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A Botulinum Toxin A Treatment Algorithm for De Novo Management of Torticollis and Laterocollis

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Title: A Botulinum Toxin A Treatment Algorithm for *De Novo* Management of Torticollis and Laterocollis

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Author contributions:

Harald Hefter and Wolfgang Jost were involved in the concept and study design, study conduct, data collection, analysis and interpretation, manuscript writing, review and critique. All other authors were involved in the study conduct and data collection, manuscript review and critique. All authors approved the final manuscript.

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Observational studies

Abstract

Objectives: Few studies have investigated the injection patterns for botulinum toxin type A (BoNT-A) for the treatment of heterogeneous forms of cervical dystonia (CD). This large, prospective, open-label, multicentre study aimed to evaluate the effectiveness and safety of 500 U botulinum toxin A (Dysport®) for the initial treatment according to a standardised algorithm of the two most frequent forms of cervical dystonia, predominantly torticollis and laterocollis.

Design: Patients (aged ≥18 years) with CD not previously treated with BoNT therapy were given one treatment with 500 U Dysport (Ipsen Biopharm Ltd.), according to a defined intramuscular injection algorithm based on clinical assessment of direction of head deviation, occurrence of shoulder elevation, occurrence of tremor (all evaluated using the Tsui rating scale) and hypertrophy of the sternocleidomastoid muscle.

Results: In this study, 516 patients were enrolled, the majority of whom (95.0%) completed treatment. Most patients had torticollis (78.1%). At Week 4, mean Tsui scores had significantly decreased by –4.01, –3.76 and –4.09 points in the total, torticollis and laterocollis populations, respectively. Symptom improvement was equally effective between groups. Tsui scores remained significantly below baseline at Week 12 in both groups. Treatment was well tolerated; the most frequent adverse events were muscular weakness (13.8%), dysphagia (9.9%) and neck pain (6.6%).

Conclusions: Dysport 500 U is effective and well tolerated for the *de novo* management of a range of heterogeneous forms of CD, when using a standardised regimen that allows tailored dosing based on individual symptom assessment.

Article summary

Article focus:

- Evaluation of the benefits of a treatment algorithm for use of Dysport for the *de novo* management of torticollis and laterocollis in a large population of patients with cervical dystonia

Key messages:

- Dysport 500 U is effective and well tolerated for the *de novo* treatment of the majority of patients suffering from the most common forms of CD
- The treatment algorithm proposed represents a clinically useful treatment algorithm to individualise Dysport treatment in approximately 90% of all CD subgroups

Strengths and limitations of this study:

- Strengths of this study include the larger patient population treatment

- The injection protocol proposed can be useful to guide initial treatment in *de novo* patients with cervical dystonia but should not replace clinical judgment and individual patient assessment

INTRODUCTION

Idiopathic cervical dystonia (CD) is the most frequent form of focal dystonia and is characterised by sustained involuntary muscle contraction and/or twitching of cervical musculature, resulting in head and neck movements as well as various undesired head positions.[1] Depending on the direction of head movement, CD can be commonly classified as torticollis (turning of the head), laterocollis (head and neck tilt), retrocollis (head and neck extension), anterocollis (head and neck flexion), or a combination of the above. More detailed analysis of the muscles that are involved in CD has recently been performed, taking into account whether the head or the neck are predominantly forced into abnormal positions [2] and this analysis may lead to new classification and terminology. However, this has yet to be widely adopted and the former classification is still routinely used in clinical practice.

Botulinum neurotoxin (BoNT) has longstanding and widespread use for the treatment of CD and is recommended as the first-line treatment option.[3] The efficacy of botulinum toxin A (Dysport) for the treatment of CD has been demonstrated in multiple randomised, placebo-controlled trials.[4-7] These studies have shown that Dysport 500 U is an effective and well-tolerated starting dose for the treatment of CD and provides symptom relief for up to 3 months.[4-7] Apart from one study specifically investigating the effects of Dysport on torticollis,[4] the other studies have included a heterogeneous CD patient population with the number of injection sites and Dysport dose at each site determined based on investigator judgment.[5-7] Careful selection of the dose of toxin used per muscle is essential as inappropriate dosing can increase the risk of adverse events such as focal muscle weakness.[8] Therefore, an injection protocol was pre-defined in this study, specifying dose and injection sites to minimise the risk of side effects and systematically evaluate the effectiveness and safety of this dosing algorithm tailored to the individual heterogeneous subtypes of CD. As such, this large, prospective, open-label, multicentre study not only aimed to confirm the effectiveness and safety of Dysport 500 U for the initial treatment of the two most frequent forms of CD (predominantly torticollis and laterocollis), but also to evaluate the treatment algorithm used in this study (Fig 1). This algorithm may help inexperienced users to inject Dysport effectively and safely.

METHODS

Study design and patients

This was a prospective, multicentre, open-label study conducted in Germany and Austria to investigate the effectiveness and safety of 500 U Dysport for the treatment of heterogeneous forms of CD. As BoNT-A is regarded as a first-line neurological therapy for the treatment of CD, this study did not include a placebo-control arm. The study was conducted in accordance with the Declaration of Helsinki, taking into account local regulatory requirements; all patients provided written informed consent to participate.

Male and female outpatients, aged ≥18 years, with CD not previously treated with BoNT therapy, were eligible for inclusion. Exclusion criteria comprised patients with pure anterocollis or retrocollis, pure tremor capitis, or pure sagittal or lateral shifts, as these are rare complex forms of CD (<10%) and may require different treatment algorithms. Additional exclusion criteria included previous treatment with botulinum toxin for any indication other than CD within the past 12 months, as well as known antibodies to BoNT.

Study treatment and treatment algorithm

All patients received 500 U Dysport (Ipsen Biopharm Ltd.), diluted in 2.5 ml 0.9% NaCl. Treatment was administered by intramuscular injections according to three pre-defined main decision steps. The investigator had to follow these steps and select (out of the 12 given injection protocols) the best suitable for the individual patient (Fig 1): 1. Main type of CD (either torticollis or laterocollis based on the Tsui score); 2. Shoulder elevation (≥2 Tsui score, subscore C) or tremor (tremor, myoclonia, corresponding to Tsui score 4, subscore D), which had to be treated as a second component; 3. Presence of hypertrophy of the sternocleidomastoid muscle (marked vs light or no hypertrophy). This decision cascade resulted in a corresponding injection protocol defining the dose and number of injection points per muscle (Fig 1). The injection protocol for shoulder elevation was used when the patient had a shoulder elevation ≥2 in Tsui subscore C. The injection protocol for tremor was used when the patients had of a tremor score of 4 in Tsui subscore D. If the patient fulfilled both these criteria, it was the investigator's decision to treat the symptoms which were the most disabling for the patient and to use the corresponding injection protocol. Electromyography (EMG) guidance for injection was left to the discretion of the investigator.

Assessments

The decision rules follow a careful assessment of severity of CD symptoms using the Tsui scale [9] under standardised conditions with the patient in a relaxed seated position. Assessment of CD symptom severity using the Tsui total score was repeated at Weeks 4 and 12 post-treatment. The primary efficacy outcome was a change from baseline to Week 4 in Tsui total score after treatment.

In addition, both investigators and patients provided a global assessment efficacy at Weeks 4 and 12 post-treatment. This was rated on a 4-point scale (1 = very good; 2 = good; 3 = moderate; 4 = insufficient).

Safety assessments included incidence of AEs, neurological and physical examinations, vital signs and patient and investigator global assessment of tolerability, rated on a 4-point scale (1 = very good; 2 = good; 3 = moderate; 4 = insufficient).

Statistical analyses

An original sample size of 600 subjects, enrolled over 24 months, was planned in order to detect a 1-point between-treatment group difference on change from baseline to Week 4 in Tsui total score with 90% power. However, this target was not reached and, as such, recruitment was stopped at 516 patients after 39 months. Following data review, the primary statistical analysis plan was regarded as exploratory, and thus no adjustments for multiplicity were made. The safety population included all patients who received study medication and had at least one safety assessment. Effectiveness analyses were conducted on the intention-to-treat population, which included all patients in the safety sample who had at least one baseline and one post-treatment Tsui total score assessment. Additionally, confirmatory analyses using the per protocol population (excluding major protocol violations) were conducted.

The primary effectiveness endpoint, mean change in Tsui total score between baseline and Week 4, was assessed by analysis of covariance (ANCOVA), with baseline Tsui total score as covariate and the main type of CD as between-group factor. Analyses were conducted for the total population and by main type of CD. The time course of the Tsui total score improvement was investigated by means of repeated-measures ANCOVA models, which included main type of CD and week of assessment as the main effects and type of CD and week of assessment as covariates. The mean percentage improvement in Tsui total scores at Weeks 4 and 12 was also evaluated for each main type of CD; this analysis was specified *post-hoc* in order to facilitate comparison of the results with other studies. Safety data were analysed descriptively.

RESULTS

Patient disposition and demographics

A total of 516 patients were enrolled in this study at 81 study sites in Germany and Austria. The safety sample consisted of 515 patients; one patient received treatment but was excluded from the safety analysis as no safety data were available. Patient disposition is shown in Figure 2. Four-hundred and eighty-nine patients (95.0%) included in the safety sample completed the study.

Patient demographics and baseline characteristics are shown in Table 1. The majority of patients had torticollis (n=402; 78.1%); 112 patients (21.7%) had laterocollis; the type of CD was unknown in one patient. Baseline characteristics were similar between patients with torticollis and laterocollis, although the proportion of males was higher in patients with torticollis (32.6%) compared to patients with laterocollis (27.7%). More than half of patients (56.5%) experienced pain associated with CD and 12.6% of patients had a documented additional sagittal or lateral shift. Twelve patients (2.3%) reported dysphagia before treatment due to head deviation (torticollis n=7 and laterocollis n=5).

Treatments and dosing

All treated patients received Dysport 500 U at baseline with the exception of three patients who received less than 500 U (non-compliance to the injection protocol). All injections were given without EMG guidance. The most frequently reported concomitant medications (>10% of patients) by therapeutic class were beta-blocking agents (19.0%), agents acting on the renin-angiotensin system (14.4%), psychoanaleptics (13.6%), thyroid therapy (13.0%) and analgesics (10.1%). Concomitant medication use was similar between CD types.

Efficacy

For the primary efficacy endpoint, Dysport significantly decreased mean Tsui total scores from baseline to Week 4 (–3.83; 95% confidence intervals [CI]: –4.01, –3.57]; p<0.0001) in the total population. Dysport also significantly decreased Tsui total scores from baseline to Week 4 for patients with torticollis (–3.76; 95% CI: –4.02, –3.51; p<0.0001) and patients with laterocollis (–4.09; 95% CI: –4.58, –3.59; p<0.0001), corresponding to a percentage improvement of 43.7±36.4% and 46.5±28.3%, respectively (total population: 44.3±34.8%). The mean treatment difference between the torticollis and laterocollis groups was not statistically significant (–0.32; 95% CI: –0.88; 0.23; p=0.255), indicating that both forms of CD equally improved at Week 4.

Significant improvements in Tsui total scores were sustained to Week 12 for both CD types (Fig 3), corresponding to similar percentage improvements in patients with torticollis (23.6±44.6%) and laterocollis (27.0±33.0%) (total population 24.3±42.4%).

Analysis of data using the per protocol population (n=490) confirmed findings from the intention-to-treat analysis (n=503).

In analyses of the total population, the mean changes in Tsui subscale scores from baseline to Week 4 were statistically significant for all Tsui subscores: amplitude of rotation, deflection (tilt) and ante-/retrocollis, subscore A: –1.4; 95% CI: –1.5, –1.3; duration of movement, subscore B: –0.3; 95% CI –0.4, –0.3; severity and duration of shoulder elevation, subscore C: –0.4; 95% CI: –0.5, –0.3; and tremor, subscore D: –0.6; 95% CI: –0.7, –0.5). The percent improvement between the mean Tsui score at baseline and V2, was greatest for severity of tremor (45% subscore D) and least for duration of movement (22%, subscore B). The percent improvement in mean values between baseline and V2 was 40% each for subscores A (amplitude) and C (shoulder elevation), respectively.

Efficacy of study medication in the total population was rated as 'very good' or 'good' by 70.0% of investigators (67.2% torticollis, 80.2% laterocollis) and 60.8% of patients (59.9% torticollis, 64.1% laterocollis) at Week 4. At Week 12, efficacy was rated as 'very good' or 'good' by 72.0% of investigators (70.4% torticollis, 77.9% laterocollis) and 64.9% of patients (63.8% torticollis, 69.3% laterocollis).

Safety and tolerability

At least one AE was experienced by 41.4% of patients, of which 30.1% were considered to be related to study medication. The most frequent AEs (>5% of patients) were muscular weakness (13.8%), dysphagia (9.9%) and neck pain (6.6%); no significant difference in the rates of these AEs was seen between patients with torticollis and laterocollis, except for severe muscular weakness (Table 2). Most AEs were mild to moderate in severity (89.7%); only 53 patients (10.3 %) experienced severe AEs. A summary of safety and tolerability by main type of CD is shown in Table 2. Overall, AEs of muscular weakness, dysphagia and neck pain were rated as severe in 17 (3.3%), three (0.6%) and 13 (2.5%) patients, respectively (Table 2). One patient experienced severe dysphagia, severe muscular weakness and severe neck pain simultaneously, and five patients experienced both severe muscular weakness and severe neck pain. Nearly all cases of severe muscular weakness (15 of 17 patients; 88.2%) and all cases of severe dysphagia (three patients) resolved without the requirement for intervention. Of the two patients with severe muscle weakness that were not classed as resolved, no information was available for one patient and one patient had to wear a cervical collar temporarily. Of the patients with severe neck pain (n=13), six (46.2%) patients had pain that was self-limiting and did not require intervention while the other seven (53.8%) required intervention.

Eleven patients (2.1%) experienced serious AEs (SAEs), although only two patients experienced SAEs that were considered possibly related to study medication. One patient with torticollis experienced a convulsive syncope together with bradycardia immediately after injection; these symptoms resolved without intervention after several hours and an electroencephalogram (EEG) revealed no pathological findings. The attending physician assessed the events as probably being an injection-related, vagal reaction. One patient with laterocollis experienced muscle weakness of the head and depression: these symptoms developed 2 days post-treatment and the patient was hospitalised 11 days post-treatment and treated with antidepressant medication. The patient recovered from both events within 3 weeks.

There were no relevant or unexpected observations in the physical and neurological examination or changes in vital signs with Dysport treatment. Tolerability of study medication, as assessed by investigators and patients, are summarised in Table 2.

DISCUSSION

This study is the largest prospectively designed study conducted to date in *de novo* patients with CD, as well as one of the largest studies conducted in patients with CD in general. The results of this study, conducted at multiple centres in Germany and Austria, demonstrate that a single dose of Dysport 500 U can be used effectively for the management of the most common forms of CD (predominantly torticollis and laterocollis), when being injected according to a standardised algorithm that allows tailored dosing based on individual symptom assessment. Dysport treatment resulted in clinically and statistically significant improvement in the symptoms of CD at Week 4, as assessed by Tsui total scores, and the magnitude of improvement was comparable between torticollis and laterocollis patients. Furthermore, in both groups, the benefit of Dysport treatment was maintained to Week 12.

The present results agree with previous studies that demonstrated the effectiveness of 500 U Dysport for the treatment of CD [4–7] and expand on these findings to demonstrate the comparable effectiveness of Dysport in the two main subtypes of CD. Dysport treatment in this study resulted in a greater than 40% improvement in CD symptoms at Week 4 in all CD types, as measured by improvement in Tsui scores. This compares well to the percentage improvement in Tsui scores at Week 4 in patients treated with Dysport in a double-blind placebo controlled study (Dysport 41% vs placebo 17%; p=0.002).[7]

Improvements in symptoms were confirmed by investigator and patient global assessment of symptoms without distinct (significant) group differences. Of note, investigator and patient ratings varied most in the laterocollis group at Week 4, which could probably be explained by the higher rate of severe muscular weakness reported in these patients.

The treatment protocol used in this study represents a clinically useful treatment algorithm to individualise treatment in approximately 90% of all CD subgroups, ie torticollis and laterocollis, both with and without shoulder elevation or tremor, also accounting for hypertrophy of the sternocleidomastoid muscle. Independently, it is still essential for treating physicians to understand the biomechanical effects of the muscles involved in the primary movements of the head in order to optimise treatment when using this algorithm. The majority of patients with CD may be treated by the present investigated, standardised injection protocol. However, this protocol may not be suitable for patients with rare, more complex forms of CD. Thus, injection algorithms may facilitate effective dosing of BoNT-A, as excess dosing into muscles not involved in CD symptoms may not improve efficacy but rather increase the risk of AEs. The findings of this study support the use of one vial of 500 U Dysport as an appropriate starting dose for patients with CD [4-7] and comply with findings of a recent long-term follow-up of Dysport in CD, suggesting that the majority of

patients can benefit from this dose over the longer-term, given careful injection technique.[9] The algorithm presented allows the optimal distribution of one 500 U vial of Dysport based on the patient's clinical picture, assessed by the Tsui score, and is practicable in a normal clinical setting.

Dysport was well tolerated for the treatment of CD in this study; most AEs were mild to moderate in severity and the majority of patients and investigators rated treatment tolerability as very good/good, regardless of torticollis or laterocollis. Interestingly, and as seen in the efficacy ratings, investigator and patient ratings of tolerability varied most in the laterocollis group at Week 4. It is possible that the statistically significant difference in severe muscular weakness between torticollis and laterocollis patients explains why laterocollis patients rated their tolerability of study treatment lower than torticollis patients at Week 4. No new safety concerns were raised by this study and the most common AEs reported, muscular weakness and dysphagia, were consistent with the known safety profile of this medication in this indication.[11]

The reported rates of muscle weakness and dysphagia were consistent with those reported for Botox in *de novo* patients,[12] although there are inherent limitations in comparing data, assessment methods and botulinum toxin A formulations between studies. Rates of dysphagia and muscular weakness presented here are lower than rates reported in previously conducted double-blind, placebo-controlled trials with Dysport,[5, 6] probably due to dose distribution of Dysport based on a pre-defined injection protocol. Specifically, with regard to dysphagia, the majority of the BoNT-A dose in this study was injected into the posterior part of the neck region. Thus, the results show that use of pre-defined injection protocols allowing individual symptom treatment may have the potential to improve treatment tolerability by providing patients with effective symptom relief while possibly limiting AEs associated with injecting non-involved muscles. Finally, it is important to point out that that injection protocol may guide initial treatment in *de novo* patients with CD. However, the dose and muscle selection of further injections should always consider the patient's individual symptoms in conjunction with the initial treatment outcomes. Careful and extensive clinical examination and diagnosis are essential in all patients, especially those presenting with symptoms of pain and dysphagia caused by head deviation.

In conclusion, Dysport 500 U is effective and well tolerated for the *de novo* treatment of the majority of patients suffering from the most common forms of CD. Analyses of additional secondary effectiveness outcomes collected in this study will provide further insight into the benefits of Dysport in this *de novo* patient group.

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Competing interests [this article]

Harald Hefter: Consultant and referent of Ipsen.

Andreas Kupsch: Speaker honoria from Ipsen.

Martina Müngersdorf: Referent of Ipsen.

Sebastian Paus: Consultant and referent of Ipsen.

Andrea Stenner: Referent of Ipsen.

Wolfgang Jost: Consultant and referent of Ipsen.

Competing interests (previous 12 months)

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Andreas Kupsch: Speaker honoria from Ipsen, Merz and Allergan.

Martina Müngersdorf: Referent of Ipsen, Merz and Allergan

Sebastian Paus: Consultant and referent of Ipsen, Merz

Andrea Stenner: Referent of Ipsen, Merz and Allergan

Wolfgang Jost: Consultant and referent of Ipsen, Merz and Allergan.

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STROBE statement: Checklist of essential items Version 3 (Sept 2005)

	Item #	Cohort study	Case-control study	Cross-sectional study
TITLE & ABSTRACT	1	(a) Identify the article as a cohort study in the title or the abstract.	(a) Identify the article as a case-control study in the title or the abstract.	(a) Identify the article as a cross-sectional study in the title or the abstract.
		(b) The abstract should be an informative and structured summary of the article, addressing key items in this checklist.		
INTRODUCTION				
Background / Rationale	2	Explain scientific background and rationale for the investigation being reported.		
Objectives	3	State specific objectives including any pre-specified hypotheses.		
METHODS				
Study design	4	Present key elements of study design. State purpose of original study, if article is one of several from an ongoing study.		
Setting	5	Describe setting, locations and dates defining periods of data collection.		
Participants	6	(a) Give inclusion and exclusion criteria, sources and methods of selection of participants.	(a) For cases and controls separately, give inclusion and exclusion criteria, sources and methods of selection.	(a) Give inclusion and exclusion criteria, sources and methods of selection of participants.
		(b) Give period and methods of follow-up.	(b) Give precise diagnostic criteria for cases, and rationale for choice of controls.	

	Item #	Cohort study	Case-control study	Cross-sectional study
			(c) For matched studies, give matching criteria and number of controls per case.	
Variables of interest	7	List and clearly define all variables of interest indicating which are seen as outcomes, exposures, potential predictors, potential confounders or effect modifiers.		
Measurement	8 *	(a) For each variable of interest give details of methods of assessment (measurement).		
		(b) If applicable, describe comparability of assessment methods across groups.		
Bias	9	Describe any measures taken to address potential sources of bias.		
Sample size	10	Describe rationale for study size, including practical and statistical considerations.		
Statistical methods	11	(a) Describe all statistical methods including those to control for confounding.		
		(b) Describe how loss to follow-up and missing data were addressed.	(b) Describe how any matching of cases and controls and missing data were addressed.	(b) Describe how any design effects and missing data were addressed.
		(c) If applicable, describe methods for subgroup analyses and sensitivity analyses.		
Quantitative variables	12	(a) Explain how quantitative variables are analyzed e.g. which groupings are chosen, and why.		
		(b) Present results from continuous analyses as well as from grouped analyses, if appropriate.		

* Give such information separately for cases and controls in case-control studies, and if applicable for exposed and unexposed groups in cohort and cross-sectional studies.

	Item #	Cohort study	Case-control study	Cross-sectional study
Funding	13	Give source of funding and role of funder(s) for the present study and, if applicable, the original study on which the present article is based.		
RESULTS				
Participants	14 *	(a) Report the numbers of individuals at each stage of the study, e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow up, and analysed.		
		(b) Give reasons for non-participation at each stage.		
		(c) A flow diagram is recommended.		
		(d) Report dates defining period of recruitment.		
			(e) For matched studies, give distribution of number of controls per case.	
Descriptive data	15 *	(a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders		
		(b) Indicate for each variable of interest the completeness of the data.		
		(c) Summarize average and total amount of follow up and dates defining follow up.		
Outcome data	16 *	Report numbers of outcome events or summary measures over time.	Report numbers in each exposure category.	Report numbers of outcome events or summary measures.

* Give such information separately for cases and controls in case-control studies, and if applicable for exposed and unexposed groups in cohort and cross-sectional studies.

	Item #	Cohort study	Case-control study	Cross-sectional study
Main results	17	(a) Give unadjusted and confounder adjusted measures of association and their precision (e.g. 95% confidence intervals). Make clear which confounders were adjusted for and on what grounds they were included and others were not. (b) For comparisons using categories derived from quantitative variables, report the range of values or median value in each group. (c) Translate relative measures into absolute differences, for a meaningful risk period that does not extend beyond the range of the data. (d) Report results standardized to confounder and modifier distributions for realistic target populations.		
Other analyses	18	Report any other analyses performed, e.g. subgroup analyses and sensitivity analyses.		
DISCUSSION				
Key findings	19	Summarize key results with reference to study hypotheses.		
Limitations	20	(a) Discuss limitations of the study, taking into account sources of potential bias or imprecision, and problems that could arise from multiplicity of analyses, exposures and outcomes. Discuss both direction and magnitude of any potential bias.		
		(b) Consider that the discussion of limitations should not be used as a substitute for quantitative sensitivity analyses.		
Generalizability	21	Discuss the generalizability (external validity) of the study findings.		
Interpretation	22	Give a cautious overall interpretation of the results in the context of current evidence and study limitations, paying attention to alternative interpretations.		

* Give such information separately for cases and controls in case-control studies, and if applicable for exposed and unexposed groups in cohort and cross-sectional studies.

Table 1: Baseline patient demographics, safety sample

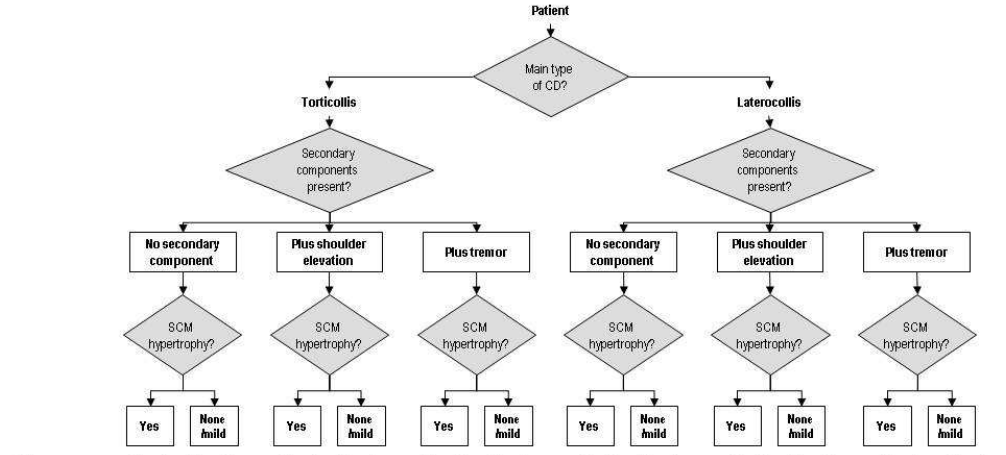
Parameter	Torticollis (n=402)	Laterocollis (n=112)	Total[a] (n=515)
Gender, n (%) male	131 (32.6)	31 (27.7)	162 (31.5)
Age, years			
Mean (SD)	51.9 (12.7)	51.9 (12.8)	51.9 (12.7)
Range	19–83	19–87	19–87
Height, cm – Mean (SD)[b]	169.1 (8.6)	168.4 (8.7)	169.0 (8.6)
Weight, kg – Mean (SD)[b]	73.2 (15.4)	70.7 (12.1)	72.6 (14.7)
BMI, kg/m² – Mean (SD)[b]	25.5 (4.6)	24.9 (3.6)	25. 3 (4.4)
Race, n (%)			
Caucasian	398 (99.0)	112 (100.0)	511 (99.2)
Asian	1 (0.2)	0 (0.0)	1 (0.2)
Oriental	3 (0.7)	0 (0.0)	3 (0.6)
Additional CD symptoms, n (%)			
Pain (p=0.0676*)	219 (54.5)	72 (64.3)	291(56.5)
Shift (sagittal or lateral, p=0.0011*)	40 (10.0)	25 (22.3)	65 (12.6)
Dysphagia (p=0.1467*)	7 (1.7)	5 (4.5)	12 (2.3)
Other	12 (3.0)	1 (0.9)	13 (2.5)
Subtypes of CD, n (%)[c]			
Without tremor/shoulder elevation (p=0.0006*)	131 (32.6)	18 (16.1)	149 (29.0)
With shoulder elevation (p=0.0024*)	126 (31.3)	53 (47.3)	179 (34.8)
With tremor (p=0.9120*)	145 (36.1)	41 (36.6)	186 (36.2)
Baseline Total Tsui score (patient in sitting position), Mean (SD)[c]	8.4 (3.5)	8.2 (3.3)	8.4 (3.5)

CD, cervical dystonia; SD, standard deviation
[a]Includes one patient in whom the main type of CD was unknown
[b]Torticollis n=399; Laterocollis n=111; Total n=510
[c]Total population n=514, main type of CD was not known in one patient
*Fisher's exact test torticollis vs laterocollis, two-sided

Table 2: Safety and Tolerability

	Torticollis (n=402)	Laterocollis (n=112)	Total[a] (n=515)
Summary of AEs, n (%)			
Patients with AEs	167 (41.5)	46 (41.1)	213 (41.4)
Patients with causally related AE	121 (30.1)	34 (30.4)	155 (30.1)
Patients with at least one severe AE	35 (8.7)	18 (16.1)	53 (10.3)
Patients with SAE	8 (2.0)	3 (2.7)	11 (2.1)
Patients with causally related SAE	1 (0.2)	1 (0.9)	2 (0.4)
AEs in >5% of patients in total population, n (%)			
Muscular weakness (p=0.0618)*	49 (12.2)	22 (19.6)	71 (13.8)
Severe (p=0.0008)*	7 (1.7)	10 (8.9)	17 (3.3)
Dysphagia (p=0.8582)*	41 (10.2)	10 (8.9)	51 (9.9)
Severe	3 (0.7)	0 (0.0)	3 (0.6)
Neck pain (p=0.8300)*	26 (6.5)	8 (7.1)	34 (6.6)
Severe, n (%)	9 (2.2)	4 (3.6)	13 (2.5)
Global Assessment of Tolerability			
Percentage investigators rating tolerability as “good” or “very good”			
Week 4	87.8	82.6	86.7
Week 12	89.2	87.9	88.8
Percentage patients rating tolerability as “good” or “very good”			
Week 4	82.5	72.5	80.3
Week 12	85.7	84.1	85.4

AE, adverse event; SAE, serious adverse event
[a]Includes one patient in whom the main type of CD was unknown
*Fisher's exact test torticollis vs. laterocollis, two-sided



Units	CL	IL	CL	IL	CL	IL	CL	IL	CL	IL	CL	IL	CL	IL	CL	IL	CL	IL	CL	IL	CL	IL
SCM (at least 2 injection points)	120		80		120		80		120		80		120		60		120		60		120		60
M. levator scapulae and/or Mm. scaleni (at least 2 injection points with at least 1 deeper)					80		80						60		60		140		140		60		60
M. splenius capitis and/or M. trapezius superior and/or M. semispinalis (at least 4 injection points)	380		420		300		340		80	300	80	340	320		380		240		300		80	240	80	300

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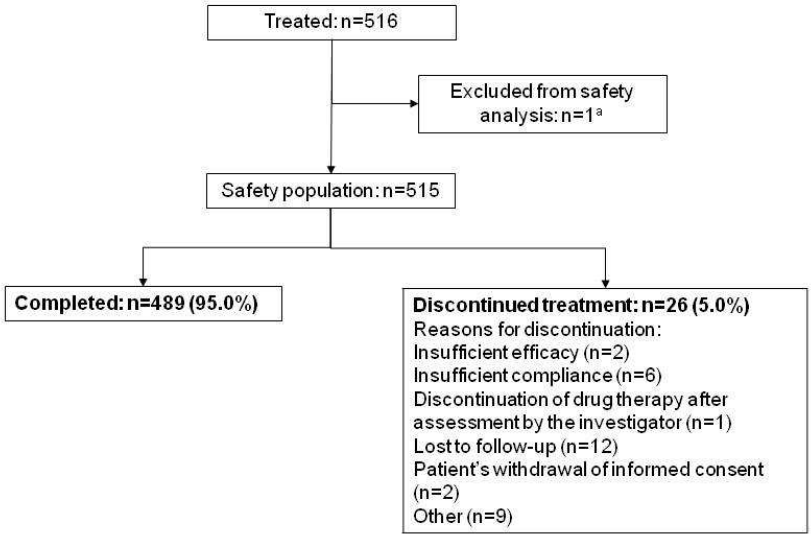

[a]One patient was excluded from the safety analysis as they discontinued treatment prematurely due to insufficient compliance. No safety data was collected for this patient.

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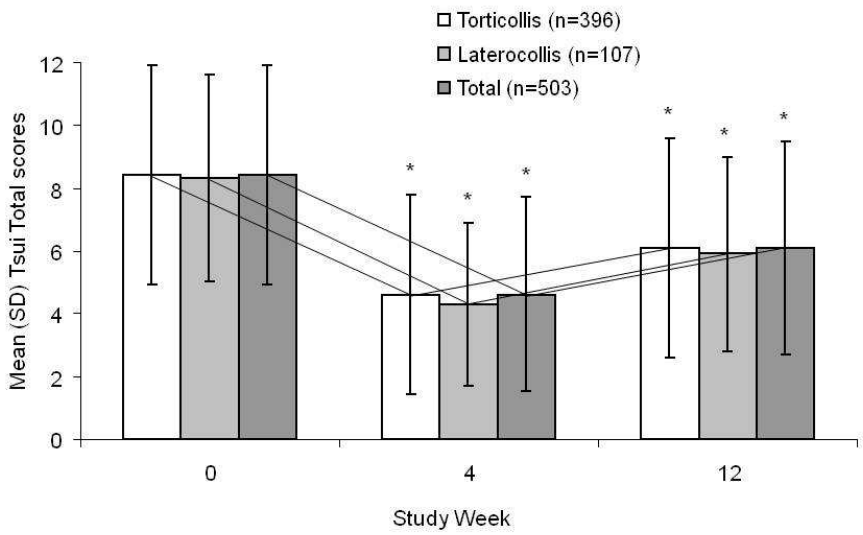

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