AbobotulinumtoxinA in the management of hallux valgus in adult patients: results of a randomized and placebo-controlled phase II trial

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PLAIN LANGUAGE SUMMARY

- Pain associated with bunions was reduced in severity following injections into muscles of the affected foot with abobotulinumtoxinA.

BACKGROUND

- Hallux valgus (HV) is a progressive foot deformity affecting around a quarter of adults.[1]
  - HV is characterized by neuromuscular forefoot pain, changes in appearance of the foot and functional disability.[1,2]
- HV is managed with orthotic interventions or corticosteroid injections, which have limited efficacy, or surgery, where there is a significant chance of recurrence.[3]
- AbobotulinumtoxinA (aboBoNT-A, Dysport®) is a neuromuscular blocking agent that inhibits peripheral and central pain neurotransmitters and local acetylcholine release to reduce pain and muscle tone.[4,5]
- Localized aboBoNT-A injections may act both locally and centrally to mitigate pain induced by the HV condition.

OBJECTIVE

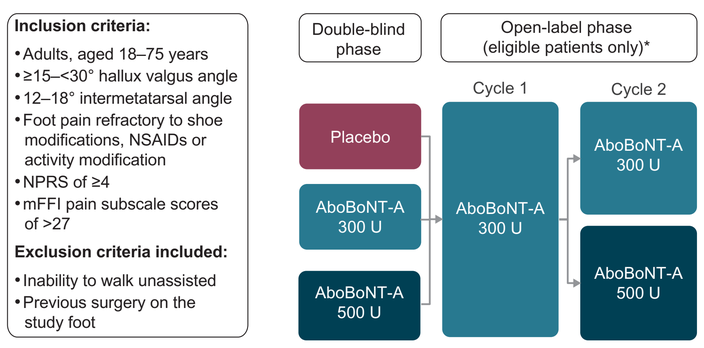
- To assess pain severity in adults with HV following aboBoNT-A treatment compared with placebo.

METHODS

Study design and treatment

- Phase II, placebo-controlled, parallel-group, multicenter study with a double-blind phase (≥12 weeks) and an open-label phase (total duration 36 weeks; NCT03569098; **Figure 1**).
  - Double-blind phase: patients received intramuscular injections of aboBoNT-A 300 U, 500 U or placebo (randomized, 1:1:1).
  - Open-label Cycle 1: aboBoNT-A 300 U (all patients).
  - Open-label Cycle 2: aboBoNT-A 300 U or 500 U, based on investigator judgement (data not shown).
- On Day 1 (baseline), and upon retreatment, the total dose was divided equally, guided by electrical stimulation, into four muscles: flexor and extensor hallucis brevis and the oblique and transverse heads of the adductor hallucis.

Figure 1. Study design



*Eligibility was dependent on requirement for retreatment at Week 12, any patients who were not eligible for retreatment were evaluated every 4 weeks at additional follow-up visits until they were eligible for retreatment, or completed the follow-up period. AboBoNT-A, abobotulinumtoxinA; mIFF, modified foot function index; NPRS, numeric pain rating scale; NSAID, non-steroidal anti-inflammatory drug.

Assessment and endpoints

- Self-reported foot pain was recorded for 7 days before baseline and before visits at 4, 8, 12, 16, 20 and 24 weeks post-injection, using the validated Numeric Pain Rating Scale (NPRS).[6]
- Primary endpoint: change from baseline in mean NPRS score (averaged over 7 days) before Week 8 (double-blind phase).
- Secondary endpoints:
  - Clinical response (proportion of patients achieving ≥20% reduction in baseline NPRS score) before visits at weeks 4, 8 and 12 (double-blind phase).
  - Change from baseline in mean NPRS score at all other time points.
- *Post hoc* analyses:
  - We also defined two new endpoints to assess the proportion of time spent with reduced pain severity at weeks 4, 8 and 12, defined as number of days a patients' NPRS score was:
    - Lower than their lowest NPRS score prior to baseline.
    - ≥2 points lower than mean baseline NPRS score.
- Incidence of adverse events (AEs) was recorded.

Statistical analysis

- A mixed model for repeated measures was used for the primary endpoint, a logistic regression model was used for *post hoc* analyses to compare treatment groups for all randomized patients (intent-to-treat population, ITT).

RESULTS

Baseline characteristics

- Patient demographic and HV characteristics were similar between treatment groups (**Table 1**).

Table 1. Baseline patient characteristics

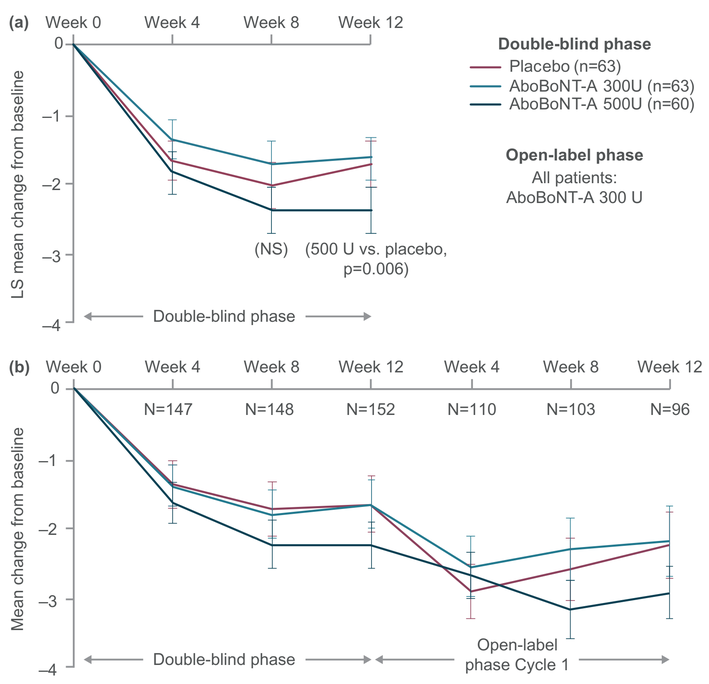
Characteristic	Placebo (n=63)	AboBoNT-A 300 U (n=63)	AboBoNT-A 500 U (n=60)
Age, mean (SD)	48.3 (±13.2)	48.4 (±14.0)	48.0 (±12.2)
Female, n (%)	55 (87.3)	60 (95.2)	56 (93.3)
HV status, n unilateral (%)	22 (34.9)	21 (33.3)	19 (31.7)
Time (years) since diagnosis, mean (SD)	5.0 (±7.1)	6.7 (±10.1)	7.4 (±8.9)
NPRS score, mean (SD)	6.6 (±1.4)	7.2 (±1.6)	6.8 (±1.7)
HV angle, mean (SD)	20.6 (±5.1)	21.3 (±5.6)	20.2 (±4.9)
IM angle, mean (SD)	11.8 (±2.2)	12.2 (±2.3)	11.8 (±2.7)

Data for the ITT population are presented. AboBoNT-A, abobotulinumtoxinA; HV, hallux valgus; IM, intermetatarsal; ITT, intent-to-treat; NPRS, Numeric Pain Rating Scale; SD, standard deviation.

Study endpoints

- At Week 8, no difference in mean change from baseline NPRS score (primary endpoint) was observed with either aboBoNT-A dose compared with placebo (**Figure 2a**).
- Clinical response rate was significantly greater for aboBoNT-A 500 U compared with placebo at Week 12 (53% versus 28%, respectively; p<0.006).
  - No significant differences were observed at weeks 4 and 8 for aboBoNT-A 300 U or 500 U (Week 4: 37% and 35%; Week 8: 44% and 53%, respectively) versus placebo (Week 4: 33%; Week 8: 42%) or at Week 12 for aboBoNT-A 300 U versus placebo (40% versus 28%, respectively).
- Further reductions in NPRS score were observed in open-label Cycle 1 (all received aboBoNT-A 300 U) (**Figure 2b**).
  - Greater benefit was observed for patients who received aboBoNT-A 500 U during the double-blind phase, with continued pain reduction over 12 weeks.

Figure 2. Change from baseline in NPRS score in (a) the double-blind phase (LS mean) (b) both phases (mean)

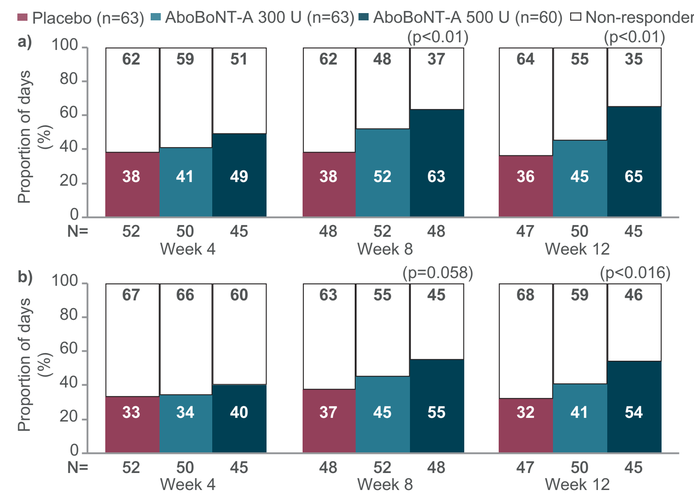


Data for the ITT population are presented. Bars represent standard error. AboBoNT-A, abobotulinumtoxinA; ITT, intent-to-treat; LS, least square; NPRS, numeric pain rating scale; NS, non-significant.

Post hoc analyses

- Patients experienced pain reduction for a significantly greater number of days with aboBoNT-A 500 U compared with placebo:
  - Lower than lowest baseline NPRS score (**Figure 3a**):
    - Pain reduction 63% and 65% of the time at Week 8 and 12, respectively (aboBoNT-A 500 U vs. placebo, p<0.01 at both timepoints).
  - ≥2-point reduction from baseline NPRS score (**Figure 3b**):
    - Pain reduction 55% and 54% of the time at Week 8 and 12, respectively (aboBoNT-A 500 U vs. placebo, p=0.058 and p=0.016, respectively).

Figure 3. Proportion of days with (a) 'lower than lowest' baseline NPRS† and (b) ≥2 point reduction from baseline NPRS‡



†Mean proportion of days with NPRS score lower than the lowest baseline daily NPRS score; ‡Mean proportion of days with an NPRS score ≥2 points lower than mean NPRS at baseline. p values are compared with placebo. AboBoNT-A, abobotulinumtoxinA; N, number of patients; NPRS, numeric pain rating scale.

Safety

- AEs observed in the active treatment groups were similar to the placebo group and no unexpected or new safety signals were reported (**Table 2**).
- No severe treatment-emergent AEs were reported.

Table 2. Common AE

Event	Placebo (n=63)	AboBoNT-A 300 U (n=63)	AboBoNT-A 500 U (n=56)
TEAEs, n (%)*	22 (36.1)	23 (36.5)	23 (41.1)
Injection site pain	1 (1.6)	1 (1.6)	3 (5.4)
Pain in extremity	3 (4.9)	3 (4.8)	3 (5.4)
Hyperkeratosis	2 (3.3)	4 (6.3)	1 (1.8)
Muscle spasms	3 (4.9)	2 (3.2)	2 (3.6)
Nasopharyngitis	3 (4.9)	2 (3.2)	1 (1.8)
TEAEs related to treatment	5 (8.2)	3 (4.8)	11 (19.6)
Severe TEAEs	0	0	0
Serious AEs	0	0	1 (1.8)
AEs of special interest	1 (1.6)	0	0

*Reported by ≥4% of patients. AboBoNT-A, abobotulinumtoxinA; AE, adverse event; ITT, intent-to-treat; TEAE, treatment-emergent adverse event.

CONCLUSIONS

- Although the primary endpoint was not met at Week 8, significant pain reduction and a clinical response were reported for patients with HV at Week 12 following aboBoNT-A 500 U injection. This may suggest that time was required for pain signals to be inhibited.
  - Pain was further reduced with repeat injection.
- *Post hoc* analyses suggest that patients spent a greater proportion of time with reduced pain following aboBoNT-A 500 U injection compared with placebo. This may be a more clinically relevant assessment of benefit than NPRS score averaged over 7 days.
- Safety results were in line with the known profile of aboBoNT-A.
- This study suggests that aboBoNT-A may mitigate pain associated with HV but that further studies are necessary to evaluate these findings.

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