AbobotulinumtoxinA in the management of hallux valgus in adult patients: reduction of pain, and the correlation between baseline pain and hallux valgus angle

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PLAIN LANGUAGE SUMMARY

- Pain caused by bunions was reduced in severity following injection of abobotulinumtoxinA into foot muscles
- Pronounced bunions (greater deformity) do not appear to cause more pain than less pronounced bunions (mild deformity)

BACKGROUND

- Around a quarter of adults are afflicted with hallux valgus (HV)[1]
  - HV is characterized by morphological changes to the foot, pain and functional disability[2]
- Hallux valgus (HV) therapy can involve surgery (usually for HV angles >20°) but recovery can take up to three months and recurrences are common[2–4]
  - Non-surgical interventions (orthoses) have limited efficacy[5]
- AbobotulinumtoxinA (aboBoNT-A, Dysport®) is a neuromuscular blocking agent that inhibits the release of local acetylcholine and peripheral and central pain neurotransmitters to reduce pain and muscle tone[6, 7]

OBJECTIVE

- To assess the effect of aboBoNT-A compared with placebo injections on pain in adults with HV, and the relationship between HV angle and severity of baseline pain

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

Assessments

- Self-reported foot pain recorded for 7 days before visits at baseline and weeks 4, 8, 12, 16, 20 and 24 post-injection, using the validated numeric pain rating scale (NPRS)[8]
- HV angle and intermetatarsal (IM) angle measured with weight-bearing anterior-posterior radiographs
- 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 (all time points)
- *Post hoc* analyses:
  - Two new endpoints to assess proportion of time spent with reduced pain severity at weeks 4, 8 and 12. Defined as the number of days a patient's NPRS score was:
    - Lower than their lowest NPRS score prior to baseline
    - ≥2 points lower than mean baseline NPRS score
  - Correlation between mean baseline NPRS score and baseline HV angle
- Incidence of adverse events (AEs) was recorded

Statistical analysis

- Mixed model for repeated measures for the primary endpoint; ANCOVA model has been used for *post hoc* analyses to compare treatment groups (all randomized patients, intent-to-treat [ITT] population); logistic regression model was used for clinical response endpoint; descriptive statistics were used for open-label data and treatment-emergent AEs; Pearson's correlation coefficient for relationship between baseline HV or IM angle and baseline (ITT population)

RESULTS

Baseline characteristics

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

Efficacy

- No difference in mean change from baseline NPRS score at Week 8 (primary endpoint) between treatment groups
  - Pain was reduced (but not statistically significantly) at Week 12 with aboBoNT-A 500 U compared with placebo (p=0.06; **Figure 2A**)
- Clinical response rate was significantly greater for aboBoNT-A 500 U compared with placebo at Week 12 (53% compared with 28%, respectively; p=0.0062)
  - No significant differences were observed at other time points, or for aboBoNT-A 300 U compared with placebo
- Further reductions in NPRS score were observed in open-label Cycle 1 (all received aboBoNT-A 300 U; **Figure 2B**), with greater benefit observed in patients who received aboBoNT-A 500 U during the double-blind phase

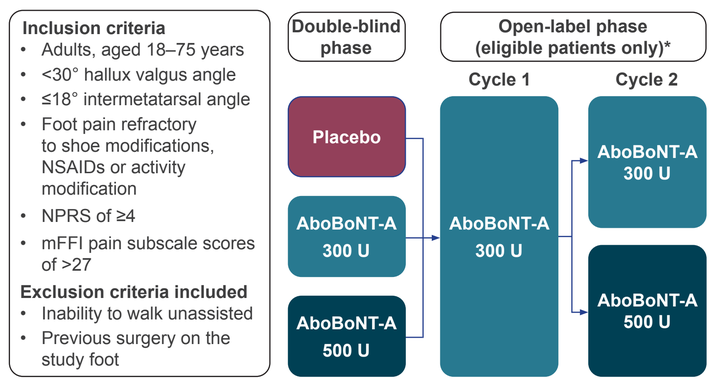
Post hoc analyses

- Pain was reduced for a significantly greater mean proportion of days with aboBoNT-A 500 U compared with placebo:
  - Lower than lowest baseline NPRS score (**Key figure A**): 63% and 65% of days at Week 8 and 12, respectively (both p<0.01)
  - ≥2-point reduction from baseline NPRS score (**Key figure B**): 55% and 54% of days at Week 8 and 12, respectively (p=0.058 and p=0.016, respectively)
- Baseline mean NPRS scores showed a lack of correlation with baseline HV angles (r=0.09; **Figure 3**) and with baseline IM angles (r=0.03)

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

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; HV, hallux valgus; IM, intermetatarsal; mFFI, modified foot function index; NPRS, numeric pain rating scale; NSAID, non-steroidal anti-inflammatory drug.

Table 1. Demographic and baseline 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 (±9.9)	7.5 (±8.8)
NPRS score, mean (SD)	6.6 (±1.4)	7.2 (±1.6)	6.9 (±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)

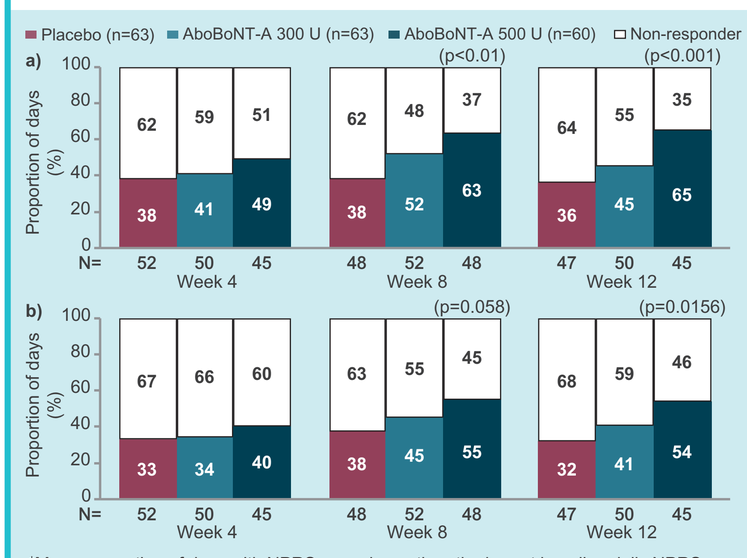
Data for the ITT population are presented. AboBoNT-A, abobotulinumtoxinA; HV, hallux valgus; IM, intermetatarsal; ITT, intent-to-treat; NPRS, numeric pain rating scale; SD, standard deviation.

Table 2. Common adverse events*

Event	Placebo (n=61)	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)	2 (3.2)	3 (5.4)
Pain in extremity	3 (4.9)	2 (3.2)	3 (5.4)
Hyperkeratosis	2 (3.3)	5 (7.9)	1 (1.8)
Muscle spasms	3 (4.9)	2 (3.2)	2 (3.6)
TEAEs related to treatment	5 (8.2)	3 (4.8)	11 (19.6)
Severe TEAEs	0	0	1 (1.8)
Serious AEs	0	0	1 (1.8)
AEs of special interest†	1 (1.6)	0	0

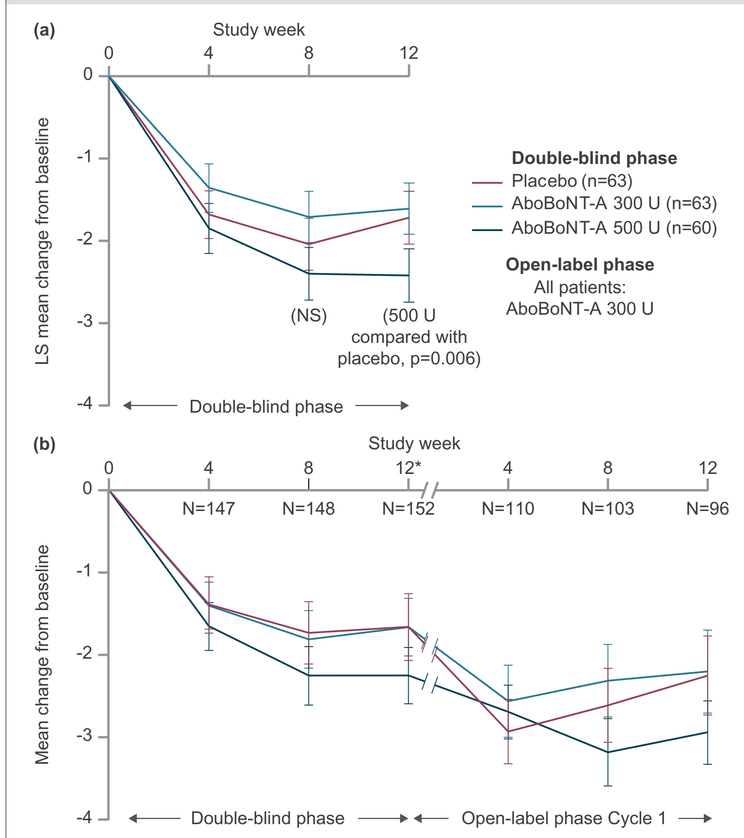
Data are shown for the double-blind phase only. *Reported by ≥4% of patients in the safety population. †AEs of special interest were possible remote spread of the toxin or hypersensitivity. AboBoNT-A, abobotulinumtoxinA; AE, adverse event; TEAE, treatment-emergent adverse event.

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



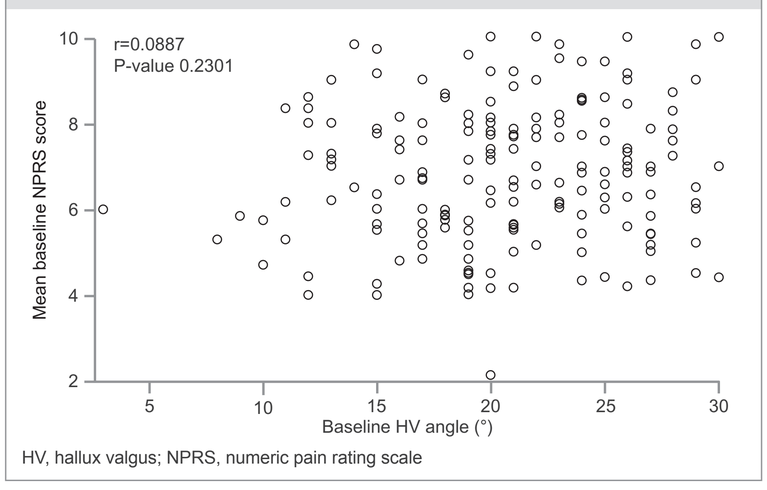
†Mean proportion of days with NPRS score lower than the lowest baseline daily NPRS score; ‡Mean proportion of days with an NPRS score ≥2 points lower than mean NPRS at baseline. P-values are compared with placebo. AboBoNT-A, abobotulinumtoxinA; N, number of patients; NPRS, numeric pain rating scale.

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. *After Week 12, patients could receive the open-label Cycle 1 injection or remain in the double-blind phase until they met the retreatment criteria. AboBoNT-A, abobotulinumtoxinA; ITT, intent-to-treat; LS, least square; NPRS, numeric pain rating scale; NS, non-significant.

Figure 3. Baseline pain and HV angle



HV, hallux valgus; NPRS, numeric pain rating scale

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 with aboBoNT-A 500 U
  - This suggests that the time course of efficacy is later than 8 weeks post-injection
  - Pain was further reduced with repeat injection
- *Post hoc* analyses suggest patients spent more time with reduced pain levels 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
- A lack of correlation with baseline pain suggests HV angle may not be of primary importance in clinical decision making
- Safety results were in line with the known profile of aboBoNT-A

References

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