Title

A Phase IV, Randomized, Double-Blind, Crossover Study to Compare the Clinical Safety and Efficacy of AbobotulinumtoxinA and OnabotulinumtoxinA in Adult Upper Limb Spasticity

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ORIGINAL RESEARCH

A Phase IV, Randomized, Double-Blind, Crossover Study to Compare the Clinical Safety and Efficacy of AbobotulinumtoxinA and OnabotulinumtoxinA in Adult Upper Limb Spasticity

Alberto Esquenazi · Theodore H. Wein · Monica Verduzco-Gutierrez · Ziyad Ayyoub · Simon Page · Sarah Harding · Pascal Maisonobe · Mathieu Beneteau · Atul Patel · the DIRECTION study group

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ABSTRACT

Introduction: Lack of head-to-head comparative safety and efficacy data for abobotulinumtoxinA (aboBoNT-A) and onabotulinumtoxinA (onaBoNT-A) represented an important gap for informed spasticity management. This study compared the safety and efficacy of aboBoNT-A and onaBoNT-A for upper limb spasticity (ULS).

Methods: DIRECTION (NCT04936542), a phase IV, randomized, double-blind, crossover study, involved 72 sites. Patients stratified by botulinum toxin A status (naïve/non-naïve) were randomized (1:1) to aboBoNT-A 900U followed by onaBoNT-A 360U (one cycle each), or vice versa. Muscles (wrist/finger flexors, biceps brachii) were injected with a fixed volume, using instrument-guided injection techniques. Participants fulfilling retreatment criteria received a second cycle at Week 12; otherwise, they were reassessed every 4 weeks (to Week 24) until requiring retreatment. Primary analyses tested non-inferiority based on treatment-emergent adverse events (TEAEs) from injection to Week 12 using a 5% non-inferiority margin [non-inferiority demonstrated if upper bound of the 80%

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The full DIRECTION study group is listed in the Acknowledgements.

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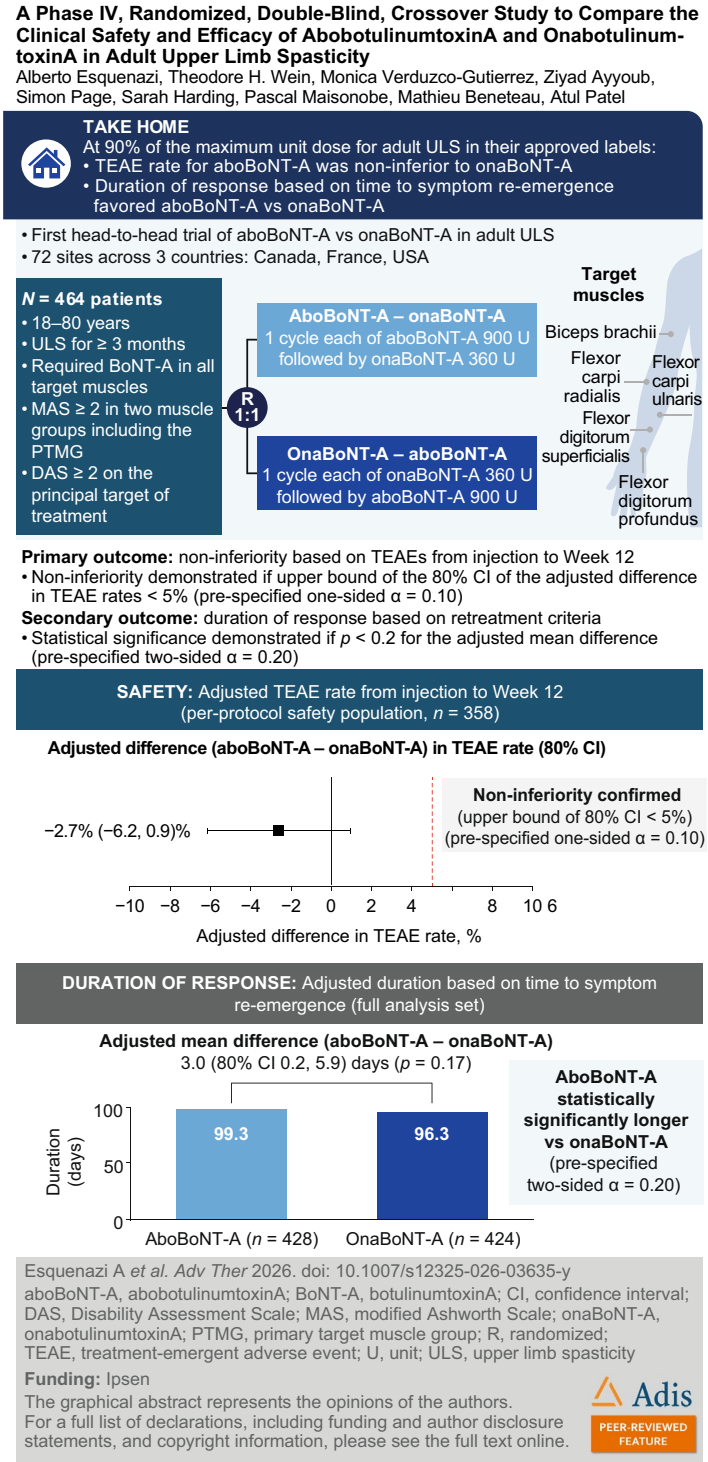
confidence interval (CI) of the adjusted difference in TEAE rates was < 5%]. Secondary analyses compared duration of response based on time to symptom re-emergence.

***Results*:** Overall, 464 patients [mean (standard deviation) age 56.8 (13.1) years, 34.1% female] were randomized (aboBoNT-A → onaBoNT-A [$n = 231$]; onaBoNT-A → aboBoNT-A [$n = 233$)]. Baseline characteristics were similar in both sequence arms. Adjusted rate of TEAEs for aboBoNT-A (20.3%) was non-inferior to onaBoNT-A (23.0%); adjusted difference (aboBoNT-A – onaBoNT-A) was – 2.7% (80%CI – 6.2%, 0.9%). Adjusted mean duration of response was 99.3 days for aboBoNT-A and 96.3 days for onaBoNT-A; adjusted difference of 3.0 (80%CI 0.2, 5.9) days favoring aboBoNT-A ($p = 0.17$; statistically significant under the pre-specified $\alpha = 0.20$ framework). Longer duration of response with aboBoNT-A versus onaBoNT-A was seen across most subgroups over a fixed-interval follow-up.

***Conclusion*:** In this first head-to-head study of aboBoNT-A and onaBoNT-A in ULS, the aboBoNT-A TEAE rate was non-inferior to onaBoNT-A. At 90% of the maximum unit dose for adult ULS in the approved label for each formulation, duration of response was 3 days longer with aboBoNT-A than onaBoNT-A. These findings may support informed therapeutic decision-making.

***Trial Registration*:** *ClinicalTrials.gov:* NCT04936542; *EudraCT:* 2023-509196-16-00.

Graphical Abstract:



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aboBoNT-A, abobotulinumtoxinA; BoNT-A, botulinumtoxinA; CI, confidence interval; DAS, Disability Assessment Scale; MAS, modified Ashworth Scale; onaBoNT-A, onabotulinumtoxinA; PTMG, primary target muscle group; R, randomized; TEAE, treatment-emergent adverse event; U, unit; ULS, upper limb spasticity

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For a full list of declarations, including funding and author disclosure statements, and copyright information, please see the full text online.

Adis
PEER-REVIEWED FEATURE

PLAIN LANGUAGE SUMMARY

Spasticity of the upper limb presents as muscle and limb stiffness that affects the arm and/or hand. It happens when parts of the brain or spinal cord that control movement are damaged. Spasticity can be painful and can make daily activities challenging. Some people with upper limb spasticity receive botulinum toxin A (BoNT-A) injections to help relax the affected muscles. BoNT-A injections work for a period, but retreatment is required when the effects start to wear off. AbobotulinumtoxinA and onabotulinumtoxinA are different types of BoNT-A. DIRECTION is the first-ever spasticity study to compare abobotulinumtoxinA and onabotulinumtoxinA directly in people with upper limb spasticity. It involved 464 people living with spasticity across the USA, France, and Canada. The study population had an average age of 57 years, two-thirds were male, and most had spasticity because of a stroke. The study found that, over the 12 weeks after BoNT-A treatment, similar numbers of patients had side-effects to abobotulinumtoxinA and onabotulinumtoxinA. In addition, it took longer for symptoms to return after treatment with abobotulinumtoxinA (99 days) compared with onabotulinumtoxinA (96 days). Longer BoNT-A treatment duration can reduce the number of days that people with upper limb spasticity have to live with symptoms before their next injection. More symptom-free days could reduce the need for patients and their caregivers to seek additional care and could reduce their overall treatment burden. These findings provide new information to help healthcare professionals make decisions about BoNT-A treatment to achieve the best outcomes for their patients with arm/hand spasticity.

Keywords: AbobotulinumtoxinA; OnabotulinumtoxinA; Upper limb spasticity; Safety; Head-to-head double-blind study; Crossover study

Key Summary Points

Why carry out this study?

There is a lack of comparative safety and efficacy data for botulinum toxin (BoNT) treatment options in adults with upper limb spasticity (ULS), representing an important knowledge gap for informed spasticity management.

To inform optimized ULS care, DIRECTION is the first head-to-head study to compare the safety and efficacy of abobotulinumtoxinA (aboBoNT-A) and onabotulinumtoxinA (onaBoNT-A) in adults with ULS.

What was learned from the study?

AboBoNT-A was non-inferior to onaBoNT-A in terms of TEAE rate from injection to Week 12 (primary endpoint).

Mean duration of response, based on time to symptom re-emergence, was 3 days longer with aboBoNT-A (99.3 days) than with onaBoNT-A (96.3 days) (key secondary endpoint).

These findings address an important evidence gap for assessing the overall benefit–risk profile of botulinum toxin therapies and may inform therapeutic decision-making for adults with ULS.

DIGITAL FEATURES

Graphical abstract available for this article https://doi.org/10.6084/m9.figshare.32204676.

INTRODUCTION

Background

Adults with central nervous system injury often present with limb spasticity, which is associated with changes in muscle tone and pain that may

lead to impaired movement and difficulty maintaining self-care, contribute to poor self-esteem and body image, and can result in pressure ulcers [1]. Impaired upper limb function due to spasticity may interfere with daily living tasks, contributing to reduced quality of life, diminished independence, and increased burden of care [2, 3].

Botulinum toxin A (BoNT-A) injections are a recommended and established first-line treatment for focal spasticity, administered as part of a comprehensive rehabilitation program to optimize functional outcomes [3–7]. The use of BoNT-A therapy is supported by a Level A recommendation in patients with upper limb spasticity (ULS) [7]. AbobotulinumtoxinA (aboBoNT-A; Dysport®, Ipsen, Paris, France) [8–11] and onabotulinumtoxinA (onaBoNT-A; Botox®, AbbVie, Irvine, CA, USA) [12–14] have demonstrated safety and efficacy versus placebo in clinical trials of patients with ULS.

The importance of duration of BoNT-A treatment response to patients was highlighted by the international Carenity survey. Of 210 survey respondents who were receiving BoNT-A treatment for spasticity, 83% reported symptom re-emergence prior to their next injection and 72% said they would like a longer-lasting BoNT-A treatment [15]. This unmet need has been echoed by subsequent patient surveys, which have described a symptom "rollercoaster", during which symptom severity and quality-of-life impacts increase as the effect of BoNT-A treatment wanes [16, 17]. Consistent with this, a US survey of 428 patients with experience of BoNT-A treatment for spasticity and 188 caregivers found that most respondents perceived less-frequent injections and longer-lasting treatment effects to be beneficial [18].

Within this context, the phase III trial of aboBoNT-A versus placebo in adults with ULS reported significant improvements in Modified Ashworth Scale (MAS) with aboBoNT-A that were sustained over 12 weeks, with 37% of patients not requiring retreatment before Week 16 in the open-label extension phase [8]. In clinical practice, the observational ULIS-III study found that aboBoNT-A was also associated with a longer interval between injections than onaBoNT-A in 953 adults with ULS [19]. It has been hypothesized that these clinical differences may reflect the greater amount of active neurotoxin found in US Food and Drug Administration-approved doses of aboBoNT-A than in other BoNT-A formulations, potentially resulting in a higher amount of neurotoxin being delivered to the injected muscles [20].

Understanding the clinical implications of differences between available BoNT-A formulations is important to inform clinical decision-making, allowing physicians to take into consideration individual patients' needs and likely treatment outcomes as well as relevant cost-effectiveness factors [21, 22]. However, the observed response to BoNT-A therapy is influenced by a range of factors, including the size of the affected muscles, anatomy of the target area, degree of spasticity, and the physician's injection technique, which—unless evaluated in a strictly controlled setting—can make it challenging to identify true therapeutic differences between BoNT-A formulations [21]. In addition, the distinct formulations and manufacturing processes of available BoNT-As result in differences in dosing, and the use of formulation-specific assays to assess biological activity mean that the units (U) assigned to each BoNT-A formulation are not directly comparable [21, 23].

The DIRECTION study (NCT04936542; EudraCT 2023-509196-16-00) is the first randomized, double-blind study comparing the safety and efficacy of aboBoNT-A and onaBoNT-A in adults with ULS [21]. The study aimed to test the hypotheses that the safety profiles of both BoNT-As are comparable (primary hypothesis) and that aboBoNT-A has a superior duration of response than onaBoNT-A resulting in longer time to symptom re-emergence (secondary hypothesis).

METHODS

Design and Setting

DIRECTION was a phase IV, multicenter, international, randomized, double-blind, crossover study comparing aboBoNT-A with onaBoNT-A

in adults with ULS. The trial eligibility criteria and design have been previously reported [21], but are briefly outlined.

Patients were enrolled across 72 sites (54 sites in the USA, 3 in Canada, and 15 in France) between June 23, 2021 and August 26, 2025. Eligible adults (aged 18–80 years) had ULS for ≥ 3 months, required BoNT-A injection in all target muscles (flexor carpi radialis, flexor carpi ulnaris, flexor digitorum profundus, flexor digitorum superficialis, and biceps brachii), had a MAS score [24] of ≥ 2 in two muscle groups [one of which was the primary target muscle group (PTMG)] and ≥ 1 in the remaining muscle group, and a Disability Assessment Scale (DAS) [25] score ≥ 2 on the principal target of treatment (one of four functional domains: dressing, hygiene, limb position, and pain). Patients were stratified by prior BoNT-A status for ULS (naïve/non-naïve) and randomized (1:1) to one cycle of aboBoNT-A 900 U followed by one cycle of onaBoNT-A 360 U (aboBoNT-A → onaBoNT-A) or vice versa (onaBoNT-A → aboBoNT-A). Owing to the non-interchangeability of potency units for aboBoNT-A and onaBoNT-A, the protocol used 90% of the maximum unit dose for adult ULS in the approved label for each formulation in the participating countries (900 U for aboBoNT-A; 360 U for onaBoNT-A) to enable fair comparison.

Visits for each injection cycle included the injection visit and Weeks 1, 4, 10, and 12. Duration of response based on time to retreatment criteria was defined for Cycle 1 as the time between Cycle 1 injection and the first Cycle 1 visit when retreatment criteria were met (from Week 10 visit), or time between Cycle 1 injection and study withdrawal if the patient discontinued from the study before Cycle 2 injection without meeting retreatment criteria. Patients began a second treatment cycle at Week 12 if retreatment criteria were fulfilled; if not, patients were reassessed every 4 weeks (at Weeks 16, 20, and 24) until they required retreatment. If a patient reached Week 24 without requiring retreatment, they were withdrawn from the study. Consistent with the Cycle 1 definition, time to retreatment for Cycle 2 was defined as the time between Cycle 2 injection and the first Cycle 2 visit when retreatment criteria were met (from Week 10 visit), or the time between Cycle 2 injection and end of study if the participant completed the study or withdrew from the study after their Cycle 2 injection without meeting retreatment criteria. If patients did not meet retreatment criteria at Week 10, they were reassessed every 4 weeks (at Weeks 16, 20, and 24) until they required retreatment. If a patient reached Week 24 without requiring retreatment, they were withdrawn from the study. To be eligible for retreatment, patients had to meet all of the following criteria: decision per investigator's clinical judgment; MAS score in PTMG returned to baseline, and no unacceptable safety risk per investigator's judgment.

The end of study for each patient was at the time of decision to retreat, or at Week 24 of Cycle 2, whichever occurred first. The target upper limb muscles were injected with a fixed dose/volume of each drug that was within their approved labels for adult ULS. A guided instrumented injection technique (electromyography, electrostimulation, or ultrasound or combination) was required and kept constant across all injection cycles.

Randomization and Blinding

Randomization was by a computer-generated system, and an interactive web response system was used to assign patients to their study treatment arm. To maintain study blinding, study medications were reconstituted to a fixed total volume (3.6 ml) by separate study staff, and the blinded injector injected the target upper limb muscles in a fixed volume (0.5 ml into each wrist and finger flexor and 1.6 ml into biceps brachii). The biceps brachii were treated with two injections, with a maximum single injection volume of 1.0 ml. Use of injection-guidance techniques to target the injection sites was mandatory.

Assessments

The primary endpoint was treatment-emergent adverse event (TEAE) rates from injection to Week 12. The key secondary endpoint was duration of response, defined per cycle as time between injection and first visit when retreatment criteria were met, or study withdrawal if

retreatment criteria were not met. Other key secondary efficacy endpoints were comparison between treatments at Week 12 of muscle tone assessed by MAS (finger, wrist, and elbow flexors based on PTMG), perceived function and pain assessed by DAS, and Physician Global Assessment (PGA) of treatment response.

Exploratory endpoints included comparison between treatments at Week 10 of other key secondary endpoints and quality-of-life assessments [12-Item Short Form Health Survey (SF-12) [26], Spasticity-related Quality of Life Tool (SQoL-6D)] at baseline, Week 4, Week 12, and end of each cycle.

Additional safety assessments included TEAE type, severity, seriousness, duration, and outcome, as well as adverse events of special interest (AESIs), including adverse events indicative of remote spread (categorized as those affecting function to eye, chewing/tongue, mouth/throat/bowel, lung, bladder, and muscle/muscle strength), and hypersensitivity (determined by standardized Medical Dictionary for Regulatory Activities query). Incidents of potential remote spread of toxin were adjudicated by the sponsor and included if confirmed as being "possible remote spread events".

Statistics/Analysis

Descriptive statistics reported number of available data (*n*) and number of missing data, mean, standard deviation (SD), median, lower quartile, upper quartile, and range for quantitative variables, and counts and percentages for each category for categorical variables. Reasons for any missing data were documented in the electronic case report form and clarified with the investigator, if required. Unless otherwise specified, there was no imputation of missing data.

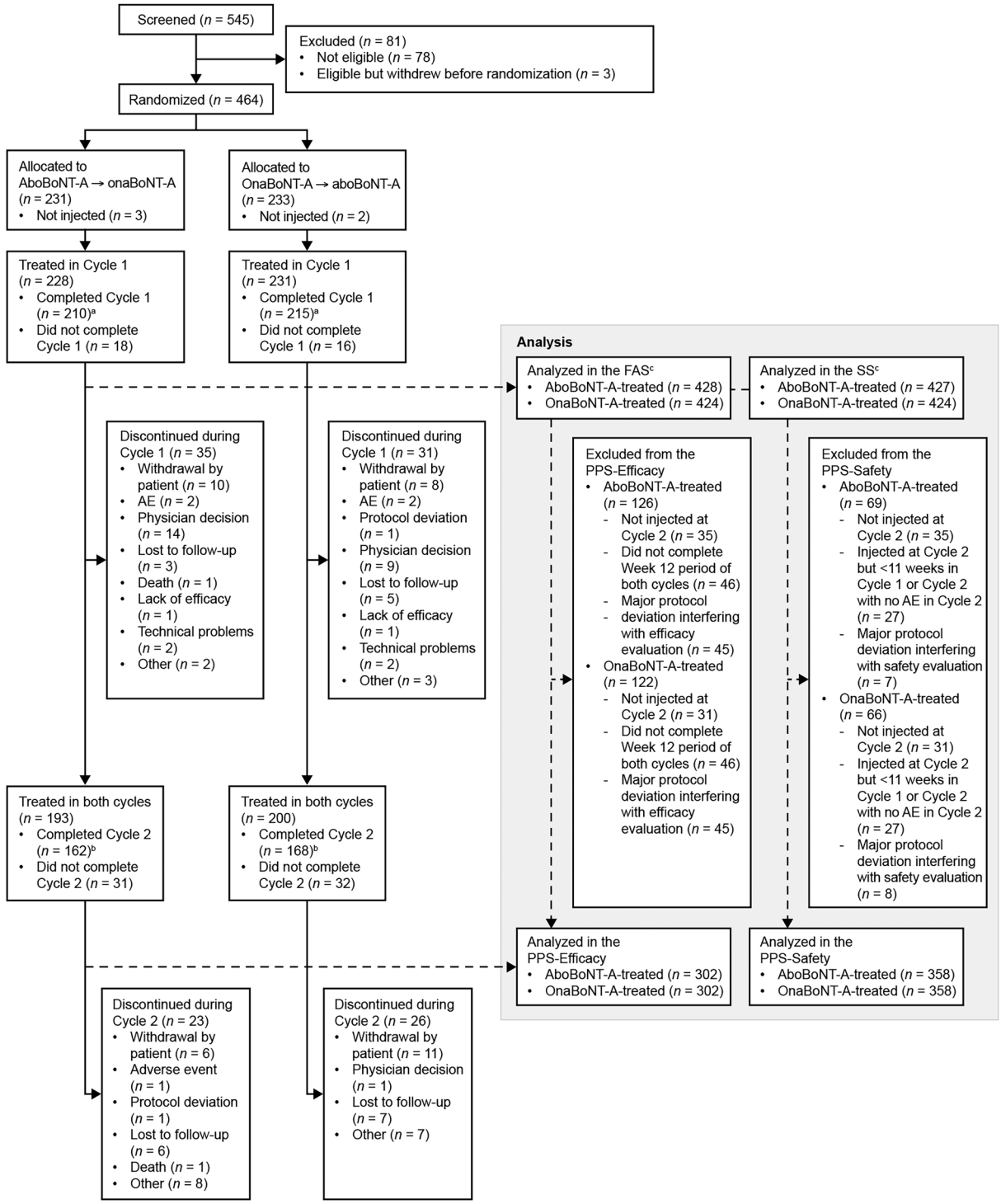
The randomized set was defined as all patients who were randomized. The full analysis set (FAS) and safety set (SS) were defined as all randomized patients who received at least one dose of aboBoNT-A or onaBoNT-A according to allocated treatment sequence and actual treatment received, respectively.

All efficacy analyses were conducted in the FAS, and some were repeated in the per-protocol efficacy set (PPS-Efficacy), which comprised all patients from the FAS who completed the 12-week period for both allocated cycles without any major protocol deviation that may have interfered with efficacy evaluation. Duration of response was based on time to fulfilment of retreatment criteria and described and compared between treatments using a mixed effects model, with cycle and treatment as fixed effects and participant as a random effect; an unstructured within-participant variance covariance matrix was assumed. The *p* value associated with cycle and treatment effects, and the estimate of the difference between treatment groups and associated two-sided confidence interval (CI), were provided, as were the number and percentage of patients retreated at Weeks 12, 16, 20, and 24.

Safety analyses were conducted in the full SS and in the per-protocol safety set (PPS-Safety), which comprised all patients from the SS who received one dose of aboBoNT-A and one dose of onaBoNT-A, and who either completed ≥ 11 weeks of the 12-week period for both cycles without any major protocol deviation that may have interfered with safety evaluation, or had a TEAE after the second injection and before study withdrawal but did not complete ≥ 11 weeks of Cycle 2. Patients who received the same treatment in both cycles were excluded from inferential safety analyses.

The primary analysis tested non-inferiority of the primary endpoint in the PPS-Safety. A generalized linear mixed-model approach was used to estimate the difference in TEAE rate between the two treatments while accounting for within-patient correlations arising from the crossover design. The fitted model included fixed effects for treatment and cycle and a random effect associated with the patient.

Prespecified sensitivity analyses were performed to assess the robustness of the primary endpoint analysis, including repetition of the primary analyses in the SS and estimation of the overall difference and SD of paired difference in TEAE rate for each patient within each sequence. If non-inferiority was demonstrated for the primary endpoint, superiority of aboBoNT-A over onaBoNT-A was tested for duration of response based on retreatment criteria; if superiority of aboBoNT-A over onaBoNT-A was demonstrated,


Screened (n = 545)
Excluded (n = 81)
• Not eligible (n = 78)
• Eligible but withdrew before randomization (n = 3)
Randomized (n = 464)
Allocated to AboBoNT-A → onaBoNT-A (n = 231)
• Not injected (n = 3)
Allocated to OnaBoNT-A → aboBoNT-A (n = 233)
• Not injected (n = 2)
Treated in Cycle 1 (n = 228)
• Completed Cycle 1 (n = 210)a
• Did not complete Cycle 1 (n = 18)
Treated in Cycle 1 (n = 231)
• Completed Cycle 1 (n = 215)a
• Did not complete Cycle 1 (n = 16)
Discontinued during Cycle 1 (n = 35)
• Withdrawal by patient (n = 10)
• AE (n = 2)
• Physician decision (n = 14)
• Lost to follow-up (n = 3)
• Death (n = 1)
• Lack of efficacy (n = 1)
• Technical problems (n = 2)
• Other (n = 2)
Discontinued during Cycle 1 (n = 31)
• Withdrawal by patient (n = 8)
• AE (n = 2)
• Protocol deviation (n = 1)
• Physician decision (n = 9)
• Lost to follow-up (n = 5)
• Lack of efficacy (n = 1)
• Technical problems (n = 2)
• Other (n = 3)
Treated in both cycles (n = 193)
• Completed Cycle 2 (n = 162)b
• Did not complete Cycle 2 (n = 31)
Treated in both cycles (n = 200)
• Completed Cycle 2 (n = 168)b
• Did not complete Cycle 2 (n = 32)
Discontinued during Cycle 2 (n = 23)
• Withdrawal by patient (n = 6)
• Adverse event (n = 1)
• Protocol deviation (n = 1)
• Lost to follow-up (n = 6)
• Death (n = 1)
• Other (n = 8)
Discontinued during Cycle 2 (n = 26)
• Withdrawal by patient (n = 11)
• Physician decision (n = 1)
• Lost to follow-up (n = 7)
• Other (n = 7)
Analysis
Analyzed in the FASc
• AboBoNT-A-treated (n = 428)
• OnaBoNT-A-treated (n = 424)
Analyzed in the SSc
• AboBoNT-A-treated (n = 427)
• OnaBoNT-A-treated (n = 424)
Excluded from the PPS-Efficacy
• AboBoNT-A-treated (n = 126)
- Not injected at Cycle 2 (n = 35)
- Did not complete Week 12 period of both cycles (n = 46)
- Major protocol deviation interfering with efficacy evaluation (n = 45)
• OnaBoNT-A-treated (n = 122)
- Not injected at Cycle 2 (n = 31)
- Did not complete Week 12 period of both cycles (n = 46)
- Major protocol deviation interfering with efficacy evaluation (n = 45)
Excluded from the PPS-Safety
• AboBoNT-A-treated (n = 69)
- Not injected at Cycle 2 (n = 35)
- Injected at Cycle 2 but <11 weeks in Cycle 1 or Cycle 2 with no AE in Cycle 2 (n = 27)
- Major protocol deviation interfering with safety evaluation (n = 7)
• OnaBoNT-A-treated (n = 66)
- Not injected at Cycle 2 (n = 31)
- Injected at Cycle 2 but <11 weeks in Cycle 1 or Cycle 2 with no AE in Cycle 2 (n = 27)
- Major protocol deviation interfering with safety evaluation (n = 8)
Analyzed in the PPS-Efficacy
• AboBoNT-A-treated (n = 302)
• OnaBoNT-A-treated (n = 302)
Analyzed in the PPS-Safety
• AboBoNT-A-treated (n = 358)
• OnaBoNT-A-treated (n = 358)

◂**Fig. 1** Screening, randomization, and analysis sets. [a] Patients were considered to have completed Cycle 1 if any of the following situations applied: patient was reinjected; patient reached Week 24 assessment and retreatment criteria were not met; patient reached at least Week 12 assessment and retreatment criteria were met at Week 12, 16, 20, or 24. [b] Patients were considered to have completed Cycle 2 if they had completed Cycle 1 and if any of the following situations applied: patient was reinjected; patient reached Week 24 assessment and retreatment criteria were not met; patient reached at least Week 12 assessment and retreatment criteria were met at Week 12, 16, 20, or 24. [c] The FAS is based on allocated treatment sequence and the SS according to treatment received. *aboBoNT-A* abobotulinumtoxinA, *aboBoNT-A → onaBoNT-A* aboBoNT-A 900 U followed by onaBoNT-A 360 U, *AE* adverse event, *FAS* full analysis set, *onaBoNT-A* onabotulinumtoxinA, *onaBoNT-A → aboBoNT-A* onaBoNT-A 360 U followed by aboBoNT-A 900 U, *PPS-Efficacy* per-protocol efficacy set, *PPS-Safety* per-protocol safety set, *SS* safety set

other key secondary efficacy endpoints at Week 12 were tested, applying Bonferroni correction for multiplicity adjustment.

For the primary analysis, a one-sided alpha level of 0.1 (α = 10%) was used, amended from the prespecified 0.05 one-sided threshold owing to sample size constraints and the observation of higher-than-expected between-patient variability at an early blinded sample size reassessment. The margin for non-inferiority was 5% (i.e., aboBoNT-A was considered non-inferior to onaBoNT-A if the upper bound of the 80% CI for the adjusted difference in TEAE rate was < 5%). For the secondary analyses, a p value of < 0.2 was considered statistically significant under the prespecified two-sided α = 0.2 framework (consistent with the one-sided α = 0.1). Post hoc analyses assessed the primary endpoint using a more conservative one-sided α of 0.025. Additionally, the secondary endpoint (duration of response) was measured in a subgroup of the FAS comprising patients without PTMG-related protocol deviations that may have impacted efficacy evaluation (PTMG was defined in the protocol as the finger, wrist, or elbow flexors with the highest MAS score at screening and should remain consistent throughout both cycles of the study; however, incorrect PTMG assignment, MAS assessments performed on a non-PTMG muscle group, or changes in PTMG between cycles were classified as major deviations and, as well as other deviations, resulted in exclusion from the PPS-Efficacy). The "correct PTMG" subgroup removed patients with PTMG-related protocol deviations from the analysis, while keeping those with the correct PTMG throughout.

Descriptive statistics were provided for the primary and key secondary endpoints within each of the following subgroups if the sample size was ≥ 30 patients in each category: sex (male/female), age (< 65/ ≥ 65 years), country (USA/Canada/France), and prior BoNT-A status for ULS (naïve/non-naïve). Statistical analyses were performed using Statistical Analysis System (SAS)® software (version 9.4 or higher).

Ethical Approval

The study was conducted in accordance with the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines and International Conference on Harmonisation Good Clinical Practice Guidelines. All patients provided written informed consent. The protocol and informed consent forms were reviewed and approved by the sponsor, the central ethics committee (Advarra), and by the applicable institutional review boards/ethical committees at participating sites with respect to scientific content and compliance with applicable regulations for research and humans (Table S1).

RESULTS

Baseline Characteristics

Overall, 545 patients were screened, of whom 464 eligible patients were randomized to receive treatment (Fig. 1): 231 patients to the aboBoNT-A → onaBoNT-A sequence and 233 to the onaBoNT-A → aboBoNT-A sequence (Table 1).

Mean patient age was 56.8 (SD 13.1) years, and 34.1% of patients were female. Most patients had a diagnosis of spasticity secondary to acquired brain injury (n = 439; 95%), most

Table 1 Baseline demographics and disease characteristics by sequence (randomized set)

Characteristic	AboBoNT-A → OnaBoNT-A (*n* = 231)	OnaBoNT-A → AboBoNT-A (*n* = 233)	Total (*N* = 464)
Age, years, mean (SD)	57.0 (12.5)	56.5 (13.7)	56.8 (13.1)
Sex, female, *n* (%)	79 (34.2)	79 (33.9)	158 (34.1)
Diagnosis of neurological condition leading to spasticity, *n* (%)[a]			
Congenital	3 (1.3)	4 (1.7)	7 (1.5)
Acquired brain injury	216 (94.3)	223 (95.7)	439 (95.0)
Spinal cord injury	2 (0.9)	4 (1.7)	6 (1.3)
Progressive neurological condition	6 (2.6)	1 (0.4)	7 (1.5)
Other	2 (0.9)	1 (0.4)	3 (0.6)
Primary etiology of spasticity, *n* (%)[a]			
Trauma	24 (10.5)	25 (10.7)	49 (10.6)
Vascular (infarct or hemorrhage)	186 (81.2)	197 (84.5)	383 (82.9)
Hypoxic	6 (2.6)	4 (1.7)	10 (2.2)
Inflammatory/infective	4 (1.7)	1 (0.4)	5 (1.1)
Tumor	1 (0.4)	2 (0.9)	3 (0.6)
Degenerative	4 (1.7)	2 (0.9)	6 (1.3)
Other	4 (1.7)	2 (0.9)	6 (1.3)
Time since event leading to spasticity, years[a]			
Mean (SD)	8.86 (9.85)	6.91 (7.90)	7.88 (8.97)
Median (range)	5.40 (0.1–52.7)	4.40 (0.0–56.3)	4.90 (0.0–56.3)
Pattern of ULS, *n* (%)[a]			
Bilateral	8 (3.5)	6 (2.6)	14 (3.0)
Unilateral	221 (96.5)	227 (97.4)	448 (97.0)
Left (% of unilateral)	122 (55.2)	123 (54.2)	245 (54.7)
Right (% of unilateral)	99 (44.8)	104 (45.8)	203 (45.3)
Also affected by LLS, *n* (%)[a]	176 (76.9)	170 (73.0)	346 (74.9)
Prior BoNT-A experience for ULS, *n* (%)[b]			
Naïve	70 (30.8)	74 (31.8)	144 (31.3)
Non-naïve	157 (69.2)	159 (68.2)	316 (68.7)

AboBoNT-A abobotulinumtoxinA, *aboBoNT-A → onaBoNT-A* aboBoNT-A 900 U followed by onaBoNT-A 360 U, *BoNT-A* botulinum toxin A, *LLS* lower limb spasticity, *OnaBoNT-A* onabotulinumtoxinA, *onaBoNT-A → aboBoNT-A* onaBoNT-A 360 U followed by aboBoNT-A 900 U, *SD* standard deviation, *ULS* upper limb spasticity

[a] *n* = 229 for patients treated with aboBoNT-A → onaBoNT-A

[b] *n* = 227 for patients treated with aboBoNT-A → onaBoNT-A

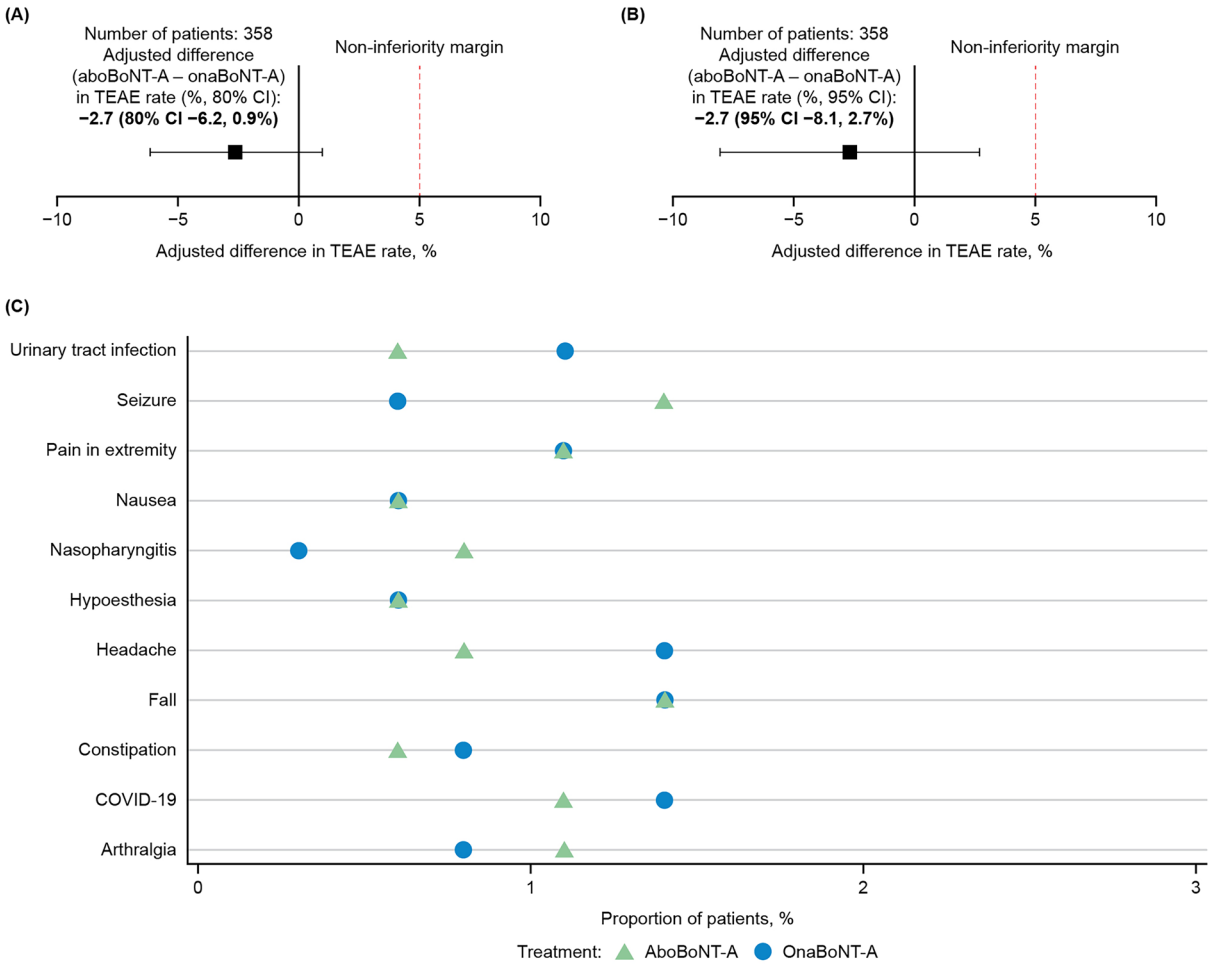


Fig. 2 Forest plot of difference of adjusted TEAE rates from injection to Week 12 for the primary (**A**)[a] and post hoc (**B**)[b] analyses (PPS-Safety), and most frequent TEAEs by preferred term from injection to Week 12 (PPS-Safety) (**C**). [a] Primary analysis using a one-sided $\alpha = 0.01$. [b] Post hoc analysis using a one-sided $\alpha = 0.025$. In (**C**) the TEAEs with the 1st to 10th highest frequency are reported, with 11 preferred terms due to ties in frequency. *aboBoNT-A* abobotulinumtoxinA, *CI* confidence interval, *onaBoNT-A* onabotulinumtoxinA, *TEAE* treatment-emergent adverse event

commonly with vascular events as the primary etiology ($n = 383$; 82.9%). Median time since the event leading to spasticity was 4.9 years (range: 0.0–56.3 years).

Most patients presented with unilateral upper limb involvement ($n = 448$; 97.0%), with the left side affected in a slightly higher proportion of patients than the right side (54.7% vs. 45.3%). Three-quarters of patients ($n = 346$; 74.9%) were also affected by lower limb spasticity (LLS) but were not concurrently treated with BoNT-A for LLS during the trial. The majority of patients had previously received BoNT-A for ULS ($n = 316$; 68.7%).

Patient baseline characteristics were broadly similar in both sequence arms with the exception of median time since the event leading to spasticity, which was slightly longer in patients treated with aboBoNT-A → onaBoNT-A (5.4 years) compared with those treated with onaBoNT-A → aboBoNT-A (4.4 years).

Treatment Exposure

Duration of BoNT-A exposure was evaluated in the SS. The mean (SD) duration of exposure was 15.11 (5.60) weeks for aboBoNT-A and 14.69 (4.98) weeks for onaBoNT-A. Mean and median exposure durations were similar for aboBoNT-A and onaBoNT-A across both treatment cycles, with mean (SD) durations in Cycle 1 of 15.20 (5.35) weeks for aboBoNT-A and 14.99 (4.71) weeks for onaBoNT-A, and of 15.00 (5.90) weeks for aboBoNT-A and 14.34 (5.28) weeks for onaBoNT-A in Cycle 2.

Safety

Primary Endpoint: Rate of TEAEs at Week 12

The primary non-inferiority endpoint was evaluated in the PPS-Safety population (aboBoNT-A, $n = 358$; onaBoNT-A, $n = 358$) and was met. The adjusted rate of TEAEs from injection to Week 12 was 20.3% for aboBoNT-A and 23.0% for onaBoNT-A. The adjusted difference in TEAE rate for aboBoNT-A compared with onaBoNT-A was − 2.7% (80% CI − 6.2%, 0.9%); the upper bound of the 80% CI of the adjusted difference was below the predefined margin of 5%,

Table 2 Subgroup analyses for the primary endpoint (TEAEs from injection to Week 12; PPS-Safety)

Subgroup	Patients experiencing TEAEs, *n*/*N* (adjusted %)		Adjusted estimated difference[a,b] (80% CI), %
	AboBoNT-A	OnaBoNT-A	
Sex			
Male	48/232 (20.6)	50/232 (21.6)	− 1.0 (− 5.3, 3.3)
Female	25/126 (19.9)	32/126 (25.4)	− 5.5 (− 11.7, 0.7)
Age[c]			
< 65 years	52/243 (21.2)	51/243 (21.2)	0.0 (− 4.1, 4.2)
≥ 65 years	21/115 (18.3)	31/115 (27.0)	− 8.7 (− 15.2, − 2.2)
Country			
USA	63/314 (20.0)	63/314 (20.1)	− 0.1 (− 3.8, 3.6)
France	9/35 (25.4)	17/35 (49.5)	− 24.1 (− 36.2, − 12.0)
Canada[d]	1/9 (NE)	2/9 (NE)	NE
BoNT-A status[c]			
Naïve	26/104 (24.6)	26/104 (25.4)	− 0.7 (− 6.8, 5.4)
Non-naïve	47/253 (18.6)	56/253 (22.1)	− 3.6 (− 7.9, 0.8)

AboBoNT-A abobotulinumtoxinA, *BoNT-A* botulinum toxin type A; *CI* confidence interval, *LS* least squares, *NE* not evaluated, *OnaBoNT-A* onabotulinumtoxinA, *PPS-Safety* per-protocol safety set, *TEAE* treatment-emergent adverse event

[a] AboBoNT-A – onaBoNT-A

[b] An upper bound of the 80% CI for the adjusted treatment difference < 5% indicates results within the non-inferiority margin (nominal, pre-specified one-sided $\alpha = 0.10$); an upper bound < 0 indicates a difference favoring aboBoNT-A versus onaBoNT-A

[c] At baseline

[d] Not evaluated owing to small sample size

Table 3 Summary of TEAEs from injection to Week 12 by treatment (SS)

Event type	AboBoNT-A (*n* = 427) *n* (%); E	OnaBoNT-A (*n* = 424) *n* (%); E
Any TEAE[a]	82 (19.2); 129	93 (21.9); 150
Severe TEAE	9 (2.1); 10	13 (3.1); 20
Related TEAE[b]	15 (3.5); 17	15 (3.5); 17
Serious TEAE	16 (3.7); 23	18 (4.2); 28
Fatal TEAE[c]	1 (0.2); 1	1 (0.2); 1
TEAE leading to study discontinuation	2 (0.5); 2	2 (0.5); 4
AESIs[d]	6 (1.4); 6	4 (0.9); 4
Of hypersensitivity[e]	4 (0.9); 4	4 (0.9); 4
Of remote spread[f]	2 (0.5); 2	0

AboBoNT-A abobotulinumtoxinA, *AESI* adverse event of special interest, *E* number of events, *OnaBoNT-A* onabotulinumtoxinA, *SS* Safety Set, *TEAE* treatment-emergent adverse event

[a] A TEAE is defined for each treatment cycle as any adverse event that occurs during the cycle if it was not present prior to treatment injection, or if it was present prior to treatment injection but the intensity increased during the cycle

[b] A TEAE was considered related to study treatment or procedure if the TEAE was categorized as definitely, probably, likely, or possibly related by the investigator. If the causality was missing, it was considered related to study treatment

[c] TEAE not related to treatment

[d] All AEs were monitored by the sponsor to determine if they met the criteria of AESIs

[e] Hypersensitivity based on standardized Medical Dictionary for Regulatory Activities query

[f] AESIs of remote spread were included if adjudicated as potential remote spread: one incident of vision blurred and one incident of muscular weakness (one patient each)

confirming non-inferiority (one-sided α = 0.1) (Fig. 2A). No significant carry-over (treatment by cycle) effect was observed. Non-inferiority was also demonstrated in the post hoc analysis at the one-sided α = 0.025 level; the upper bound of the 95% CI for the adjusted treatment difference (aboBoNT-A – onaBoNT-A) remained below the predefined margin of 5% [– 2.7% (95% CI – 8.1%, 2.7%)] (Fig. 2B).

Sensitivity analyses conducted in the full SS (patients treated with aboBoNT-A, *n* = 421; patients treated with onaBoNT-A, *n* = 418) showed similar results to the PPS-Safety, confirming the non-inferiority of aboBoNT-A versus onaBoNT-A (Fig. S1). The adjusted 12-week TEAE rate was 19.5% for aboBoNT-A and 22.3% for onaBoNT-A, with an estimated difference of – 2.9% (80% CI – 6.1%, 0.4%); as per the primary analysis, the upper bound of the confidence interval was < 5%, confirming non-inferiority. Estimation of the paired differences in TEAE rate from injection to Week 12 further supported the non-inferiority of aboBoNT-A versus onaBoNT-A. The overall difference in TEAE rates (aboBoNT-A – onaBoNT-A) was – 2.51% (80% CI – 6.04, 1.01) across 358 patients.

Subgroup analysis of TEAEs in the PPS-Safety population, stratified by patient sex, age, country, and prior BoNT-A status, demonstrated generally comparable safety profiles for the aboBoNT-A and onaBoNT-A treatments. Non-inferiority of aboBoNT-A versus onaboNT-A was established in all subgroups of clinical interest except the BoNT-A-naïve group. Although included in the main analysis, no subgroup analyses were performed for the patient group from Canada owing to the small sample size (< 30 patients) (Table 2).

Other Safety Assessments

In the SS (aboBoNT-A, *n* = 427; onaBoNT-A, *n* = 424), 129 TEAEs were reported from injection to Week 12 in 82 (19.2%) patients treated with aboBoNT-A and 150 TEAEs in 93 (21.9%) patients treated with onaBoNT-A (Table 3). TEAEs considered by the investigator to be related to treatment were reported in 15 (3.5%) patients (17 events) receiving aboBoNT-A and in 15 (3.5%) patients (17 events) treated with onaBoNT-A. The most commonly reported TEAEs considered by the investigator to be related to aboBoNT-A were muscular weakness (3 events),

headache (3 events), and hypoaesthesia, asthenia and nausea (2 events each). In patients receiving onaBoNT-A, the most commonly reported TEAEs considered by the investigator to be related to treatment were injection site pain (3 events), muscular weakness (2 events), and pain in extremity (2 events) (Table S2). Discontinuation of BoNT-A treatment owing to TEAEs occurred in 2 (0.5%) patients receiving aboBoNT-A and 2 (0.5%) receiving onaBoNT-A.

AESIs were reported in 6 (1.4%) patients (6 events) treated with aboBoNT-A and in 4 (0.9%) patients (4 events) treated with onaBoNT-A. Hypersensitivity AESIs were reported in 4 (0.9%) patients treated with aboBoNT-A and 4 (0.9%) treated with onaBoNT-A (4 events each); additionally, two adjudicated incidents of remote spread occurred in 2 (0.5%) patients treated with aboBoNT-A. The AESIs of potential remote spread included one incident of blurred vision and one incident of muscular weakness (one participant each). Both events were considered non-serious. The case of muscular weakness was moderate and considered to be related to study treatment by the investigator; it had not resolved at time of study discontinuation and led to study treatment withdrawal. The incident of blurred vision was mild, was not considered to be treatment-related by the investigator, resolved, and did not lead to any changes in dose.

Overall, two patients experienced TEAEs that led to death during the study. One patient (0.2%) experienced a fatal myocardial infarction after treatment with aboBoNT-A and one patient (0.2%) experienced a fatal cardiac arrest after onaBoNT-A treatment. Both events were considered not related to study treatment.

The safety profile in the SS for the whole cycle duration was broadly consistent with that from injection to Week 12 (Table S3). Rates of serious TEAEs, TEAEs leading to study treatment discontinuation, and AESIs were similar to those from injection to Week 12. Fatal events unrelated to study treatment were reported in 1 (0.2%) patient treated with aboBoNT-A and in 1 (0.2%) patient treated with onaBoNT-A.

In the PPS-Safety population (aboBoNT-A, $n=358$; onaBoNT-A, $n=358$), the safety profile of aboBoNT-A and onaBoNT-A was comparable between injection and Week 12; TEAEs were reported in 20.4% of patients treated with aboBoNT-A in 22.9% of patients treated with onaBoNT-A. The most commonly reported TEAEs from injection to Week 12 were urinary tract infection, seizure, pain in extremity, nausea, nasopharyngitis, hypoesthesia, headache, fall, constipation, COVID-19, and arthralgia, affecting 0.5–1.5% of patients across treatments (Fig. 2C). Serious TEAEs were reported in 12 (3.4%) and 14 (3.9%) patients after treatment with aboBoNT-A and onaBoNT-A, respectively (Table S4).

Efficacy

Key Secondary Endpoint: Duration of Treatment Response Based on Time to Symptom Re-emergence

Efficacy was evaluated in the FAS, which comprised 428 patients treated with aboBoNT-A and 424 patients treated with onaBoNT-A. The adjusted mean duration of response based on time to symptom re-emergence was 99.3 days for aboBoNT-A and 96.3 days for onaBoNT-A. The adjusted mean difference in duration for aboBoNT-A – onaBoNT-A was 3.0 (80% CI 0.2, 5.9) days ($p=0.17$), which was statistically significant under the pre-specified $\alpha=0.20$ framework. No significant carry-over (treatment by cycle) effect was observed. Among patients in the FAS without PTMG-related protocol deviations (aboBoNT-A, $n=388$; onaBoNT-A, $n=383$), the adjusted mean duration of response was 4.2 days longer with aboBoNT-A than with onaBoNT-A (99.9 vs. 95.7 days, respectively), with a lower p value than that observed in the full FAS ($p=0.0685$) (Fig. S2).

In this fixed-interval follow-up protocol, a general trend toward a numerically longer time to symptom re-emergence was observed for aboBoNT-A than for onaBoNT-A across prespecified subgroups, with statistical significance under the pre-specified $\alpha=0.20$ framework shown for the male ($p=0.1886$) and USA ($p=0.1571$) subgroups (Table 4).

Table 4 Subgroup analyses for the key secondary endpoint (duration of response based on time to symptom re-emergence; FAS)

Subgroup (*n*, AboBoNT-A/OnaBoNT-A)	Duration of response, adjusted mean, days		LS mean difference[a,b] (80% CI), days *p* value
	AboBoNT-A	OnaBoNT-A	
Sex			
Male (280/275)	99.5	96.1	3.38 (0.09, 6.68) $p = 0.1886$
Female (148/149)	99.1	97.2	1.90 (− 3.47, 7.28) $p = 0.6492$
Age[c]			
< 65 years (295/287)	98.1	95.8	2.31 (− 1.05, 5.67) $p = 0.3781$
≥ 65 years (133/137)	102.0	97.4	4.65 (− 0.68, 9.99) $p = 0.2633$
Country			
USA (371/375)	98.3	95.0	3.25 (0.31, 6.19) $p = 0.1571$
France (48/40)	111.0	108.7	2.39 (− 8.83, 13.61) $p = 0.7825$
Canada (9/9)	84.0	84.9	− 0.92 (− 9.85, 8.02) $p = 0.8887$
BoNT-A status[c]			
Naïve (131/134)	99.9	96.6	3.25 (− 2.51, 9.00) $p = 0.4688$
Non-naïve (296/289)	99.0	96.5	2.56 (− 0.61, 5.73) $p = 0.3002$

AboBoNT-A abobotulinumtoxinA, *BoNT-A* botulinum toxin type A, *CI* confidence interval, *FAS* full analysis set, *LS* least squares, *OnaBoNT-A* onabotulinumtoxinA

[a] Lower bounds of the two-sided 80% CI > 0 indicate results favoring aboBoNT-A (nominal, pre-specified two-sided $\alpha = 0.20$)

[b] AboBoNT-A – onaBoNT-A

[c] At baseline

Other Key Secondary Efficacy Endpoints

At Week 12, there was no other significant difference between aboBoNT-A and onaBoNT-A for any other key secondary efficacy endpoints. The adjusted mean MAS score for the PTMG was 2.4 in patients treated with aboBoNT-A and in those treated with onaBoNT-A [estimated difference − 0.04 (80% CI − 0.09, 0.02; $p = 0.4182$; Bonferroni-adjusted $p > 0.9999$)].

The adjusted mean DAS score was 1.8 in patients treated with aboBoNT-A and in those treated with onaBoNT-A [estimated difference – 0.00 (– 0.06, 0.05; $p = 0.9792$; Bonferroni-adjusted $p > 0.9999$)]. The adjusted PGA mean score was 0.7 in patients treated with aboBoNT-A and 0.6 in those treated with onaBoNT-A [estimated difference 0.02 (– 0.08, 0.12; $p = 0.8215$; Bonferroni-adjusted $p > 0.9999$)].

Exploratory Endpoints

Comparable improvements from baseline were observed for both treatments across most SF-12 domains (Table S5) and with SQoL-6D (Table S6).

DISCUSSION

The primary objective of this randomized, double-blind, crossover study was to demonstrate non-inferiority of aboBoNT-A compared with onaBoNT-A in terms of safety, based on the TEAE rate from injection to 12 weeks after treatment (one-sided $\alpha = 0.1$). The study met this primary endpoint. The demonstration of the non-inferiority of aboBoNT-A compared with onaBoNT-A in terms of 12-week TEAE rate was confirmed and strengthened by the sensitivity and prespecified subgroup analyses and by a post hoc analysis that used a more stringent, conventional alpha level (one-sided $\alpha = 0.025$). Overall, aboBoNT-A was well tolerated and demonstrated a similar safety profile to onaBoNT-A, with no unexpected safety signals. The study also met its key secondary efficacy endpoint: when administered at 90% of the maximum unit dose for adult ULS in the approved label for each formulation, time to symptom re-emergence was 3 days longer with aboBoNT-A than with onaBoNT-A (statistically superior; two-sided $\alpha = 0.2$), based on predefined, physician-assessed objective retreatment criteria and a 4-week, fixed-interval follow-up protocol. At Week 12, there was no evidence of differences between aboBoNT-A and onaBoNT-A using MAS, DAS, or PGA measures. Overall, similar improvements from baseline in most SF-12 domains and the spasticity-specific quality-of-life measure SQoL-6D were observed for both treatments.

When recommending treatment options to patients with limb spasticity, healthcare professionals and healthcare systems assess overall benefit–risk balance, with safety profile being a key consideration. In this context, DIRECTION addresses a critical clinical knowledge gap, not only reassuring physicians that both BoNT-As are well tolerated but also that this finding holds true across a wide range of patients; non-inferiority of aboBoNT-A compared with onaBoNT-A in terms of TEAE rates was confirmed across age (< 65/ ≥ 65 years), sex (male/female), prior BoNT-A treatment status for ULS (non-naïve), and country (USA/France) subgroups. There have been suggestions within the literature that aboBoNT-A may have an inferior safety profile to onaBoNT-A, particularly in terms of immunogenicity and spread [27–31]. DIRECTION is the first head-to-head trial known to the authors to assess this; rates of spread were low with aboBoNT-A and absent for onaBoNT-A, and rates of hypersensitivity were very low for both.

From an efficacy perspective, duration of response based on time to symptom re-emergence was 3 days longer with aboBoNT-A than with onaBoNT-A. In post hoc analyses excluding PTMG-related protocol deviations, this difference favoring aboBoNT-A was numerically longer and associated with a lower p value, despite the reduced sample size. The lower p value in this context highlights the potential influence of incorrect PTMG selection, including incorrect PTMG assignment, MAS assessments performed on a non-PTMG muscle group, and/or changes in PTMG between cycles on the overall efficacy assessment. A minimal clinically important difference (MCID) in BoNT-A duration has not been established, perhaps reflecting methodological challenges in defining and measuring what constitutes an MCID given the heterogeneity of spasticity endpoints, the individualized and goal-directed nature of treatment, and substantial confounding from dosing strategy, reinjection practices, and rehabilitation. However, it is reasonable to posit that any extension in duration of response translates to fewer days with symptom recurrence for patients

across the year and that each additional day of symptom relief can represent meaningful benefit to patients and caregivers living with/managing chronic spasticity. Even brief extensions to patient-centered endpoints and functional maintenance can prevent regressions that might otherwise require additional therapy, caregiver time, or result in unplanned and potentially costly care visits. At a health system level, a 3-day extension of symptom relief, particularly when aggregated across annual treatment cycles, could translate into meaningful savings in healthcare resource. In many health systems, aboBoNT-A has lower acquisition costs than onaBoNT-A, potentially offering improved treatment value when combined with a longer interval before retreatment. Further analyses may reveal which patient profiles in DIRECTION experienced greatest duration of response and could explore additional potential economic implications.

From a societal cost perspective, most (96–98%) participants in the Carenity study were of working age, and 44% (188/427) of those living with spasticity and 29% (55/188) of spasticity caregivers reported an impact of spasticity on their professional status; the majority (52–53%) reported missing ≥ 5 days' work annually for BoNT-A injections [15]. Among respondents living with spasticity, the greatest perceived benefits of fewer treatments were longer periods with improved mobility and without worrying about symptoms; among caregivers, the greatest perceived benefits were longer periods without worrying about symptoms, more quality time with family and friends, and less logistical burden and impact on work activities [15]. Also noteworthy is that the extension to treatment response offered by aboBoNT-A versus onaBoNT-A in DIRECTION was observed in the context of a rigid 4-week fixed assessment period after Week 12, and was an average for the study population; numerically longer treatment duration extensions were observed in the BoNT-A naïve, older (aged ≥ 65 years), male, and USA subgroups. Indeed, treatment with aboBoNT-A provided patients aged ≥ 65 years an average 4.65 days longer before retreatment was necessary than treatment with onaBoNT-A. The cumulative benefit of this prolonged treatment duration (approximately 20 days annually) may be particularly beneficial for older patients with ULS who often have greater concomitant medical issues and caregiver reliance than younger patients.

The protocol-defined longer duration of response observed with aboBoNT-A compared with onaBoNT-A should be interpreted alongside the absence of statistically significant between-treatment differences in MAS, DAS, and PGA at Week 12, and in changes from baseline in SF-12 and SQoL-6D; the results are not contradictory. These clinical and patient-reported outcomes were evaluated before the adjusted mean duration of response was reached for either BoNT formulation; therefore, assessments occurred while both treatments remained within their expected therapeutic plateau. Consequently, these measures were likely to be relatively insensitive to modest between-treatment differences at their respective assessment points.

A clear strength of the study is the use of a robust crossover trial design, which enables outcomes to be attributed to true treatment effects rather than between-patient differences. Other strengths include the use of aboBoNT-A and onaBoNT-A at 90% of their maximum unit dose for adult ULS in their approved labels to allow fair comparison of the two BoNT formulations, and the minimal per-protocol variability permitted in injection practices, muscle selection, and follow-up assessments per toxin cycle, which reduced potential confounding and ensured fair comparability of aboBoNT-A and onaBoNT-A.

However, the strict study protocol resulted in some limitations and challenges when interpreting the findings. Patients had to receive standardized treatment with fixed doses of BoNT-A administered to five protocol-defined muscles, which is a treatment modality that likely differs from clinical practice. In practice, physicians individualize muscle selection and dosing regimens according to patients' spasticity presentation and therapeutic goals. For example, real-world evidence studies, such as ULIS-III in ULS [19] and AboLiSh in LLS [32], which permitted treatment personalization, demonstrated substantially longer durations of response for aboBoNT-A compared with other BoNT-A formulations than those seen in DIRECTION.

Consequently, direct extrapolation of the longer treatment duration with aboBoNT (vs. onaBoNT) observed in DIRECTION may underestimate the full difference achievable when physicians optimize BoNT-A dosing and muscle selection to individual patient presentation, a possibility that may have been further confounded by the fixed protocol-defined follow-up schedule. Given the potential for subjectivity in patient-perceived symptom re-emergence to attenuate measurable differences between BoNT-A treatments, duration of response was assessed by physicians using objective clinical assessment tools and did not include a patient-reported component. However, patients living with spasticity and their caregivers were consulted on the study design through a structured patient advisory meeting [33]. Insights from this consultation supported logistical assistance with appointment scheduling and transportation, and the development of patient materials to facilitate understanding of the trial's retreatment criteria. Further research that more explicitly incorporates patient experience within duration-of-response assessments in an experimental setting would be welcomed.

Challenges with recruitment arising from the highly specific trial eligibility criteria were exacerbated by COVID-19-related inclusion and retreatment criteria. However, despite the highly selective eligibility criteria, an early blinded sample-size reassessment indicated that between-patient variability was higher than originally anticipated. Together with the recruitment challenges, this led to the pre-specification of a more permissive alpha, enabling study completion while maintaining adequate statistical power. However, it is reassuring that non-inferiority of the adjusted difference in 12-week TEAE rate was also demonstrated in a post hoc analysis applying the more stringent one-sided $\alpha = 0.025$ level.

CONCLUSION

This is the first head-to-head study known to the authors of aboBoNT-A and onaBoNT-A in adults with ULS. It found that aboBoNT-A treatment was non-inferior to onaBoNT-A with respect to the 12-week TEAE rate; rates of AESIs, including spread and hypersensitivity reactions, were low for both aboBoNT-A and onaBoNT-A, and numerically similar between the two BoNT-A formulations. When dosed at 90% of the maximum unit dose for adult ULS in their approved labels, duration of response (based on time to symptom re-emergence) was 3 days longer with aboBoNT-A than onaBoNT-A. Overall, aboBoNT-A demonstrated a more durable duration of response than onaBoNT-A, without an increase in adverse event rates. These findings address an important evidence gap in the assessment of the overall benefit–risk profile of botulinum toxin therapies and support more informed therapeutic decision-making for patients.

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Data Availability. Qualified researchers with a valid research question may request anonymized patient-level data by contacting an Ipsen representative. Further information on Ipsen's Data Sharing policy is available here (Clinical Data Transparency–Global: https://www.ipsen.com/clinical-data-transparency/).

Declarations

Conflict of interest. Alberto Esquenazi: Consulting: Allergan and Ipsen; Research grants: Allergan, Bristol Myers Squibb, and Ipsen. Theodore H. Wein: Research: Ipsen, AbbVie, Canadian Institutes of Health Research/Eurospocnet; Consulting, honoraria/payment and travel support: AbbVie, Ipsen; Advisory Boards: Ipsen; Data Safety Monitoring Board: Pacira Biosciences, PharmaZzz. Monica Verduzco-Gutierrez: Consulting: AbbVie, Ipsen, Merz, Piramal, Revance. Research grants: Ipsen; Data Safety Monitoring Board: Pacira Biosciences. Ziyad Ayyoub: Consulting: honoraria from AbbVie, Ipsen, and Revance Therapeutics, Inc. Simon Page: Employee and shareholder of Ipsen. Sarah Harding: Employee and shareholder of Ipsen. Pascal Maisonobe: Employee of Ipsen. Mathieu Beneteau: Employee of Ipsen. Atul Patel: Consulting: AbbVie, Ipsen, and Revance; Speaker's Bureau: AbbVie and Ipsen; Research: (to institution) AbbVie, Ipsen, and Pacira; Treasurer (during the study)/Vice President (at the time of writing) of the American Academy of Physical Medicine and Rehabilitation.

Ethical Approval. The study was conducted in accordance with the Declaration of Helsinki and Council for International Organizations

of Medical Sciences International Ethical Guidelines and International Conference on Harmonisation Good Clinical Practice Guidelines. All patients provided written informed consent. The protocol and informed consent forms were reviewed and approved by the sponsor, the central ethics committee (Advarra), and by the applicable institutional review boards/ethical committees at participating sites with respect to scientific content and compliance with applicable regulations for research and humans (Table S1).

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