# Rationale and design for a Phase 2 trial of abobotulinumtoxinA (Dysport) in the management of Hallux valgus

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## INTRODUCTION

- Hallux valgus (bunion) is a progressive foot deformity, affecting up to 35% of adults and characterised by pain, morphological changes in foot appearance, and functional disability.[1]
- While hallux valgus is typically managed initially by orthotic applications such as splints, inserts or braces used to correct foot biomechanics, the efficacy of these interventions is widely considered to be largely ineffective with substantial evidence suggesting that these devices are no more effective than no treatment at all.[2] Surgery is common, but is associated with a prolonged recovery, post-surgical pain and a significant chance of recurrence.[3]
- Evidence suggests that the underlying cause of hallux valgus is related to a progressive imbalance among specific foot muscles, resulting in lateral deviation of the hallux and osseous changes with subsequent development of a pressure-sensitive prominence on the medial side of the first metatarsal which limits mobility.[4, 5]
- Based on this aetiology, localised injections of abobotulinumtoxinA (AboBoNT-A), have the potential to correct the underlying muscle imbalance, thereby reducing foot pain and improving functional mobility.[6, 7]

## PRIMARY OBJECTIVE

- This ongoing Phase 2 study aims to assess reduction in pain in adult subjects with hallux valgus following treatment with AboBoNT-A vs. placebo.

## METHODS

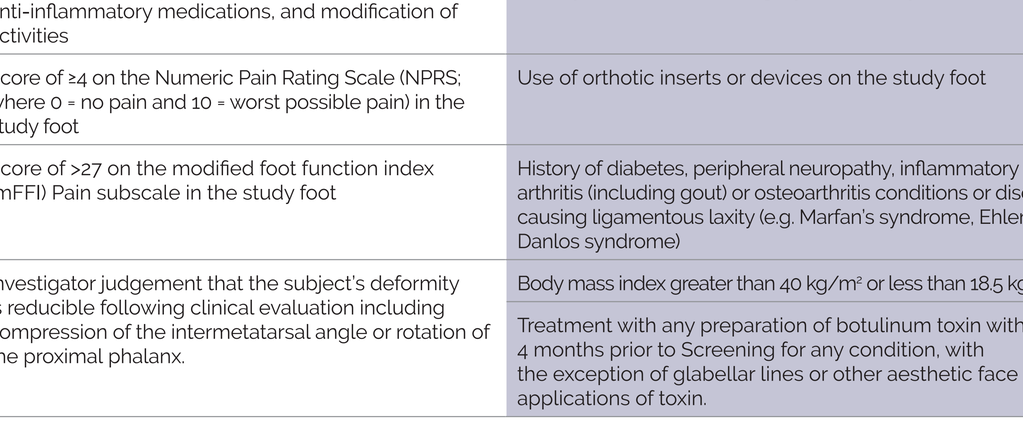
### Table 1; Subjects

| Key inclusion criteria | Key exclusion criteria |
|---|---|
| Male or female, aged 18 to 75 years | Hallux valgus angle of <15˚ or ≥30˚ in the study foot |
| Clinical diagnosis of hallux valgus as determined by the investigator based on evidence of lateral deviation of either great toe (left or right) | Inability to walk unassisted |
| Hallux valgus angle between ≥15˚ and <30˚ in the study foot great toe | Presence of flat or square metatarsal head, metatarsus primus elevates and/or severe cavus/planus in the study foot |
| Intermetatarsal angle of 12˚ to 18˚, inclusive in the study foot great toe | Any other podiatric or orthopedic condition which may interfere with the accurate evaluation of pain and/or function |
| Foot pain refractory to shoe modifications, nonsteroidal anti-inflammatory medications, and modification of activities | History of ankle or foot surgery in the study foot |
| Score of ≥4 on the Numeric Pain Rating Scale (NPRS; where 0 = no pain and 10 = worst possible pain) in the study foot | Use of orthotic inserts or devices on the study foot |
| Score of >27 on the modified foot function index (mFFI) Pain subscale in the study foot | History of diabetes, peripheral neuropathy, inflammatory arthritis (including gout) or osteoarthritis conditions or disease causing ligamentous laxity (e.g. Marfan's syndrome, Ehlers-Danlos syndrome) |
| Investigator judgement that the subject's deformity is reducible following clinical evaluation including compression of the intermetatarsal angle or rotation of the proximal phalanx. | Body mass index greater than 40 kg/m² or less than 18.5 kg/m² |
| | Treatment with any preparation of botulinum toxin within 4 months prior to Screening for any condition, with the exception of glabellar lines or other aesthetic face applications of toxin. |

### Study design

- This is a randomised, placebo-controlled, parallel-group, multicentre study conducted in two periods: a double-blind period lasting for at least 12 weeks, followed by an open-label period which will last up to 24 weeks (**Figure 1**).
- Eligible subjects will be randomised (1:1:1) to treatment with AboBoNT-A (2 dose groups), or placebo.
- Following completion of double-blind Cycle 1, subjects who meet retreatment criteria will be eligible for open-label treatment. Subjects who do not meet retreatment criteria at 12 weeks post-injection will be re-evaluated at the next scheduled visit (every 28 days) to determine eligibility to commence open-label treatment.

**Figure 1. Study design**

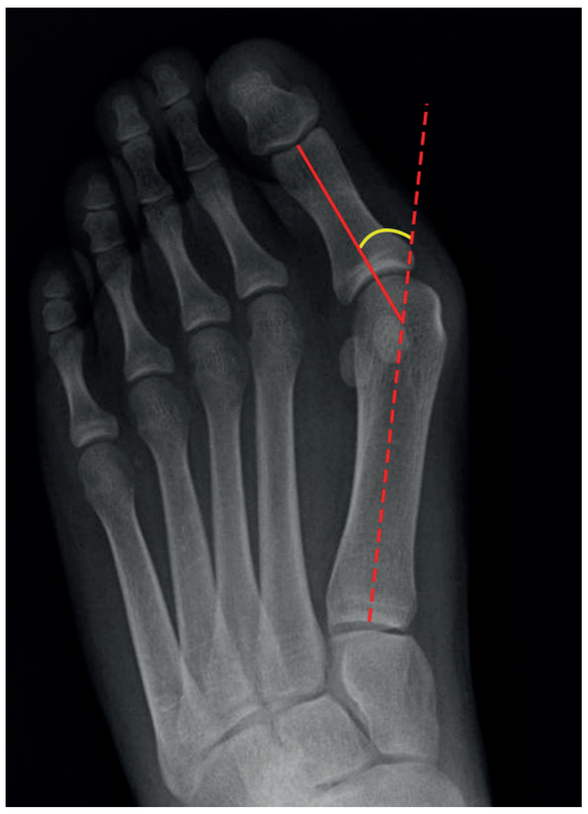



*Retreatment eligibility depends on (1) subject willingness to continue AboBoNT-A, (2) clinician judgement that reinjection is in the best interest of the subject (3) foot pain on NPRS≥3 in the 24 hours prior to assessment (4) no unacceptable risk that requires postponement of the injection (5) minimum of 12 weeks since the last AboBoNT-A injection. No subject will receive treatment after the Week 24 study visit.*

### Study treatment and assessments

- Subjects will receive four intramuscular injections (divided equally) in the study foot under electrical stimulation guidance on Day 1 of double-blind Cycle 1.
- Evaluations of efficacy will be based solely on the foot selected for treatment meeting the study entry criteria. For subjects with bilateral hallux valgus, the most affected foot will be selected for double-blind treatment.
- Safety is assessed through adverse event reporting, and clinical evaluations (including physical examination of the study foot).

### Metatarsophalangeal angle



### Table 2: Assessments

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|---|
| **Primary efficacy endpoint** |
| Change from baseline in self-reported foot pain experienced by the subject as measured by daily Numeric Pain Rating Scale (NPRS) averaged over 7 days prior to Week 8. |
| **Secondary efficacy endpoints (Change from baseline)** |
| Daily mFFI disability, pain, activity limitation and total scores |
| SF-36 score |
| Hallux valgus angle as measured directly by weight-bearing anterior-posterior radiographs |
| Intermetatarsal angle as measured directly by weight-bearing anterior-posterior radiographs |
| Time to retreatment |
| Patient Global Impressions (Improvement and Severity) of:<br>- Foot pain<br>- Disability |
| **Exploratory efficacy endpoint** |
| Use of protocol-approved pain medications during the study |

## RESULTS

- Study (NCT03569098) is currently recruiting. A total of 165 subjects are planned to be enrolled in the study. Subjects enrolled during the double-blind period will roll over into the open-label period.

## CONCLUSIONS

- Treatment with AboBoNT-A is a new potential intervention for patients suffering from hallux valgus who have very limited pharmacological treatment options for this painful condition.

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### Author Contributions

Substantial contributions to study conception/design: DGA, LD, BB, RS, PP. Drafting of the publication, or revising it critically for important intellectual content: DGA, LD, BB, RS, PP. Final approval of the publication: DGA, LD, BB, RS, PP.

### Disclosures

Dr Armstrong and Dr Baravarian are investigators for the current study and report consultancy (advisory board) for Ipsen. Dr DiDomenico is an investigator for the current study. Dr Silva & Dr Picaut are Ipsen employees.

### Medical Writing Support

The authors thank Anita Chadha-Patel PhD of ACP Clinical Communications Ltd (Hertfordshire, UK) for providing medical writing support, which was funded by Ipsen (Abingdon, UK) in accordance with Good Publication Practice guidelines.



Presented at TOXINS 2019: Basic Science and Clinical Aspects of Botulinum and Other Neurotoxins, 16-19 January, 2019, Copenhagen, Denmark.

This study was sponsored by Ipsen