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Pain Reduction With AbobotulinumtoxinA for the Treatment of Hallux Valgus in Adult Participants: Results of a Randomized and Placebo-Controlled Phase 2 Trial

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ABSTRACT

AbobotulinumtoxinA (aboBoNT-A, Dysport® [Ipsen, Paris, France]) inhibits acetylcholine release at the neuromuscular junction and may modulate pain signaling in hallux valgus (HV). This randomized study (NCT03569098) included a double-blind phase (aboBoNT-A 300U, 500U or placebo injections into forefoot muscles) and an open-label aboBoNT-A treatment period in participants with an HV diagnosis and no HV surgery. The primary endpoint was change from baseline in numeric pain rating scale (NPRS) score at week 8. Secondary endpoints included change in NPRS (other time points) and proportion of participants with ≥20% reduction from baseline NPRS (responders). Post-hoc analyses assessed number of days in a 7-day evaluation period that participants spent in a lower pain state than at baseline. Participants received aboBoNT-A 300U (n = 63), 500U (n = 60) or placebo (n = 63). Superiority to placebo was not observed with either aboBoNT-A dose at week 8, thus the primary endpoint was unmet. At week 12, a trend toward efficacy was observed with aboBoNT-A 500U versus placebo and the proportion of participants with ≥20% reduction from baseline NPRS was greater with aboBoNT-A 500U versus placebo (p = .006). Participants in the aboBoNT-A 500U group spent more days with lower NPRS than their lowest baseline score, and with NPRS ≥2 points lower than their mean baseline NPRS at weeks 8 and 12 versus placebo (all $p < .05$; post-hoc). AboBoNT-A was well tolerated. Although the primary endpoint was unmet, other endpoints showed a nominal advantage for aboBoNT versus placebo for treatment of HV-related pain, particularly at week 12. Further clinical evaluation is needed to establish whether botulinum toxins represent a viable non-operative treatment option for HV-associated pain.

Plain language summary: Hallux valgus is the medical name for a bunion, a foot deformity that can worsen over time. Patients with bunions experience pain and walking can become difficult, which can affect their quality of life. Foot support aids (e.g., braces, splints and inserts) are available, but surgery is the standard treatment.

This study looked at how injections of a specific type of botulinum toxin, called abobotulinumtoxinA or "aboBoNT-A", into the foot may help to reduce pain in patients with bunions. The study included 186 patients aged 18 to 75 years who had not had surgery on their bunion. The researchers looked at how well the injections worked using scales that measure the pain levels the patient experienced.

The main outcome was whether patients who had aboBoNT-A injections had less pain after 8 weeks than they did before treatment. The study included patients who were injected with saltwater (no treatment) to check that any treatment effect was real. Researchers also looked at the results after 12 weeks, as well as how many patients had

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Conflict of Interest: DGA and BB are investigators for the current study and report consultancy (advisory board) for Ipsen. LAD is an investigator for the current study. SGP has no disclosures to declare. MV is an Ipsen employee. RS was an Ipsen employee during the study and manuscript preparation.

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less pain after treatment than before and how many days in a given week patients experienced less pain after treatment than they did before.
There was no reduction in pain levels with aboBoNT-A injections after 8 weeks compared with no treatment. However, the other study outcomes suggested that aboBoNT-A resulted in a small benefit compared with no treatment, especially after 12 weeks. Further medical research is needed to establish whether botulinum toxins represent an alternative treatment to surgery for the pain associated with bunions.

Globally, approximately 23% of adults below 65 years of age are afflicted with hallux valgus (HV) (1), a progressive deformity characterized by lateral deviation of the great toe (the hallux) and medial deviation of the first metatarsal head, which causes a prominence commonly known as a "bunion" (2,3). The etiology of HV is thought to involve an imbalance between the abductor (decreased activity) and adductor hallucis muscles, whereby the latter gains a mechanical advantage and the hallux is pulled laterally causing the HV forefoot morphology (4,5). Subsequent structural changes in the joint can lead to significant and chronic pain, often related to extrinsic factors (such as pressure of a shoe over the medial eminence), severe mobility limitations (6), emergence of ancillary pain conditions (e.g., transfer metatarsalgia (6) and sensory nerve dysfunction) (7), and functional impairments in gait and balance (8,9), all of which negatively impact quality of life (10-13).

Together with morphological changes in the foot, forefoot pain and disability are key indicators of HV severity and treatment outcomes (14,15). Early medical management of HV involves orthotic interventions (16), such as braces, splints or inserts. However, with limited effect in clinical trials in correcting the biomechanics of the foot, reducing HV-related pain or preventing HV progression, orthoses may be no more effective than no treatment at all (16-18). Currently, the standard of care is operative correction, which generally includes rebalancing soft tissue, reducing angular deviation, and realigning the articular surface of the metatarsal (6,17). However, postoperative pain and swelling, a recovery period of up to 12 weeks (6) and a risk of recurrence (5,19) complicate risk/benefit decisions regarding surgery for participants with HV. There is a dearth of effective non-operative treatments for HV for those who cannot, or who choose not to, undergo operative procedures.

Botulinum toxins (BoNTs) are neuromuscular blocking agents that inhibit release of presynaptic acetylcholine at the neuromuscular junction, reducing localized muscle tone in the injected muscle (20). Pain signaling in the periphery, the dorsal root ganglia and spinal cord is also impaired following BoNT injection, leading to peripheral and central pain desensitization (20-22). BoNTs have reliably shown efficacy in the treatment of pain conditions such as migraine (23), trigeminal neuralgia (22), hypertrophic scar pain (24) and plantar fasciitis (25). Prior studies in participants with HV have demonstrated robust, clinically meaningful changes in foot pain and functional mobility following direct injection of BoNT type A (BoNT-A) into specific forefoot muscles governing the hallux and related metatarsal structures (26-28). In addition to reducing pain, there is some evidence that BoNT injections can reduce HV-associated angular deviation owing to the temporary paralysis of muscle and subsequent elimination of one of the deforming forces (26-28).

AbobotulinumtoxinA (aboBoNT-A, Dysport® [Ipsen, Paris, France]) is approved in several countries for the treatment of spasticity, cervical dystonia and facial esthetics (29-31). Based on its mechanism of action, it was hypothesized that aboBoNT-A would reduce pain in participants with HV. The primary aim of the present randomized controlled study was therefore to assess pain reduction in adults with HV who had not undergone surgery, following injections of aboBoNT-A 300U and 500U compared with placebo, using the numeric pain rating scale (NPRS) (32,33). Secondary objectives were to assess the effect of aboBoNT-A on functional impairment, activity limitation, angular displacement, quality of life and participants' global impressions of severity and improvement, and to evaluate the safety and tolerability of aboBoNT-A in patients with HV who had not undergone surgery.

Participants/Materials and Methods

Study Design

This was a randomized, double-blind, placebo-controlled, parallel-group, multicenter, phase 2 study (NCT03569098 [ClinicalTrials.gov]; Fig. 1). The total duration was 39 weeks, and comprised a double-blind period of at least 12 weeks (cycle 1) and an open-label period lasting up to 24 weeks (cycles 2 and 3). The study was approved by appropriate health authorities and by independent ethics committees/institutional review boards, and was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization Consolidated Guideline on Good Clinical Practice and all local regulatory guidelines. Written informed consent was provided by all participants prior to enrollment.

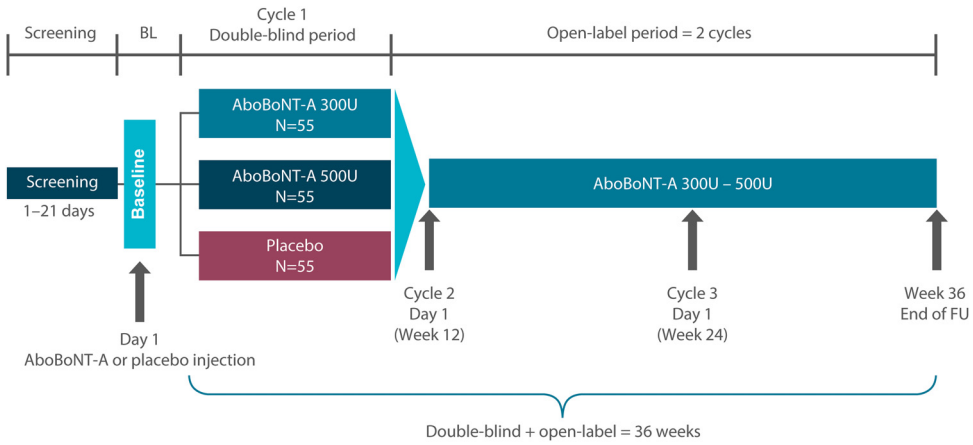

Fig. 1. Study design.
Abbreviations: AboBoNT-A, abobotulinumtoxinA; BL, baseline; FU, follow-up; N, number of participants; U, units.

Randomization and Blinding

Participants, investigators and study and sponsor personnel were blinded to treatment assignment throughout the study. All treatments were similar in size, color, smell, taste and appearance, allowing the blinded conditions of the study to be maintained. The placebo treatment (saline) was provided in glass vials and was indistinguishable from the active product.

Randomization numbers were produced in blocks on a balanced ratio (1 placebo:1 aboBoNT-A 300U:1 aboBoNT-A 500U) and stratified by unilateral and bilateral HV. After eligibility was confirmed at baseline, participants were assigned a randomization number and allocated to the associated treatment arm. Randomization and assignment of treatment number were managed by an independent person using an interactive response technology system.

Participants

Participants were recruited at each investigator's institution, as listed in Supplementary Appendix 1. Supplementary Appendix 2 lists full inclusion and exclusion criteria. In order to ensure that variability was minimized and potential confounding factors eliminated, the entry criteria restricted the inclusion of participants with pre-existing medical conditions and those reliant on treatments not permitted in the study. Key inclusion criteria were: age 18 to 75 years; unilateral or bilateral HV diagnosis; HV angle <30 degrees; first intermetatarsal (IM) angle <18 degrees associated with the hallux of the study foot; reducible deformity (investigator judgment); and foot pain refractory to shoe modifications, non-steroidal anti-inflammatory medications and activity modification. Participants must have recorded scores of ≥4 on the NPRS and >27 on the modified foot function index (mFFI) pain and disability subscales in the study foot. Key exclusion criteria included: an inability to walk unassisted; any other podiatric/orthopedic condition interfering with pain and/or function evaluation; history of ankle or foot surgery in the study foot; diabetes, peripheral neuropathy, inflammatory arthritis, osteoarthritis, disease causing ligamentous laxity; or a body mass index >40 kg/m^2 or <18.5 kg/m^2. Use of orthotic inserts/devices on the study foot (except over-the-counter orthoses used for 30 days prior to screening) and BoNT treatment <4 months prior to screening for any condition (except esthetic facial applications) were not permitted. Participants with severe HV (HV angle ≥30 degrees or IM angle ≥18 degrees) were excluded because they are potential candidates for surgery; also, the upper limit on the HV angle was anticipated to reduce the need for "rescue" surgery. Participants with fixed deformity were excluded because it was postulated that BoNT treatment may improve structural disease, but only if the HV was semi-reducible or reducible.

Treatment

In the double-blind period (cycle 1), participants were randomized 1:1:1 to receive aboBoNT-A 300U, aboBoNT-A 500U or placebo (Fig. 1). These doses were based on the demonstrated safety and efficacy of aboBoNT-A in reducing hypertonia in muscles of similar size and volume to those planned for evaluation in the current study (34,35). Twelve weeks after treatment in cycle 1, participants from each group who met retreatment criteria entered the open-label period and received aboBoNT-A 300U (cycle 2), regardless of treatment received in the double-blind period. Participants who met retreatment criteria again at least 12 weeks later received either aboBoNT-A 300U or aboBoNT-A 500U (investigator judgment) in cycle 3. Retreatment criteria were: participant consent; investigator's clinical judgment; clinically significant foot pain (NPRS ≥3) in the preceding 24 hours; and no unacceptable risk experienced by the participant (investigator judgment). The decision to increase the dose to 500U at the beginning of cycle 3 was based on an evaluation of safety and tolerability (treatment-related adverse events [AEs] and any significant changes in the study foot), severity of pain (NPRS score) and disability (mFFI disability subscale score). From week 12 of each treatment cycle, participants not meeting these criteria were clinically re-evaluated every 4 weeks to assess eligibility for retreatment.

Each participant received up to 3 administrations (i.e., cycles) of study treatment (one double-blind and up to 2 open-label), each with a minimum 12-week follow-up period, to assess the effect of repeated treatment cycles. For each cycle, study treatments were administered by the investigator with assistance from sub-investigators (if relevant) at each clinical site, and consisted of a single set of 4 intramuscular injections to the study foot of aboBoNT-A 75U (total dose 300U), aboBoNT-A 125U (total dose 500U) or placebo. The total dose of aboBoNT-A was divided equally among the oblique and transverse heads of the adductor hallucis muscle, the flexor hallucis brevis muscle and the extensor hallucis brevis muscle. The appropriate target muscles were identified using a peripheral electrical stimulator, with or without complementary techniques. A Teflon-coated, 27- to 30-gauge, open-lumen needle was used to stimulate the target muscle once per second (repetitive square wave pulses, 0.25 msec in duration), and injection was performed when either a continuous or stretch of muscle was located. For participants with bilateral HV, only the foot with the most severe pain, based on NPRS and clinical evaluation at baseline, was treated and evaluated. The same investigator at each site administered interventions and assessed for retreatment eligibility (DGA, LAD, BB), with assistance from sub-investigators when relevant.

Assessments

For all 3 cycles, study visits were conducted at baseline and weeks 1, 4, 8 and 12, with additional visits conducted every 4 weeks thereafter in cycles 1 and 2 to assess eligibility for retreatment, as needed. Participants, who were blinded to treatment allocation, used electronic diaries to self-record daily NPRS and mFFI scores for 7 consecutive days prior to baseline and at each post-baseline study visit. The NPRS is an 11-point scale (0-10, no pain to worst possible pain) (36). The mFFI consists of 21 items (modified from 23 items (37,38) to exclude 2 relating to use of assisted devices) grouped into 3 11-point subscales: pain (0-10, no pain to worst possible pain), disability (0-10, no difficulty to so difficult unable) and activity limitation (0-10, none of the time to all of the time). Patient Global Impression of Improvement (PGI-I) and Patient Global Impression of Severity (PGI-S) scores for disability and pain were reported by the participants on site at weeks 4, 8 and 12. The PGI-S (4-point Likert scale [0: no pain; 3: severe pain]) and PGI-I (7-point Likert scale [−3: very much worse; 3: very much improved]) scales, respectively evaluate severity of a given symptom and the degree to which it has improved following treatment (39-41). Functional outcomes and perceived well-being in mental, social and physical aspects of life were measured using the 36-item Short-Form Health Survey (SF-36) (42-44), completed by participants at baseline and weeks 8 and 12 in each treatment cycle. Radiographic measurements were based on guidelines set forth by the American Orthopedic Foot and Ankle Society ad hoc Committee on Angular Measurements (45). HV and IM angles were measured directly from weightbearing anteroposterior radiographs, with the X-ray beam angled at 15 degrees toward the heel centered on the second tarsometatarsal joint. Images were to be taken by the same radiology technician at each site, who was not involved in the administration of aboBoNT-A and was blinded to treatment allocation. Angle measurements were performed by a blinded central reader.

Any AEs were reported. AEs that suggested a possible remote spread of the effect of the toxin (Supplementary Appendix 3) or hypersensitivity were of special interest.

Objectives and Endpoints

The primary objective was to assess pain reduction with aboBoNT-A compared with placebo using the NPRS. Secondary objectives were to assess: functional improvement (mFFI disability subscale); foot pain reduction (mFFI pain subscale); activity limitation (mFFI activity limitation subscale); quality of life (SF-36); hallux angular displacement (radiographs); PGI-I and PGI-S for foot pain and disability; and safety and tolerability of aboBoNT-A.

For NPRS and mFFI, mean scores were calculated for the 7 days prior to each time point. Participants must have completed at least 4 of the 7 daily scores for diaries to be considered valid. The primary endpoint was change from baseline in foot pain measured by mean NPRS at week 8 in cycle 1. This time point was chosen because it reflects good-quality care and follow-up in general clinical practice. Secondary endpoints included the change from baseline in mean NPRS at all other time points, the proportion of responders (participants who reported ≥20% reduction from baseline in mean NPRS), change from baseline in mean mFFI, PGI and SF-36 scores, change from baseline in HV and IM angle, and time to retreatment. To evaluate the number of days in a 7-day evaluation period that participants spent in a "reduced pain state" following treatment, 2 post-hoc analyses were performed. The first assessed the number of days in a 7-day evaluation period that participants reported an NPRS that was lower than their lowest (lowest degree of pain) daily baseline NPRS; the second assessed the number of days in a 7-day evaluation period that participants reported an NPRS at least 2 units lower than their individual mean NPRS at baseline.

Statistical Analyses

All statistical analyses were conducted on the intent-to-treat population (all randomized participants). To demonstrate superiority of each aboBoNT-A dose compared with placebo, a sample size of 165 randomized participants was estimated assuming a 1.5 point difference in mean change from baseline in NPRS at week 8 between aboBoNT-A and placebo (based on previously reported minimum clinically important difference [MCID] values, as measured by the NPRS in post-bunionectomy pain trials) (32,33,46), a treatment group ratio of 1:1:1, a common standard deviation of 2.5, a power of 80% and a one-sided type I error rate of 2.5%. There was no control of type I error rate for secondary endpoints.

For the primary endpoint, a mixed model for repeated measures (MMRM) was used. Visit (weeks 4, 8 and 12), treatment-group-by-visit interaction, the stratification parameter (unilateral and bilateral HV) and the baseline value were included in the model. For participants without available post-baseline scores, week 8 data were imputed by the mean of the placebo group at week 8 for participants who discontinued because of lack of efficacy, or by the mean of the participants' treatment group at week 8 for those who discontinued for other reasons or completed the study but had no valid post-baseline diaries.

An interim analysis was performed after the first 110 randomized participants had been followed for at least 12 weeks to assess both futility and potential for early stopping due to efficacy for each aboBoNT-A group compared with placebo. The overall type I error for each comparison was controlled at the one-sided 0.025 level using O'Brien Fleming spending per Lan-DeMets spending function specification (47). Treatment comparison with an O'Brien Fleming spending corresponds to a nominal one-sided alpha of 0.0062 at the interim analysis. Significance levels were adjusted using the Hochberg procedure to reduce the risk of false positive results due to multiple comparison, under the following decision rules: (1) if the larger of the 2 p values is less than .0062, stop and declare evidence of effect for each arm; and (2) if the larger of the 2 p values is greater than .0062

and the smaller of the 2 *p* values is less than .0031, then conclude evidence of effect for the arm with the smallest *p* value. The nonbinding futility boundary was set to declare futility in the interim analysis if the one-sided *p* value for a comparison was greater than .30. If futility was concluded for the primary endpoint, the secondary endpoint of mFFI pain subscale score (mean change from baseline in the daily mFFI pain subscale score at week 8) was analyzed using the MMRM model. If a one-sided *p* value was equal to or lower than .05, evidence of a trend was to be declared for the corresponding arm; otherwise, no evidence of a trend for the corresponding arm was concluded. The interim analysis was conducted and reviewed by an independent data monitoring committee; the statistician and programmer were unblinded at the individual participant level for the interim analysis, remained independent from the study, and did not otherwise participate in any study procedures.

The primary analysis was subsequently conducted after all participants had completed week 12 of the double-blind period, but participant entry to the open-label phase was not contingent on the results. The null hypothesis of "no difference between treatment with aboBoNT-A 300U and 500U versus placebo with respect to change from baseline in mean daily NPRS score at week 8" was tested against the alternative hypothesis of "there is a difference between aboBoNT-A 300U or 500U versus placebo." A Hochberg procedure was applied to control the global type I error at the one-sided 2.5% significance level, using the following decision rules: compare larger *p* value to .0231; if this is less than .0231, then stop and declare evidence of effect for each arm; if this is not less than .0231, then compare the smaller of the 2 *p* values to .01155; if this is less than .01155, then conclude evidence of effect for the treatment arm with the smallest *p* value.

The proportion of "responder" participants with a clinically significant reduction in pain (defined as ≥20% reduction in NPRS from baseline) was calculated for the double-blind phase and analyzed with a logistic regression model, with the treatment group, stratification parameter and baseline value as covariates. For analysis on mFFI, HV and IM angle, an MMRM model was used. An mFFI was considered valid if at least 4 of the diary days had at least 50% of items in each subscale completed. No imputation of missing data was done. For PGI and SF-36 data, an analysis of covariance (ANCOVA) model was used and included treatment group, stratification parameter and the baseline value as covariates. Survival curves are presented for time to retreatment data, and a log-rank test performed to compare placebo with the treated groups. An ANCOVA model was used for analysis of post-hoc endpoints. Descriptive statistics are presented for open-label efficacy data and safety data.

Results

Participant Disposition and Baseline Characteristics

This study was conducted at 31 clinical sites in the United States (Supplementary Appendix 1) from June 2018 to May 2020; 27 sites recruited at least one participant. Overall, 531 participants were screened and 345 were screening failures, of whom 335 did not meet the inclusion criteria. Overall, 186 participants were randomized to receive placebo (n = 63), aboBoNT-A 300U (n = 63) or aboBoNT-A 500U (n = 60) in the double-blind phase (cycle 1; 32 randomized participants were from authors' practices [DGA, n = 1; LDD, n = 6; BB, n = 25]) and 180 were treated (n = 61, 63 and 56, respectively) (Fig. 2). In the open-label phase, 146 participants were eligible for retreatment with aboBoNT-A 300U in cycle 2; in cycle 3, 8 and 56 participants were eligible for retreatment with aboBoNT-A 300U or aboBoNT-A 500U, respectively. Treatment cycles 1, 2 and 3 were completed by 157 (84.4%), 111 (76.0%) and 57 (89.1%) participants, respectively. Emergency unblinding was not required during the study.

Baseline demographics and disease characteristics were similar across the groups (Table 1). Mean (standard deviation [SD]) age was 48.2 (13.1) years, 91.9% of participants were female, and approximately two-thirds of participants had bilateral HV. The mean (SD) HV and IM angles in the study foot were 20.7 (5.2) degrees and 11.9 (2.4) degrees, respectively. Mean (SD) NPRS at baseline was 6.9 (1.6) and mean (SD) time from diagnosis to first injection was 6.4 (8.7) years.

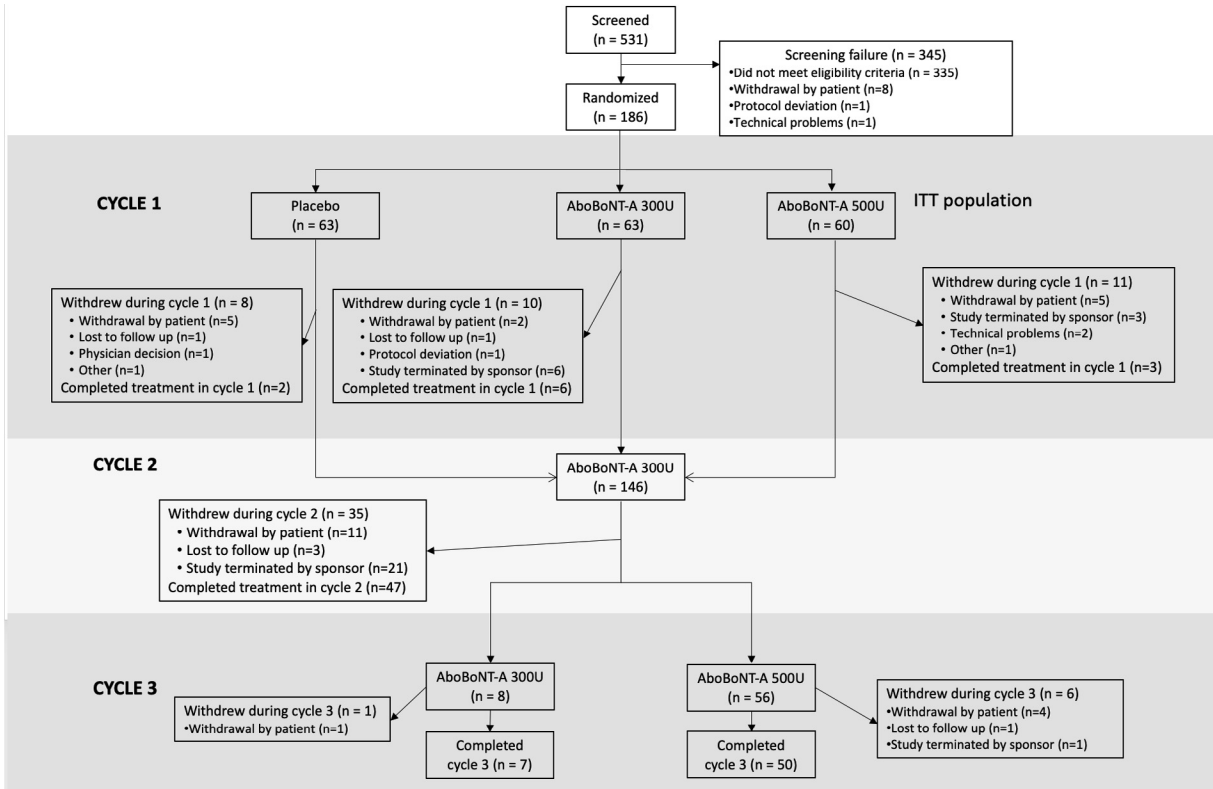

Fig. 2. Participant disposition (screened participants).

If a participant did not meet criteria for additional treatment, they remained in the current cycle. Retreatment was allowed from week 12 onward. In total, 6 participants were lost to follow-up: 2 participants after week 20 of cycle 1; 1 participant after week 4 of cycle 2; 2 participants after week 8 of cycle 2; and 1 participant after week 4 of cycle 3.

Abbreviations: AboBoNT-A, abobotulinumtoxinA; ITT, intent-to-treat.

Table 1
Baseline demographics and disease characteristics

Characteristic	Placebo (n = 63)	AboBoNT-A 300U (n = 63)	AboBoNT-A 500U (n = 60)	All Participants (N = 186)
Age, mean (SD), y	48.3 (13.2)	48.4 (14.0)	48.0 (12.2)	48.2 (13.1)
p value versus placebo[*]		*p = .9583*	*p = .8897*	
Female, n (%)	55 (87.3)	60 (95.2)	56 (93.3)	171 (91.9)
p value versus placebo[†]		*p = .1146*	*p = .2598*	
HV status, n (%)				
Unilateral	22 (34.9)	21 (33.3)	19 (31.7)	62 (33.3)
Bilateral	41 (65.1)	42 (66.7)	41 (68.3)	124 (66.7)
p value versus placebo[†]		*p = .8510*	*p = .7020*	
Time since diagnosis, mean (SD), y	5.0 (7.1)	6.7 (9.9)	7.5 (8.8)	6.4 (8.7)
p value versus placebo[*]		*p = .2870*	*p = .0890*	
HV angle in degrees, mean (SD)	20.6 (5.1)	21.3 (5.6)	20.2 (4.9)	20.7 (5.2)
p value versus placebo[*]		*p = .4529*	*p = .6275*	
IM angle in degrees, mean (SD)	11.8 (2.2)	12.2 (2.3)	11.8 (2.7)	11.9 (2.4)
p value versus placebo[*]		*p = .3056*	*p = .9586*	
NPRS[‡], mean (SD)	6.6 (1.4)	7.2 (1.6)	6.9 (1.7)	6.9 (1.6)
p value versus placebo[*]		*p = .0304*	*p = .2997*	

Abbreviations: AboBoNT-A, abobotulinumtoxinA; HV, hallux valgus; IM, intermetatarsal; ITT, intent-to-treat; NPRS, numeric pain rating scale; SD, standard deviation.
Data are for the ITT population.
[*] Based on pooled *t*-test.
[†] Based on Chi-Square test.
[‡] Mean of the daily NPRS scores over the 7 consecutive days prior to the baseline visit. A mean is calculated if there are at least 4 days of e-diary completed.

Cycle 1 (Placebo-Controlled Phase)

A decision to continue with the study was concluded based on the outcome of the interim analysis. A table presenting summary statistics of the primary endpoint can be found in the supplementary material (Supplementary Table 1). The primary analysis includes all participants from the intent-to-treat population. All visits performed at weeks 4, 8 and 12 were included in the statistical model (MMRM analysis). For the primary analysis, superiority was not achieved for either aboBoNT-A dose compared with placebo at week 8 in cycle 1, as measured by the change from baseline NPRS (least-squares [LS] mean [95% confidence interval (CI)]: aboBoNT 300U (N = 63), −1.7 [−2.3, −1.1], *p* = .77; aboBoNT 500U (N = 63), −2.4 [−3.0, −1.8], *p* = .21; placebo (N = 60), −2.0 [−2.7, −1.4]) (Fig. 3). Given that the primary endpoint was not met, the study was terminated by the sponsor. This decision was not related to any safety or tolerability issues with aboBoNT-A or any other study-related information other than the primary efficacy endpoint interim analysis. The proportion of responders was not significantly different at week 8 with either dose of aboBoNT-A compared with placebo (odds ratio [95% CI]: aboBoNT-A 300U, 1.08 [0.53, 2.20], *p* = .84; aboBoNT-A 500U, 1.53 [0.75, 3.14], *p* = .24) (Fig. 4).

A trend toward efficacy was observed at week 12 in the aboBoNT-A 500U group, with a greater reduction from baseline in mean NPRS compared with placebo (LS mean [95% CI] change from baseline: aboBoNT-A 300U, −1.6 [−2.2, −1.0], *p* = .59; aboBoNT-A 500U, −2.4 [−1.6, 0.2], *p* = .06; placebo, −1.7 [−2.4, −1.1] (Fig. 3). A significantly higher proportion of responders compared with placebo was also observed for the aboBoNT-A 500U dose group (53% vs 28%, respectively; odds ratio [95% CI] 2.873 [1.349, 6.118]; *p* = .0062 (Fig. 4). No significant differences in responder rates were observed for either dose of aboBoNT-A compared with placebo at weeks 4 and 8 (Fig. 4).

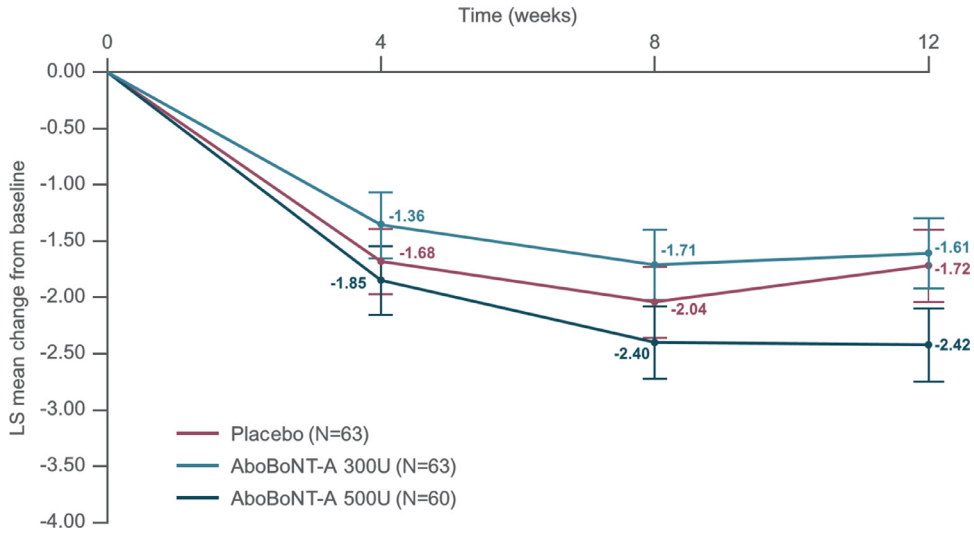

Fig. 3. Change from baseline in NPRS in the double-blind phase.
Results were from a mixed model including week 4, 8 and 12 visits. All participants from the ITT population were included, with any missing values for week 8 imputed. Bars represent standard error.
Abbreviations: AboBoNT-A, abobotulinumtoxinA; ITT, intent-to-treat; LS, least-squares; NPRS, numeric pain rating scale.

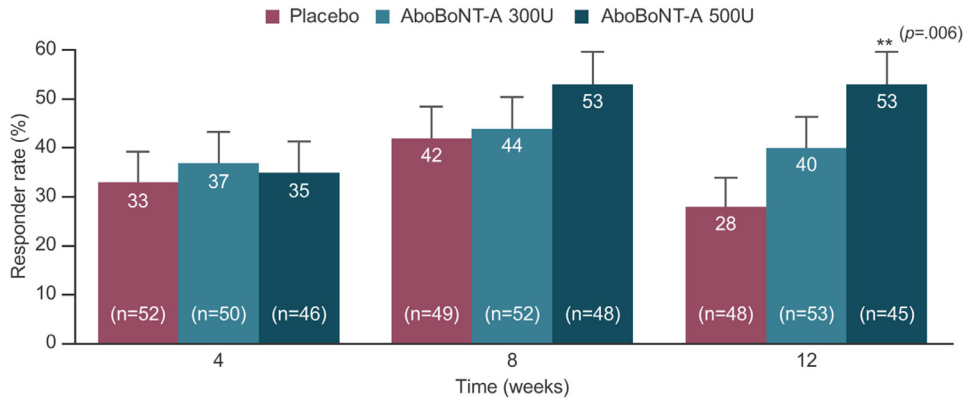

Fig. 4. Proportion of participants achieving a clinical response in the double-blind phase[a].
Data are for the ITT population. Bars represent standard error. [a]Clinical response is defined as the mean reduction from baseline in NPRS of ≥20% at each time point.
Abbreviations: AboBoNT-A, abobotulinumtoxinA; ITT, intent-to-treat; NPRS, numeric pain rating scale.

There were no significant differences observed between either aboBoNT-A 300U or aboBoNT-A 500U treatment groups compared with placebo at any time points during the double-blind phase in mean change from baseline in mFFI pain, disability or activity subscales or PGI subscales (baseline values are shown in Supplementary Table 2 and the LS mean [95% CI] change values from baseline are shown in Supplementary Table 3). A significant improvement from baseline was observed for the SF-36 Bodily Pain domain with aboBoNT-A 300U compared with placebo at week 12 (LS mean difference [95% CI] 7.52 [−0.87, 15.92], $p < .05$; Supplementary Table 3). There were no significant differences from baseline between aboBoNT-A treatment groups and placebo in HV or IM angles at any time point (Supplementary Table 3).

Cycles 2 and 3 (Open-Label Phases)

In open-label cycle 2 (aboBoNT-A 300U only), mean NPRS was further nominally reduced from baseline across all groups (n = 152) regardless of treatment received in the double-blind phase (Fig. 5; Supplementary Table 4). In cycle 3 (aboBoNT-A 300U or 500U), mean NPRS reduced again in both aboBoNT-A dose groups; the greatest mean reduction from baseline was reported with aboBoNT-A 500U – 300U – 500U administered per cycle; however, the number of participants who required a third treatment cycle within the duration of the study was low (n = 3-18; Supplementary Table 4).

Time to Retreatment

The time to retreatment was statistically significantly longer for aboBoNT-A groups compared with placebo (median time [95% CI] to retreatment with placebo was 12.6 [12.29, 12.86] weeks vs 13.1 [12.57, 16.14] weeks for aboBoNT-A 300U, $p = .0189$ and 13.1 [12.57, 15.43] weeks for aboBoNT-A 500U, $p = .0328$) (Supplementary Fig. 1).

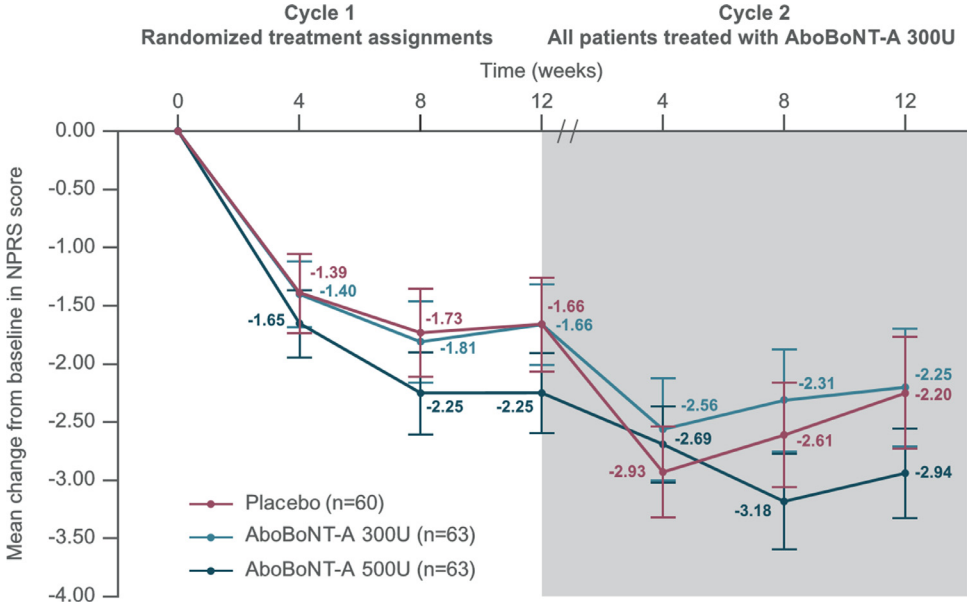

Fig. 5. Change from baseline in NPRS across 2 treatment cycles according to treatment assignment. Data are for the ITT population. Bars represent standard error. Note that data for cycle 3 are not shown because participant numbers were low (n = 3 to 18).
Abbreviations: AboBoNT-A, abobotulinumtoxinA; ITT, intent-to-treat; NPRS, numeric pain rating scale.

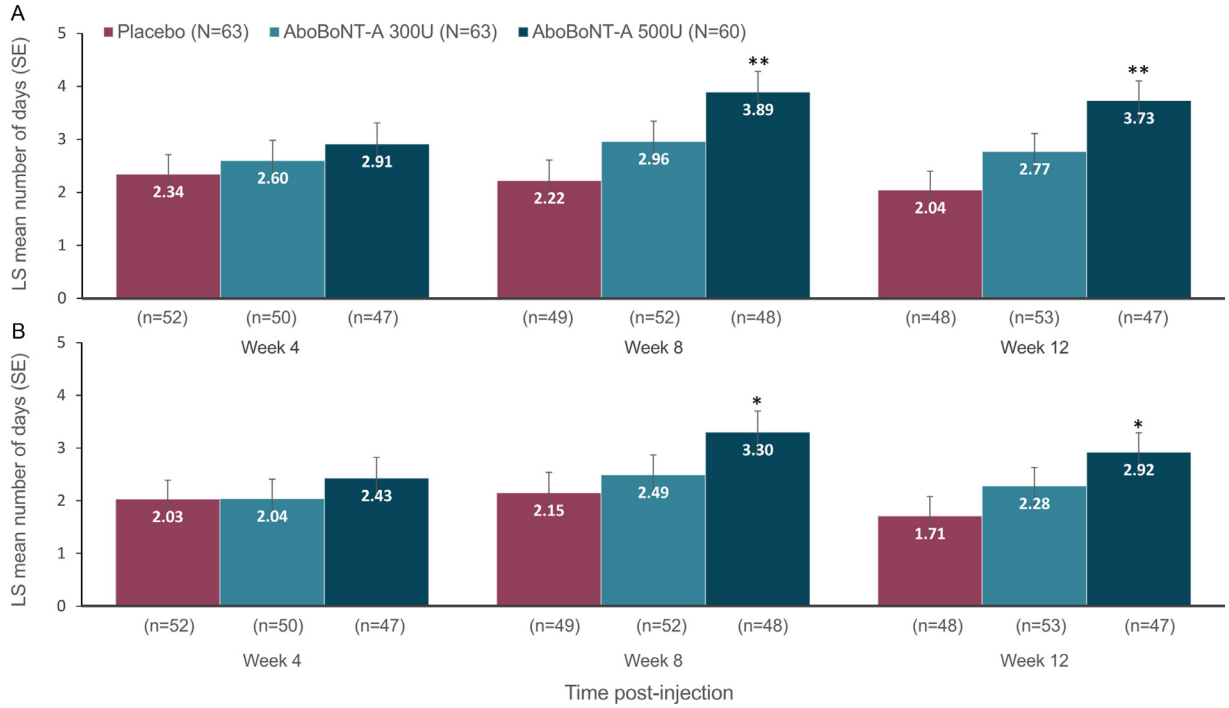

Fig. 6. Least squares mean number of days during a 7-day evaluation period with (*A*) "lower than lowest" baseline daily NPRS, and (*B*) ≥2-point reduction from mean baseline NPRS.
*$p < .05$ versus placebo; **$p < .005$ versus placebo.
Participants must have completed at least 4 of the 7 daily NRPS scores for diaries to be considered valid.
Abbreviations: AboBoNT-A, abobotulinumtoxinA; LS, least-squares; N, number of participants; n, number of participants with available data; NPRS, numeric pain rating scale; SE, standard error.

Post-Hoc Efficacy Analyses

Post-hoc analyses demonstrated that aboBoNT-A 500U treatment was associated with a trend toward significantly more time spent in a "reduced pain state" compared with placebo treatment in the double-blind phase. First, participants treated with aboBoNT-A 500U spent more days in a 7-day evaluation period with a lower NPRS score than their lowest score at baseline compared with placebo at week 8 (LS mean [95% CI] 3.89 [3.00, 4.78] vs 2.22 [1.35, 3.10], respectively; p = .0028) and week 12 (3.73 [2.89, 4.57] vs 2.04 [1.22, 2.86], respectively; p = .0012) (Fig. 6*A*). Second, participants spent more days in a 7-day evaluation period with a NPRS score ≥2 points lower than their mean baseline NPRS score with aboBoNT-A 500U compared with placebo at week 8 (LS mean [95% CI] 3.30 [2.40, 4.21] vs 2.15 [1.26, 3.04], respectively; p = .0400) and week 12 (2.92 [2.08, 3.77] vs 1.71 [0.88, 2.54], respectively; p = .0208) (Fig. 6*B*).

The clinical significance of these results can be extended by calculating the number needed to treat (NNT), which is a measure of effect size that answers the question "How many participants would one need to treat with an experimental treatment instead of placebo before encountering one additional outcome of interest?" (48,49). At week 8, comparing aboBoNT-A 500U with placebo, the (1) proportion of participants showing a clinical response (20%) and (2) proportion of participants achieving the MCID for HV (≥1.5 reduction in NPRS) corresponded to NNT scores of 9.1 and 5.7, respectively. At week 12, the same NNT analyses (clinical response and MCID) resulted in NNT scores of 4.0 and 4.0, respectively.

Safety

In cycle 1, treatment-emergent AEs (TEAEs) were reported in 36.5%, 41.1% and 36.1% of participants in the aboBoNT-A 300U, aboBoNT-A 500U and placebo groups, respectively, the majority being mild-to-moderate in severity (Table 2). The most common TEAEs (in ≥4% of participants) were injection-site pain, pain in extremity, hyperkeratosis, muscle spasms and nasopharyngitis. No unexpected or new safety signals were observed with aboBoNT-A. TEAEs considered possibly related to treatment by the investigator were observed in 3 (4.8%; aboBoNT-A 300U), 11 (19.6%; aboBoNT-A 500U) and 5 (8.2%; placebo) participants (Table 2). One participant randomized to the placebo group had a serious AE of aphasia during treatment in cycle 3 with aboBoNT-A 500U. The event was considered severe in intensity and unrelated to treatment, and the participant recovered. One AE of special interest (hypersensitivity) was reported in one participant (1.6%) who received placebo.

Discussion

To our knowledge, this is the first large, double-blind, placebo-controlled, clinical study to evaluate the efficacy and safety of intramuscular foot injections of aboBoNT-A, a potential and alternative non-operative treatment for pain associated with HV. The study, which was conducted in participants who had not undergone HV surgery, showed no significant difference from baseline in mean NPRS following treatment with aboBoNT-A 300U or 500U compared with placebo at week 8 in cycle 1 (primary endpoint). However, results of secondary and post-hoc analyses showed that clinically relevant pain reduction was achieved with aboBoNT-A 500U treatment, as suggested by the findings from the trial showing a greater proportion of participants demonstrating a clinically significant reduction in forefoot pain; as measured by multiple pain assessment endpoints, including responder analysis, evaluation of effectiveness under long-term treatment conditions, as well as an alternative pain endpoint measuring the number of days that patients achieved profound pain reduction (severity lower than clinical

Table 2
Summary of adverse events

Adverse Event	Placebo (n = 61)	AboBoNT-A 300U (n = 63)	AboBoNT-A 500U (n = 56)
TEAEs, n (%)			
Any	22 (36.1)	23 (36.5)	23 (41.1)
Not related	20 (32.8)	21 (33.3)	21 (37.5)
Related	5 (8.2)	3 (4.8)	11 (19.6)
Arthralgia	1 (1.6)	0 (0.0)	0 (0.0)
Burning sensation	1 (1.6)	0 (0.0)	0 (0.0)
Contusion	0 (0.0)	0 (0.0)	1 (1.8)
Ecchymosis	0 (0.0)	1 (1.6)	0 (0.0)
Hypoesthesia	0 (0.0)	0 (0.0)	1 (1.8)
Injection-site discoloration	0 (0.0)	0 (0.0)	2 (3.6)
Injection-site hemorrhage	0 (0.0)	0 (0.0)	1 (1.8)
Injection-site irritation	1 (1.6)	0 (0.0)	2 (3.6)
Injection-site pain	1 (1.6)	1 (1.6)	2 (3.6)
Injection-site rash	1 (1.6)	0 (0.0)	0 (0.0)
Joint stiffness	0 (0.0)	0 (0.0)	2 (3.6)
Metatarsalgia	0 (0.0)	0 (0.0)	1 (1.8)
Muscle spasms	1 (1.6)	0 (0.0)	1 (1.8)
Pain in extremity	2 (3.3)	1 (1.6)	1 (1.8)
Paresthesia	0 (0.0)	0 (0.0)	1 (1.8)
Skin hyperpigmentation	0 (0.0)	0 (0.0)	1 (1.8)
Intensity of TEAEs, n (%)			
Mild	20 (32.8)	20 (31.7)	19 (33.9)
Moderate	2 (3.3)	3 (4.8)	3 (5.4)
Severe	0 (0.0)	0 (0.0)	1 (1.8)
TEAEs leading to discontinuation, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Most common TEAEs (>4%)*, n (%)			
Hyperkeratosis	2 (3.3)	5 (7.9)	1 (1.8)
Injection-site pain	1 (1.6)	2 (3.2)	3 (5.4)
Muscle spasms	3 (4.9)	2 (3.2)	2 (3.6)
Nasopharyngitis	3 (4.9)	2 (3.2)	1 (1.8)
Pain in extremity	3 (4.9)	2 (3.2)	3 (5.4)
SAE	0 (0.0)	0 (0.0)	1 (1.8)
AESI, n (%)			
Hypersensitivity	1 (1.6)	0 (0.0)	0 (0.0)
Remote spread of toxin	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: AboBoNT-A, abobotulinumtoxinA; AESI, adverse event of special interest; n, number of participants; SAE, serious adverse event; TEAE, treatment-emergent adverse event.
Data are for the safety population and are shown for the double-blind phase only.
* Cut-off applies to all treatment groups.

presentation at baseline). Time to retreatment was also longer in the aboBoNT-A 300U or 500U groups compared with placebo, using a priori retreatment criteria based on clinical symptomatology. This suggests that aboBoNT-A may offer an advantage in the need for pain relief treatment. Furthermore, NNT scores (clinical response and MCID) were shown to be similar to those achieved with numerous therapies for chronic pain conditions (50,51), suggesting that the degree of pain reduction observed following treatment in this trial is equivalent to that observed with well-established pain medications. The MCID values were based on those reported previously (as measured by the NPRS in post-bunionectomy pain trials) (32,33,46), suggesting that, for those patients who reached the MCID, this was a clinically relevant finding. These multiple lines of evidence support the conclusion that BoNT-As may be a beneficial intervention for pain relief in HV.

Pain evaluation is subjective and many pain-rating methods are currently in use, including the Visual Analogue Scale (VAS), the Manchester Foot Pain and Disability Index, and the FFI (37,52-54). The NPRS was used in the present study because it is widely applied in both research and therapeutic settings, and is also one of the few validated unidimensional measures of self-reported pain (55), and is recognized by global health authorities as such. Although continuous rating scales are widely used in both research and clinical practice, they may not adequately describe the treatment benefit in individuals and may result in misleading conclusions about a patient's perception of pain relief. For example, studies in fibromyalgia, acute pain and arthritis often result in U-shaped distribution efficacy curves, with participants either achieving excellent pain relief or little to none, thereby describing the actual experience of almost nobody in the trial (50). More recently, alternative, dichotomous methods for evaluating pain have emerged. For example, in various pain disorders, including musculoskeletal disorders, a mean reduction of approximately 10% to 30% on the NPRS is representative of an MCID in pain intensity, thereby underscoring its clinical significance (56,57). This corresponds to approximately 1 to 3 points on the 11-point NPRS and thus served as the basis for the priori MCID in this trial (1.5 points on NPRS), which was homologous to the NPRS MCID observed in several bunionectomy trials (32,33,46), as well as a related foot pain syndrome of plantar fasciitis (25). In the current study, we detected differences between treatment groups using 2 alternative, dichotomous measures based on the NPRS to assess the number of days spent in a "reduced pain state," which supported the results of responder analyses. Dichotomous measures may be more relevant for clinicians and patients in the assessment of pain in HV than weekly mean changes on a continuous scale such as the NPRS.

With the exception of small pharmacodynamic studies, such as those involving BoNT injections to the extensor digitorum brevis muscle (58), there is a paucity of published data on the effects of BoNT-A injections into the foot for the control of foot pain or dysfunction. A significant reduction in foot pain (Pain VAS and Pain Relief VAS) at 3 and 8 weeks post-injection was reported in a small study of 27 participants with plantar fasciitis injected with BoNT-A compared with saline in the contralateral foot (25). In one of the first studies directly evaluating changes in foot function in HV following BoNT-A treatment, Radovic and Shah reported clinically significant reductions in pain as well as reductions in HV angle (27). Moreover, in a small, placebo-controlled study of participants with mild/moderate HV, foot pain (as measured by the FFI) was significantly reduced after a single injection into selected forefoot muscles from 8 weeks that persisted for up to 6 months (28); results of the present study support and extend these findings, showing that long-term pain control may be achievable in HV with repeated BoNT-A injections.

In addition to HV-related pain, patients with HV experience significant impairments in their disability status or in general mobility (8,9). Although the results from the FFI disability scale and FFI activity limitation scale showed nominal improvement over time in these domains following treatment with aboBoNT-A compared with placebo, the changes were not statistically significant and thus suggest that the impact of aboBoNT-A is limited. The present study is the first, to our knowledge, to evaluate disability outcomes in HV using the PGI-S and PGI-I scales. The failure to detect a change in disability status may be due to lack of efficacy for either aboBoNT-A dose or, alternatively, the PGI may be insensitive to subtle changes in HV disability symptoms and thus may not be an ideal tool to evaluate functional changes in this population. The failure of aboBoNT-A to demonstrate benefit in HV-related disability is in line with the only other study to date to evaluate disability in participants with HV following BoNT-A treatment (28), but is in contrast to that reported with BoNT-A treatment in plantar fasciitis, which significantly improved overall foot function compared with placebo (25). Further work is needed to evaluate the impact of BoNT-A treatment on disability associated with HV.

Although pain remains a central consideration for HV diagnosis and treatment, an endpoint of significant clinical interest is the degree to which the lateral angular deviation of the hallux is reduced by treatment. Addressing morphological changes in HV is typically the principal goal of HV surgery, and involves returning the hallux to midline or approximating normal HV and IM angular ranges (0-15 degrees for HV and <12 degrees for IM). This is typically achieved via operative resection and structural stabilization of the hallux. Therefore, it remains important to compare the degree to which any non-operative treatment can achieve

this morphological "gold standard." In the present trial, a small reduction in HV angle (−0.99 degrees) was observed with aboBoNT-A 300U compared with placebo at week 12. Although this was not clinically significant, it may reflect a lack of worsening in the aboBoNT-A 300U group, because participants treated with placebo in the present study showed an increase in HV angle (+0.30 degrees) by the same week 12 time point. This suggests that more time may be required to show an impact of aboBoNT-A treatment on HV and IM angle reduction. In contrast, other studies have shown substantial improvement in angular deviation over time with BoNT-A compared with placebo (26,27).

In terms of safety, the AE profile observed in this trial was largely similar to that reported by participants treated with placebo, and the safety profile was in line with the known profile of aboBoNT-A (29,30). The most frequently reported TEAEs for participants who received aboBoNT-A (300U or 500U) during the double-blind period were hyperkeratosis (5.0%), pain in extremity (4.2%) and injection-site pain (4.2%). The most frequently reported TEAEs in the placebo group were pain in extremity, muscle spasms and nasopharyngitis (4.9% each). There was no pattern indicating a unique safety signal following treatment in this study.

The study is subject to a number of potential limitations, some of which reduce the generalizability of the findings. The study population was limited to nonsurgical participants with mild to moderate angular deformity and without arthritic immobility or hypermobility. In addition, only general forefoot pain was assessed. It therefore remains to be determined whether specific types of HV pain (e.g., medial eminence pain, metatarsalgia, first metatarsophalangeal pain, midfoot pain) are more responsive to aboBoNT-A. However, because the underlying mechanisms of pain in disparate foot regions are mediated by the general nociceptive principles of localized inflammation and subsequent afferent pain signal propagation (59), it is plausible that the efficacy signal observed in this trial could be reproduced in other neuromuscular podiatric pain conditions. Another potential limitation in the generalizability of the findings in the trial is that only one foot per participant was treated, thus pain reporting may have been confounded by undiscernible and multiple pain foci in the contralateral foot in patients with bilateral HV, which represents a sizable portion of the global HV population. It is also noted that participants were not required to wear the same or a certain type of shoe over the study period, thus making the variability in shoe wear among patients during the trial a potential confounding factor, with those opting for looser fitting shoes potentially more likely to report lower pain scores during the trial. Lastly, the superiority of the aboBoNT-A 500U dose group at week 12 compared with placebo on the NPRS corresponded to a 2-point advantage compared with placebo on the 11-point NPRS used as the primary endpoint scale in this trial (approximately 20% change), which, while very similar to the observed perceived pain benefit in bunionectomy trials (32,33,46), may not be clinically relevant to some patients suffering from mild to moderate HV. The study provides valuable insights in an area where large, randomized, controlled trials are lacking and further clinical studies are warranted.

In conclusion, although the primary endpoint (mean change in NPRS from baseline at week 8) was not met, several other lines of evidence from the present trial, including robust efficacy at week 12, higher efficacy signals observed at the aboBoNT-A 500U dose, the proportion of treatment responders and the number of days spent in a "reduced pain state" compared with placebo, suggest that pain associated with HV may be ameliorated by treatment with aboBoNT-A 500U in participants who have not undergone HV surgery. Further clinical evaluation is needed to establish whether BoNT-A represents a viable non-operative treatment option for HV-associated pain.

Authors' Contributions

Substantial contributions to study design and data acquisition: DGA, LAD, BB, MV and RS. Data analysis or interpretation: MV and SGP. Drafting of the publication or revising it critically for important intellectual content: all authors. Final approval of the publication: all authors.

Data Sharing

When participant data can be anonymized, Ipsen will share all individual participant data that underlie the results reported in this article with qualified researchers who provide a valid research question. Study documents, such as the study protocol and clinical study report, are not always available. Proposals should be submitted to DataSharing@Ipsen.com and will be assessed by a scientific review board. Data are available beginning 6 months and ending 5 years after publication; after this time, only raw data may be available.

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Supplementary Materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1053/j.jfas.2022.07.002.

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