-office at each treatment visit for Cycles 2 through 4 and at the study termination visit. It was assessed by phone interview at Week 8 of all four cycles.

The PNRS assessed pain during the previous 24 h on a scale of 0 (no pain) to 10 (worst possible pain). The PNRS was scored at each office visit and by phone interview 4 weeks after treatment for Cycles 2 through 4.

Satisfaction with treatment was assessed using the modified TSQM, an instrument with 6 questions assessing global satisfaction and effectiveness. Each question is rated on a 7-point scale ranging from "Extremely Satisfied" to "Extremely Dissatisfied". The modified TQSM was administered in-office at Week 4 of Cycle 1 and at the treatment visit for Cycles 2 through 4. It was also administered by phone at Week 4 of Cycles 2 through 4, and at the study termination visit.

The CDIP-58 is a validated 58-item patient-reported questionnaire assessing eight domains: head and neck symptoms, pain and discomfort, upper limb activities, walking, sleep, annoyance, mood, and psychosocial functioning. CDIP-58 was assessed at baseline, at the Cycle 3 treatment visit, and at the study termination visit.

Investigators were asked to report adverse drug reactions (ADRs, AEs thought to have a causative relationship to the drug) directly to the safety department of the study sponsor. AEs were reported to the study sponsor according to the regulations governing postmarketing reporting of spontaneous cases. In this paper, we include all ADRs and AEs reported to the sponsor from April 27, 2011 through April 22, 2014.

2.3. Statistical reporting

This was an observational study and thus did not include statistical significance testing. The response rate was calculated as the number of responders divided by the number of patients who completed TWSTRS and PGIC assessments at Week 4 of Cycle 1. An exact 95% confidence interval (CI) was calculated using the binomial distribution without a continuity correction. The 95% CIs of mean change were calculated using the normal approximation to the distribution of the sample mean. Demographic and efficacy data collected as continuous measures were summarized by mean, SD, median, 25th percentile, 75th percentile, minimum, and maximum.

3. Results

3.1. Patient disposition and baseline characteristics

A total of 350 patients from 41 sites in the United States were enrolled in the study. Seventy-five percent were women. The mean age at enrollment was 59.0 ± 13.6 years, with a mean age at diagnosis of 52.9 ± 14.1 years. Most patients (67.2%) had a mixed-type CD with 25.6% having had pure torticollis (Table 1). Most patients had received previous BoNT treatment for CD (72.6%). The most common reason for switching to abobotulinumtoxinA was efficacy (82/347, 57.3%). The second most common cause for switching was cost/reimbursement (31/347, 21.7%).

Of the 350 patients enrolled, 347 (99%) received at least 1 dose (any amount) of abobotulinumtoxinA treatment and constituted the full study population. Of the 347 patients treated, 127 (36.6%) discontinued over the 4 treatment cycles: 19.6% after Cycle 1, 7.5% after Cycle 2, 5.2% after Cycle 3, and 4.3% after Cycle 4. Fig. 1 describes the reasons for discontinuation. The most common reason for discontinuation was patient decision (40/68 [58%], 15/26 [57.7%], 8/18 [44.4%], and 4/15 [26.7%] of patients at Cycles 1–4, respectively). Other common reasons for discontinuation included lost to follow-up and investigator decision.

3.2. Treatment exposure

For the full study population, median dose of abobotulinumtoxinA injected, the total volume injected, and the total number of muscles injected remained relatively constant across treatment cycles. For Cycle 1, the cycle used for the primary efficacy analysis, the median dose (range) administered was 500 U (100–1500 U) and the median number of muscles injected was 4 (1–7). The splenius capitis was the most commonly injected muscle, followed by the levator scapulae and trapezius (Table 2).

Table 1
Baseline characteristics.

	N = 347
Male/female, n (%)	86/261 (25/75)
Age at first visit (years; mean ± SD)	59.0 ± 13.6
Age at symptom onset (years; mean ± SD)	48.9 ± 15.6
Age at diagnosis (years; mean ± SD)	52.9 ± 14.1
Type of CD posture, n (%)	
None selected	1 (0.3)
Torticollis	89 (25.6)
Laterocollis	13 (3.7)
Retrocollis	4 (1.2)
Anterocollis	5 (1.4)
Lateral shift	1 (0.3)
Other	1 (0.3)
Mixed types	233 (67.2)
Previous exposure to BoNT products, n (%)	
No	95 (27.4)
Yes	252 (72.6)
Concomitant treatments, n (%)[a]	
Concomitant medications	269 (77.5)
Analgesics	157 (45.2)
Benzodiazepines	141 (40.6)
Antiepileptics	66 (19)
Baclofen	17 (4.9)
Dopamine antagonist	7 (2.0)
Beta blockers	54 (15.6)
Anticholinergics	12 (3.5)
Other muscle relaxants	99 (28.5)
Nonpharmacologic treatments	
Physical therapy	86 (24.8)
Transdermal electrical nervestimulation	76 (21.9)
Acupuncture	69 (19.9)

[a] Multiple categories could be selected.

3.3. Primary efficacy endpoint

3.3.1. Patient response rate

The response rate for the full study population who completed both TWSTRS and PGIC assessments at Week 4 (n = 304) was 30.6% (95% CI, 25.5–36.1), n = 93 (Table 2). The proportion of responders was comparable for BoNT-naïve (32.4% [95% CI, 21.8–44.5]; n = 23/71) and previously treated with BoNT (30.0% [95% CI, 24.2–36.4]; n = 70/233) patients.

3.4. Secondary efficacy endpoints

3.4.1. TWSTRS

The TWSTRS Total score decreased 27.4% (SD = 28.9) during Cycle 1 (n = 304), with improvements noted in the Severity, Disability, and Pain TWSTRS subscale scores (Fig. 2), indicating overall improvements in these domains. The mean percent reduction in TWSTRS Total score was comparable for BoNT-naïve patients (25.6%, SD 31.5), and patients previously treated with BoNT (27.9%, SD 28.1).

3.4.2. PGIC

"Much improved" or "very much improved" PGIC was rated by 43.6% of the patients at Week 4 of Cycle 1 and was maintained in injection cycles 2 through 4 (43.3%, 48.9%, and 52.8%, respectively (Fig. 2)). Similar improvements in PGIC (42.5% and 44.1%) were observed for BoNT-naïve patients and patients previously treated with BoNT.

3.4.3. CGIC

At Cycle 1, Week 4, approximately two-thirds (n = 192) of patients with responses (n = 316) were assessed by their physician as "very much improved" (n = 41) or "much improved" (n = 151) relative to baseline. Additionally, 4.6% and 4.9% of patients had "no change" or worsening symptoms, respectively (see Supplementary Table 1).

3.4.4. Other secondary endpoints

The Global Satisfaction domain score of the modified TSQM increased from 48.7% at Cycle 1, Week 4, to 57.3% at Cycle 4, Week 4, indicating an overall increase in satisfaction with treatment as patients progressed through the four treatment cycles. Patients also reported improvements in the PNRS and all domains of the CDIP-58 (see Supplementary Table 2).

3.5. Safety data

Seventeen patients (5%) experienced a total of 39 AEs, of which 11 (n = 5 patients) were serious AEs. The most common AEs were dysphagia (n = 6, 1.7%), muscular weakness (n = 4, 1.2%), neck pain (n = 3, 0.9%), and rhinorrhea (n = 2, 0.6%). Three patients withdrew as a result of AEs, 2 with dysphagia and 1 with blurred vision and chewing difficulty.

Of the 39 AEs, 31 (n = 13 patients) were thought to be related to the study drug (ADRs). Of the 11 serious AEs, 6 were serious ADRs (n = 3; asthenia, dysphagia, diplopia, dizziness, fall, joint injury). One patient died of an unknown cause 2 days after study completion. The death was deemed not related to study drug by the investigator. Full safety data for the registry are presented in Supplementary Table 3.

4. Discussion

ANCHOR-CD was a prospective, observational registry study designed to evaluate the response to abobotulinumtoxinA treatment for idiopathic CD in routine clinical practice in the United States. The results of this study support the clinical utility of abobotulinumtoxinA for managing CD-associated pain and disability in a real-world setting.

In the registry, the percentage of responders and the TWSTRS total and subscale scores were similar between BoNT-naïve and previously

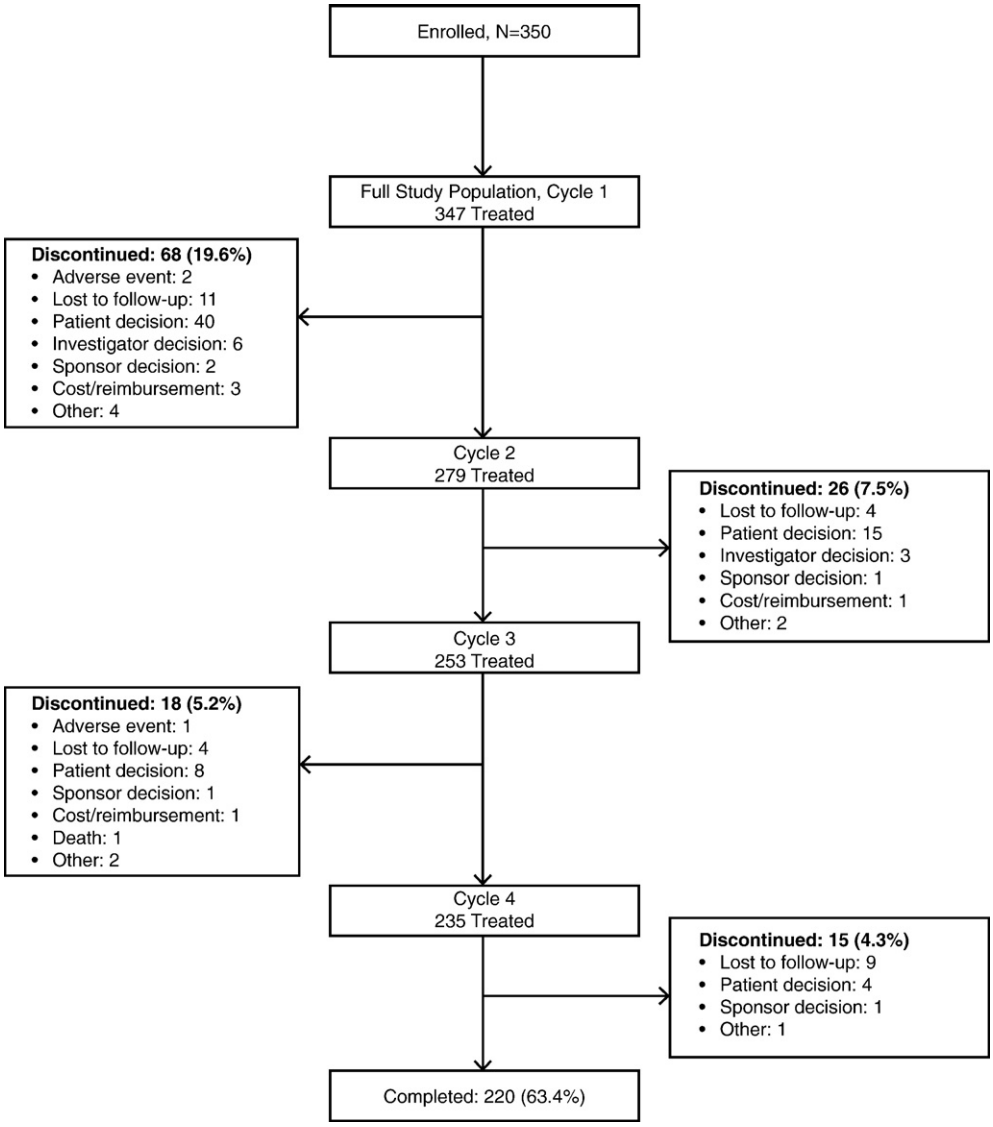

Fig. 1. Patient disposition.

treated subgroups. These results suggest that BoNT-naïve patients and patients previously treated with BoNTs may have a similar response to abobotulinumtoxinA treatment.

In terms of safety, abobotulinumtoxinA was generally well-tolerated by patients in the registry. The most common AEs that were reported were dysphagia, muscular weakness, neck pain, and rhinorrhea, which appear to be consistent with the known profile in the product labeling [10].

The results from the registry were consistent with the results from two pivotal randomized, double-blind, placebo-controlled trials of abobotulinumtoxinA for the treatment of CD [11,12]. For example, the percent decrease in TWSTRS Total score from baseline to Week 4 of the first cycle was similar across all 3 trials: 27.4%, 22.0%, and 35.6% in the ANCHOR-CD, Truong 2005, and Truong 2010, respectively [11,12].

Registry studies for two other BoNT-A products have also been performed. CD-PROBE was a prospective, observational study of onabotulinumtoxinA for CD (1046 patients) [13,14], and XCiDaBLE was a prospective observational study of incobotulinumtoxinA for blepharospasm and CD (145 patients) [15]. All three registry studies had comparable patient populations and similar patterns of muscles injected, although a higher percentage of patients in the CD-PROBE registry were BoNT-naïve [14,15]. See Supplementary Table 4 for additional details.

Although the three registries differed in terms of the timing and type of assessments performed, patients in ANCHOR-CD and CD-PROBE achieved similar reductions in TWSTRS Total score and subscale scores (TWSTRS was not assessed for XCiDaBLE). For example, 4 weeks after the first treatment in ANCHOR-CD (Cycle 1, Week 4), the TWSTRS Total score was reduced by 27.4%. Jankovic 2015 did not report on the TWSTRS results in CD-PROBE after the first treatment, but 4–6 weeks after the second treatment (Visit 3), the reduction from baseline in TWSTRS Total score was 20.2% (TWSTRS Total score 39.2 at baseline and 31.3 at Visit 3) [14]. In addition, all three registries had similar patient-reported outcomes as assessed by PGIC (data not shown) [14,15].

Registries have inherent limitations, including the lack of a control group or a prespecified statistical analysis plan, which may affect the strength of their findings.

A total of 127 patients (36.6%) discontinued treatment before the end of the study. The most common reason was patient decision ($n = 67$). Five additional patients withdrew due to cost/reimbursement issues and 3 as a result of AEs (see Fig. 1 for a complete breakout). The overall dropout rate was lower in ANCHOR-CD than in the CD-PROBE

Table 2
Treatment exposure and patient response during Cycle 1.

	N = 347
AbobotulinumtoxinA treatment	
Median dose [range]	500 U [100–1502 U]
Mean dose [SD]	504 U (228.6)
Median number of muscles injected [range]	4 [1–7]
Injection site, n (%)[a]	
Splenius capitis	318 (91.6)
Levator scapulae	244 (70.3)
Trapezius	236 (68.0)
Sternocleidomastoid	213 (61.4)
Semispinalis capitis	192 (55.3)
Longissimus	104 (30.0)
Scalenus (medius and anterior)	54 (15.6)
Other	156 (45.0)
Patient response rate, n (%) [95% CI]	
At least 25% reduction in TWSTRS Severity score at Week 4, Cycle 1 (n = 304[b])	199 (65.5%) [59.8, 70.8]
PGIC score of +2 or +3 (much or very much improved) at Week 4, Cycle 1 (n = 307[a])	134 (43.6%) [38.0, 49.4]
Responders (25% reduction in TWSTRS Severity and PGIC scores of +2 or +3) (n = 304[a])	93 (30.6%) [25.5, 36.1]

[a] Multiple categories could be selected.
[b] Calculated for patients with complete data.

registry, 36.6% vs 52.0%, even though ANCHOR-CD had one more treatment cycle than CD-PROBE.

Finally, because of the need for an in-office follow-up visit (Cycle 1, Week 4), the registry population may have been limited to patients geographically near the study sites. If local patients differ in important ways from the overall population with CD, the registry may not reflect the experience of the larger patient population. Nevertheless, the size and diversity of the patient population in ANCHOR-CD is consistent with the heterogeneous clinical presentation of CD and provides real-world information to supplement what can be obtained during randomized controlled trials.

5. Conclusion

Treatment of adult idiopathic CD with abobotulinumtoxinA in routine clinical practice revealed improvements in TWSTRS Total score and subscale scores, and in patient-rated measures of improvement similar to those reported in previous controlled clinical trials. AbobotulinumtoxinA was generally well tolerated and no new safety concerns were identified.

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Declaration of interest

Dr. Trosch received personal compensation as a consultant or speaker from Ipsen Biopharmaceuticals, Inc., Impax Pharmaceuticals, Allergan Inc. and Acadia Pharmaceuticals. He has served as a clinical investigator

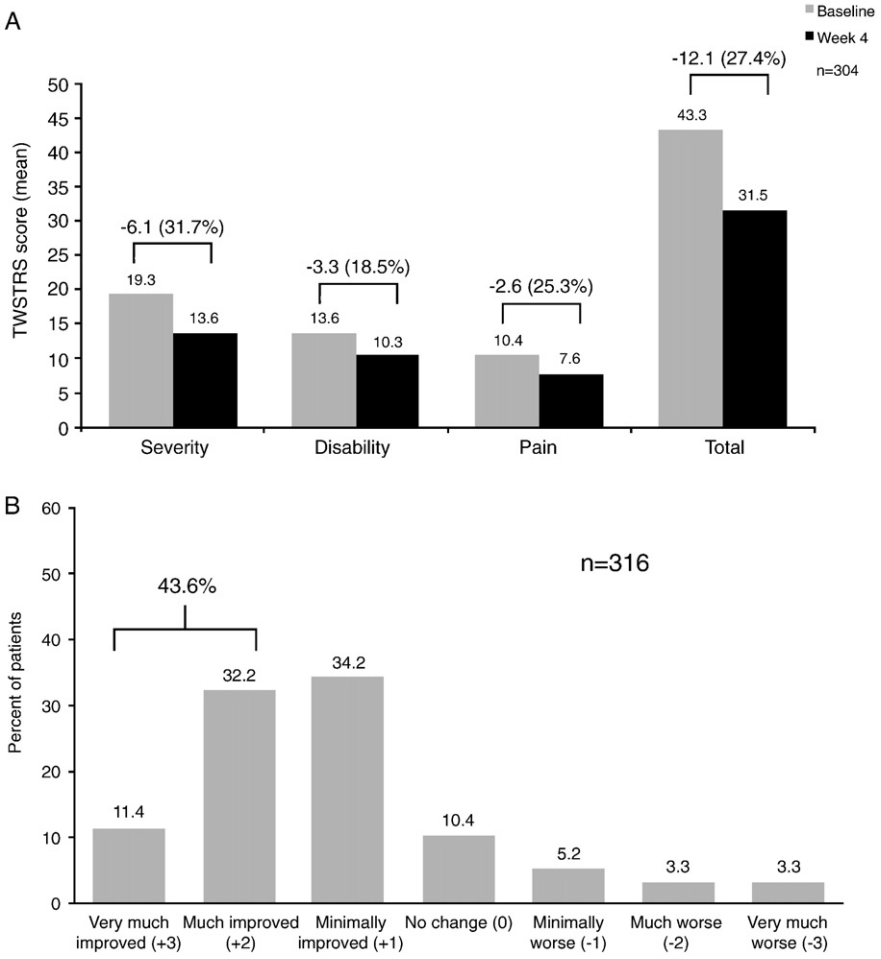

Fig. 2. Change in TWSTRS mean scores (A) and Patient Global Impression of Change (B) at Week 4, Cycle 1.

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Dr. LeWitt is a consultant/advisor for Acadia, Civitas, Concit, Depomed, Impax, Insightec, Intec, Ipsen, Knopp Biosciences, Lundbeck, Merck, Merz, NeuroDerm, Noven, Osmotica, Parkinson Study Group, Pfizer, ProStrakan, Teva, USWorldMeds, and XenoPort; has received grants/honoraria from Adamas, Addex, Allergan, Biotie, Great Lakes Neurotechnologies, Kyowa Hakko, The Michael J. Fox Foundation for Parkinson's Research, Pharma 2B, Phytopharm, UCB, and USWorldMeds; and received other financial or commercial support from The International Parkinson's Disease and Movement Disorders Society, Lundbeck, Tremor Research Group, USWorldMeds, and the World Parkinson Congress.

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Mr. Marchese is an employee of Ipsen Biopharmaceuticals. Mr. Marchese owns stock greater than $10,000 in Amicus Therapeutics. Mr. Marchese had owned stock in Questcor Pharmaceuticals and Chelsea Therapeutics greater than $10,000.

Dr. Comella serves on the editorial board of *Clinical Neuropharmacology, Sleep Medicine*, and *Continuum*. She receives research support from the NIH R01NS074343, U54NS065701, Dystonia Medical Research Foundation, Allergan Inc. Ipsen Biopharmaceuticals, Inc., Merz Pharmaceuticals and Biotie Inc. She receives compensation/honoraria for services as a consultant or an advisory committee member from: Acorda Therapeutics, Allergan, Inc.; Impax Pharmaceuticals; Ipsen Biopharmaceuticals, Inc.; Lundbeck Ltd.; Medtronic Inc.; Merz Pharmaceuticals; Acadia Pharmaceuticals; Teva Neurosciences; Neurocrine Biosciences Inc., Revance Therapeutic; and Ultragenyx Pharmaceuticals. She receives royalties from Cambridge, Humana Press, and Wolters Kluwer. She receives research support from the Parkinson's Disease Foundation.

Author's Contribution

Richard M Trosch, MD, was a site investigator and contributed to the critical review of the manuscript.

Alberto J Espay, MD, MSc, was a site investigator and contributed to the critical review of the manuscript.

Daniel Truong, MD, was a site investigator and contributed to the critical review of the manuscript.

Ramon Gil, MD, was a site investigator and contributed to the critical review of the manuscript.

Carlos Singer, MD, contributed to the critical review of the manuscript.

Peter A LeWitt, MD, contributed to the critical review of the manuscript.

Mark F Lew, MD, contributed to the critical review of the manuscript.

Michele Tagliati, MD, contributed to the critical review of the manuscript.

Charles H. Adler, MD, PhD, contributed to the critical review of the manuscript.

Jack J Chen, PharmD, FCCP, BCPS, CGP, contributed to the critical review of the manuscript.

Dominic Marchese, RPh, contributed to the critical review of the manuscript.

Cynthia L Comella, MD, was involved in study design and contributed to the critical review of the manuscript.

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Appendix – study sites

Allegheny General Hospital Department of Neurology, Pittsburgh, Pennsylvania, United States; Arizona Dystonia Institute, Scottsdale, Arizona, United States; Baptist Neurology Center – Lexington, Lexington, Kentucky, United States; Capital Neurology Services & MS Institute, Gahanna, Ohio, United States; Cleveland Clinic Center for Neurological Restoration, Cleveland, Ohio, United States; Cleveland Clinic Florida, Reston, Florida, United States; Coastal Neurological Medical Group, Inc., La Jolla, California, United States; Coastal Neurology, PA, Port Royal, South Carolina, United States; Colorado Springs Neurological Associates, Colorado Springs, Colorado, United States; Columbia Pain Management, PC, Hood River, Oregon, United States; East Bay Physicians Medical Group, Berkeley, California, United States; Elks Rehab Hospital - Movement Disorders Center, Boise, Idaho, United States; Emerald Coast Center for Neurological Disorders, Pensacola, Florida, United States; Empire Neurology PC, the MS Center of Northeastern New York, Latham, New York, United States; Evergreen Hospital Medical Center/Booth Gardner Parkinson's Care Center, Kirkland, Washington, United States; Georgetown University Hospital, Washington, District of Columbia, United States; Gershon Pain Specialists, Virginia Beach, Virginia, United States; Gundersen Clinic, Ltd., LaCrosse, Wisconsin, United States; Harvinder S. Birk, Redding, California, United States; Headache Center, Encinitas, California, United States; Infinity Clinical Research, LLC, Hollywood, Florida, United States; Kansas City Bone & Joint Clinic, PA Overland Park, Overland Park, Kansas, United States; Methodist Rehabilitation Center, Jackson, Mississippi, United States; Neuro-Pain Medical Center, Fresno, California, United States; Neurological Associates of Tulsa, Tulsa, Oklahoma, United States; Neurology Center of San Antonio, San Antonio, Texas, United States; Neurology Offices of South Florida, Boca Raton,

Florida, United States; Palm Beach Gardens Medical Center, North Palm Beach, Florida, United States; Parkinson's Disease and Movement Disorders Center of Boca Raton, Boca Raton, Florida, United States; Parkinson's Treatment Center of SW Florida, Port Charlotte, Florida, United States; Raleigh Neurology Associates, Raleigh, North Carolina, United States; Rehabilitation Consultants, PA, Eagan, Minnesota, United States; Riverhills Neuroscience, Cincinnati, Ohio, United States; Rush University Medical Center Department of Neurological Sciences, Chicago, Illinois, United States; South Puget Sound Neurology, Tacoma, Washington, United States; The Neuro Medical Center, Baton Rouge, Louisiana, United States; The Parkinson's & Movement Disorder Institute, Fountain Valley, California, United States; The Parkinson's and Movement Disorders Center, Southfield, Michigan, United States; University Neurology, Inc., Cincinnati, Ohio, United States; University of Colorado Denver, Denver, Colorado, United States; University of Miami, Dept. of Movement Disorders Clinic, Miami, Florida, United States; University of Nevada School of Medicine, Reno, Nevada, United States, 89502 USF Health Parkinson's Disease and Movement Disorders Center, Tampa, Florida, United States; Valley Parkinson Clinic, Los Gatos, California, United States; Victorium Clinical Research, San Antonio, Texas, United States.

Appendix A. Supplementary data

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