PROTOCOL TITLE: A MULTIPLE-DOSE, DOUBLE-BLIND, RANDOMISED, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF DYSPORT FOR THE TREATMENT OF PAIN ASSOCIATED WITH HALLUX ABDUCTO VALGUS

STUDY PROTOCOL

STUDY NUMBER: D-FR-52120-237

DYSPORT

FINAL Version 6.0: 03 July 2019 (Amendment 5)

Study Sponsor:
Ipsen Innovation
Z.I. de Courtaboeuf
5 Avenue du Canada
91940 Les Ulis, Cedex France
Tel: +33 (0)1 60 92 20 00
PPD

Sponsor Signatory:
PPD
Ipsen Bioscience Inc
650 East Kendall Street
Cambridge, Massachusetts 02142, USA
PPD

Pharmacovigilance/Emergency Contact:
PPD
Ipsen Innovation
Z.I. de Courtaboeuf
5 Avenue du Canada
91940 Les Ulis, Cedex France
PPD

For serious adverse events (SAEs) reporting:
PPD
In USA and Latin America
PPD

INVESTIGATOR'S AGREEMENT

Investigator Agreement and Signature:

I have read and agree to Protocol D-FR-52120-237 entitled "A Multiple-dose, Double-blind, Randomised, Placebo-controlled Study to Evaluate the Efficacy and Safety of Dysport for the Treatment of Pain Associated with Hallux Abducto Valgus". I am aware of my responsibilities as an investigator under the guidelines of Good Clinical Practice (GCP), local regulations (as applicable) and the study protocol. I agree to conduct the study according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in the study.

NAME:
TITLE: SIGNATURE:

DATE:
OFFICE:

Sponsor's Representative Signature:

NAME: PPD

TITLE: PPD SIGNATURE: PPD

DATE: July 9th, 2019
OFFICE: Ipsen Bioscience, Inc
650 East Kendall Street
Cambridge, Massachusetts 02142
United States of America

Summary of Changes

The current version of the protocol was released on 7 September 2018 and includes Amendment 3. For all protocol amendments, amendment forms were prepared and are provided in Appendix 2: Summary of Changes (see Table 1).

Table 1 List of Protocol Amendments

Amendment	Release date	Amendment form
1	22 May 2018	Appendix 2
2	25 May 2018	Appendix 2
3	7 September 2018	Appendix 2
4	15 February 2019	Appendix 2
5	03 July 2019	Appendix 2

SYNOPSIS

Name of sponsor/company: Ipsen Innovation
Name of finished product: Dysport **Name of active ingredient(s)**: Clostridium botulinum type A toxin-haemagglutinin complex (BTX-A-HAC)
Title of study: A Multiple-dose, Double-blind, Randomised, Placebo-controlled Study to Evaluate the Efficacy and Safety of Dysport for the Treatment of Pain Associated with Hallux Abducto Valgus **Study number**: D-FR-52120-237
Number of planned centres: Approximately 30 centres
Study type: Multiple-dose, randomised, parallel-group, double-blind, placebo-controlled study, followed by an open-label period.
Objectives: Primary Study Objective: To assess reduction in pain in adult subjects with hallux abducto valgus (HAV) with Dysport (300 U and 500 U) as compared with placebo using a Numeric Pain Rating Scale (NPRS). Secondary Study Objectives: • To assess functional improvement in Dysport (300 U and 500 U) as compared with placebo using the modified Foot Function Index (mFFI) disability subscale. • To assess reduction in foot pain in Dysport (300 U and 500 U) as compared with placebo using the mFFI pain subscale. • To assess improvement in activity limitation associated with foot pain in Dysport (300 U and 500 U) as compared with placebo using the mFFI activity limitation subscale. • To evaluate the quality of life using the 36-item Short Form (SF-36). • To evaluate angular displacement of the hallux using radiographs. • To evaluate the patient's global impression of improvement and severity associated with foot pain and disability. • To evaluate the clinical safety and efficacy of Dysport following repeated treatment cycles. Exploratory Study Objectives: • CCI [redacted]
Methodology: This is a randomised, placebo-controlled, parallel-group, multicentre study conducted in two periods: a double-blind (DB) period lasting for at least 12 weeks, followed by an open-label (OL) period which will last up to 24 weeks. Adult subjects with HAV will be randomly assigned to 1 of 3 DB treatment groups: Dysport 300 U, Dysport 500 U, or placebo in a 1:1:1 ratio. Subjects will receive four intramuscular injections of blinded study treatment in the HAV affected foot (i.e. study foot) on Day 1 of the study during the DB period (i.e. Cycle 1). The muscles to be injected are: 1) the oblique head of the adductor hallucis muscle; 2) the transverse head of the adductor hallucis muscle; 3) flexor hallucis brevis muscle; and 4) the extensor hallucis brevis muscle. The evaluation of efficacy (DB) and effectiveness (OL) will be based solely on the foot selected for treatment at Screening

(i.e. study foot) meeting the study entry criteria. For each subject, the study foot (i.e. the foot that will be treated with study treatment during the study) will be evaluated for all efficacy analyses, regardless of the presence of HAV in the contralateral foot. For subjects presenting with bilateral HAV at Screening, the investigator will determine which foot is of greater severity based on his/her clinical judgment following clinical evaluation of the degree of pain (including assessment of NPRS score for each foot during Screening), degree of disability and clinical evaluation of the degree of angular deviation of the hallux, as well as meeting all other study entry criteria. In these subjects, the foot with the greatest severity of HAV, based on clinical evaluation by the investigator (and meeting all other study entry criteria), will be selected for treatment with DB study treatment in this study.

Following completion of the DB period (i.e. completion of Cycle 1), subjects who meet retreatment criteria will be eligible to participate in the OL period. All retreatment-eligible subjects will receive OL treatment with Dysport 300 U at the first retreatment cycle (Cycle 2) in the HAV study foot selected during the DB period. At the second retreatment cycle (Cycle 3), subjects will be treated with either Dysport 300 U or 500 U in the HAV study foot based on investigator judgment and following clinical evaluation at the time of retreatment. The decision to increase the dose at the beginning of Cycle 3 will be based on 1) evaluation of safety and tolerability (review related AEs and consideration of any significant changes in the study foot) and 2) severity of pain (considering NPRS score) and disability (considering mFFI Disability subscale score) experienced by the subject at the time of evaluation. The muscles to be injected and procedures for injection are identical to those targeted in the DB period.

As in the DB period, each treatment cycle in the OL period (Cycles 2 and 3) will be separated by at least 12 weeks. After Cycle 1 of the DB period, subjects who do not meet the retreatment criteria will be evaluated by the investigator at the next scheduled study visit (every 28 days) to determine eligibility to receive retreatment with Dysport in the OL period. Subjects who do not meet the retreatment criteria by Week 24 will not be eligible for retreatment in the OL period. As such, the maximum duration of participation in the study for a given subject will be 36 weeks.

Subjects will be considered to have completed the study after they complete all of the assessments required for the Week 36 visit. The study will be considered complete after the last subject has completed their last follow-up visit.

Number of subjects planned:

A total of 165 subjects are planned to be enrolled in the study. Subjects enrolled during the DB period will roll over into the OL period.

Diagnosis and criteria for inclusion:

Inclusion criteria:

Subjects must meet all inclusion criteria at Screening and Baseline and none of the exclusion criteria to be considered for enrolment in the study.

(1) Subjects must provide written informed consent prior to any study related procedure

(2) Male or female, aged 18 years or older

(3) Clinical diagnosis of HAV as determined by the investigator based on evidence of lateral deviation of either great toe (left or right), as well as assessment of NPRS scores for each foot (in bilateral subjects).

(4) Subjects must present with a score of ≥4 on the NPRS in the study foot at Baseline

(5) Subjects must present with a score of >27 on the mFFI Pain subscale in the study foot at Baseline

(6) Subjects must present with a score of >27 on the mFFI Disability subscale in the study foot at Baseline

(7) Subjects must present with hallux valgus (HV) angle ≤30° in the study foot great toe using radiographic measurements based on guidelines set forth by the AOFAS ad hoc Committee on Angular Measurements at Screening only

(8) Subjects must present with an intermetatarsal angle of ≤18°, inclusive in the study foot great toe using radiographic measurements based on guidelines set forth by the American Orthopedic Foot and Ankle Society ad hoc Committee on Angular Measurements at Screening only

(9) Subject's foot pain associated with HAV condition is refractory to shoe modifications, nonsteroidal anti-inflammatory medications, and modification of activities

(10) In the opinion of the investigator the subject's deformity is reducible following clinical evaluation including compression of the intermetatarsal angle or rotation of the proximal phalanx.

(11) Female subjects of childbearing potential must have a negative pregnancy test result at Screening and be willing to use reliable contraceptive measures throughout study participation.

Reliable forms of contraception include but are not limited to:

- hormonal contraceptives (e.g. oral, patch, injection)
- double barrier (e.g. male condom plus spermicide, or female diaphragm plus spermicide)
- intrauterine device
- male partner has had a vasectomy
- total abstinence from intercourse with male partners (periodic abstinence is not acceptable).

Female subjects meeting any of the following criteria are <u>not</u> considered to be of childbearing potential:

- postmenopausal (≥ 47 years of age and amenorrhoeic for at least 12 consecutive months)
- have been sterilised surgically (e.g. bilateral tubal ligation)
- have had a hysterectomy
- have had a bilateral oophorectomy.

(12) Ability to complete all study requirements in the opinion of the investigator

(13) Subject can read well enough to understand the informed consent form and other subject materials.

Exclusion criteria:

(1) Subject has an HV angle of >30° in the study foot

(2) Evidence of cognitive impairment

(3) Inability to walk unassisted

(4) Subject presents with a flat or square metatarsal head in the study foot

(5) Subject presents with metatarsus primus elevatus in the study foot

(6) Subject presents with severe cavus/planus in the study foot

(7) Subject suffers from any other podiatric or orthopaedic condition which, in the opinion of the investigator would interfere with the accurate evaluation of pain and/or function

(8) Subject presents with medical history or clinical evidence of peripheral vascular disease

(9) Subject has a body mass index greater than 40 kg/m^2 or less than 18.5 kg/m^2

(10) Any medical history of a diabetic condition

(11) Subject has glycated haemoglobin level of ≥6.5% at Screening

(12) Any history of ankle or foot surgery in the study foot

(13) Subject is using an orthotic device (including over-the-counter toe-spacers) which could influence the functioning of the hallux of the study foot in any way, or any other device intended for this purpose. Over-the-counter shoe inserts for the study foot are permitted if used for at least 30 days prior to screening.

(14) Subject has medical history or clinical evidence of peripheral neuropathy or fibromyalgia

(15) Subject has metatarsus adductus

(16) Subject has a history of conditions or disease causing ligamentous laxity (e.g. Marfan's syndrome, Ehlers-Danlos syndrome)

(17) Subject has a history of allergic reaction or has a known or suspected sensitivity to any substance that is contained in the study treatment formulation (including cow's milk protein)

(18) Any medical condition or disease that might interfere with neuromuscular function, e.g. diagnosed myasthenia gravis, Lambert-Eaton syndrome or amyotrophic lateral sclerosis.

(19) Subject demonstrates evidence of inflammatory arthritis (including gout) in the study foot or osteoarthritis based in the study foot on either history or clinical evaluation

(20) Subject demonstrates evidence of degenerative arthritis of the first metatarsophalangeal joint based on either history or clinical evaluation

(21) Subject has an acute or chronic medical condition (other than HAV) that in the opinion of the investigator could confound clinical assessments or interfere with the ability of the subject to participate in the study.

(22) Subject has a clinically significant abnormality on screening evaluation including physical examination, vital signs, or laboratory tests that the investigator considers to be inappropriate to allow participation in the study.

(23) Subject is currently participating or has participated in a clinical study within the last 90 days or has participated in more than two clinical studies within the past year. This includes studies using marketed compounds or devices.

(24) Subject is an investigational study site staff member or the relative of an investigational study site staff member.

(25) 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. Subjects who have previously received an injection with botulinum toxin in the foot are not eligible to participate in the study.

(26) Any concomitant therapy usage that, in the investigator's opinion, would interfere with the evaluation of safety or efficacy of the investigational medicinal product, and/or confound the study results.

(27) Subject has planned or ongoing use of opioids; use of antipsychotics or antidepressants dose that is not stable for at least 30 days prior to Screening; use of anticholinergic treatments that are not stable for at least 6 weeks prior to randomisation; or requires continuous treatment with any medication restricted by this protocol.

(28) Evidence of clinically significant chronic drug or alcohol abuse within the last year.

(29) Use of medications that affect neuromuscular transmission, such as curare-like depolarising agents, lincosamides, polymyxins, anticholinesterases and aminoglycoside antibiotics within the last 3 months before Screening.

(30) Subject is medically unable to discontinue treatment with medications with anticoagulant/antiplatelet effects (e.g. warfarin and other coumadin derivatives, acetylsalicylic acid and clopidogrel/ticlopidine) for at least 3 days before randomisation/injection of study treatment. Subjects are permitted restart anticoagulant/antiplatelet medications one day after injection of study treatment (or longer at the discretion of the investigator).

(31) Any condition or situation which, in the investigator's opinion, puts the subject at significant risk, may confound the study results, or may interfere with the subject's participation in the study.

Test product, dose, mode of administration:

A blinded kit will be used in this study to maintain the blinding of the study during the DB period. Each blinded kit will contain two vials regardless of treatment assignment. The two vials in each kit will contain either a Dysport 300 U vial + a placebo vial, a Dysport 500 U vial + a placebo vial or two placebo vials, based on treatment assignment. Investigators will be blinded to which vial contains Dysport and which vial contains placebo.

The blinded active study treatment, Dysport, will be provided as a white, lyophilised powder in vials containing 300 U or 500 U of BTX-A-haemagglutinin complex (abobotulinumtoxinA). Before each administration, the powder in each vial in the blinded kit will be reconstituted at the investigational site with 1.0 mL of 0.9% sterile (preservative free) sodium chloride for injection. The contents of each vial will be combined for a total volume of 2.0 mL (150 U/mL for Dysport 300 U and 250 U/mL for Dysport 500 U). Investigators will inject 0.5 mL of the reconstituted solution containing study treatment into each of four specified muscles of the foot (2.0 mL total volume) under guidance with a peripheral electrical stimulator. Subjects assigned to receive 300 U of Dysport will be treated with 75 U of Dysport per muscle (300 U dose divided equally among each of four specified muscles of the foot). Subjects assigned to receive 500 U of Dysport will be treated with 125 U of Dysport per muscle (500 U dose divided equally among each of four specified muscles of the foot).

To administer the study treatment, a peripheral electrical stimulator (with or without complementary techniques for identifying target muscles) will be used to locate the muscles in the foot.

Duration of treatment: DB and OL periods: 36 weeks

Reference therapy, dose and mode of administration:

A blinded kit will be used in this study to maintain the blinding of the study during the DB period as described above. The placebo study treatment (administered only during the DB period) will be provided as a white, lyophilised powder and will be indistinguishable from the active product. Placebo will contain only the excipients of Dysport. There will be two matching placebo vials: one matching the 500 U Dysport vial and one matching the 300 U Dysport vial. A blinded kit will be used in this study to maintain the blinding of the study.

The procedures for reconstitution of blinded placebo study treatment will be identical to that described above for the active study treatment. Before each administration, the powder from the vials will be reconstituted at the investigational site with 0.9% sterile (preservative free) sodium chloride for injection, to a total volume of 2.0 mL. The total treatment volume will be divided equally across the four specified muscles of the foot (i.e. 0.5 mL per injection site).

To administer the study treatment, a peripheral electrical stimulator (with or without complementary techniques for identifying target muscles) will be used to locate the muscles in the foot.

Criteria for evaluation (endpoints):

Efficacy:

Primary Endpoint: the change from baseline in foot pain as measured by the daily NPRS score averaged over the 7 consecutive days prior to the Week 8 DB visit.

Secondary Endpoints:

- The change from baseline as measured by the daily NPRS score averaged over the 7 consecutive days prior to Week 4 and Week 12 DB visits and at each scheduled visit in the OL period.
- The change from baseline in the daily mFFI Disability subscale score averaged over the 7 consecutive days prior to Week 4, Week 8 and Week 12 DB visits and at each scheduled visit in the OL period.
- The change from baseline in the daily mFFI Pain subscale score averaged over the 7 consecutive days prior to Week 4, Week 8 and Week 12 DB visits and at each scheduled visit in the OL period.
- The change from baseline in the daily mFFI total score averaged over the 7 consecutive days prior to Week 4, Week 8 and Week 12 DB visits and at each scheduled visit in the OL period.
- The change from baseline in the daily mFFI activity limitation subscale score averaged over the 7 consecutive days prior to Week 4, Week 8 and Week 12 DB visits, and at each scheduled visit in the OL period.
- The change from baseline in quality of life as measured by the SF-36 at Week 8 and Week 12 DB visit and at each scheduled visit in the OL period.
- The change from baseline in HV angle as measured directly by weight-bearing anterior-posterior radiographs at Week 4 and Week 12 DB visits and at each scheduled visit in the OL period.
- The change from baseline in intermetatarsal angle as measured directly by weight-bearing anterior-posterior radiographs at Week 4, Week 8 and Week 12 DB visits and at each scheduled visit in the OL period.
- Time to retreatment
- Patient Global Impression of Improvement of foot pain score at the Week 4, Week 8 and Week 12 DB visits and at each scheduled visit in the OL period.

- Patient Global Impression of Improvement in disability score at the Week 4, Week 8 and Week 12 DB visits and at each scheduled visit in the OL period.
- The change from baseline in the Patient Global Impression of Severity of foot pain score to Week 4, Week 8 and Week 12 DB visits and each scheduled visit in the OL period.
- The change from baseline in the Patient Global Impression of Severity disability score to Week 4, Week 8 and Week 12 DB visits and at each scheduled visit in the OL period.

Exploratory Endpoint:

- CCI [redacted]

Safety:

- The incidence of AEs, serious AEs (SAEs), AEs leading to discontinuations and AEs of special interest (AESI)
- Evaluation of concomitant medications and therapies.
- Clinical evaluations (vital signs, physical examinations (including physical examination of the foot), presence of binding and neutralising antibodies).

Statistical Methods:

Statistical Analyses

The primary efficacy endpoint is the change from baseline in foot pain as measured by the daily NPRS score averaged over the 7 consecutive days prior to the Week 8 DB visit. The baseline is defined as the daily NPRS score averaged over the 7 consecutive days prior to the baseline visit (Day 1).

The estimate of the treatment effect will be the difference in mean change from baseline in the daily NPRS score averaged over the 7 consecutive days prior to the Week 8 DB visit between each Dysport dose group and the placebo group. The primary estimand will be "treatment policy" based. A mixed model for repeated measures will be used to evaluate the estimand and compare treatment groups.

Sample Size Calculation:

A sample size of 165 randomised subjects is required to demonstrate the superiority of each of the Dysport doses (300 U and 500 U) over placebo. This calculation is based on the following assumptions: a difference of 1.5 points observed in the mean change from baseline in foot pain as measured by the daily NPRS score averaged over the 7 consecutive days prior to the Week 8 DB visit between Dysport and Placebo, a treatment group ratio of 1:1:1, a common standard deviation of 2.5, a power of 80% and a two-sided type I error rate of 2.5% (corresponding to multiplicity adjustment that controls the experiment wise rate at two-sided 5%).

An interim analysis will be conducted after the first 110 randomised subjects have been followed up for at least 12 weeks. The aim of this interim analysis is to both assess futility and the potential for early stopping due to efficacy for each Dysport group as compared to the Placebo group. A decision to continue with an arm will be determined by an independent Data Monitoring Committee (DMC) based on the outcome of the interim analysis. No interruption to recruitment will occur whilst the decision-making process is ongoing.

A primary analysis will be conducted once all subjects have completed the Week 12 of the DB period. At this point, all subjects will have completed the Week 8 visit and had adequate safety follow-up.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ABBREVIATION	Wording Definition
AE	Adverse event
AESI	Adverse Event of Special Interest
AOFAS	American Orthopedic Foot and Ankle Scale
BTX	Botulinum Toxin
BTX-A	Botulinum Toxin Type A
BTX-A-HAC	Botulinum Toxin Type A Hemagglutinin Complex
CA	Competent Authorities
CMC	Chemistry Manufacturing Control
CFR	Code of Federal Regulations (United States of America)
CRO	Contract research organisation
CSR	Clinical Study Report
DB	Double-blind
DMC	Data Monitoring Committee
EC	Ethics Committee
eCRF	Electronic case report form
FDA	Food and Drug Administration
FFI	Foot Function Index
GCP	Good Clinical Practice
HAV	Hallux Abducto Valgus
HV	Hallux Valgus (angle)
ICH	International Conference on Harmonisation
IEC	Independent ethics committee
IMP	Investigational Medicinal Product
IRB	Institutional review board
IRT	Interactive response technology
ITT	Intention-to-treat
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model for Repeated Measures
mFFI	Modified Foot Function Index
NPRS	Numeric Pain Rating Scale
OL	Open-label

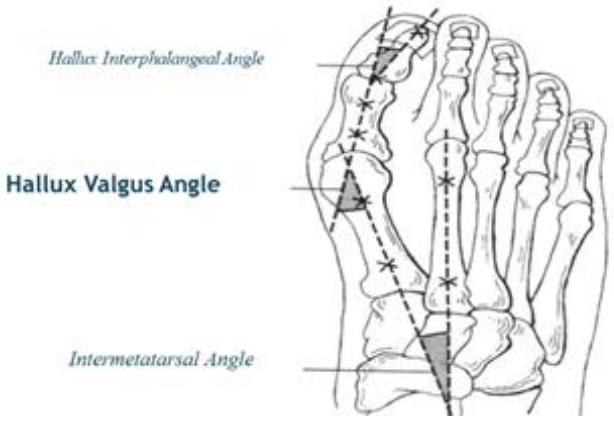
ABBREVIATION	Wording Definition
PP	Per protocol
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS®	Statistical Analysis System®
SD	Standard deviation
SF-36	36-item Short Form
SOP	Standard Operating Procedure
SUSARs	Suspected Unexpected Serious Adverse Reactions
TEAE	Treatment emergent adverse event
US(A)	United States (of America)
WHO	World Health Organisation

1 BACKGROUND INFORMATION

1.1 Introduction

Hallux abducto valgus (HAV or bunion) is a highly prevalent and chronic foot deformity characterized by lateral deviation of the great toe (hallux) causing debilitating foot pain, morphological changes in the appearance of the foot, functional impairments in gait and balance, as well as significantly impaired quality of life. Although HAV affects approximately 23% of adults worldwide [1], very few effective treatments exist to treat this condition. The morphological changes observed in HAV patients present clinically as lateral deviations of hallux which can be measured directly using the hallux valgus (HV) angle and intermetatarsal angle (Figure 1).

Figure 1 Hallux Abductus Angle



Adapted from: Coughlin and Jones [2]

Clinical evaluation of HAV includes establishment of the functional status of the patient including pain and the degree of disability [3] in addition to the morphological changes observed in the foot. While HAV 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 [4]. The standard of care for HAV patients is limited to surgical intervention in which the deformed bone and/or soft tissue is removed to ameliorate the deformity. However, recovery time and required physical therapy following surgery are significant and the procedure is associated with post-surgical pain of significant duration [5]. Moreover, a proportion of patients fail to derive long-term benefit with surgical interventions and experience recurrence of HAV [6].

Development of HAV is associated with extrinsic factors (high heeled or constricting shoes, excessive weight bearing) as well as intrinsic factors, including genetics, age, and a number of morphological and muscular podiatric abnormalities (e.g. pes planus) [6]. There is strong evidence to suggest that the structural abnormalities and subsequent mechanical dysfunction that result in the development of HAV are related to progressive changes in the muscles of the affected foot. For example, muscle imbalance of the abductor and adductor hallucis muscles have been shown to be apparent in HAV patients, with the abductor hallucis muscle showing decreased activity compared with the adductor hallucis muscle in these patients [7]. This imbalance allows the adductor hallucis muscle to gain mechanical advantage thereby pulling the hallux laterally forcing the first metatarsal head to drift medially off of the sesamoid apparatus, causing the proximal phalanx to move into a valgus position as it is tethered at its

base to the sesamoids, the deep transverse ligament (via the plantar plate), and the adductor hallucis tendon [6; 8]. The extensor and flexor hallucis longus tendons appear to bowstring laterally [9], increasing the valgus displacement and occasionally acting as dorsiflexors of the proximal phalanx. As the metatarsal head sits on the medial sesamoid as a result of lateral displacement of the hallux, erosion of the cartilage and the crista have been observed. Functionally, these structural changes cause the bursa overlying the medial eminence to thicken because of the pressure effect of footwear on a prominent medial eminence, leading to significant and chronic pain and severe mobility limitations.

Given the considerable involvement of these specific musculoskeletal abnormalities of the foot in the development and progression of HAV, it is reasonable to consider the utility of targeted local injections of botulinumtoxinA for the treatment of HAV, given the demonstrated ability of these toxins to reduce localized hypertonia in injected muscles. Intramuscular botulinumtoxinA injections reduce muscle hypertonicity by blocking the release of presynaptic acetylcholine at the neuromuscular junction. BotulinumtoxinA injections have been proven useful in treating muscle imbalance, muscle spasms and in providing significant pain reduction in patients with foot disorders such as plantar fasciitis [8; 10; 11]. Moreover, there is direct evidence to suggest that injection of botulinumtoxinA into specific muscles of the foot results in clinically meaningful changes in hallux valgus angle, foot pain and functional mobility [8; 10]. In a double blind, randomised, placebo-controlled study of botulinumtoxinA, Wu, et al. injected botulinumtoxinA divided across the oblique and transverse heads of the adductor hallucis, the flexor hallucis brevis, and the extensor hallucis longus muscles in patients with a diagnosis of HAV. The primary outcome measures in this study were subscales on pain and disability in the Taiwan Chinese version of the Foot Function Index (FFI). The results of this study showed robust improvements in pain ($p<0.001$) and disability ($p<0.05$) in the group treated with botulinumtoxinA compared with those treated with normal saline (placebo). An immediate reduction in pain intensity was noted in the botulinumtoxinA group, reaching a plateau in the second month and persisting for up to six months post injection. [10]. Reduction in foot pain following treatment with botulinumtoxinA as demonstrated in these studies is of particular relevance in HAV. Several studies have demonstrated that foot pain is the primary outcome measure used to define efficacy in HAV (i.e. following surgical correction) [11] and the use of the Numeric Pain Rating Scale (NPRS) for foot pain is a reliable and widely used instrument for this purpose [13; 14; 15].

Hallux abducto valgus remains a highly prevalent and debilitating foot abnormality for which the standard of care, surgical correction, is associated with a significant recovery time, considerable patient burden and elevated risk. Long-term outcomes for this treatment also suggest recurrence is common. Given the underlying involvement of selected foot muscles in the development of HAV, targeted injections Dysport in the foot has the potential to be a safe and effective intervention for the treatment of HAV. The clinical efficacy observed in HAV patients following treatment with botulinumtoxinA in prior studies, strongly suggests that this treatment would be an important addition to the current treatment armamentarium.

1.2 Study Rationale

Intramuscular botulinumtoxinA injections reduce muscle hypertonicity by blocking the release of presynaptic acetylcholine at the neuromuscular junction. BotulinumtoxinA injections have been proved useful in treating muscle imbalance, muscle spasms and in providing significant pain reduction in patients with foot disorders such as plantar fasciitis. There is also evidence showing that botulinumtoxinA injection was effective for the treatment of pain and disability associated with HAV.

Several studies have compared HAV subjects with their normal counterparts and found pathologic and electromyographic evidence of HAV-related muscle degeneration [6; 16; 17].

These findings imply that it is possible to manage HAV-related pain and deformities through management of the muscle groups that act on the first metatarsophalangeal joint. Muscle imbalance of the abductor and adductor hallucis muscles has been demonstrated in HAV patients. When the adductor hallucis is dysfunctional, the action of the abductor hallucis is exaggerated and pulls the phalanx into pronation. The muscles that coordinate the movement of the first metatarsophalangeal joint consist of the oblique and transverse head of the adductor hallucis, extensor hallucis brevis, and flexor hallucis brevis. In patients with HAV, early onset of stance phase activities was found in these four muscles. Hoffmeyer et al. examined the relationship between muscle pathology and HAV and found not only enlarged mitochondria with paracrystalline inclusions but also myogenic and neurogenic alterations in patients with HAV [18]. An ultrasonic evaluation of the abductor hallucis muscle in patients with HAV also suggested that morphological changes may occur early in the development of the deformity. These findings suggest that a treatment strategy focused on intervention in HAV-related muscle groups may provide pain and disability relief, and may even suppress the progression of HAV. Therefore, the efficacy and tolerability of Dysport injections for the treatment of HAV in adult subjects will be evaluated in the present study.

1.3 Name and Description of Investigational Medicinal Product

The investigational medicinal product being evaluated is Clostridium botulinum toxin type A haemagglutinin complex (BTX-A-HAC), (United States generic name, abobotulinumtoxinA) hereafter referred to as Dysport. Dysport is a protein complex derived from Clostridium BTX-A consisting of the neurotoxin and other proteins. Dysport is supplied as a white lyophilised powder, for reconstitution.

The selection of Dysport doses to be evaluated in the present study (300 U and 500 U) are based on the demonstrated safety and efficacy of these doses in reducing hypertonia in muscles of similar size and volume to those planned for evaluation in this study (see Section 3.1) in the context of adult upper and lower limb spasticity with no unacceptable safety findings observed.

A more detailed description of the product is given in Section 3.4.

1.4 Findings from Nonclinical and Clinical Studies

In nonclinical studies, in vivo experiments demonstrate the efficacy of low doses of botulinum toxin (BTX) in various cholinergic pathways. Pharmacokinetic and distribution studies performed with BTX-A have demonstrated that the majority of the toxin remained localised at the injection site, supporting the local effect of the toxin as the principal location of action.

The results of the single- or repeat dose toxicity studies in animal models demonstrated that BTX-A administered in striated muscle possesses no potential for producing toxicity unrelated to its pharmacological activity or specific target organ. The effects on injected muscles (decrease in muscle and myofibre size) were related to the pharmacological activity of BTX-A, and were consistent with the results of the pharmacodynamic Rat Muscle Force Test. Intramuscular administration of Dysport in healthy juvenile rats did not alter male or female rat fertility with toxicological profiles in juvenile animals observed to be similar to adults.

No clinical studies have been conducted with Dysport for the treatment of adults with HAV. However, Dysport has been in clinical use since 1990 and is now licensed in more than 80 countries worldwide for various therapeutic indications including: blepharospasm, hemifacial spasm, upper and lower limb spasticity in adults, cervical dystonia (spasmodic torticollis), paediatric leg spasticity associated with cerebral palsy, and axillary hyperhidrosis. Studies conducted in these indications have shown Dysport to provide greater improvement in symptoms of these conditions compared with placebo, as well as demonstrating an acceptable safety profile.

Further details may be found in the investigator’s brochure (IB).

1.5 Known and Potential Risks and Benefits to Human Subjects

Dysport has proved to be an effective treatment for a number of therapeutic indications, and to have an acceptable benefit-risk ratio. The posology and safety of Dysport has been established in numerous clinical studies and over 20 years of postmarketing experience. The majority of treatment-emergent adverse events (TEAEs) reported for Dysport are mild to moderate in intensity and of limited duration. This safety profile is thought to be related to the pharmacology of the toxin, which may potentially result in excess paralysis of the injected and adjacent muscles in some patients. Dysport is generally well-tolerated, although temporary paralysis of non-targeted muscle groups may occur. AEs resulting from a possible remote spread of the toxin from its site of injection have been very rarely reported (including excessive muscle weakness, dysphagia, and aspiration pneumonia). Local spread of the toxin from the injection site has also been reported and therefore the safety profile is dependent on the site of injection. The profile of adverse reactions reported during postmarketing use reflects the pharmacology of the product and AEs seen during clinical studies. There have been occasional reports of hypersensitivity. In order to minimize the risk of serious reactions representing remote distribution of the effect of toxin, the guidance provided in the IB and/or in this protocol must be strictly followed. Additional information regarding risks and benefits to human subjects may be found in the IB.

1.6 Selection of Investigational Medicinal Products and Dosages

The safety and efficacy of Dysport is already well established in various indications including adult upper and lower limb spasticity, and cervical dystonia. The doses to be evaluated in this study (i.e. Dysport 300 U and 500 U) were selected based on the demonstrated safety and efficacy of these doses in reducing hypertonia in muscles of similar size and volume in the context of adult upper and lower limb spasticity including, but not limited to, the flexor digitorum longus, flexor hallucis longus, flexor digitorum profundus, flexor digitorum superficialis, flexor carpi radialis, flexor hallucis brevis and flexor carpi ulnaris muscles. In previous studies, each of these muscles were injected with 100 U to 200 U of Dysport in Studies Y-55-52120-140, Y-55-52120-142, Y-52-52120-145 and Y-52-52120-148, with no unacceptable safety findings observed.

A more detailed description of administration procedures is given in Section 6.1.

1.7 Compliance Statement

The study will be conducted in compliance with independent ethics committees/institutional review boards (IECs/IRBs), informed consent regulations, the Declaration of Helsinki and International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines. Any episode of noncompliance will be documented.

In addition, the study will adhere to all local regulatory requirements.

Before initiating a study, the investigator/institution should have written and dated approval/favourable opinion from the IEC/IRB for the study protocol/amendment(s), written informed consent form, any consent form updates, subject emergency study contact cards, subject recruitment procedures (e.g. advertisements), any written information to be provided to subjects and a statement from the IEC/IRB that they comply with GCP requirements. The IEC/IRB approval must identify the protocol version as well as the documents reviewed.

1.8 Population to Be Studied

The study will enrol adult male and female subjects aged 18 years or older suffering from clinically significant HAV who have not undergone surgery for their condition.

2 PURPOSE OF THE STUDY AND STUDY OBJECTIVES

2.1 Purpose of the Study

Given the underlying involvement of the selected foot muscles to be injected in this study (i.e. 1) the oblique head of the adductor hallucis muscle; 2) the transverse head of the adductor hallucis muscle; 3) flexor hallucis brevis muscle; and 4) the extensor hallucis brevis muscle) in the development of HAV, targeted injections of Dysport in the foot have the potential to be a safe and effective intervention for the treatment of pain associated with HAV. The clinical efficacy observed in HAV patients following treatment with botulinumtoxinA in prior studies has shown a reduced localized hypertonia in injected muscles (see Section 1.1), and strongly suggests that Dysport may be an important addition to the current treatment armamentarium. For this reason, the purpose of conducting this study is to investigate the short and long-term efficacy and safety of single- and repeat-treatment with Dysport in adults suffering from clinically significant pain associated with HAV who have not undergone surgery for their condition, during two treatment periods. The first period will be DB with the primary aim to assess the efficacy of Dysport 300 U and 500 U versus placebo. The second period will be OL and will mainly assess the long-term safety of treatment with Dysport in adult subjects with HAV.

2.2 Study Objectives

2.2.1 Primary Objective

The primary objective of this study is to assess reduction in pain in adult subjects with HAV with Dysport (300 U and 500 U) as compared with placebo using the NPRS.

2.2.2 Secondary Objectives

The secondary objectives of the study are:

- To assess functional improvement in Dysport (300 U and 500 U) as compared with placebo using the mFFI disability subscale.
- To assess reduction in foot pain in Dysport (300 U and 500 U) as compared with placebo using the mFFI pain subscale.
- To assess improvement in activity limitation associated with foot pain in Dysport (300 U and 500 U) as compared with placebo using the mFFI activity limitation subscale.
- To evaluate the quality of life using the SF-36.
- To evaluate angular displacement of the hallux using radiographs.
- To evaluate the patient's global impression of improvement and severity associated with foot pain and disability.
- To evaluate the clinical safety and efficacy of Dysport following repeated treatment cycles

2.2.3 Exploratory Objective

The exploratory objective of this study is:

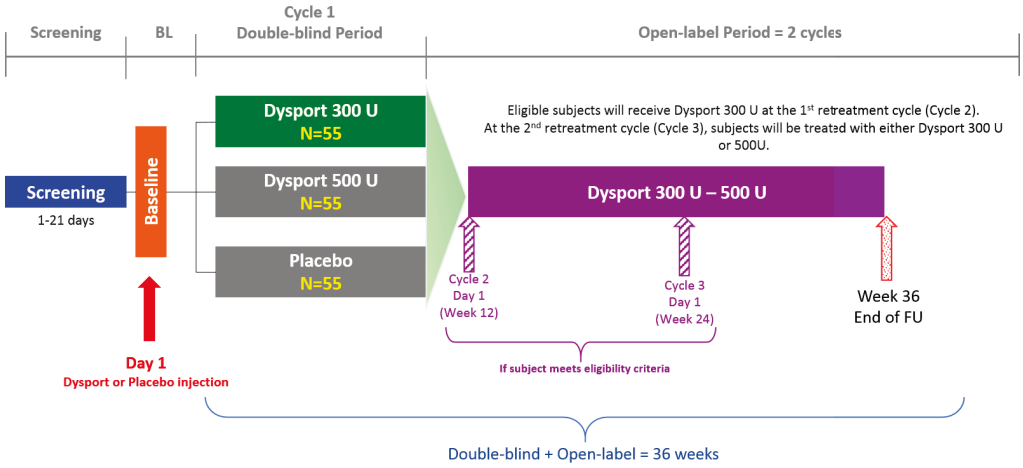
- CCI [redacted]

3 STUDY DESIGN

3.1 General Design and Study Schematic

This is a multiple-dose, randomised, parallel-group, DB, placebo-controlled study to evaluate the efficacy and safety of Dysport at doses of 300 U and 500 U compared with placebo in adult subjects suffering from clinically significant HAV who have not undergone surgery for their condition. The study will consist of a screening period, followed by a DB period where subjects will receive a single treatment with either Dysport or placebo (Cycle 1) followed by an OL extension period where subjects may receive up to two additional cycles of Dysport. As such, the maximum duration of participation in the study for a given subject will be 36 weeks. See Figure 2 for further details of the study design.

Figure 2 Study Design



BL=baseline; FU=follow up; N=number of subjects in a treatment group; U=units

* In the open-label period, eligible subjects will be administered injections of Dysport 300 U on Day 1 of Cycle 2. On Day 1 of Cycle 3, eligible subjects will be treated with either 300 U or 500 U of Dysport, based on investigator judgment. The decision to increase the dose at the beginning of Cycle 3 will be based on 1) evaluation of safety and tolerability (review related AEs and consideration of any significant changes in the study foot) and 2) severity of pain (considering NPRS score) and disability (considering mFFI Disability subscale score) experienced by the subject at the time of evaluation. Only subjects who meet the protocol-defined retreatment criteria will be eligible to receive treatment with Dysport at these intervals. Subjects who meet the protocol-defined retreatment criteria will be administered injections of Dysport 300 U (Cycle 2) in an open-label fashion. Subsequent treatment with Dysport (Cycle 3) will also be based on subjects' meeting the retreatment criteria and will occur at least 12 weeks after receiving the prior injection of Dysport. Subjects who do not meet retreatment criteria at any point will not receive subsequent treatment cycles beyond Cycle 1 and will be clinically evaluated every 4 weeks to determine retreatment eligibility. No subject will receive treatment with Dysport after the Week 24 study visit.

3.1.1 Double-blind Period (Cycle 1):

Subjects will be evaluated for eligibility during a screening period of up to 21 days, during which they will be tapered off all medications prohibited by this protocol in a manner that is consistent with labelling recommendations and conventional medical practice.

Following the screening period, subjects will be randomised to one of three treatment groups (i.e. Dysport 300 U, Dysport 500 U or placebo) in a 1:1:1 ratio during the DB period. Subjects will receive four intramuscular injections of blinded study treatment (Dysport 300 U, Dysport 500 U or placebo) in the HAV affected foot (i.e. study foot) on Day 1 of the study during the DB period (i.e. Cycle 1). The muscles to be injected are: 1) the oblique head of the adductor

hallucis muscle; 2) the transverse head of the adductor hallucis muscle; 3) flexor hallucis brevis muscle; and 4) the extensor hallucis brevis muscle. The evaluation of efficacy (DB) and effectiveness (OL) will be based solely on the foot selected for treatment at Screening (i.e. study foot) meeting the study entry criteria. For each subject, the study foot (i.e. the foot that will be treated with study treatment during the study) will be evaluated for all efficacy analyses regardless of the presence of HAV in the contralateral foot. For subjects presenting with bilateral HAV at Screening, the investigator will determine which foot is of greater severity based on the clinical judgment of the investigator following clinical evaluation of the degree of pain (including assessment of the NPRS scores for each foot during Screening), degree of disability and angular deviation of the hallux, and meeting all other study entry criteria. In these subjects, the foot with the greatest severity of HAV will be selected for treatment with DB study treatment in this study.

During the DB period, study visits will proceed at the following intervals following study treatment administration and assessments on Day 1:

- Week 1 (Day 8) (clinic visit)
- Week 4 (Day 29 (clinic visit)
- Week 8 (Day 57) (clinic visit)
- Week 12 (Day 85) (clinic visit*)
- Additional visits every 4 weeks

(*Note: Subjects will be evaluated for retreatment with Dysport 300 U in an OL fashion).

3.1.2 Open-label Period (Cycles 2 to 3):

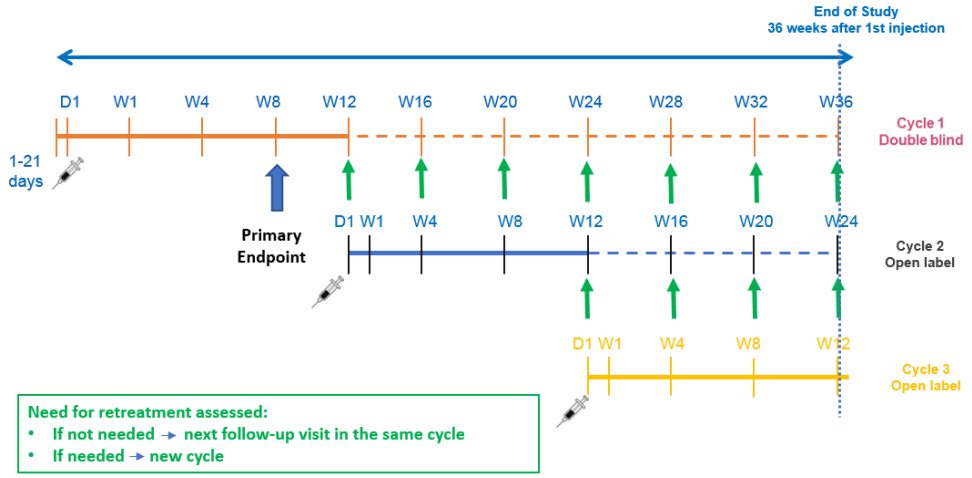
Following completion of all protocol-specified procedures for the DB period (i.e. completion of Cycle 1), subjects who meet retreatment criteria (see Section 3.1.2.1) will be treated during the OL period with Dysport (300 U) in the HAV study foot determined in the DB period. The muscles to be injected and procedures for injection are identical to those targeted in the DB period.

During the OL period, subjects may be treated with up to two additional cycles of Dysport with intervals of at least 12 weeks between each treatment cycle (see Figure 3). All retreatment-eligible subjects will receive OL treatment with Dysport 300 U at the first retreatment cycle (Cycle 2) in the HAV study foot determined in the DB period. At the second retreatment cycle (Cycle 3), subjects will be treated in the HAV study foot with either Dysport 300 U or 500 U based on investigator judgment following clinical evaluation of the subject at the time of retreatment. The decision to increase the dose at the beginning of Cycle 3 will be based on 1) evaluation of safety and tolerability (review related AEs and consideration of any significant changes in the study foot) and 2) severity of pain (considering NPRS score) and disability (considering mFFI Disability subscale score) experienced by the subject at the time of evaluation.

During the OL period, each treatment cycle (Cycles 2 and 3) will include the following study visits after the retreatment injection with Dysport at the beginning of each treatment cycle:

- Week 1 (Day 8) (clinic visit)
- Week 4 (Day 29) (clinic visit)
- Week 8 (Day 57 (clinic visit)
- Week 12 (Day 85) (clinic visit)
- Additional visits every 4 weeks

Figure 3 Open-label Period Retreatment Scheme



3.1.2.1 Retreatment Criteria

Prior to receiving retreatment with Dysport in each of the two retreatment cycles in the OL period (Cycles 2 and 3), subjects will be required to meet all the following retreatment criteria:

- Subject is willing to receive a new treatment cycle with Dysport
- Treatment with Dysport is in the best interest of the subject based on the investigator's clinical judgment.
- Subject's foot pain is clinically significant as evidenced by an NPRS score ≥3 within 24-48 hours immediately prior to the retreatment visit.
- Subject has not experienced any unacceptable risk judged by the investigator to require postponement of the treatment cycle to the next visit
- At least 12 weeks have passed since the subject's last treatment with Dysport (or blinded study treatment)

Subjects who do not meet the retreatment criteria will be evaluated by the investigator at the next scheduled study visit (every 4 weeks) to determine eligibility to receive retreatment with Dysport (300 U to 500 U) in the OL period. Subjects who do not meet the retreatment criteria by Week 24 will not be eligible for retreatment in the OL period, as treatment is not available beyond Week 24 in the study.

3.2 Primary and Secondary Endpoints and Evaluations

3.2.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the change from baseline in the daily NPRS score averaged over the 7 consecutive days prior to the Week 8 DB visit.

The baseline is defined as the daily NPRS score averaged over the 7 consecutive days prior to the baseline visit (Day 1).

3.2.2 Secondary Efficacy Endpoints

The secondary efficacy evaluations and endpoints are presented in Table 2.

Table 2 Secondary Efficacy Evaluations and Endpoints

Evaluations	Secondary Efficacy Endpoints
NPRS	The change from baseline in the daily NPRS score averaged over the 7 consecutive days prior to Week 4 and Week 12 DB visits and each scheduled visit in the OL period.
mFFI	The change from baseline in the daily mFFI disability subscale score averaged over the 7 consecutive days prior to Week 4, Week 8 and Week 12 DB visits and each scheduled visit in the OL period.
	The change from baseline in the daily mFFI pain subscale score averaged over the 7 consecutive days prior to Week 4, Week 8 and Week 12 DB visits and each scheduled visit in the OL period.
	The change from baseline in the daily mFFI total score averaged over the 7 consecutive days prior to Week 4, Week 8 and Week 12 DB visits and each scheduled visit in the OL period.
	The change from baseline in the daily mFFI activity limitation subscale score averaged over the 7 consecutive days prior to Week 4, Week 8 and Week 12 DB visits at each scheduled visit in the OL period.
Hallux angular measurements	The change from baseline in HV angle as measured directly by weight-bearing anterior-posterior radiographs at Week 4, Week 8 and Week 12 DB visits and each scheduled visit in the OL period.
	The change from baseline in intermetatarsal angle as measured directly by weight-bearing anterior-posterior radiographs at Week 4, Week 8 and Week 12 DB visits and each scheduled visit in the OL period.
Time between injections	The time to retreatment
PGI-S	The change from baseline in PGI-S of foot pain score to Week 4, Week 8 and Week 12 DB visits and each scheduled visit in the OL period.
	The change from baseline in PGI-S disability score to Week 4, Week 8 and Week 12 DB visits and at each schedule visit in the OL period.
PGI-I	The PGI-I-foot pain score at the Week 4, Week 8 and Week 12 DB visits and at each scheduled visit in the OL period.
	The PGI-I disability score at the Week 4, Week 8 and Week 12 DB visits and at each scheduled visit in the OL period.
SF-36	The change from baseline in quality of life as measured by the SF-36 at Week 8 and Week 12 DB visits and each scheduled visit in the OL period.

DB=double blind; HV=hallux valgus; mFFI=modified foot function index; NPRS=numeric pain rating scale; PGI-I=patient global impression of improvement; PGI-S=patient global impression of severity; SF-36=36-item short form

3.2.3 Exploratory Efficacy Endpoint

CCI

3.2.4 Safety Endpoints and Evaluations

The safety endpoints and evaluations are as follows:

- The incidence of AEs, serious AEs (SAEs), AEs leading to discontinuations and AEs of special interest (AESIs) (i.e. remote effects of toxin and hypersensitivity-like reactions)
- Evaluation of concomitant medications and therapies
- Clinical evaluations:
  - vital signs (absolute value and change from baseline)

- physical examinations (including physical examination of the foot)
- presence of binding and neutralising antibodies (seroconversion)
- haematology and chemistry (absolute value and change from baseline).

3.3 Randomisation and Blinding

All IMP will be similar in size, colour, smell, taste and appearance allowing the blinded conditions of the study to be maintained. Subjects and investigators will remain blinded to treatment assignment during the study.

The sponsor's randomisation manager who is a statistician independent from the study will prepare:

- A list of randomisation numbers (List A). It will be produced in blocks, on a balanced ratio (1 placebo: 1 Dysport 300 U: 1 Dysport 500 U) and will be stratified by unilateral and bilateral HAV.
- A list of treatment numbers/treatment which will be dispatched to the sites (list B). It will be produced in blocks, on a balanced ratio (1 placebo: 1 Dysport 300 U: 1 Dysport 500 U).

The randomisation, as well as the treatment number(s) assignation at drug dispensation, will be managed by an Interactive Response Technology (IRT). After eligibility is confirmed, at baseline, subjects will be assigned to a randomisation number and to the associated treatment arm, in sequential order within each centre and within each level of strata.

Subjects meeting the randomisation criteria will be assigned to a randomisation number, and will be allocated to the associated treatment arm, by IRT. A treatment number will be also allocated by IRT each time drug is dispensed during the DB and OL cycles. The IRT will also manage all the logistical aspects of treatments (e.g.: drug supplies, replacement of lost, damaged, quarantined, expiring and expired kits).

This service provides investigators, site co-ordinators and project team members with a 24-hour per day, 7-day per week service (additional details may be found in the IRT reference manual provided to each site). In case of medical or technical randomisation or dispensation queries, a 24-hour helpline is available – see supporting information in the investigator site file. Recruitment will stop once 165 evaluable subjects have been randomised.

Randomised subjects who terminate their study participation for any reason before administration of the first dose of randomised study drug will retain their randomisation and treatment numbers (i.e. these numbers will not be reused). The next subject will be given another randomisation number and another treatment number, even if he/she should receive the same treatment. Subjects who leave the study early will not be replaced.

The sponsor's randomisation manager will keep the master lists. A copy of the list of treatment numbers (list B) will be confidentially supplied to the CMC Supply Chain (Beaufour Ipsen Industrie SAS, rue d'Ethe Virton, 28100 Dreux, France) and to the Contract Research Organisation (CRO) in charge of IRT. Similarly, a copy of the list of randomisation numbers (list A) will be also confidentially supplied to the CRO in charge of IRT. The master list(s) and the copy(ies) supplied to the CMC Supply Chain and CRO in charge of IRT will be kept confidential in a secure location. Access to the randomisation lists must be restricted until authorisation is given to release them for final analysis.

3.4 Maintenance of Randomisation and Blinding

In an emergency situation, which requires the identification of the study treatment group, the investigator may break the treatment code immediately, or as quickly as possible, if he/she finds it is in the best interest of the trial subject. The investigators have direct and immediate access to break the treatment code through the IRT. At the earliest opportunity, the investigator is

requested to inform the blinded monitor in charge of his/her centre that the blind has been broken for an emergency.

In addition, a set of hard copy sealed code break envelopes will be held by Global Patient Safety at Ipsen, in case of IRT failure (this set will be prepared by the Ipsen Randomisation manager).

If code-break was performed using the IRT, the investigator must store the email notification revealing unblinded treatment in a sealed envelope. The investigator will then sign, date and provide the reason for the code break on the emergency code break form and on the sealed envelope. The date and reason for identifying the treatment group will be recorded in the eCRF.

3.5 Study Treatments and Dosage

The term IMP refers to both active drugs and placebo.

The study treatment, Dysport, will be provided as a white, lyophilised powder in vials containing 300 U or 500 U of BTX-A-HAC (abobotulinumtoxinA). Before each administration, the powder from the Dysport vial (300 U or 500 U) will be reconstituted at the investigational site with 0.9% sterile (preservative free) sodium chloride for injection, to a total volume of 2.0 mL. Investigators will inject 0.5 mL of the reconstituted vial from a syringe into each of the four muscles in the study foot (i.e. the oblique head of the adductor hallucis muscle; the transverse head of the adductor hallucis muscle; flexor hallucis brevis muscle; and the extensor hallucis brevis muscle). Subjects assigned to receive 300 U of Dysport will be treated with 75 U of Dysport per muscle (300 U dose divided equally among the four described muscle muscles). Subjects assigned to receive 500 U of Dysport will be treated with 125 U of Dysport per muscle (500 U dose divided equally among the described four muscles).

A more detailed description of administration procedures is given in Section 6.2.

The reference therapy in this study is a matching placebo for the DB period. Placebo will be provided as a white, lyophilised powder in vials containing only excipients of BTX-A-HAC and undistinguishable from the active BTX-A-HAC product. Reconstitution and administration of the placebo will be as described for the active BTX-A-HAC product. A more detailed description of administration procedures is given in Section 6.2.

The study treatment will be packaged and released by Beaufour Ipsen Industrie and delivered to the investigational sites or interim storage facilities. A sufficient quantity of study treatment will be supplied as well as an acknowledgement of receipt form.

The sponsor's representative will receive; a Certificate of Analysis for which batch of IMP has been used under their study, and a Certificate of Compliance which reflects the product release statement and will provide them to sites according to local requirement.

The core label texts for all packaging units will be translated or adjusted, to follow applicable regulatory requirements (e.g. Good Manufacturing Practice guidelines (Volume 4 Annex 13)), national laws in force and in accordance with the local regulations.

The investigator, or designee, will only dispense IMPs to subjects included in this study. Each subject will only be given the IMP with his/her treatment number. The dispensing for each subject will be documented in the electronic case report form (eCRF).

3.6 Study Duration

The duration of the study per subject will be up to 39 weeks. This study will consist of a screening period (up to 3 weeks), a DB single-dosing period (Cycle 1) followed by a repeated dose OL period where subjects can receive up to two additional cycles of Dysport (Cycles 2 and 3) depending on retreatment eligibility (36 weeks). Each subject will receive up to three administrations (i.e. cycles) of study treatment with a 12-week follow up period after each treatment in the DB and OL periods.

The study will be considered to have started when the first subject has been screened/provided signed informed consent.

The study will be considered complete after the last subject has completed 36 weeks in the study.

3.7 Stopping Rules and Discontinuation Criteria

There are no formal rules for early termination of this study. During the conduct of the study, SAEs will be reviewed (see Section 8.1.5) as they are reported from the study centre to identify safety concerns. A specific site can be discontinued or the entire study may be terminated at any time if the sponsor judges it necessary for any reason. In that case, all scheduled procedures and assessments for subjects who are still in the study will be performed. Possible reasons for the closure of a study site may include:

- failure of the investigator staff to comply with the protocol or with the GCP guidelines;
- New and significant safety concerns;
- inadequate subject recruitment.

A subject may discontinue participation in the study at any time for any reason (e.g. lack of efficacy, withdrawal of consent, AE). The investigator and/or sponsor can withdraw a subject from the study at any time for any reason (e.g. protocol violation or deviation as defined in Section 13.1.2, noncompliance with the protocol conditions, AE or if the investigator feels it is not in the best interest of the subject to continue in the study). All cases of discontinuation will be discussed between the investigator and the sponsor.

3.8 Source Data Recorded on the Case Report Form

Data will be collected in the eCRF in compliance with FDA 21 CFR Part 11. As required by GCP, the sponsor assigned monitor will verify, by direct reference to the source documents, that the data required by the protocol are accurately reported on the eCRF.

The source documents must, as a minimum, contain a statement that the subject is included in a clinical study, the date that informed consent was obtained prior to participation in the study, the identity of the study, diagnosis and eligibility criteria, visit dates (with subject status), IMP administration, and any AEs and associated concomitant medication.

As required by ICH GCP Section 6.4.9, if some items are recorded directly on the eCRF and are considered as source data, the identification of these data must be documented and agreed between the investigator and the sponsor.

Definition for source data and source documents are given below:

- **Source Data**: All original records and certified copies of original records of clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).
- **Source Documents**: Original documents, data and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x rays, subject files, and records kept at the pharmacy, at the laboratories and at medicotechnical departments involved in the clinical study).

The subject must have consented to their medical records being viewed by the sponsor's authorised personnel, and by local, and possibly foreign, CAs. This information is included in the informed consent.

4 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Inclusion Criteria

All subjects must fulfil all the following criteria at Screening and Baseline to be included in the study:

(1) Subjects must provide written informed consent prior to any study related procedures.

(2) Male or female, aged 18 years or older

(3) Clinical diagnosis of HAV as determined by the investigator based on evidence of lateral deviation of either great toe (left or right), as well as assessment of NPRS Pain scores for each foot (in bilateral subjects).

(4) Subjects must present with a score of ≥4 on the NPRS in the study foot at Baseline

(5) Subjects must present with a score of >27 on the mFFI Pain subscale in the study foot at Baseline

(6) Subjects must present with a score of >27 on the mFFI Disability subscale in the study foot at Baseline

(7) Subjects must present with HV angle ≤ 30° in the study foot great toe using radiographic measurements based on guidelines set forth by the AOFAS ad hoc Committee on Angular Measurements at Screening only

(8) Subjects must present with an intermetatarsal angle of ≤ 18°, inclusive, in the study foot great toe using radiographic measurements based on guidelines set forth by the American Orthopedic Foot and Ankle Society Ad hoc Committee on Angular Measurements at Screening only

(9) Subject's foot pain associated with HAV deformity is refractory to shoe modifications, nonsteroidal anti-inflammatory medications, and modification of activities

(10) In the opinion of the investigator the subject's deformity is reducible following clinical evaluation including compression of the intermetatarsal angle or rotation of the proximal phalanx.

(11) Female subjects of childbearing potential must have a negative pregnancy test result at Screening and be willing to use reliable contraceptive measures throughout study participation.

a) Reliable forms of contraception include but are not limited to:

- Hormonal contraceptives (e.g. oral, path, injection)
- Double barrier (e.g. male condom plus spermicide, or female diaphragm plus spermicide)
- Intrauterine device
- Male partner has had a vasectomy
- Total abstinence from intercourse with male partners (periodic abstinence is not acceptable)

b) Female subject meeting any of the following criteria are not considered to be of childbearing potential:

- Postmenopausal (≥47 years of age and amenorrhoeic for at least 12 consecutive months)
- Have been sterilised surgically (e.g. bilateral tubal ligation)
- Have had a hysterectomy
- Have had a bilateral oophorectomy

(12) Ability to complete all study requirements in the opinion of the investigator

(13) Subject can read well enough to understand the informed consent form and other subject materials.

Subjects must be willing and able to comply with study restrictions and to remain at the clinic for the required duration during the study period and willing to return to the clinic for the follow up evaluation as specified in the protocol.

4.2 Exclusion Criteria

Subjects will not be included in the study if the subject:

(1) Subject has an HV angle of >30° in the study foot

(2) Evidence of cognitive impairment

(3) Inability to walk unassisted

(4) Subject presents with a flat or square metatarsal head in the study foot

(5) Subject presents with metatarsus primus elevatus in the study foot

(6) Subject presents with severe cavus/planus in the study foot

(7) Subject suffers from any other podiatric or orthopaedic condition which, in the opinion of the investigator would interfere with the accurate evaluation of pain and/or function

(8) Subject presents with medical history or clinical evidence of peripheral vascular disease

(9) Subject has a body mass index greater than 40 kg/m^2 or less than 18.5 kg/m^2

(10) Any medical history of a diabetic condition

(11) Subject has a glycated haemoglobin level of ≥6.5% at Screening

(12) Any history of ankle or foot surgery in the study foot

(13) Subject is using an orthotic device (including over-the-counter toe-spacers) which could influence the functioning of the hallux of the study foot in any way, or any other device intended for this purpose. Over-the-counter shoe inserts for the study foot are permitted if used for at least 30 days prior to screening

(14) Subject has medical history or clinical evidence of peripheral neuropathy or fibromyalgia

(15) Subject has metatarsus adductus

(16) Subject has a history of conditions or disease causing ligamentous laxity (e.g. Marfan's syndrome, Ehlers-Danlos syndrome)

(17) Subject has a history of allergic reaction or has a known or suspected sensitivity to any substance that is contained in the study treatment formulation (including cow's milk protein)

(18) Any medical condition or disease that might interfere with neuromuscular function, e.g. diagnosed myasthenia gravis, Lambert-Eaton syndrome or amyotrophic lateral sclerosis.

(19) Subject demonstrates evidence of inflammatory arthritis (including gout) in the study foot or osteoarthritis in the study foot based on either history or clinical evaluation

(20) Subject demonstrates evidence of degenerative arthritis of the first metatarsophalangeal joint based on either history or clinical evaluation

(21) Subject has an acute or chronic medical condition (other than HAV) that in the opinion of the investigator could confound clinical assessments or interfere with the ability of the subject to participate in the study.

(22) Subject has a clinically significant abnormality on screening evaluation including physical examination, vital signs, or laboratory tests that the investigator considers to be inappropriate to allow participation in the study.

(23) Subject is currently participating or has participated in a clinical study within the last 90 days or has participated in more than two clinical studies within the past year. This includes studies using marketed compounds or devices.

(24) Subject is an investigational study site staff member or the relative of an investigational study site staff member.

(25) 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. Subjects who have previously received an injection with botulinum toxin in the foot are not eligible to participate in the study.

(26) Any concomitant therapy usage that, in the investigator's opinion, would interfere with the evaluation of safety or efficacy of the investigational medicinal product, and/or confound the study results.

(27) Subject has planned or ongoing use of opioids; use of antipsychotics or antidepressants that are not stable for at least 30 days prior to Screening; use of anticholinergic therapies that are not stable for at least 6 weeks prior to randomisation; or requires continuous treatment with any medication restricted by this protocol.

(28) Evidence of clinically significant chronic drug or alcohol abuse within the last year.

(29) Use of medications that affect neuromuscular transmission, such as curare-like depolarising agents, lincosamides, polymyxins, anticholinesterases and aminoglycoside antibiotics within the last 3 months before Screening.

(30) Subject is medically unable to discontinue treatment with medications with anticoagulant/antiplatelet effects (e.g. warfarin and other coumadin derivatives, acetylsalicylic acid and clopidogrel/ticlopidine) for at least 3 days before randomisation/injection of study treatment. Subjects are permitted restart anticoagulant/antiplatelet medications one day after injection of study treatment (or longer at the discretion of the investigator).

(31) Any condition or situation which, in the investigator's opinion, puts the subject at significant risk, may confound the study results, or may interfere with the subject's participation in the study

4.3 Rationale for Inclusion / Exclusion Criteria

The selection of the specific subject population defined by the inclusion/exclusion criteria above was based on the known aetiology and course of HAV in adult patients seeking treatment for this condition. The typical clinical presentation for HAV primarily includes clinically significant pain, mobility dysfunction and angular deviation of the hallux. As such, the entry criteria have been specifically chosen to allow for generalizability of this clinical study population to the larger adult HAV population. For the purposes of ensuring that variability is minimised and potential confounding factors are eliminated, the entry criteria include several provisions restricting subjects who have pre-existing medical conditions or are reliant upon treatments which will not be permitted in the study.

4.4 Subject Withdrawal Criteria and Procedures

4.4.1 Withdrawal from the Study

In accordance with the Declaration of Helsinki (in accordance with the applicable country's acceptance), each subject is free to withdraw from the study at any time. The investigator also has the right to withdraw a subject from the study in the event of concurrent illness, AEs, or other reasons concerning the health or wellbeing of the subject, or in the case of lack of cooperation. In addition, a subject may be withdrawn from the study as described in Sections 3.7, 5.2.3, 6.3, 8.1.6 and 8.1.8.

If a subject decides to withdraw from the study after administration of IMP, or should the investigator decide to withdraw the subject, all efforts will be made to complete and report the observations up to the time of withdrawal as thoroughly as possible. A complete final evaluation at the time of the subject's withdrawal should be made (see Sections 5.2.3) and an explanation given of why the subject is withdrawing or being withdrawn from the study.

The reason for and date of withdrawal from the study must be recorded on the eCRF. If a subject withdraws consent, every attempt will be made to determine the reason. If the reason for withdrawal is an AE or a clinically significant laboratory test abnormality, monitoring will continue until the event has resolved or stabilised, until the subject is referred to the care of a local health care professional, or until a determination of a cause unrelated to the IMP or study procedure is made. The specific AE or test result(s) must be recorded on the eCRF. All evaluations should be performed, according to the protocol, on the last day the subject receives IMP, or as soon as possible thereafter.

4.4.2 Withdrawal from Study Treatment

Discontinuation of the study treatment does not represent withdrawal from the study. However, a subject may permanently discontinue study treatment at any time. If a subject discontinues from the study treatment, the subject will continue to be followed up for efficacy and safety evaluations. Criteria for permanent discontinuation of study treatment include:

- The subject requests to discontinue study treatment
- The subject has a medical condition or personal circumstance which in the opinion of the investigator and/or Sponsor would place the participant at unnecessary risk from continued administration of study treatment.
- The participant has a confirmed positive urine pregnancy test
- Chronic failure to comply with dosing, evaluations, or other requirements of the study, despite documentation at the study site of repeated efforts to reinforce compliance.

Discontinuation from the study treatment is permanent. Once a subject is discontinued, he/she will not be allowed to restart study treatment.

5 STUDY PROCEDURES

5.1 Study Schedule

The schedule of procedures and assessments during the double-blind and open-label periods of the study are summarised in Table 3 and Table 4, respectively.

Table 3 Study Procedures and Assessments: Double-blind Period

Procedures and Assessments	Screening 1 (Days -21 to Day -1)[a]	Baseline Day 1	Day 8 Week 1	Day 29 Week 4	Day 57 Week 8	Day 85[b] Week 12	Additional Visit every 4 weeks[d]	End of Study or Early Withdrawal[c]
Visit Number	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	-	-
Visit Window	**NA**	**NA**	**± 1 day**	**± 3 days**	**± 3 days**	**+ 1 week[e]**	**± 7 days**	**N/A**
Obtain informed consent/assent	X							
Inclusion/exclusion criteria	X	X						
Demographics[f]	X							
Assessment of unilateral/ bilateral HAV[g]	X							
Randomisation		X						
Injection of study treatment		X						
Weight-bearing foot radiograph and measurement of HV and IM angles and tibial sesamoid position[h]	X			X	X	X	X	X
NPRS	X	X[i]		X[i]	X[i]	X[i]	X[i]	X[i]
mFFI	X	X[i]		X[i]	X[i]	X[i]	X[i]	X[i]
SF-36		X			X	X		X
PGI-I for pain and PGI-I for disability[n]				X	X	X		X
PGI-S for pain and PGI-S for disability[n]	X	X		X	X	X		X
Prior/concomitant medications/non-drug therapies	X[j]	X	X	X	X	X	X	X
Adverse event monitoring	X	X	X	X	X	X	X	X

Procedures and Assessments	Screening 1 (Days -21 to Day -1)[a]	Baseline Day 1	Day 8 Week 1	Day 29 Week 4	Day 57 Week 8	Day 85[b] Week 12	Additional Visit every 4 weeks[d]	End of Study or Early Withdrawal[e]
Visit Number	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	-	-
Visit Window	**NA**	**NA**	**± 1 day**	**± 3 days**	**± 3 days**	**+ 1 week[c]**	**± 7 days**	**N/A**
Medical history	X							
Physical examination	X		X			X		X
Examination of injected foot[j]		X	X	X	X	X	X	X
Height and weight[k]	X					X		X
Vital signs[l]	X		X			X		X
Hematology and chemistry	X					X		X
Blood sampling for BTX-A Abs- testing		X						X
Urine drug screen	X	X		X		X		X
Urine pregnancy test	X	X						
Eligibility for retreatment						X	X	

BTX-A-Abs=botulinum toxin type A antibodies; HV= hallux valgus; IM=intermetatarsal; mFFI=modified foot function index; NA=not applicable; NPRS=numeric pain rating scale; PGI-I=Patient Global Impression of Improvement; PGI-S=Patient Global Impression of Severity; SF-36=36-item short form survey

a Screening assessments are to be performed at the study site, including NPRS, mFFI and PGI-S.
b Assessments outlined for Day 85 are the same as those for Day 1 of the subsequent cycle and do not need to be repeated.
c Repeat study treatment must not be administered any sooner than 12 weeks after the last dose.
d Any subjects who are not eligible for retreatment will be evaluated every 4 weeks at additional follow-up visits until they are eligible for retreatment, or have completed the study.
e A subject will be considered to have completed the study if he/she has completed a total of 36 weeks follow-up in the study from the first study treatment injection (Treatment Cycle 1, Day 1) and has completed the Day 85 visit following the last injection.
f Demographic data will include sex, age/date of birth, ethnicity and race.
g Subjects should be assessed for the presence of unilateral or bilateral HAV and the status recorded in the electronic case report form.
h Subjects will record daily measurements for 7 consecutive days (preferably in the evening) using an electronic diary prior to Baseline (i.e. Day -7 to Day -1) and prior to the following visits: Week 4, Week 8 and Week 12.
i Prior and concomitant medications will include all medications administered within 30 days before the screening visit.
j Assessment to include complete physical examination of the injection sites on the study foot specifically evaluating the foot for any dermatologic, neurologic or musculoskeletal abnormalities (see Section 8.4 for further details).
k Height is to be collected at Screening only.
l Vital signs will include sitting blood pressure and sitting heart rate.

Procedures and Assessments	Screening 1 (Days -21 to Day -1)[a]	Baseline Day 1	Day 8 Week 1	Day 29 Week 4	Day 57 Week 8	Day 85[b] Week 12	Additional Visit every 4 weeks[d]	End of Study or Early Withdrawal[c]
Visit Number	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	-	-
Visit Window	NA	NA	± 1 day	± 3 days	± 3 days	+ 1 week[c]	± 7 days	N/A

m The PGI-I and PGI-S assessments will be completed by the subject at the study site during the study visit. Subjects are to complete these self-assessments using the electronic diary which will be accessed at the site during the visit. Site staff should not help subjects answer questions but must ensure that the subject can access the eDiary to complete the assessment while at the site

Table 4 Study Procedures and Assessments: Open-label Period

Procedures and Assessments	Cycle 2 to 3 Day 1[c]	Cycle 2 to 3 Day 8	Cycle 2 to 3 Day 29	Cycle 2 to 3 Day 57	Cycle 2 to 3 Day 85[d]	Additional Visit every 4 weeks[f]	End of Study or Early Withdrawal[g]
Visit Number	**Visits 7 & 12**	**Visits 8 & 13**	**Visits 9 & 14**	**Visits 10 & 15**	**Visits 11 & 16**	-	-
Visit Window	**+ 2 days**	**± 1 day**	**± 3 days**	**± 3 days**	**+ 1 week[e]**	**± 7 days**	**N/A**
Weight-bearing foot radiograph and measurement of HV and IM angles and tibial sesamoid position	X		X		X		X
Injection of study treatment	X[a, b]						
NPRS[h]	X		X	X	X	X	X
mFFI[h]	X		X	X	X	X	X
SF-36	X			X	X		X
PGI-I for pain and PGI-I for disability[i, k]	X			X			X
PGI-S for pain and PGI-S for disability[i, k]	X			X			X
Prior/concomitant medication review	X	X	X	X	X	X	X
Adverse event monitoring	X	X	X	X	X	X	X
Physical examination	X				X		X
Examination of injected foot[j]	X	X	X	X	X	X	X
Vital signs	X	X	X				X
Weight	X						X
Hematology and chemistry	X				X		X
Blood sampling for BTX-A-Abs testing							X
Urine drug screen	X		X		X		X

Procedures and Assessments	Cycle 2 to 3 Day 1[c]	Cycle 2 to 3 Day 8	Cycle 2 to 3 Day 29	Cycle 2 to 3 Day 57	Cycle 2 to 3 Day 85[d]	Additional Visit every 4 weeks[f]	End of Study or Early Withdrawal[g]
Visit Number	**Visits 7 & 12**	**Visits 8 & 13**	**Visits 9 & 14**	**Visits 10 & 15**	**Visits 11 & 16**	-	-
Visit Window	**+ 2 days**	**± 1 day**	**± 3 days**	**± 3 days**	**+ 1 week[e]**	**± 7 days**	**N/A**
Urine pregnancy test	X						
Eligibility to retreatment					X	X	

BTX-A-Abs=botulinum toxin type A antibodies; HV= hallux valgus; IM=intermetatarsal; mFFI=modified foot function index; NPRS=numeric pain rating scale; U=units

a Dysport 300 U or 500 U will be administered to eligible subjects based on investigator judgment and ONLY if the subject meets the protocol-specified retreatment criteria.

b Treatment with Dysport in the open-label period will be administered in 12-week treatment cycles. All eligible subjects will receive open-label treatment with Dysport 300 U at the first retreatment cycle (Cycle 2) in the study foot. At the second retreatment cycle (Cycle 3), subjects will be treated with either Dysport 300 U or 500 U in the study foot based on investigator judgment following clinical evaluation of the subject at the time of retreatment. The decision to increase the dose at the beginning of Cycle 3 will be based on 1) evaluation of safety and tolerability (review of related AEs and consideration of any significant changes in the study foot) and 2) severity of pain (considering NPRS score) and disability (considering mFFI Disability subscale score) experienced by the subject at the time of evaluation.

c This visit must occur on the same day as the last visit of the previous cycle.

d Assessments outlined for Day 85 are the same as those for Day 1 of the subsequent cycle and do not need to be repeated.

e Repeat study treatment must not be administered any sooner than 12 weeks after the last dose.

f Any subject not eligible for retreatment will be evaluated every 4 weeks at additional follow-up visits until they are eligible for retreatment or have completed the study.

g A subject will be considered to have completed the study if he/she has completed a total of 36 weeks follow-up in the study from the first study treatment injection (Treatment Cycle 1, Day 1) and has completed the Day 85 visit following the last injection.

h Subjects will record daily measurements for 7 consecutive days (preferably in the evening) for Cycles 2 and 3 during the open-label period prior to the following visits: Day 1, Week 4, Week 8 and Week 12 using an electronic diary.

i The PGI-I and PGI-S assessments will be completed by the subject at the study site during the study visit. Subjects are to complete these self-assessments using the electronic diary which will be accessed at the site during the visit. Site staff should not help subjects answer questions but must ensure that the subject can access the eDiary to complete the assessment while at the site

j Assessment to include a complete physical examination of the injection sites on the study foot specifically evaluating the foot for any dermatologic, neurologic or musculoskeletal abnormalities (see Section 8.4 for further details).

k The PGI-I and PGI-S assessments will be completed by the subject at the study site during the study visit. Subjects are to complete these self-assessments using the electronic diary which will be accessed at the site during the visit. Site staff should not help subjects answer questions but must ensure that the subject can access the eDiary to complete the assessment while at the site

5.2 Study Visits

Activities to be performed at visits during the DB and OL periods are outlined in Table 3 and Table 4, respectively. Additional details for study visits are provided below as appropriate.

5.2.1 Screening and Enrolment

A signed and dated informed consent form will be obtained before screening procedures during the DB period occur.

After informed consent is obtained, subjects who are screened will be allocated a subject number. All screened subjects must be identifiable throughout the study. The investigator will maintain a list of subject numbers and names to enable records to be found at a later date if required.

If the initial foot evaluated for study entry fails to meet the entry criteria, bilateral HAV subjects are allowed to be rescreened only once for entry in the study using the contralateral foot.

Following confirmation of eligibility for the study, subjects will be given a randomisation/treatment allocation number and allocated to one of the dosing groups specified in Section 6.1.

Each investigator will also maintain a record of all subjects screened into the study (i.e. who signed the informed consent form). Records up to the time of premature termination should be completed. In the event that the subject was not receiving IMP, the primary reason will be recorded.

5.2.2 Additional Follow-up Visits (Double-blind and Open-label Periods)

Additional follow-up visits will be performed every 4 weeks after Visit 6 during the DB period, and after Visits 11 and 16 during the OL period to determine eligibility for retreatment.

5.2.3 End of Study or Early Withdrawal Visit

Subjects who participate in the study in compliance with the protocol for at 36 weeks (DB and OL periods) will be considered to have completed the study.

For subjects who complete the study, or for those who withdraw prematurely from the study, final evaluations will be performed on the last day the subject receives the study treatment, or as soon as possible afterwards. Subjects with ongoing AEs or clinically significant laboratory test abnormalities (as determined by the investigator) will be monitored as described in Section 8.1.4 and Section 8.1.2.4, respectively.

6 TREATMENT OF SUBJECTS

6.1 Investigational Medicinal Product Preparation Storage and Accountability

6.1.1 Investigational Medicinal Product Storage and Security

The investigator, or an approved representative (e.g. pharmacist), will ensure that all IMP and any other study related material is stored in a secured area, under recommended temperature monitored storage conditions, in accordance with applicable regulatory requirements.

To prevent theft or diversion, the IMP will be stored in a securely locked, substantially constructed cabinet or enclosure appropriate for the study treatment. Any actual or suspected theft or diversion must be reported immediately.

6.1.2 Investigational Medicinal Product Preparation

The investigator, or an approved representative (e.g. pharmacist), will ensure that all IMP is reconstituted and dispensed by qualified staff members. Detailed instructions for the preparation before administration of study medication (Dysport and matching Placebo) will be provided in the study IMP Handling manual or similar documentation

6.1.3 Investigational Medicinal Product Accountability

All IMP and any other study related material is to be accounted for on the IMP accountability log provided by the sponsor. It is essential that all used and unused supplies are retained for verification (by the sponsor or sponsor's representative). The investigator should ensure adequate records are maintained in the IMP accountability log.

All used and unused IMP and any other related material is to be destructed at the investigational sites and/or at the Interim Storage facility according to local procedures, regulations and laws.

6.2 Study Drugs Administered

At Screening during the DB period, subjects will be allocated a subject number. Following confirmation of eligibility for the study, subjects will be allocated to treatment with Dysport 300 U, Dysport 500 U or placebo during the DB period.

A blinded kit will be used in this study to maintain the blinding of the study during the DB period. Each blinded kit will contain two vials regardless of treatment assignment: one vial 300 U or placebo and one vial 500 U or placebo. The two vials in each kit will contain either a Dysport 300 U vial + a placebo vial, a Dysport 500 U vial + a placebo vial or two placebo vials, based on treatment assignment. Investigators will be blinded to which vial contains Dysport and which vial contains placebo.

Before each administration, the powder in each vial in the blinded kit will be reconstituted at the investigational site with 1.0 mL of 0.9% sterile (preservative free) sodium chloride for injection. The contents of each vial will be combined for a total volume of 2.0 mL (150 U/mL for Dysport 300 U and 250 U/mL for Dysport 500 U). Investigators will inject 0.5 mL of the reconstituted solution (2.0 mL total volume) containing study treatment into each of the four targeted muscles. Subjects assigned to receive 300 U of Dysport will be treated with 75 U of Dysport per muscle (300 U dose divided equally among, 1) the oblique head of the adductor hallucis muscle; 2) the transverse head of the adductor hallucis muscle; 3) flexor hallucis brevis muscle; and 4) the extensor hallucis brevis muscle muscles); subjects assigned to receive 500 U of Dysport will be treated with 125 U of Dysport per muscle (500 U dose divided equally among the described four muscles); subjects treated with placebo will receive four injections of reconstituted product containing only the excipients described in Dysport, without the addition of toxin (see Section 6.2.2).

During the OL period, subjects will receive treatment with Dysport 300 U or 500 U. At the first retreatment cycle (Cycle 2) during the OL period, subjects will receive Dysport 300 U in the

HAV study foot determined in the DB period. At the second retreatment cycle (Cycle 3), subjects will be treated with either Dysport 300 U or 500 U in the HAV study foot. The Dysport dose to be administered in the HAV study foot will be based on investigator judgment following clinical evaluation of the subject at the time of retreatment. The decision to increase the dose at the beginning of Cycle 3 will be based on 1) evaluation of safety and tolerability (related AEs and if any significant changes occurred in the injected foot) and 2) severity of pain (considering NPRS score) and disability (considering mFFI Disability subscale score) experienced by the subject at the time of evaluation.

6.2.1 Dysport

Dysport is provided in glass vials containing 300 U or 500 U of BTX-A-HAC as a white lyophilised powder for reconstitution. The composition the Dysport 300 U and 500 U vials are provided in Table 5.

Table 5 Dysport Composition (300 U and 500 U Vial)

Active Constituent Per Vial		
Clostridium BTX-A-HAC	500 U	300 U
Other Constituents Per Vial		
Human Serum Albumin	125 µg	125 µg
Lactose monohydrate	2.5 mg	2.5 mg

One unit (U) is defined as the median lethal intraperitoneal dose in mice.

Dysport drug product should be stored at the recommended temperature, in a refrigerator between 2°C and 8°C (36 °F to 46°F). Dysport should not be frozen and protected from light.

The drug product does not contain any microbial agent. Therefore, it is recommended that the product be used within 24 hours after reconstitution.

6.2.2 Placebo

Placebo is provided in glass vials and will be undistinguishable from the active product. Placebo will contain only the excipient described in Dysport, without the addition of toxin, as white lyophilized powder for reconstitution. There will be two matching placebo vials: one matching the 500 U Dysport vial and one matching the 300 U Dysport vial. The constituents in both placebo vials are identical:

- **Constituent per vial**:
  - Human Serum Albumin: 125 µg
  - Lactose monohydrate: 2.5 mg

Placebo product should be stored at the recommended temperature (between 2°C and 8°C).

The drug product does not contain any microbial agent. Dysport should not be frozen and protected from light.

6.2.3 Injection –Guided Technique

To administer the study treatment, a peripheral electrical stimulator (with or without complementary techniques for identifying target muscles) will be used to locate the muscles in the foot. A Teflon coated, 22 to 30-gauge, open lumen needle will be used to stimulate the targeted muscle once per second (repetitive square wave pulses, 0.25 msec in duration). Injection will be performed when either a continuous or stretch of muscle has been induced by the electrical stimulator confirming the location of the targeted muscle.

Further details of the use of electrical stimulator are provided in the study injection manual.

6.3 Concomitant Medication/Therapy

Any prior or concomitant therapy or medication given to a subject within 30 days before IMP administration or during IMP administration will be indicated on the eCRF. Dose and generic name or tradename will be indicated.

The following concomitant medications are not permitted during this study:

- Botulinum toxin for administration into any site of the body other than Dysport for HAV, with the exception of glabellar lines or other aesthetic face applications of toxin.
- Any investigational new drug or device or off label use of any drug.
- Aminoglycoside antibiotics or other drugs that interfere with neuromuscular transmission.
- Opioids
- Any medication not specifically permitted by the protocol which has antinociceptive (pain relieving) properties. This includes any and all narcotic pain relievers, as well as pregabalin and gabapentin.
- Subjects who require treatment with antipsychotic (e.g. D2 antagonists) or antidepressant (e.g. selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors) medications will need to demonstrate evidence of stable dose regimen in the 30 days prior to Screening and will maintain that dose for the duration of the study.

The following concomitant medications are permitted during this study but they must be monitored closely and every effort should be made to keep their dose and dose regimen constant throughout the course of the study.

- Concomitant use of anticholinergic drugs (which may potentiate systemic anticholinergic effect) is permitted if the dosage has been stable for 6 weeks prior to study treatment and is expected to remain at this stable dose throughout the study.
- Concomitant use of over-the-counter medications for the symptomatic treatment of minor ailments (e.g. common cold). Specifically, these include non-steroidal anti-inflammatory medications (e.g. aspirin, ibuprofen), anti-pyretic agents (e.g. acetaminophen), antihistamines (e.g. loratadine) and expectorants (e.g. guaifenesin).
- After consultation with prescribing physician, anticoagulant medications must be stopped 3 days prior to administration of study treatment. These medications can be restarted one day after administration of study treatment and can be stopped for a longer period if deemed necessary in the opinion of the investigator, and in compliance with standard medical practice and the manufactures' discontinuation recommendations for the medication. Anticoagulant medications permitted during the study include, but are not limited to:
  - warfarin and other coumadin derivatives
  - acetylsalicylic acid (including low-dose aspirin)
  - clopidogrel/ticlopidine

  If medically indicated, lower molecular weight heparins are permitted providing the last dose was within 24 hours prior to administration of study treatment, and may be restarted one day following administration of study treatment.
- Topical or oral anaesthesia for pain management of the injection site.

6.4 Lifestyle Restrictions/Recommendations

Besides restrictions already presented in the exclusion criteria, subjects should not use an orthotic device or 'over-the-counter shoe-insert' which could influence the functioning of the hallux of the study foot in any way during the study. This includes toe-spacers or any other

device intended for this purpose. Over-the-counter shoe inserts will be permitted during the study only for subjects who have used these for at least 30 days prior to screening.

6.5 Procedures for Monitoring Subject Compliance

The study treatment will be administered at the investigational site; therefore, compliance is not likely to be an issue.

6.6 Priority Order on Study Procedures

The following priority order should be followed in case study procedures are scheduled at the same time point:

1. NPRS*
2. mFFI*
3. PGI-I and PGI-S (pain and disability)
4. SF-36
5. Weight-bearing radiographs

*These assessments are assessed at home after baseline.

7 ASSESSMENT OF EFFICACY

For the timing of assessments in this study, refer to the schedule in Table 3 and Table 4.

7.1 Methods and Timing of Assessing, Recording, and Analysing Efficacy Data

Methods for assessing efficacy data is described below. Timing of efficacy assessments are discussed in Section 5. Procedures for recording efficacy data are discussed in Section 15.1, and methods of analyses are discussed in Section 11.4.3. For all assessments related to pain, the subject is to be instructed by the investigator to report severity specifically for his/her study foot when completing the questionnaires using the e-diary. The Sponsor will provide a device (to complete the e-diary questionnaires) in the clinical trial if requested by subjects or in situations in which the subject is not willing or able to use their own device. The device will be returned to the site at the completion of the subjects' participation in the trial. Also, it is critical that investigators and site staff instruct and remind subjects to complete home-based self-assessments (eg, NPRS, mFFI) in the evening.

7.1.1 Numeric Pain Rating Scale

The NPRS is a widely used and validated unidimensional measure of pain intensity in adults. Subjects will be asked to rate the intensity of their foot pain during physical activity (e.g. walking, standing or running) based on an 11-point scale ranging from 0 to 10, where 0 equals “no pain” and 10 equals “worst possible pain”. They will be asked to rate their daily pain intensity by responding directly to the following question: "Please rate the average intensity of the pain in your **treated** foot while performing physical activities (e.g. standing, walking or running) over the past 24 hours".

Daily pain intensities will be recorded by the subject using an electronic diary for 7 consecutive days prior to the study visits as outlined in Section 5.1. The electronic diary should be completed by the subject at the same time each day, **preferably in the evening**. The subject should be instructed by the investigator to focus on his/her study foot when completing the questionnaire. This instruction is critical in subjects with bilateral disease.

7.1.2 Modified Foot Function Index

The FFI was developed to assess foot-related pain, disability and activity limitations, and later revised to include foot-related health and quality of life [19; 20; 21]. A modified version of the FFI specific to this study is provided in Appendix 1. It is a self-administered specific patient-reported outcome measure of foot pain plus evoked foot pain, and the impact of foot pathologies on disability and activity limitations. The mFFI consists of a total of 21 items grouped into three subscales: pain (seven questions), disability (nine questions), and activity limitation (five questions). The mFFI items are rated using numeric rating scales ranging from 0 to 10 and cover a period of the 'past' 24 hours. The poles are labelled "no pain" and "worst pain imaginable" (pain), "no difficulty" and "so difficult unable to do" (disability), and "none of the time" and "all of the time" (limitations). For each item, the subject is asked to record the number value which best corresponds to the effect of the foot complaints. To obtain a subscale score, the item scores for a given subscale (i.e. pain, disability or activity limitation subscales) are totalled and divided by the maximum total possible and then multiplied by 100. Each subscale score, as well as the total score, will range from 0 to 100. If a patient did not perform the task listed in the question, they will be instructed to mark the item as not applicable (N/A).

Daily pain intensities, disability and activity limitations will be recorded by the subject using an electronic diary for 7 consecutive days prior to the study visits as outlined in Section 5.1. The electronic diary should be completed by the subject at the same time each day, **preferably in the evening**. The subject should be instructed by the investigator to focus on his/her study foot when completing the questionnaire. This instruction is critical in subjects with bilateral disease. In addition, all subjects should be educated on the proper use of the "not applicable" option. For example, subjects that do not stand on their tiptoes in the course of their daily lives should mark "not applicable" for that particular item. However, if the subject does not stand on his or her tiptoes due to their disease, then he or she should choose the option "so difficult unable to do".

7.1.3 Intermetatarsal Angle, Hallux Valgus Angle and Sesamoid Position

Intermetatarsal angle, HV angle and tibial sesamoid position will be measured directly on weight-bearing anteriorposterior radiographs, in which the X-ray beam is angled 15° towards the heel centered on the second tarsometatarsal joint with a source to image-receptor distance of 100 cm. Radiographic measurements will be conducted by following the General Acquisition Guidelines document provided to sites by the Sponsor to ensure accurate reproducibility of image acquisition across sites. Images should be taken by the same radiology technician. Angle measurements will be performed by a blinded central reader.

7.1.4 36-Item Short Form Health Survey

The SF-36 is a 36-item questionnaire which measures the extent to which physical health impacts an individual's functional ability and perceived well-being in mental, social and physical aspects of life. The SF-36 has eight individual subscales divided across physical and psychological domains: physical function, role physical, bodily pain, global health, vitality, social function, role emotional and mental health. Scores on these subscales can be combined to form two higher-order summary scores, the Physical Component Summary and Mental Component Summary. The Physical Component Summary is calculated by positively weighting the four subscales in the physical domain (physical function, role physical, bodily pain and global health) and the remaining psychological domain subscales negatively. In contrast, the Mental Component Summary is calculated by positively weighting the four mental domain subscales (mental health, vitality, social function and role emotional), and negatively weighting the four physical domain subscales.

7.1.5 Patient Global Impression of Improvement of Foot Pain

An assessment of PGI-I of foot pain will be conducted by the subject using a 7-point Likert scale (from -3: very much worse to +3: very much improved). The PGI-I will be assessed by the subject answering the following question: “Compared to your foot pain prior to the study treatment initiation, your foot pain while performing physical activities (e.g. standing, walking or running) now is: +3=very much improved; +2=much improved; +1=minimally improved; 0=no change; -1=minimally worse; -2=much worse; -3=very much worse”). Also, an additional question will be included in the PGI-I assessment which will ask patients the following: "If you experienced a change, was this change meaningful to you? (Yes/No)"

The PGI-I of foot pain will be recorded by the subject using an electronic diary during the study visits at site as outlined in Section 5.1. The subject should be instructed by the investigator to focus on his/her study foot when completing the questionnaire. This instruction is critical in subjects with bilateral disease.

7.1.6 Patient Global Impression of Severity of Foot Pain

An assessment of PGI-S of foot pain will be conducted by the subject using a 4-point Likert scale (from 0: no pain to 3: severe pain). The PGI-S will be assessed by the subject by answering the following question: “How severe was your foot pain while performing physical activities (e.g. standing, walking or running) over the past week?” (0=no pain; 1=mild pain; 2=moderate pain; 3=severe pain).

The PGI-S of foot pain will be recorded by the subject using an electronic diary during the study visits on site as outlined in Section 5.1. The subject should be instructed by the investigator to focus on his/her study foot when completing the questionnaire. This instruction is critical in subjects with bilateral disease.

7.1.7 Patient Global Impression of Improvement of Disability

An assessment of PGI-I of the subject's disability will be conducted by the subject using a 7-point Likert scale (from -3: very much worse to +3: very much improved). The PGI-I will be assessed by the subject answering the following question: “Compared to your disability prior to the study treatment initiation, your disability while performing physical activities (e.g. standing, walking or running) now is: +3=very much improved; +2=much improved; +1=minimally improved; 0=no change from baseline; -1=minimally worse; -2=much worse; -3=very much worse”). In addition, an additional question will be included in the PGI-I assessment which will ask patients the following: "If you experienced a change, was this change meaningful to you? (Yes/No)"

The PGI-I of disability will be recorded by the subject using an electronic diary during the study visits on site as outlined in Section 5.1.

7.1.8 Patient Global Impression of Severity of Disability

An assessment of PGI-S of disability will be conducted by the subject using a 4-point Likert scale (from 0: no disability to 3: severe disability). The PGI-S will be assessed by the subject by answering the following question: “How severe was your disability while performing physical activities (e.g. standing, walking or running) over the past week?” (0=no disability; 1=mild disability; 2=moderate disability; 3=severe disability).

The PGI-S of disability will be recorded by the subject using an electronic diary during the study visits on site outlined in Section 5.1.

8 ASSESSMENT OF SAFETY

8.1 Adverse Events

Adverse events will be monitored from the time that the subject gives informed consent and throughout the study until at least 14 days after the last dose of study treatment. Information will be elicited by direct, nonleading questioning or by spontaneous reports. Further details for AE reporting can be found in Section 8.1.2.

The investigator will be responsible for a clinical safety assessment of the study participants during the whole participation of the subjects in the study, from informed consent up to discharge from the study, and for the setup of a discharge plan if needed.

The sponsor medical monitor and the global patient safety physician will monitor safety data throughout the course of the study.

8.1.1 Definition of an Adverse Event

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g. nausea, chest pain), signs (e.g. tachycardia, enlarged liver) or the abnormal results of an investigation (e.g. laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run in or washout periods, even if no IMP has been administered.

This definition includes events occurring from the time of the subject giving informed consent until the end of the study (as defined in Section 3.6).

8.1.2 Categorisation of Adverse Events

8.1.2.1 Intensity Classification

Adverse events will be classified as mild, moderate or severe according to the following criteria:

- **Mild**: symptoms do not alter the subject's normal functioning
- **Moderate**: symptoms produce some degree of impairment to function, but are not hazardous, uncomfortable or embarrassing to the subject
- **Severe**: symptoms definitely hazardous to wellbeing, significant impairment of function or incapacitation.

8.1.2.2 Causality Classification

The relationship of an AE to IMP administration will be classified according to the following:

- **Related**: reports including good reasons and sufficient information (e.g. plausible time sequence, dose response relationship, pharmacology, positive dechallenge and/or rechallenge) to assume a causal relationship with IMP administration in the sense that it is plausible, conceivable or likely.
- **Not related**: reports including good reasons and sufficient information (e.g. implausible time sequence and/or attributable to concurrent disease or other drugs) to rule out a causal relationship with IMP administration.

8.1.2.3 Assessment of Expectedness

The reference document for assessing expectedness of AEs/event in this study will be the current Dysport Therapeutics IB.

8.1.2.4 Laboratory Test Abnormalities

Abnormalities in laboratory test values should only be reported as AEs if any of the following apply:

- They result in a change in IMP schedule of administration (change in dosage, delay in administration, IMP discontinuation),
- They require intervention or a diagnosis evaluation to assess the risk to the subject,
- They are considered as clinically significant by the investigator.

8.1.2.5 Abnormal Physical Examination Findings

Clinically significant changes, in the judgement of the investigator, in physical examination findings (abnormalities) will be recorded as AEs.

8.1.2.6 Other Investigation Abnormal Findings

Abnormal test findings as judged by the investigator as clinically significant that result in a change in study drug dosage or administration schedule, or in discontinuation of the study drug, or require intervention or diagnostic evaluation to assess the risk to the subject, should be recorded as AEs.

8.1.3 Adverse Events of Special Interest

Adverse events of special interest (AESIs) for Dysport are AEs that suggest a possible remote spread of effect of the toxin or events suggestive of hypersensitivity like reactions. The effects of Dysport and all BTX products may spread away from the area of injection to produce symptoms consistent with remote spread of BTX effects. These symptoms have been reported hours to weeks after injection. The events of remote spread of toxin maybe severe and affects swallowing and breathing, can be life threatening, and there have been reports of death. The risk of symptoms is increased in subjects who have underlying conditions (e.g. disorders of the neuromuscular junction) that would predispose them to these symptoms. Dysport is contraindicated in individuals with known hypersensitivity to any BTX preparation or to any of the components in the formulation.

A list of preferred terms of AESIs will be provided in the Statistical Analysis Plan (SAP). All AEs will be monitored by the sponsor to determine if they meet the criteria of AESIs. These AESIs will be further analysed to determine if there is a plausible possibility that they represent remote spread of toxin or hypersensitivity like reactions. In order to perform the analysis, variables including alternative aetiology (medical history, concomitant medication, or diagnosis which could account for the symptoms), location of Dysport administration, and temporal relationship to Dysport administration will be considered by the sponsor.

8.1.4 Recording and Follow up of Adverse Events

At each visit, the subject should be asked a nonleading question such as: “How have you felt since starting the new treatment/the last assessment?”

All observed or volunteered AEs, regardless of treatment group or suspected causal relationship to IMP, will be recorded on the AE page(s) of the eCRF. Events involving drug reactions, accidents, illnesses with onset during the treatment phase of the study, or exacerbations of pre-existing illnesses should be recorded.

Any AEs already recorded and designated as ‘continuing’ should be reviewed at each subsequent assessment.

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a SAE requiring immediate notification to the sponsor or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE (i.e. IMP or other illness). The investigator is required to assess causality and record that assessment on the eCRF. Follow up of the AE, after the date of IMP discontinuation, is required if the AE or its sequelae persist. Follow up is required until the event or its sequelae resolve or

stabilise at a level acceptable to the investigator and the sponsor's clinical monitor or his/her designated representative.

8.1.4.1 Reporting of Adverse Events

Any AE occurring during the study, from informed consent until 14 days after the end of study/early discontinuation must be reported to the Sponsor.

Any AE considered related to IMP administration that the investigator becomes aware of after completion of the end of study/early discontinuation visit must be reported to the sponsor and will be recorded in the clinical database.

8.1.5 Reporting of Serious Adverse Events

All SAEs (as defined below) regardless of treatment group or suspected relationship to IMP must be reported immediately (within 24 hours of the investigator's knowledge of the event) using the e-mail address specified at the beginning of this protocol. If the immediate report is submitted by telephone, this must be followed by detailed written reports using the SAE report form.

A SAE is any AE that:

(1) Results in death,

(2) Is life threatening, that is any event that places the subject at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death,

(3) Results in in-patient hospitalisation or prolongation of existing hospitalisation, excluding admission for social or administrative reasons (see further),

(4) Results in a persistent or significant disability/incapacity, where disability is a substantial disruption of a person's ability to conduct normal life functions,

(5) Results in congenital anomaly/birth defect in the offspring of a subject who received the IMP,

(6) Is an important medical event that may not result in death, be life threatening, or require hospitalisation when, based upon appropriate medical judgement, may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalisation, or the development of drug dependency or drug abuse.

In addition to the above criteria, any additional AE that the sponsor or an investigator considers serious should be immediately reported to the sponsor and included in the corporate SAEs database system.

- Hospitalisation is defined as any in-patient admission (even if less than 24 hours). For chronic or long-term in-patients, in-patient admission also includes transfer within the hospital to an acute/intensive care in-patient unit.
- **Prolongation of hospitalisation** is defined as any extension of an in-patient hospitalisation beyond the stay anticipated/required in relation to the original reason for the initial admission, **as determined by the investigator or treating physician**. For protocol-specified hospitalisation in clinical studies, prolongation is defined as any extension beyond the length of stay described in the protocol. Prolongation in the absence of a precipitating, treatment emergent, clinical AE (i.e. not associated with the development of a new AE or worsening of a pre-existing condition) may meet criteria

for "seriousness" but is not an adverse experience and thus is not subject to immediate reporting to the sponsor.

- Preplanned or elective treatments/surgical procedures should be noted in the subject's screening documentation. Hospitalisation for a preplanned or elective treatment/surgical procedure should not be reported as an SAE unless there are complications or sequelae which meet the criteria for seriousness described above.

Any SAE must be reported immediately (within 24 hours), using the e-mail address specified at the beginning of this protocol, independent of the circumstances or suspected cause, if it occurs or comes to the attention of the investigator at any time during the study period.

Any AE/SAE with a suspected causal relationship to IMP administration occurring at any other time after completion of the study must be promptly reported.

The following information is the minimum that must be provided to the sponsor within 24 hours for each SAE:

- Study number
- Centre number
- Subject number
- AE
- Investigator's name and contact details

The additional information included in the SAE form must be provided to the sponsor or representative as soon as it is available. The investigator should always provide an assessment of causality for each event reported to the sponsor. Upon receipt of the initial report, the sponsor will ask for the investigator's causality assessment if it was not provided with the initial report.

The investigator should report a diagnosis or a syndrome rather than individual signs or symptoms. The investigator should also try to separate a primary AE considered as the foremost untoward medical occurrence from secondary AEs which occurred as complications.

8.1.6 Pregnancy

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IMP has interfered with a contraceptive method. If pregnancy occurs during the study, the outcome of the pregnancy will then need to be collected post study and it may be necessary to discontinue administration of the IMP.

Information regarding pregnancies must be collected on the AE page of the eCRF. The sponsor will request further information from the investigator as to the course and outcome of the pregnancy using the Standard Pregnancy Outcome Report Form.

The investigator must instruct all female subjects to inform them immediately should they become pregnant during the study. The investigator should counsel the subject, discuss the risks of continuing with the pregnancy and the possible effects on the foetus. Monitoring of the subject should continue until conclusion of the pregnancy, which may involve follow up after the subject's involvement in the study has ended.

Pregnancies with a conception date during the study period (or within 12 weeks of the subject being dosed with IMP, if early discontinuation) must also be reported to the investigator for onward reporting to the sponsor.

8.1.7 Deaths

All AEs resulting in death either during the study period or within 12 weeks (84 days) after the last dose of IMP, must be reported as an SAE within 24 hours of the investigator's knowledge of the event.

The convention for recording death is as follows:

- Adverse event term: lead cause of death (e.g. multiple organ failure, pneumonia, myocardial infarction),
- Outcome: fatal.

The **only exception** is if the cause of death is unknown (i.e. sudden or unexplained death), in which case the AE term may be "death" or "sudden death".

8.1.8 Discontinuation/Withdrawal due to Adverse Events/Serious Adverse Events

Discontinuation/withdrawal due to AEs should be distinguished from discontinuation/withdrawal due to insufficient response to the IMP (see Section 4.4).

If the IMP is discontinued due to a SAE, it must be reported immediately to the sponsor's designated representative (see Section 8.1.5).

In all cases, the investigator must ensure the subject receives appropriate medical follow up (see Section 8.1.4).

8.1.9 Reporting to Competent Authorities/IECs/IRBs/Other Investigators

The sponsor will ensure that processes are in place for submission of reports of Suspected Unexpected Serious Adverse Reactions (SUSARs) occurring during the study to the Competent Authorities (CA), IECs and other investigators concerned by the IMP. Reporting will be done in accordance with the applicable regulatory requirements.

For study centres in the USA, Investigational New Drug Application Safety Reports will be submitted directly to the investigators. It is the investigators' responsibility to notify their IRB in a timely manner.

8.2 Clinical Laboratory Tests

Blood and urine samples will be collected during the DB and OL periods as described in the study procedures and assessments in Table 3 and Table 4 for the evaluation of haematology and serum chemistry and urine examination.

The total volume of blood drawn for all evaluations throughout this study is approximately 54 mL for each subject.

The investigator will review the safety laboratory test results, document the review, and record any clinically relevant changes occurring or observed during the study in the AE section of the eCRF (see Section 8.1.2.4 for abnormal laboratory tests that should be recorded as AEs).

8.2.1 Haematology

Blood samples will be collected in a potassium ethylenediamine tetra-acetic acid tube to assess the following variables: red blood cell count, haemoglobin, haematocrit, mean corpuscular volume, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration, white blood cell count with differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils) and platelet count.

8.2.2 Blood Biochemistry

Blood samples will be collected in an activator gel tube to assess the following parameters:

- urea, creatinine, total bilirubin, conjugated bilirubin
- chloride, bicarbonate, sodium, potassium, calcium, phosphate
- alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transferase
- albumin total protein, total cholesterol, triglycerides, glycated haemoglobin

Blood samples will be collected in a citrated tube to assess the following coagulation variables: activated partial thromboplastin time, prothrombin time and its derived measures of prothrombin ratio and international normalised ratio.

8.2.3 Pregnancy Test

A human chorionic gonadotrophin urine test will be performed for all female subjects of childbearing potential at Screening (Visit 1), as well as at other timepoints as indicated in the study procedures and assessments (Table 3 and Table 4), and if clinically indicated thereafter. Any subject becoming pregnant during the study will be withdrawn. All pregnancies that occur during the study are to be reported as described in Section 8.1.6.

8.2.4 Drug of Abuse Testing

Urine drug screen testing for opiates, cannabis, cocaine and amphetamines will be performed as specified in Table 3 and Table 4 at the study site, and at any time at the discretion of the investigator.

8.2.5 Immunogenicity

Blood samples will be collected for the detection of antibodies to BTX-A (6 mL samples per timepoint). Each sample will be left to stand for 30 minutes at room temperature and the tubes should be centrifuged at approximately 1300 g for 10 minutes at 4°C. The serum will be removed and transferred into three aliquots in clean plastic tubes (approximately 0.5 mL, 0.5 mL, 3 mL, respectively). This sample process has to be made in the most sterile possible conditions. The resulting serum will be stored at -20°C or below. Each tube should be labelled with the sample identification, study number, site number, subject number and initials, and visit number (when applicable). Serum samples will be sent to the central laboratory for storage up to analysis by the bioanalytical CRO.

Batch shipping to the bioanalytical CRO will be arranged by the central laboratory at appropriate interval.

All samples will be tested initially for the presence of binding antibodies using a validated immunoassay. Samples found positive for the presence of binding antibodies will be analysed for the presence of neutralising antibodies using a functional assay. Additional aliquots (i.e. back-up samples) will be archived at the central laboratory. Archived samples will be destroyed at the end of the study.

Full details regarding required the processing, labelling and shipment processes for these samples are provided in the Study Manual.

The determination of antibodies against BTX-A will be evaluated using a validated method:

- RS16-077-IP: Validation of the ECLA method for the detection of binding antibodies to Dysport in human serum samples by KYMOS PHARMA SERVICES, S.L.
- RS15-574-IP: Validation of a Cell Based Assay (CBA) for the detection of neutralising antibodies to BoNT/A in human serum samples by KYMOS PHARMA SERVICES, S.L.

8.3 Physical Examination

Physical examinations, including body weight, will be conducted as outlined in Table 3 and Table 4 and height will be measured at Baseline.

Any new clinically significant physical examination findings (abnormalities) observed during the study will be reported as AEs. Any physical examination findings (abnormalities) persisting at the end of the study will be followed by the investigator until resolution or until reaching a clinically stable endpoint.

8.4 Examination of the Study Foot

A complete physical examination of the study foot will be conducted as outlined in Table 3 and Table 4 for the DB and OL periods. The examination will include evaluation of the a) dermatologic, b) neurologic and c) musculoskeletal condition of the study foot. For dermatologic and musculoskeletal foot examinations, the Investigator will record whether a given abnormality or deformity is present. For neurological examinations, the Investigator will record whether the specified neurological parameters are "normal" or "abnormal" based on clinical presentation.

Any findings that were not present at Baseline based on examination of the study will be recorded as AEs. As for all AEs reported during the study, the investigator should use his/her medical judgment to determine if treatment of the study foot is required based on an abnormal finding, and/or if the subject should be withdrawn from the study due to an abnormal finding in the study foot.

Details for each of the study foot examination parameters required during the study are provided in the sections below.

8.4.1 Dermatologic Examination

The dermatologic examination will consist of a global inspection of the study foot and injection sites for injection site irritations, ulcerations, bleeding, discolorations, calluses, wounds, fissures, lesions, macerations, nail dystrophy, hyperpigmentation, erythema, oedema or paronychia. Inspection of the toes should include a search for fungal, ingrown or elongated nails, as well as areas between the toes for the presence of deeper lesions. The investigator will evaluate and record whether these or other dermatological conditions are present in the study foot and will record new findings as AEs that were not present at Baseline resulting from the dermatologic examination.

8.4.2 Neurologic Examination

The neurological examination will consist of the evaluation of protective sensation using the Ipswich Touch Test [22], as subjects who develop neuropathies with loss of sensation at are increased risk for unrecognized injury. The subject will be instructed to close their eyes while the investigator lightly rests his/her finger on each of the subject's first, third and fifth toes of the study foot for 1 to 2 seconds. Subjects will be instructed to respond "yes" when they feel the investigator's touch. The investigator will evaluate and record whether the neurological condition of the study foot is "normal" or "abnormal" based on their medical judgment regarding the degree of loss of sensation in the study foot and will record new findings as AEs that were not present at Baseline resulting from the neurological examination.

8.4.3 Musculoskeletal Examination

The musculoskeletal examination will include a visual inspection of the study foot, as well as direct evaluation via palpation, range of motion (ie, dorsiflexion, plantar flexion), motor strength and muscle tone to identify the presence of abnormalities or foot deformities (except for HAV). The investigator will specifically look for the presence of bony prominences, asymmetry, wasting, fasciculations or the presence of foot deformities (except for HAV) including but not limited to hammer toe, claw toe, Charcot's neuroarthropathy, pes planus, cavus planus, Morton's neuroma, or hallux limitus. The investigator will evaluate and record whether these or other musculoskeletal conditions of the study foot are present and will record

new findings as AEs that were not present at Baseline resulting from the musculoskeletal examination.

8.5 Vital Signs

Blood pressure and heart rate will be assessed with an automated device so that measurements are independent of the observer. Blood pressure and heart rate will be recorded after five minutes' rest in sitting position. Absolute values and change from Baseline will be analysed.

Respiratory rate and temperature oral will be recorded.

9 ASSESSMENTS OF PHARMACOKINETICS/PHARMACODYNAMICS

Pharmacokinetics and pharmacodynamics are not assessed in this study.

10 EXPLORATORY BIOMARKERS AND BIOBANKING

No exploratory biomarkers or biobanking will be performed during this study.

11 STATISTICS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a SAP, which will be dated and completed before the interim analysis. The SAP may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint and/or its analysis will also be reflected in a protocol amendment.

Statistical evaluation will be performed using Statistical Analysis System (SAS)® (version 9.1 or higher)

11.1 Analyses Populations

The following populations will be used during statistical analyses:

- **Screened population**: All subjects screened (i.e. who signed the informed consent).
- **Safety population**: All subjects who received at least one dose of IMP administration (including only partial administration).
- **Intention-to-treat (ITT) population**: All randomised subjects (i.e. who were randomly allocated to a treatment group by IRT).
- **Per protocol (PP) population**: All subjects in the ITT population for whom no major protocol deviations (which may interfere with efficacy evaluation) occurred until Week 8 of the DB period.
- **Open-label (OL) population**: All randomised subjects who received at least one dose of Dysport (including only partial administration) during the OL period.
- **Active Treatment population**: All randomised subjects who received at least one dose of Dysport (including only partial administration) during the DB or OL period

11.1.1 Populations Analysed

The primary analysis based on the primary efficacy endpoint will be performed on the ITT population. In addition, PP analysis will be performed as confirmatory. Secondary analyses based on secondary efficacy endpoints will be performed on the ITT population (for the DB period) and on the Active Treatment population (for analysis by active treatment cycle).

The analyses of safety data will be performed based on the safety population.

11.1.2 Reasons for Exclusion from the Analyses

Any major protocol deviation (see Section 13.1.2 for definition) will be described and its impact on inclusion in PP population for any subject will be specified. The final list of protocol deviations impacting the PP population will be reviewed prior to database lock, before any unblinding of treatment groups. The list may be updated, up to the point of database lock.

11.2 Sample Size Determination

Several lines of evidence have established that a reduction of approximately 2 points or 10% to 30% on the NPRS represents a clinically important difference for evaluations of pain intensity in numerous musculoskeletal disorders [23; 24; 25; 26; 27; 28], as well as specifically in HAV patients following treatment [13; 29]. Several interventional studies have demonstrated treatment-placebo differences in the NPRS ranging from 1.5 to 2.0 points in HAV patients [13; 30]. Based on these findings, a difference of 1.5 points between Dysport and Placebo is anticipated in the change from baseline in the mean daily NPRS score averaged for the 7 consecutive days prior to the Week 8 DB visit.

A sample size of 165 subjects (55 subjects per treatment group) is required to demonstrate the superiority of each of the two Dysport doses (300 U and 500 U) over placebo. This calculation is based on the following assumptions:

- a mean difference of 1.5 points observed between the Dysport and placebo groups in the mean daily NPRS score averaged for the 7 consecutive days prior to the Week 8 visit in the DB period;
- a common standard deviation of 2.5,
- a treatment group ratio of 1:1:1,
- a Hochberg procedure is implemented to control the family-wise Type 1 error rate at one-sided 2.5% level for comparisons of two Dysport doses versus placebo,
- a minimal power of 80%, corresponding for a comparison based on power using a Type I error rate from a one-sided test at 1.25% level.

An interim analysis will be conducted after the first 110 randomised subjects have been followed up for at least 12 weeks. To account for this interim analysis, the overall type I error for each comparison is controlled at the one-sided 0.025 level using O'Brien Fleming spending per Lan-DeMets spending function specification. Treatment comparison with an O'Brien Fleming spending corresponds to a nominal one-sided alpha of 0.0062 at the interim and 0.0231 at the final analysis.

To implement the Hochberg procedure, decision rules are the following:

- At interim look:
  Compare larger p-value to 0.0062
  - if <larger of 2 p-values> <0.0062 then stop and declare evidence of effect for each arm,
  - If not, compare <smaller of 2 p-values> to 0.0062/2. If <smaller of 2 p-values> <0.0062/2, then conclude evidence of effect for arm with the smallest p-value
- At final look (if outcome of interim analysis is to continue):
  Compare larger p-value to 0.0231
  - if <larger of 2 p-values> <0.0231 then stop and declare evidence of effect for each arm
  - If not, compare <smaller of 2 p-values> to 0.0231/2. If <smaller of 2 p-values> <0.0231/2, then conclude evidence of effect for arm with the smallest p-value

The non-binding futility boundary is set to declare futility if the one-sided p-value for a comparison is above 0.30.

Considering the Hochberg adjustment for two experimental arms, this interim analysis plan results in a minimal power of at least 80 % to detect a treatment effect of 1.5 units in a Dysport arm.

Details regarding operational aspects of the interim analysis are described in an Interim Analysis Charter.

11.3 Significance Testing and Estimations

The primary efficacy hypotheses are as follow:

- H_0: there is no difference between treatment with Dysport 300 U and Dysport 500 U versus treatment with Placebo with respect to the change from baseline in the mean daily NPRS score averaged for the 7 consecutive days prior the DB Week 8 visit.
- H_1: There is a difference between treatment with Dysport 300 U or Dysport 500 U and treatment with Placebo with respect to the change from baseline in the mean daily NPRS score averaged for the 7 consecutive days prior the DB Week 8 visit.

For the primary efficacy analysis, a Hochberg procedure will be applied to control the global type I error at one-sided 2.5% significance level.

For other efficacy analyses, all statistical tests will be performed one-sided with a type I error rate set at 2.5%. For safety analyses, no formal statistical analyses will be carried out; only descriptive statistics will be provided.

11.4 Statistical/Analytical Methods

Statistical analyses will be performed by an external CRO, managed by the sponsor's biometry department.

11.4.1 Demographic and Other Baseline Characteristics

In order to assess balance of treatment groups, descriptive summary statistics (n, mean, standard deviation (SD), median, minimum, maximum) or frequency counts of demographic and baseline data (medical history, concomitant disease, etc.) will be presented by treatment group and overall.

11.4.2 Subject Disposition and Withdrawals

The numbers and percentages of subjects enrolled and included in each analysis populations will be tabulated by centre. The reasons for subject exclusions from each of the populations will also be tabulated. In addition, the numbers of subjects who discontinued and completed at each of the study periods (DB and OL period) will be tabulated. Primary reasons for discontinuation of study treatment will be tabulated.

11.4.3 Efficacy Evaluation

11.4.3.1 Analysis of the Primary Efficacy Endpoint

The primary efficacy endpoint is the change from baseline in foot pain as measured by the daily NPRS score averaged over the 7 consecutive days prior to the Week 8 DB visit. Baseline is defined as the daily NPRS score averaged over the 7 consecutive days prior to the baseline visit.

The NPRS score data collected over the 7 consecutive days prior to a visit will be retrieved using an electronic diary (see Section 7.1.1).

The estimate of the treatment effect will be the difference in mean change from baseline in the daily NPRS score averaged over the 7 consecutive days prior to the Week 8 DB visit between each Dysport dose group and the placebo group.

The primary estimand will be based on "treatment policy" strategy, which is the estimate of the treatment effect regardless of whether the subject has an intercurrent event during the study. Potential intercurrent events are the following:

(1) Use of prohibited pain medication,

(2) Surgery for HAV.

No treatment switch or interruption is possible as the primary efficacy endpoint is evaluated following a single injection of study treatment. Intercurrent event (1) is unlikely to occur, as the evaluation period for the primary efficacy endpoint is up to Week 8 (short period).

Intercurrent event (2) is also unlikely to occur. All subjects with this level of pain severity and angular displacement are considered surgical candidates theoretically. However, the upper limit on HV angle (30 degrees) will likely limit the need for a "rescue" surgery.

Subjects are expected to continue follow-up assessments regardless of these two intercurrent events. NPRS scores will be used as observed.

A mixed model for repeated measures (MMRM) on change from baseline in foot pain as measured by the daily NPRS score averaged over the 7 consecutive days prior to each scheduled assessment timepoint of the DB period (up to Week 12) will be used to evaluate the estimand and compare treatment groups.

This model will include the fixed categorical effects of treatment group, visit, treatment-group-by-visit interaction, the stratification parameter as fixed categorical covariates and the baseline value as fixed continuous covariate. The treatment group factor will have three levels (Dysport 300 U, Dysport 500 U and placebo), the factor visit three levels (Week 4, Week 8 and Week 12) and the stratification parameter two levels (unilateral and bilateral HAV).

Average scores will be calculated if there is at least 5-day e-diary completed. No missing baseline is expected as NPRS assessment is part of the inclusion criteria. Subjects will have reminders to complete the electronic diary, and site staff will be alerted if they miss a day. Therefore, the risk of having missing days is minimized. However, if subjects have no post-baseline efficacy assessment, Week 8 score will be imputed (imputation method will be described in the SAP). Other missing data will be considered missing at random (MAR).

Sensitivity analysis

Two sensitivity analyses will be performed to investigate the robustness of the primary efficacy analysis. First, the primary efficacy analysis will be re-run imputing missing data as described in Table 6.

Table 6 Rules for Missing Data Associated with the NPRS

Reason for missing data	Imputation of the missing NPRS score
More than 2 days missing in the 7-day NPRS e-diary assessment	Multiple imputation based on subject with similar characteristics on the same treatment group.
Subject withdrawal before Week 8 of the DB period due to lack of efficacy	NPRS score imputed as the mean of placebo value at Week 8
Subject withdrawal before Week 8 of the DB period due to other reason	Multiple imputation based on subject with similar characteristics in the same treatment group
Subjects not withdrawn before Week 8 of the DB period with a missing NPRS at Week 8	Multiple imputation based on subject with similar characteristics within the same treatment group

DB=double blind; e-diary=electronic diary; NPRS=numeric pain rating scale

Then, a tipping point analysis will be performed (analysis will be detailed in the Statistical Analysis Plan).

Supplementary analyses

Supplementary analyses will be performed in order to complement the primary estimand. The primary efficacy analysis will be first re-run on the PP population. In addition, two other estimands will be considered:

- Proportion of responders in the NPRS pain score at Week 8 DB. A responder is defined as a subject with at least a 20% decrease from baseline (30%, 40% and 50% cut-off will also be considered).
- The mean change in the area under the curve of the daily NPRS score averaged over the 7 consecutive days prior to each visit up to Week 8 of the DB period.

11.4.3.2 Analysis of Secondary Efficacy Endpoints

Double-blind Period

Table 7 summarises the secondary efficacy endpoints, their associated estimates and estimands during the DB period.

Table 7 Analysis of Secondary Efficacy Endpoints (Double-blind Period)

Secondary Efficacy Endpoints	Estimate of Treatment Effect	Estimand
The change from baseline in the daily NPRS score averaged over the 7 consecutive days prior to Week 4 and Week 12 DB visits.	Difference between each Dysport doses and the placebo group, in the mean change from baseline in the mean daily NPRS score averaged for the 7 consecutive days prior to Week 4 and Week 12 DB visits.	For each estimate, the associated estimand will be based on "treatment policy" strategy, which is the estimate of the treatment effect regardless of whether the subject has an intercurrent event during the study.
The change from baseline in the daily mFFI disability subscale score averaged over the 7 consecutive days prior to Week 4, Week 8 and Week 12 DB visits.	Difference between each Dysport doses and the placebo group in the mean change from baseline in the mean daily mFFI disability subscale score averaged for the 7 consecutive days prior to Week 4, Week 8 and Week 12 DB visits.	
The change from baseline in the daily mFFI pain subscale score averaged over the 7 consecutive days prior to Week 4, Week 8 and Week 12 DB visits.	Difference between each Dysport dose and the placebo group in the mean change from baseline in the mean daily mFFI pain subscale score averaged for the 7 consecutive days prior to Week 4, Week 8 and Week 12 DB visits.	
The change from baseline in the daily mFFI total score averaged over the 7 consecutive days prior to Week 4, Week 8 and Week 12 DB visits.	Difference between each Dysport doses and the placebo group in the mean change from baseline in the mean daily mFFI total score averaged for the 7 consecutive days prior to Week 4, Week 8 and Week 12 DB visits.	
The change from baseline in the daily mFFI activity limitation subscale score averaged over the 7 consecutive days prior to Week 4, Week 8 and Week 12 DB visits.	Difference between each Dysport doses and the placebo group in the mean change from baseline in the mean daily mFFI activity limitation subscale score averaged for the 7 consecutive days prior to Week 4, Week 8 and Week 12 DB visits.	
The change from baseline in the PGI-S pain and disability scores, respectively, averaged over the 7 consecutive days prior to Week 4, Week 8 and Week 12 DB visits.	Difference between each Dysport doses and the placebo group in the change from baseline in the mean daily PGI-S pain and disability scores, respectively, averaged for the 7 consecutive days prior to Week 4, Week 8 and Week 12 DB visits.	
PGI-I pain and disability scores, respectively, at Week 4, Week 8 and Week 12 DB visits.	Difference between each Dysport doses and the placebo group in the mean daily PGI-I pain and disability scores, respectively, averaged for the 7 consecutive days prior to Week 4, Week 8 and Week 12 DB visits.	
The change from baseline in HV angle as measured directly by weight-bearing	Difference between each Dysport doses and the placebo group in then mean change from baseline in HV angle at	

Secondary Efficacy Endpoints	Estimate of Treatment Effect	Estimand
anterior-posterior radiographs at Week 4, Week 8 and Week 12 DB visits.	Week 4, Week 8 and Week 12 DB visits.	
The change from baseline in intermetatarsal angle as measured directly by weight-bearing anterior-posterior radiographs at Week 4, Week 8 and Week 12 DB visits.	Difference between each Dysport doses and the placebo group in then mean change from baseline in intermetatarsal angle at Week 4, Week 8 and Week 12 DB visits.	
The change from baseline in quality of life as measured by the SF-36 at Week 8 and Week 12 DB visits.	Difference between each Dysport doses group and the placebo group in the SF-36 scores to Week 8 and Week 12 DB visits (analysis will be detailed in the statistical analysis plan)	
Time to retreatment	Difference between each Dysport doses group and the placebo group in the median time to retreatment between the first and the second injection.	

DB=double blind; HV=hallux valgus; mFFI=modified foot function index; NPRS=numeric pain rating scale; PGI-I=patient global impression of improvement; PGI-S=patient global impression of severity; SF-36=36-item short form

Subjects are expected to continue follow-up assessments regardless of the intercurrent events define above. Scores will be used as observed. No imputation of missing data will be done.

According to the scale, an MMRM model or a mixed-linear-generalized model on change from baseline including each scheduled timepoint up to Week 12 will be used to evaluate the estimands and compare treatment groups. Missing data will be considered as MAR.

Only descriptive statistics will be used to present the estimands after Week 12 visit.

Active Treatment Cycles

Table 8 summarises the secondary efficacy endpoints, their associated estimates and estimands during the active treatment cycles.

Table 8 Analysis of Secondary Efficacy Endpoints (active treatment cycles)

Secondary Efficacy Endpoints	Estimate of Treatment Effect	Estimand
The change from baseline as measured by the daily NPRS score averaged over 7 consecutive days prior to each scheduled assessment timepoint.	The mean change from baseline in the mean daily NPRS score averaged for the 7 consecutive days prior to each scheduled assessment timepoint.	
The change from baseline in the daily mFFI Disability subscale score averaged over the 7 consecutive days prior each scheduled assessment timepoint.	The mean change from baseline in the mean daily mFFI disability subscales score averaged for the 7 consecutive days prior to each scheduled assessment timepoint.	
The change from baseline in the daily mFFI Pain subscale score averaged over the 7 consecutive days prior to each scheduled assessment timepoint.	The mean change from baseline in the mean daily mFFI pain subscale score averaged for the 7 consecutive days prior to each scheduled assessment timepoint.	For each estimate, the associated estimand will be based on "treatment policy" strategy, which is the estimate of the treatment effect
The change from baseline in the daily mFFI total score averaged over the	The mean change from baseline in the mean daily mFFI total score averaged	

Secondary Efficacy Endpoints	Estimate of Treatment Effect	Estimand
7 consecutive days prior to each scheduled assessment timepoint.	for the 7 consecutive days prior to each scheduled assessment timepoint.	regardless of whether the subject has an intercurrent event during the study.
The change from baseline in the daily mFFI activity limitation subscale score averaged over the 7 consecutive days prior to each scheduled assessment timepoint.	The mean change from baseline in the mean daily mFFI activity limitation subscale score averaged for the 7 consecutive days prior to each scheduled assessment timepoint.	
The change from baseline in the PGI-S pain and disability scores, respectively, averaged over the 7 consecutive days prior to each scheduled assessment timepoint.	The change from baseline in the mean daily PGI-S pain and disability scores, respectively, averaged for the 7 consecutive days prior to each scheduled assessment timepoint.	
PGI-I pain and disability scores, respectively, averaged over the 7 consecutive days prior to each scheduled assessment timepoint.	The mean daily PGI-I pain and disability scores, respectively, averaged for the 7 consecutive days prior to each scheduled assessment timepoint.	
The change from baseline in HV angle as measured directly by weight-bearing anterior-posterior radiographs at each scheduled assessment timepoint.	The mean change from baseline in HV angle at each scheduled assessment timepoint.	
The change from baseline in intermetatarsal angle as measured directly by weight-bearing anterior-posterior radiographs at each scheduled assessment timepoint.	The mean change from baseline in intermetatarsal angle at each scheduled assessment timepoint.	
The change from baseline in quality of life as measured by the SF-36 at each scheduled assessment timepoint.	Difference between each Dysport doses group and the placebo group in the SF-36 scores at each scheduled assessment timepoint. (analysis will be detailed in the statistical analysis plan)	
Time to retreatment	Difference between each Dysport doses group and the placebo group in the median time to retreatment between each OL injection cycle.	

HV=hallux valgus; mFFI=modified foot function index; NPRS=numeric pain rating scale; OL=open label; PGI-I=patient global impression of improvement; PGI-S=patient global impression of severity; SF-36=36-item short form

Only descriptive statistics will be performed for the active treatment cycles.

11.4.3.3 Analysis of Exploratory Efficacy Endpoints

Table 9 summarises the exploratory efficacy endpoint, and the associated estimate and estimand.

CCI

[redacted]

CCI

[redacted]

11.4.4 Adjustment for Centre Effect

Descriptive analysis will be carried out to evaluate/describe any possible centre/country effect.

11.4.5 Safety Evaluation

All safety data will be included in the subject data listings.

All AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) (current version at the time of database lock) and will be classified by MedDRA preferred term and system organ class. AE listings will be presented by subject, system organ class and preferred term.

Incidence of all reported AEs/treatment emergent AEs (TEAE) and SAEs will be tabulated by treatment group. In addition, summary tables will be presented by maximum intensity, drug relationship and AEs associated with premature withdrawal of study medication.

A TEAE is defined as any AE that occurs during the active phase of the study if:

- it was not present prior to receiving the first dose of IMP, or
- it was present prior to receiving the first dose of IMP but the intensity increased during the active phase of the study.

All TEAEs will be flagged in the AEs listings.

Summary statistics (mean, median, SD and range as appropriate) by treatment group and by overall will be presented for vital signs, clinical laboratory tests at each assessment with change from Baseline. For laboratory data, abnormal values will be flagged in the data listings and a list of clinically significant abnormal values will be presented. Shift tables will be presented of the number and percentage of subjects with low, normal or high values and normal or abnormal exams.

Descriptive statistics will be provided for study foot examination (i.e. dermatological, neurological and musculoskeletal). Results of these assessments will include whether a given dermatologic or musculoskeletal deformity is present in the study foot, or whether the neurological foot evaluation domain evaluated is “normal” or “abnormal”. For each of the three parameters summaries will be provided by treatment group for both the DB and OL periods.

11.5 Subgroup Analyses

Descriptive statistics for the primary efficacy endpoint will be provided on the stratification parameter (unilateral or bilateral HAV) on the ITT population. Other subgroup analyses may be planned according to clinical interest and will be detailed in the SAP.

11.6 Interim Analyses

An interim analysis will be conducted after the first 110 randomised subjects have been followed up for at least 12 weeks. The aim of this interim analysis is to both assess futility and the potential for early stopping due to efficacy of one of the Dysport group as compared to the Placebo group. A decision to continue with the study will be determined by an independent DMC based on the outcome of the interim analysis. No interruption to recruitment will occur whilst the decision-making process is ongoing.

11.7 Primary Analyses

A primary analysis will be conducted once all subjects have completed the Week 12 of the DB period. At this point, all subjects will have completed the Week 8 visit and had adequate safety follow-up.

12 DIRECT ACCESS TO SOURCE DATA AND DOCUMENTS

Authorised personnel from external CAs and sponsor authorised Quality Assurance personnel may carry out inspections and audits. The purpose of an audit is to ensure that ethical, regulatory and quality requirements are fulfilled in all studies performed by the sponsor.

Auditors and inspectors must have direct access to study documents and site facilities as specified in Section 13.4, and to any other locations used for the purpose of the study in question (e.g. laboratories).

In the event of the site being notified directly of a regulatory inspection, the investigator must notify the sponsor's representative as soon as possible, to assist with preparations for the inspection.

13 QUALITY CONTROL AND QUALITY ASSURANCE

13.1 Protocol Amendments and Protocol Deviations

13.1.1 Protocol Amendments

No changes from the final approved (signed) protocol will be initiated without the prior written approval or favourable opinion of a written amendment by the IEC/IRB, except when necessary to eliminate immediate safety concerns to the subjects or when the change involves only logistics or administration. The principal investigator and the sponsor will sign the protocol amendment.

13.1.2 Protocol Deviations and Exceptions

All protocol deviations will be identified and recorded by the sponsor or sponsor's representative.

A major protocol deviation is any significant divergence from the protocol, i.e. nonadherence on the part of the subject, the investigator, or the sponsor to protocol specific inclusion/exclusion criteria, primary objective evaluation criteria, and/or GCP guidelines.

Generally, a protocol deviation qualifies as major if:

(1) The deviation has harmed or posed a significant or substantive risk of harm to the research subject

(2) The deviation compromises the scientific integrity of the data collected for the study

(3) The deviation is a wilful or knowing breach of human subject protection regulations, policies, or procedures on the part of the investigator(s)

(4) The deviation involves a serious or continuing noncompliance with any applicable human subject protection regulations, policies, or procedures

(5) The deviation is inconsistent with Ipsen's research, medical, and ethical principles.

See also Section 11.1.2 for details on the impact of major protocol deviations on the inclusion of subjects in each analysis population.

A minor protocol deviation is any significant divergence from the protocol that does not impact the study results.

As a matter of policy, the sponsor will not grant exceptions to protocol specific entry criteria to allow subjects to enter a study. If under extraordinary circumstances such action is considered ethically, medically, and scientifically justified for a particular subject, prior approval from the sponsor and the responsible IRB/IEC, in accordance with the Standard Operating Procedure (SOP), is required before the subject will be allowed to enter the study. If investigative centre personnel learn that a subject who did not meet protocol eligibility criteria was entered in a study (a protocol violation), they must immediately inform the sponsor. Such subjects will be discontinued from the study, except in an exceptional instance following review and written approval by the sponsor and the responsible IRB/IEC, according to the applicable SOP.

13.2 Information to Study Personnel

To ensure accurate, complete and reliable data, the sponsor or its representatives will provide instructional material to the study sites, as appropriate. A study initiation visit will be conducted prior to screening start to instruct the investigators and study coordinators. This session will give instruction on the protocol, the completion of the eCRF and all study procedures. The investigator is responsible for giving information about the study to all staff members involved in the study or in any element of subject management, both before starting any study procedures and during the course of the study (e.g. when new staff become involved). The investigator must assure that all study staff members are qualified by education, experience, and training to perform their specific responsibilities. These study staff members must be listed on the study

centre authorisation form, which includes a clear description of each staff member's responsibilities. This list must be updated throughout the study, as necessary.

The study monitor is responsible for explaining the protocol to all study staff, including the investigator, and for ensuring their compliance with the protocol. Additional information will be made available during the study when new staff become involved in the study and as otherwise agreed upon with either the investigator or the study monitor.

13.3 Study Monitoring

The investigator is responsible for the validity of all data collected at the site.

The sponsor is responsible for monitoring these data to verify that the rights and wellbeing of subjects are protected, that study data are accurate (complete and verifiable to source data) and that the study is conducted in compliance with the protocol, GCP and regulatory requirements.

Sponsor assigned monitors will conduct regular site visits. The investigator will allow direct access to all relevant files (for all subjects) and clinical study supplies (dispensing and storage areas) for the purpose of verifying entries made in the eCRF, and assist with the monitor's activities, if requested. Adequate time and space for monitoring visits should be made available by the investigator.

The site must complete the eCRFs on an ongoing basis to allow regular review by the study monitor, both remotely by the internet and during site visits. The CRO study monitor will use functions of the electronic data capture system to address any queries raised while reviewing the data entered by the study site personnel in a timely manner.

Whenever a subject name is revealed on a document required by the sponsor (e.g. laboratory print outs) the name must be blacked out permanently by the site personnel, leaving the initials visible, and annotated with the subject number as identification.

13.4 Investigator's Regulatory Obligations

All clinical work under this protocol will be conducted according to GCP rules. This includes that the study may be audited at any time by a quality assurance personnel designated by the sponsor, or by regulatory bodies. The investigator must adhere to the GCP principles in addition to any applicable local regulations.

If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable EC with direct access to any original source documents.

The investigator(s) should demonstrate due diligence in recruitment and screening of potential study subjects. The enrolment rate should be sufficient to complete the study as agreed with the sponsor. The sponsor should be notified of any projected delays, which may impact the completion of the study.

13.5 Audit and Inspection

Authorised personnel from external CAs and the sponsor's authorised Quality Assurance personnel may carry out inspections and audits (see Section 12).

13.6 Data Quality Assurance

Monitored eCRFs shared between the investigational site and Data Management CRO will be reviewed (Data Review) for completeness, consistency, legibility and protocol compliance.

Reasons should be given on the relevant eCRF for any missing data and other protocol deviations. Any electronic queries and items not adequately explained will require additional electronic manual queries to be raised to the investigator by the monitor for clarification/correction. The investigator must ensure that queries are dealt with promptly. All data changes and clarifications can be viewed in the audit trail function of the eCRF.

14 ETHICS

14.1 Compliance with Good Clinical Practice and Ethical Considerations

This study will be conducted in compliance with IECs/IRBs, informed consent regulations, the Declaration of Helsinki and ICH GCP Guidelines (Section 1.7).

In addition, this study will adhere to all local regulatory requirements.

Before initiating a study, the investigator/institution should have written and dated approval/favourable opinion from the IEC/IRB for the study protocol/amendment(s), written informed consent form, any consent form updates, subject emergency study contact cards, subject recruitment procedures (e.g. advertisements), any written information to be provided to subjects and a statement from the IEC/IRB that they comply with GCP requirements. The IEC/IRB approval must identify the protocol version as well as the documents reviewed.

After IEC/IRB approval, changes will require a formal amendment. Once the study has started, amendments should be made only in exceptional circumstances. Changes that do not affect subject safety or data integrity are classified as administrative changes and generally do not require ethical approval. If ethically relevant aspects are concerned, the IEC/IRB must be informed and, if necessary, approval sought prior to implementation. Ethical approval on administrative changes will be obtained if required by local/site IEC/IRB.

14.2 Informed Consent for Participation in the Study

Prior to study entry, the investigator, or a person designated by the investigator, will explain the nature, purpose, benefits and risks of participation in the study to each subject, subject's legally acceptable representative or impartial witness. Written informed consent must be obtained prior to the subject entering the study (before initiation of any study-related procedure and administration of the IMP). Sufficient time will be allowed to discuss any questions raised by the subject.

The sponsor will provide a sample informed consent form. The final version-controlled form must be agreed to by the sponsor, and the IEC/IRB and must contain all elements included in the sample form, in language readily understood by the subject. Each subject's original consent form, personally signed and dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion, will be retained by the investigator. The investigator will supply subjects with a copy of their signed informed consent.

The consent form may need to be revised during the study should important new information become available that may be relevant to the safety of the subject or as a result of protocol amendments. In this instance approval should always be given by the IEC/IRB. It is the investigator's responsibility to ensure that all subjects subsequently entered into the study and those currently in the study sign the amended form. This is documented in the same way as previously described. Subjects who have completed the study should be informed of any new information that may impact on their welfare/wellbeing.

The investigator should, with the consent of the subject, inform the subject's primary physician about their participation in the clinical study.

14.3 Health Authorities and Independent Ethics Committees/Institutional Review Boards

As required by local regulations, the sponsor's Regulatory Affairs group will ensure all legal regulatory aspects are covered, and obtain approval of the appropriate regulatory bodies, prior to study initiation in regions where an approval is required.

The following documents should be submitted to the relevant ethics committee(s) (EC) for review and approval to conduct the study (this list may not be exhaustive):

- Protocol/amendment(s) approved by the sponsor,
- Currently applicable IB or package labelling,
- Relevant investigator's curriculum vitae,
- Subject information and informed consent document(s) and form(s),
- Subject emergency study contact cards,
- Recruitment procedures/materials (advertisements), if any.

The EC(s) will review all submission documents as required, and a written favourable opinion for the conduct of the study should be made available to the investigator before initiating the study. This document must be dated and clearly identify the version number(s) and date(s) of the documents submitted/reviewed and should include a statement from the EC that they comply with GCP requirements.

The study may begin at the investigative site(s) only after receiving this dated and signed documentation of the EC approval or favourable opinion.

During the study, any update to the following documents will be sent to the EC either for information, or for review and approval, depending on how substantial the modifications are: (1) IB; (2) reports of SAEs; (3) all protocol amendments and revised informed consent(s), if any.

At the end of the study, the EC will be notified about the study completion.

14.4 Confidentiality Regarding Study Subjects

The investigator must assure that the privacy of the subjects, including their personal identity and all personal medical information, will be maintained at all times. In CRFs and other documents or image material submitted to the sponsor, subjects will be identified not by their names, but by an identification code (e.g. initials and identification number).

Personal medical information may be reviewed for the purpose of verifying data recorded on the eCRF. This review may be conducted by the study monitor, properly authorised persons on behalf of the sponsor, the quality assurance unit, or regulatory authorities. Personal medical information will always be treated as confidential.

15 DATA HANDLING AND RECORD KEEPING

15.1 Data Recording of Study Data

In compliance with GCP, the medical records/medical notes, etc., should be clearly marked and permit easy identification of a subject's participation in the specified clinical study.

The investigator must record all data relating to protocol procedures, IMP administration, laboratory data, safety data and efficacy ratings on the eCRFs provided for the study. The investigator, by completing the signature log, may formally designate authority to complete, to appropriately qualified staff having certified user access to the eCRF. The investigator must, as a minimum, provide an electronic signature (e-signature) to each case report book to attest to the accuracy and completeness of all the data. If any changes are made to the eCRF, after a form has been locked and electronically signed, the investigator will be required to perform an additional e-signature authorising agreement with any new information or changes to the eCRF.

All corrections on the eCRF will be automatically tracked and a reason for change is always required. In the eCRF, the audit trail function will allow the changes made to be viewed on each item entered.

15.2 Data Management

Electronic data capture will be utilised for collecting subject data. Each site is required to have a computer and internet connection available for site entry of clinical data. All entries in the eCRF will be done under the electronic signature of the person performing the action. This electronic signature consists of an individual and confidential username and password combination. It is declared to be the legally binding equivalent of the handwritten signature. Only sponsor authorised users will have access to the eCRF as appropriate to their study responsibilities. Users must have successfully undergone software application training prior to entering data into the eCRF.

Data management will be conducted by a CRO directed by the sponsor's Biometry department. All data management procedures will be completed in accordance with the sponsor and the contracted CRO SOPs. Prior to data being received in-house at the assigned CRO, they will be monitored at the investigator site, (for further details please see Section 13.3 Monitoring Procedures). The eCRF and other data documentation removed from the investigator site(s) will be tracked by the CRO and the monitor.

The sponsor will ensure that an appropriate eCRF is developed to capture the data accurately, and suitable queries are raised to resolve any missing or inconsistent data. The investigator will receive their data, from the clinical study, in an electronic format (PDF files) which will be an exact copy of the eCRF, and will include the full audit trail, for archiving purposes and future reference.

Any queries generated during the data management process will also be tracked by the contracted Biometry CRO. It is the central study monitor's responsibility to ensure that all queries are resolved by the relevant parties.

The sponsor will also ensure that SAE data collected in the eCRF are consistent with information provided to the sponsor's pharmacovigilance department (and vice versa).

The coding of an AE, medical history, surgical procedures and concomitant medication terms will be performed by the contracted CRO, directed by the sponsor's Biometry department, and reviewed and approved by the sponsor. Concomitant medications will be coded using WHODRUG and AEs/medical history terms will be coded using MedDRA.

Only data from enrolled subjects will be reported in the eCRFs and collected in the sponsor's database.

For screen failure subjects, at least the Unique Subject Identifier, the date of informed consent signature and the potential AEs which occurred during the screening phase will be reported in the eCRFs and collected in the sponsor's database.

15.3 Record Archiving and Retention

During the prestudy and initiation visits, the monitor must ensure the archiving facilities are adequate and archiving/retention responsibilities of the investigator have been discussed.

Study documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or planned marketing applications in an ICH region (that is at least 15 years) or at least 2 years have elapsed since the formal discontinuation of clinical development of the product. However, these documents should be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. The investigator should take measures to prevent accidental or premature destruction of these documents. The final archiving arrangements will be confirmed by the monitor when closing out the site. The sponsor will inform the investigator, in writing, as to when these documents no longer need to be retained.

If the principal investigator relocates or retires, or otherwise withdraws his/her responsibility for maintenance and retention of study documents, the sponsor must be notified (preferably in writing) so that adequate provision can be made for their future maintenance and retention.

16 FINANCING AND INSURANCE

16.1 Contractual and Financial Details

The investigator (and/or, as appropriate, the hospital administrative representative) and the sponsor will sign a clinical study agreement prior to the start of the study, outlining overall sponsor and investigator responsibilities in relation to the study. Financial remuneration will cover the cost per included subject, based on the calculated costs of performing the study assessments in accordance with the protocol, and the specified terms of payment will be described in the contract. The contract should describe whether costs for pharmacy, laboratory and other protocol required services are being paid directly or indirectly.

Financial Disclosure Statements will need to be completed, as requested by FDA 21 CFR Part 54.

16.2 Insurance, Indemnity and Compensation

The sponsor will provide Product Liability insurance for all subjects included in the clinical study. Where required, a hospital specific indemnity agreement will be used.

17 REPORTING AND PUBLICATIONS OF RESULTS

17.1 Publication Policy

The sponsor encourages acknowledgement of all individuals/organisations involved in the funding or conduct of the study, including medical writers or statisticians subject to the consent of each individual and entity concerned, including acknowledgement of the sponsor.

The results of this study may be published or communicated to scientific meetings by the investigators involved in the study. For multicentre studies, a plan for scientific publication and presentation of the results may be agreed and implemented by the study investigators or a Steering Committee. The sponsor requires that reasonable opportunity be given to review the content and conclusions of any abstract, presentation, or paper before the material is submitted for publication or communicated. This condition also applies to any amendments that are subsequently requested by referees or journal editors. The sponsor will undertake to comment on the draft documents within the time period agreed in the contractual arrangements, including clinical trial agreements, governing the relationship between the sponsor and authors (or the author's institution). Requested amendments will be incorporated by the author, provided they do not alter the scientific value of the material.

If patentability would be adversely affected by publication, this will be delayed until (i) a patent application is filed for the content of the publication in accordance with applicable provisions of the clinical trial agreement concerned, (ii) the sponsor consents to the publication, or (iii) the time period as may be agreed in the contractual arrangements, including clinical trial agreements, governing the relationship between the sponsor and authors (or authors' institution) after receipt of the proposed publication by the sponsor, whichever of (i), (ii) or (iii) occurs first.

The author undertakes to reasonably consider the sponsor's request for delay to the proposed publication should the sponsor reasonably deem premature to publish the results obtained at the then stage of the study.

17.2 Clinical Study Report

A final clinical study report (CSR) will be prepared according to the ICH guideline on structure and contents of CSRs. A final CSR will be prepared where any subject has signed informed consent, regardless of whether the study is completed or prematurely terminated. Where appropriate an abbreviated report may be prepared. The CSR will comply with any applicable regulatory requirements, national laws in force and will be in English.

18 REFERENCES

1. Nix S, Smith M, Vicenzio B. Prevalence of hallux valgus in the general population: a systematic review and meta-analysis. J Foot and Ankle Res. 2010;3(21):1-9.
2. Coughlin MJ, Jones CP. Hallux Valgus: demographics, etiology, and radiographic assessment. Foot Ankle Int. 2007;28(7):759 77.
3. Pinsker E, Daniels TR. AOFAS position statement regarding the future of the AOFAS clinical rating systems. Foot Ankle Int. 2011;32(9):841-2.
4. Ferrari J, Higgins JPT, Prior TD. Interventions for treating hallux valgus (abductovalgus) and bunions. Cochrane Database Syst Rev 1: CD000964, 2004.
5. Schuh R, Hofstaetter SG, Adams SB et al. Rehabilitation after hallux valgus surgery: importance of physical therapy to restore weight bearing of the first ray during the stance phase. Phys Ther. 2009;89(9):934-45.
6. Perera AM, Mason L, Stephens MM. The pathogenesis of hallux valgus, J Bone Joint Surg Am. 2011;93:1650-61.
7. Arinci IN, Genc H, Erdem HR et al. Muscle imbalance in hallux valgus: an electromyographic study. Am J Phys Med Rehabil. 2003;82(5):345-9.
8. Radovic, PA, Shah E. Nonsurgical treatment for hallux abducto valgus with botulinum toxin A. J Am Pod Med Assoc. 2008;98:61-5.
9. Haines RW, McDougall A. The anatomy of hallux valgus. J Bone Joint Surg Br. 1954;36 B(2):272-93.
10. Wu KPH, Chen CK, Lin SC et al. Botulinum toxin type A injections for patients with painful hallux valgus: a double-blind, randomized controlled study. Clin Neurol and Neurosurg. 2015;129 S1:S58-S62.
11. Babcock MS, Foster L, Pasquina P et al. Treatment of pain attributed to plantar fasciitis with botulinum toxin a: a short-term, randomized, placebo-controlled, double-blind study. Am J Phys Med Rehabil. 2005;84:649-54.
12. Schrier JC, Palmen LN, Verheyen CC et al. Patient-reported outcome measures in hallux valgus surgery. A review of literature. Foot Ankle Surg. 2015;21(1):11-5.
13. Riff DS, Duckor S, Gottlieb I et al. Diclofenac potassium liquid-filled soft gelatin capsules in the management of patients with postbunionectomy pain: a phase III, multicentre, randomized, double-blind, placebo-controlled study conducted over 5 days. Clin Ther. 2009;31(10):2072-85.
14. Daniels SE, Baum DR, Francis C et al. Diclofenac potassium liquid-filled soft gelatin capsules for the treatment of postbunionectomy pain. Curr Med Res Opin. 2010;26(10):2375-84.
15. Golf M, Daniels SE, Onel E. A phase 3, randomized, placebo-controlled trial of DepoFoam® bupivacaine (extended-release bupivacaine local analgesic) in bunionectomy. Adv Ther. 2011;28(9):776-88.
16. Shimazaki K, Takebe K. Investigations on the origin of hallux valgus by electromyographic analysis. Kobe J Med Sci. 1981;27(4):139-58.
17. Saltzman CL, Aper RL, Brown TD. Anatomic determinants of first metatarsophalangeal flexion movements in hallux valgus. Clin Orthop Rel Res. 1997;339:261-69.
18. Hoffmeyer P, Cox JN, Blanc Y et al. Muscle in hallux valgus. Clin Orthop Relat Res. 1988;232:112-8.
19. Budiman-Mak E, Conrad KJ, Roach KE. The foot function index: a measure of foot pain and disability. J Clin Epidemlol. 1991;44(6):561-70.

20. Budiman-Mak E, Conrad KJ, Stuch R et al. Theoretical model and rasch analysis to develop a revised foot function index. Foot Ankle Int. 2006;27(7):519-27.
21. Budiman-Mak E, Conrad KJ, Mazza J et al. A review of the foot function index and the foot function index – revised. J Foot Ankle Res. 2013;6(1):5.
22. Raymond G, Prashanth R, Baker N et al. The Ipswich Touch Test: a simple and novel method to identify in patients with diabetes at risk of foot ulceration. Diabetes Care. 2011;34(7):1517-8.
23. Dworkin RH, Turk DC, Wyrwich KW et al. Interpreting the clinical importance of treatment outcomes in chronic pain trials: IMMPACT recommendations. Pain. 2009;146(3):238-44.
24. Farrar JT, Young JP, LaMoreaux L et al. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain. 2001;94(2):149-58.
25. Hanley MA, Jensen MP, Ehde DM et al. Clinically significant change in pain intensity ratings in persons with spinal cord injury or amputation. Clin J Pain. 2006;22(1):25-31.
26. Kendrick DB, Stout TD. The minimum clinically significant difference in patient-assigned numeric scores for pain. Am J Emerg Med. 2005;23(7):828-32.
27. Salaffi F, Stancati A, Silvestri CA et al. Minimal clinically important changes in chronic musculoskeletal pain intensity measured on a numerical rating scale. Eur J Pain. 2004;8(4):283-91.
28. Childs JD, Piva SR, Fritz JM. Responsiveness of the numeric pain rating scale in patients with low back pain. Spine (Phila Pa 1976). 2005;30(11):1331-4.
29. van der Swaard BC, van der Horst HE, Knol DL et al. Treatment of forefoot problems in older people: a randomized clinical trial comparing podiatric treatment with standardized shoe advice. Ann Fam Med. 2014;12(5):432-40.
30. Halstead J, Chapman GJ, Gray JC et al. Foot orthoses in the treatment of symptomatic midfoot osteoarthritis using clinical and biochemical outcomes: a randomised feasibility study. Clin Rheum. 2016;35(4):987-96.

19 LIST OF APPENDICES

Appendix 1 Modified Foot Function Index

Modified Foot Function Index (mFFI)

Subject ID Number: _____ Date: _____

mFFI Pain Subscale

This questonnaire has been designed to give your clinician information as to how your foot pain has affected your ability to manage in everyday life. For each of the following questions, we would like you to score each question on a scale from 0 (no pain) to 10 (worst pain imaginable) that best describes your study foot over the past 24 hours. Please read each question and place a number from 0 to 10 in the corresponding box. If you did not perform the task listed in the question, please mark the item as not applicable (N/A).

No Pain 0 1 2 3 4 5 6 7 8 9 10 **Worst Pain Imaginable**

How severe was your foot pain:	
1. Foot pain at its worst?	
2. Foot pain in the morning?	
3. Pain walking barefoot?	
4. Pain standing barefoot?	
5. Pain walking with shoes?	
6. Pain standing with shoes?	
7. Foot pain at end of day?	
Pain Subscale Score:	**Total_____/Possible_____x100 =_____**

mFFI Disability Subscale

For each of the following questions, we would like you to score each question on a scale from 0 (no difficulty) to 10 (so difficult that you are unable to do) that best describes your study foot over the past 24 hours. Please read each question and place a number from 0 to 10 in the corresponding box. If you did not perform the task listed in the question, please mark the item as not applicable (N/A).

No Difficulty 0 1 2 3 4 5 6 7 8 9 10 **So difficult unable to do**

How much difficulty did you have:	
8. Difficulty walking in house?	
9. Difficulty walking outside?	
10. Difficulty walking 4 blocks?	
11. Difficulty climbing stairs?	
12. Difficulty descending stairs?	
13. Difficulty standing tip toe?	
14. Difficulty getting up from chair?	
15. Difficulty climbing curbs?	
16. Difficulty walking fast?	
Disability Subscale Score:	**Total_____/Possible_____x100 =_____**

mFFI Activity Limitation Subscale

For each of the following questions, we would like you to score each question on a scale from 0 (none of the time) to 10 (all of the time) that best describes your study foot over the past 24 hours. Please read each question and place a number from 0 to 10 in the corresponding box. If you did not perform the task listed in the question, please mark the item as not applicable (N/A).

None of the time 0 1 2 3 4 5 6 7 8 9 10 **All of the time**

How much of the time did you:	
17. Stay inside all day because of feet?	
18. Stay in bed because of feet?	
19. Limit activities because of feet?	
20. Use assistive device indoors?	
21. Use assistive device outdoors?	
Activity Limitation Subscale Score:	**Total_____/Possible_____x100 =_____**
mFFI TOTAL SCORE:	**Total of 3 Subscale Scores_____/3=_____**

Adapted from Budiman-Mak E, Conrad KJ, Roach K. The Foot Function Index: A measure of foot pain and disability. J. Clin. Epidemiology. 4(6): 561-570. 1991.

Appendix 2 : Protocol Amendment Forms

STUDY NUMBER:	D-FR-52120-237
PROTOCOL TITLE:	A MULTIPLE-DOSE, DOUBLE-BLIND, RANDOMISED, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF DYSPORT FOR THE TREATMENT OF PAIN ASSOCIATED WITH HALLUX ABDUCTO VALGUS
AMENDED PROTOCOL VERSION NUMBER & DATE	Protocol Version 5.0 (Amendment 4) 15 February 2019

THE FOLLOWING AMENDMENTS ARE PROPOSED:

Version Date		**15 FEBRUARY 2019**	**03 JULY 2019**
Page	**Section**	**WAS**	**IS**
10 & 64/65	Synopsis: sample size calculation Sections 11.6		**An interim analysis will be conducted after the first 110 randomized subjects have been followed up for at least 12 weeks. The aim of this interim analysis is to both assess futility and the potential for early stopping due to efficacy for each Dysport group as compared to the Placebo group. A decision to continue with an arm will be determined by an independent Data Monitoring Committee (DMC) based on the outcome of the interim analysis. No interruption to recruitment will occur whilst the decision-making process is ongoing.** **A primary analysis will be conducted once all subjects have completed the Week 12 of the DB period. At this point, all subjects will have completed the Week 8 visit and had adequate safety follow-up.**
38	Table 4 Study Procedures and Assessments: Open-label Period	Table 4 → Study Procedures and Assessments: Open-label Period Procedures and Assessments: Visit Number: Visits 7 & 12; Visit Window: ±1 day; Weight-bearing foot radiograph and measurement of HV and IM angles and tibial sesamoid position: X Cycle 2 to 3 Day 1; Cycle 2 to 3 Day 8; Cycle 2 to 3 Day 29; Cycle 2 to 3 Day 57; Cycle Day	Procedures and Assessments: Visit Number: Visits 7 & 12; Visit Window: +2 days; Weight-bearing foot radiograph and measurement of HV and IM angles and tibial sesamoid position: X Cycle 2 to 3 Day 1; Cycle 2 to 3 Day 8; Cycle 2 to 3 Day 29; Cycle 2 to 3 Day 57; Cycle 2 to Day 85

<table>
<tr><td>39</td><td></td><td><table><tr><td>Procedures and Assessments</td><td>Cycle 2 to 3 Day 1[c]</td><td>Cycle 2 to 3 Day 8</td><td>Cycle 2 to 3 Day 29</td><td>Cycle 2 to 3 Day 57</td><td>Cycl Da</td></tr><tr><td>Visit Number</td><td>Visits 7 & 12</td><td>Visits 8 & 13</td><td>Visits 9 & 14</td><td>Visits 10 & 15</td><td>Visits</td></tr><tr><td>Visit Window</td><td>±1 day</td><td>±1 day</td><td>±3 days</td><td>±3 days</td><td>+1</td></tr></table></td><td><table><tr><td>Procedures and Assessments</td><td>Cycle 2 to 3 Day 1[c]</td><td>Cycle 2 to 3 Day 8</td><td>Cycle 2 to 3 Day 29</td><td>Cycle 2 to 3 Day 57</td><td>Cycl Da</td></tr><tr><td>Visit Number</td><td>Visits 7 & 12</td><td>Visits 8 & 13</td><td>Visits 9 & 14</td><td>Visits 10 & 15</td><td>Visits</td></tr><tr><td>Visit Window</td><td>+2 days</td><td>±1 day</td><td>±3 days</td><td>±3 days</td><td>+1</td></tr></table></td></tr>
<tr><td>39</td><td>Table 4 Footnotes</td><td>h ~~Radiographic assessments should be performed using a standard foot positioner.~~</td><td></td></tr>
<tr><td>57</td><td>Section 11 Statistics</td><td>Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a SAP, which will be dated and completed before the ~~unblinding for the primary analysis at the latest~~. The SAP may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint and/or its analysis will also be reflected in a protocol amendment.</td><td>Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a SAP, which will be dated and completed before the interim analysis. The SAP may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint and/or its analysis will also be reflected in a protocol amendment.</td></tr>
</table>

58	Section 11.2 Sample size Determination	• a Hochberg procedure ~~to apply~~ to control the family-wise Type 1 error rate at 5% ~~as~~ compar~~ing~~ two Dysport doses versus placebo, • ~~a type I error rate two-sided test of 2.5%, corresponding to the second step of the Hochberg procedure,~~ • a power of 80%	• a Hochberg procedure **is implemented** to control the family-wise Type 1 error rate at **one-sided 2.**5% l**evel for** compari**sons of** two Dysport doses versus placebo, • a **minimal** power of 80%, **corresponding for a comparison based on power using a Type I error rate from a one-sided test at 1.25% level.** **An interim analysis will be conducted after the first 110 randomized subjects have been followed up for at least 12 weeks. To account for this interim analysis, the overall type I error for each comparison is controlled at the one-sided 0.025 level using O'Brien Fleming spending per Lan-DeMets spending function specification. Treatment comparison with an O'Brien Fleming spending corresponds to a nominal one-sided alpha of 0.0062 at the interim and 0.0231 at the final analysis.** **<u>To implement the Hochberg procedure, decision rules are the following:</u>** • **<u>At interim look:</u>** **Compare larger p-value to 0.0062** • **if <larger of 2 p-values> <0.0062 then stop and declare evidence of effect for each arm,** • **If not, compare <smaller of 2 p-values> to 0.0062/2. If <smaller of 2 p-values> <0.0062/2, then conclude evidence of effect for arm with the smallest p-value** • **<u>At final look (if outcome of IA is to continue):</u>** **Compare larger p-value to 0.0231** • **if <larger of 2 p-values> <0.0231 then stop and declare evidence of effect for each arm** • **If not, compare <smaller of 2 p-values> to 0.0231/2. If <smaller of 2 p-values> <0.0231/2,**

			then conclude evidence of effect for arm with the smallest p-value **The non-binding futility boundary is set to declare futility if the one-sided p-value for a comparison is above 0.30.** **Considering the Hochberg adjustment for two experimental arms, this interim analysis plan results in a minimal power of at least 80 % to detect a treatment effect of 1.5 units in a Dysport arm.** **Details regarding operational aspects of the interim analysis are described in the Interim Analysis Charter.**
59	Section 11.3 Significance Testing and Estimations	For the primary efficacy analysis, a Hochberg procedure will be applied to control the global type I error at 5% significance level. For other efficacy analyses, all statistical tests will be performed ~~two~~ sided with a type I error rate set at 5%. For safety analyses, no formal statistical analyses will be carried out; only descriptive statistics will be provided.	For the primary efficacy analysis, a Hochberg procedure will be applied to control the global type I error at **one-sided 2.**5% significance level. For other efficacy analyses, all statistical tests will be performed **one-**sided with a type I error rate set at **2.**5%. For safety analyses, no formal statistical analyses will be carried out; only descriptive statistics will be provided.
	Section 11.6 Interim Analyses		An interim analysis will be conducted after the first 110 randomised subjects have been followed up for at least 12 weeks. The aim of this interim analysis is to both assess futility and the potential for early stopping due to efficacy of one of the Dysport group as compared to the Placebo group. A decision to continue with the study will be determined by an independent DMC based on the outcome of the interim analysis. No interruption to recruitment will occur whilst the decision-making process is ongoing.

SUMMARY & OUTCOME OF CHANGES:

STUDY NUMBER	D-FR-52120-237	
AMENDED PROTOCOL VERSION NUMBER & DATE	Protocol Version 5.0 (Amendment 4) 15 February 2019	
SUBSTANTIAL ☒	**NON-SUBSTANTIAL** ☐	
REASON(S) FOR CHANGES	Implementation of an interim analysis plan	
OTHER ACTION REQUIRED?	CRF UPDATE	Yes ☐ No ☒ *(tick one)*
	LOCAL CONSENT FORM UPDATE	Yes ☐ No ☒ *(tick one)*
	DATABASE UPDATE	Yes ☐ No ☒ *(tick one)*
	STATISTICAL ANALYSIS PLAN (SAP) UPDATE	Yes ☒ No ☐ *(tick one)*

STUDY NUMBER:	D-FR-52120-237
PROTOCOL TITLE:	A MULTIPLE-DOSE, DOUBLE-BLIND, RANDOMISED, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF DYSPORT FOR THE TREATMENT OF PAIN ASSOCIATED WITH HALLUX ABDUCTO VALGUS
AMENDED PROTOCOL VERSION NUMBER & DATE	Protocol Version 4.0 (Amendment 3) 07 September 2018

THE FOLLOWING AMENDMENTS ARE PROPOSED: (deleted text is indicated with strikethrough; new text is indicated in bold)

Version Date		**07 SEPTEMBER 2018**	**15 FEBRUARY 2019**
Page	**Section**	**WAS**	**IS**
1	n/a	FINAL Version ~~4.0~~: 7 ~~September 2018~~ (Amendment ~~3~~)	FINAL Version **5.0**: **15 February 2019** (Amendment **4**)
3	Table 1	|	|	|	**4** | **15 February 2019** | **Appendix 2**
5 & 30	Synopsis & 4.1 **Inclusion Criteria** (3)	Clinical diagnosis of HAV as determined by the investigator based on evidence of lateral deviation of either great toe (left or right), as well as assessment of NPRS scores for each foot	Clinical diagnosis of HAV as determined by the investigator based on evidence of lateral deviation of either great toe (left or right), as well as assessment of NPRS scores for each foot **(in bilateral subjects)**.
6 & 30	Synopsis & 4.1 **Inclusion Criteria** (7)	Subjects must present with hallux valgus (HV) angle between ~~≥ 15° and <~~30° in the study foot great toe using radiographic measurements based on guidelines set forth by the AOFAS ad hoc Committee on Angular Measurements at Screening only	Subjects must present with hallux valgus (HV) angle ≤ 30° in the study foot great toe using radiographic measurements based on guidelines set forth by the AOFAS ad hoc Committee on Angular Measurements at Screening only

Version Date		07 SEPTEMBER 2018	15 FEBRUARY 2019
Page	**Section**	**WAS**	**IS**
6 & 30	Synopsis & 4.1 **Inclusion Criteria** (8)	Subjects must present with an intermetatarsal angle of ~~9° to~~ 18°, inclusive in the study foot great toe using radiographic measurements based on guidelines set forth by the American Orthopedic Foot and Ankle Society ad hoc Committee on Angular Measurements at Screening only	Subjects must present with an intermetatarsal angle of ≤ 18°, inclusive in the study foot great toe using radiographic measurements based on guidelines set forth by the American Orthopedic Foot and Ankle Society ad hoc Committee on Angular Measurements at Screening only
6 & 32	Synopsis & 4.2.1 **Exclusion Criteria** (1)	Subject has an HV angle of ~~<15° or ≥~~30° in the study foot	Subject has an HV angle of >30° in the study foot
7 & 31	Synopsis & 4.2 **Exclusion Criteria** (13)	Subject is using an orthotic device ~~of any kind~~ (including over-the-counter toespacers) which could influence the functioning of the hallux of the study foot in any way, or any other device intended for this purpose.	Subject is using an orthotic device (including over-the-counter toespacers) which could influence the functioning of the hallux of the study foot in any way, or any other device intended for this purpose.
8 & 32	Synopsis & 4.2.28 **Exclusion Criteria** (28)	~~History of chronic drug or alcohol abuse.~~	**Evidence of clinically significant chronic drug or alcohol abuse within the last year.**
25	3.1.2.1 **Retreatment Criteria**	• Subject's foot pain is clinically significant as evidenced by an NPRS score ≥3 ~~for the~~ 24-hour ~~period~~ immediately prior to the retreatment visit.	• Subject's foot pain is clinically significant as evidenced by an NPRS score ≥3 **within** 24-**48** hours immediately prior to the retreatment visit.

Version Date		07 SEPTEMBER 2018	15 FEBRUARY 2019
Page	**Section**	**WAS**	**IS**
36	Table 3 **Footnotes**	~~h Radiographic assessments should be performed using a standard foot positioner.~~ * note footnotes reordered due to deletion	
43	6.4 **Lifestyle Restrictions/Recommendations**	Besides restrictions already presented in the exclusion criteria, subjects should not use an orthotic device or 'over-the-counter shoe-insert' ~~of any kind~~ which could influence the functioning of the hallux of the study foot in any way during the study	Besides restrictions already presented in the exclusion criteria, subjects should not use an orthotic device or 'over-the-counter shoe-insert' which could influence the functioning of the hallux of the study foot in any way during the study
44	7.1 **Methods and Timing of Assessing, Recording, and Analysing Efficacy Data**	For all assessments related to pain, the subject is to be instructed by the investigator to report severity specifically for his/her study foot when completing the questionnaires. Also, it is critical that investigators and site staff instruct and remind subjects to complete home-based self-assessments (eg, NPRS, mFFI) in the evening.	For all assessments related to pain, the subject is to be instructed by the investigator to report severity specifically for his/her study foot when completing the questionnaires **using the e-diary. The Sponsor will provide a device (to complete the e-diary questionnaires) in the clinical trial if requested by subjects or in situations in which the subject is not willing or able to use their own device. The device will be returned to the site at the completion of the subjects' participation in the trial.** Also, it is critical that investigators and site staff instruct and remind subjects to complete home-based self-assessments (eg, NPRS, mFFI) in the evening.

Version Date		07 SEPTEMBER 2018	15 FEBRUARY 2019
Page	**Section**	**WAS**	**IS**
46	7.1.5 **Patient Global Impression of Improvement of Foot Pain**	The PGI-I will be assessed by the subject answering the following question: "Compared to your foot pain prior to the study treatment initiation, your foot pain while performing physical activities (e.g. standing, walking or running) now is: +3=very much improved; +2=much improved; +1=minimally improved; 0=no change; -1=minimally worse; -2=much worse; -3=very much worse").	The PGI-I will be assessed by the subject answering the following question: "Compared to your foot pain prior to the study treatment initiation, your foot pain while performing physical activities (e.g. standing, walking or running) now is: +3=very much improved; +2=much improved; +1=minimally improved; 0=no change; -1=minimally worse; -2=much worse; -3=very much worse"). **Also, an additional question will be included in the PGI-I assessment which will ask patients the following: "If you experienced a change, was this change meaningful to you? (Yes/No)"**
46	**7.1.7 Patient Global Impression of Improvement of Disability**	The PGI-I will be assessed by the subject answering the following question: "Compared to your disability prior to the study treatment initiation, your disability while performing physical activities (e.g. standing, walking or running) now is: +3=very much improved; +2=much improved; +1=minimally improved; 0=no change from baseline; -1=minimally worse; -2=much worse; -3=very much worse").	The PGI-I will be assessed by the subject answering the following question: "Compared to your disability prior to the study treatment initiation, your disability while performing physical activities (e.g. standing, walking or running) now is: +3=very much improved; +2=much improved; +1=minimally improved; 0=no change from baseline; -1=minimally worse; -2=much worse; -3=very much worse"). **In addition, an additional question will be included in the PGI-I assessment which will ask patients the following: "If you experienced a change, was this change meaningful to you? (Yes/No)"**

SUMMARY & OUTCOME OF CHANGES:

STUDY NUMBER	D-FR-52120-237	
AMENDED PROTOCOL VERSION NUMBER & DATE	Protocol Version 4.0 (Amendment 3) 07 September 2018	
SUBSTANTIAL ☐	**NON-SUBSTANTIAL** ☒	
REASON FOR CHANGES	Additional questions are being included and an e-diary device will be now available to the subject upon request. The minimum HV and IM angle criteria have also been further amended."	
OTHER ACTION REQUIRED?	CRF UPDATE	Yes ☒ No ☐ *(tick one)*
	EPRO UPDATE	Yes ☒ No ☐ *(tick one)*
	LOCAL CONSENT FORM UPDATE	Yes ☒ No ☐ *(tick one)*
	DATABASE UPDATE	Yes ☐ No ☒ *(tick one)*
	REPORTING & ANALYSIS PLAN (RAP) UPDATE	Yes ☐ No ☒ *(tick one)*

STUDY NUMBER:	D-FR-52120-237
PROTOCOL TITLE:	A MULTIPLE-DOSE, DOUBLE-BLIND, RANDOMISED, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF DYSPORT FOR THE TREATMENT OF PAIN ASSOCIATED WITH HALLUX ABDUCTO VALGUS
AMENDED PROTOCOL VERSION NUMBER & DATE	Protocol Version 4.0 (Amendment 3) 7 September 2018

THE FOLLOWING AMENDMENT(S) IS/ARE PROPOSED: (DELETED TEXT IS INDICATED WITH STRIKETHROUGH; NEW TEXT IS INDICATED IN BOLD)

Version Date		**25 MAY 2018**	**7 SEPTEMBER 2018**
Page	**Section**	**WAS**	**IS**
4 & 22	Synopsis Objectives And 2.2.2 Secondary Objectives	• To evaluate the clinical safety and efficacy of Dysport following repeated treatment cycles ~~in adult subjects with HAV.~~	• To evaluate the clinical safety and efficacy of Dysport following repeated treatment cycles.
5 & 24	3.1.1 Double-blind Period (Cycle 1):	For subjects presenting with bilateral HAV at Screening, the investigator will determine which foot is of greater severity based on the clinical judgment of the investigator following clinical evaluation of the degree of pain (including assessment of the NPRS scores for each foot during Screening), degree of disability and angular deviation of the hallux, and meeting all other study entry criteria. In these subjects, the foot with the greatest severity of HAV~~, based on clinical evaluation by the investigator (and meeting all other study entry criteria),~~ will be selected for treatment with DB study treatment in this study.	For subjects presenting with bilateral HAV at Screening, the investigator will determine which foot is of greater severity based on the clinical judgment of the investigator following clinical evaluation of the degree of pain (including assessment of the NPRS scores for each foot during Screening), degree of disability and angular deviation of the hallux, and meeting all other study entry criteria. In these subjects, the foot with the greatest severity of HAV will be selected for treatment with DB study treatment in this study.

Version Date		25 MAY 2018	7 SEPTEMBER 2018
Page	**Section**	**WAS**	**IS**
6 & 31	Synopsis & Section 4.1 Inclusion Criteria	(8) Subjects must present with an intermetatarsal angle of ~~12~~° to 18°, inclusive in the study foot great toe using radiographic measurements based on guidelines set forth by the American Orthopedic Foot and Ankle Society ad hoc Committee on Angular Measurements at Screening only	(8) Subjects must present with an intermetatarsal angle of **9°** to 18°, inclusive in the study foot great toe using radiographic measurements based on guidelines set forth by the American Orthopedic Foot and Ankle Society ad hoc Committee on Angular Measurements at Screening only
9	Synopsis Secondary Efficacy Evaluations and Endpoints	• Patient Global Impression of Improvement of foot pain score ~~averaged over the 7 consecutive days prior to~~ Week 4, Week 8 and Week 12 DB visits and at each scheduled visit in the OL period • Patient Global Impression of Improvement in disability score ~~averaged over the 7 consecutive days prior to~~ Week 4, Week 8 and Week 12 DB visits and at each scheduled visit in the OL period. • The change from baseline in the Patient Global Impression of Severity of foot pain score~~ averaged over the 7 consecutive days prior~~ to Week 4, Week 8 and Week 12 DB visits ~~and~~ each scheduled visit in the OL period. • The change from baseline in the Patient Global Impression of Severity disability score ~~averaged over the 7 consecutive days prior~~ to Week 4, Week 8 and Week 12 DB visits and at each scheduled visit in the OL period.	• Patient Global Impression of Improvement of foot pain score **at the** Week 4, Week 8 and Week 12 DB visits and at each scheduled visit in the OL period • Patient Global Impression of Improvement in disability score **at the** Week 4, Week 8 and Week 12 DB visits and at each scheduled visit in the OL period. • The change from baseline in the Patient Global Impression of Severity of foot pain score to Week 4, Week 8 and Week 12 DB visits **at** each scheduled visit in the OL period. • The change from baseline in the Patient Global Impression of Severity disability score to Week 4, Week 8 and Week 12 DB visits and at each scheduled visit in the OL period.
16	Abbreviations	~~mITT: modified Intention-to-treat~~	ITT: Intention-to-treat

Version Date		25 MAY 2018	7 SEPTEMBER 2018
Page	Section	WAS	IS
22	2.2.2 Secondary Objectives	The secondary objectives of the study are: • To assess functional improvement Dysport (300 U and 500 U) as compared with placebo using the mFFI disability subscale.	The secondary objectives of the study are: • To assess functional improvement **in** Dysport (300 U and 500 U) as compared with placebo using the mFFI disability subscale.
23	3.1 Figure 2 Study Design footnote	Subjects who meet the protocol-defined retreatment criteria will be administered injections of Dysport 300 U (Cycle 2) in open-label fashion. Subsequent treatment with Dysport (Cycle 3) will also be based on subjects' meeting the retreatment criteria and will occur at least 12 weeks after receiving the prior injection of Dysport.	Subjects who meet the protocol-defined retreatment criteria will be administered injections of Dysport 300 U (Cycle 2) in **an** open-label fashion. Subsequent treatment with Dysport (Cycle 3) will also be based on subjects' meeting the retreatment criteria and will occur at least 12 weeks after receiving the prior injection of Dysport.
24	3.1.1 Double-blind Period (Cycle 1):	In these subjects, the foot with the greatest severity of HAV, ~~based on clinical evaluation by the investigator (and meeting all other study entry criteria),~~ will be selected for treatment with DB study treatment in this study.	In these subjects, the foot with the greatest severity of HAV will be selected for treatment with DB study treatment in this study.
24	3.1.2 Open-label Period (Cycles 2 to 3):	Following completion of all protocol-specified procedures for the DB period (i.e. completion of Cycle 1), subjects who meet retreatment criteria (see Section 3.1.2.1) will be treated with Dysport (300 U) in the HAV study foot determined in the DB period ~~during the OL period~~.	Following completion of all protocol-specified procedures for the DB period (i.e. completion of Cycle 1), subjects who meet retreatment criteria (see Section 3.1.2.1) will be treated with Dysport (300 U) in the HAV study foot determined in the DB period..
24	3.1.2 Open-label Period (Cycles 2 to 3	At the second retreatment cycle~~s~~ (Cycle 3), subjects will be treated with either Dysport 300 U or 500 U ~~in the HAV study foot~~ based on investigator judgment following clinical evaluation of the subject at the time of retreatment.	At the second retreatment cycle (Cycle 3), subjects will be treated **in the HAV study foot** with either Dysport 300 U or 500 U based on investigator judgment following clinical evaluation of the subject at the time of retreatment.

Version Date		25 MAY 2018	7 SEPTEMBER 2018
Page	**Section**	**WAS**	**IS**
24	3.1.2 Open-label Period (Cycles 2 to 3	• Week 12 (Day 85) (clinic visit~~*~~) ~~(*Note: Subjects will be evaluated for retreatment with Dysport (300 U or 500 U) in an OL fashion.)~~	Week 12 (Day 85) (clinic visit)
25	Figure 3		Alignment of 'D1' in cycle 2 and arrows replaced => signs
36	Table 3 SF-36 In End of Study or Early Withdrawal Column	X‡	**X**

Version Date		25 MAY 2018	7 SEPTEMBER 2018
Page	**Section**	**WAS**	**IS**
36	Table 3 PGI-I for pain and PGI-I for disability[n] All timepoints including Early Withdrawal[e] Column	PGI-S for pain and PGI-S for disability X[i]	PGI-S for pain and PGI-S for disability[n] **X**
36	Table 3 PGI-S for pain and PGI-S for disability (All timepoints)	PGI-S for pain and PGI-S for disability X[i]	PGI-S for pain and PGI-S for disability[n] **X**

Version Date		25 MAY 2018	7 SEPTEMBER 2018
Page	**Section**	**WAS**	**IS**
36	Table 3 PGI-S for pain and PGI-S for disability Screening 1 (Days -21 to Day -1)a		**X**
38	Table 3 Footnote		**n The PGI-I and PGI-S assessments will be completed by the subject at the study site during the study visit. Subjects are to complete these self-assessments using the electronic diary which will be accessed at the site during the visit. Site staff should not help subjects answer questions but must ensure that the subject can access the eDiary to complete the assessment while at the site**
39	Table 4	PGI-I for pain and PGI-I for disability[j]	PGI-I for pain and PGI-I for disability[j, l]
39	Table 4	PGI-S for pain and PGI-S for disability[j]	PGI-S for pain and PGI-S for disability[j, l]
39	Table 4 footnote	b The decision to increase the dose at the beginning of Cycle 3 will be based on 1) evaluation of safety and tolerability (review related AEs and consideration of any significant changes in the study foot) and 2) severity of pain (considering NPRS score) and disability (considering mFFI Disability subscale score) experienced by the subject at the time of evaluation.	b The decision to increase the dose at the beginning of Cycle 3 will be based on 1) evaluation of safety and tolerability (review **of** related AEs and consideration of any significant changes in the study foot) and 2) severity of pain (considering NPRS score) and disability (considering mFFI Disability subscale score) experienced by the subject at the time of evaluation.

Version Date		25 MAY 2018	7 SEPTEMBER 2018
Page	**Section**	**WAS**	**IS**
39	Table 3 & footnote		**n The PGI-I and PGI-S assessments will be completed by the subject at the study site during the study visit. Subjects are to complete these self-assessments using the electronic diary which will be accessed at the site during the visit. Site staff should not help subjects answer questions but must ensure that the subject can access the eDiary to complete the assessment while at the site**
39	Table 4 footnote	j ~~To be recorded by the subject daily for 7 consecutive days prior to Week 8 using an electronic diary. These assessments are assessed at home after baseline~~	j **The PGI-I and PGI-S assessments will be completed by the subject at the study site during the study visit. Subjects are to complete these self-assessments using the electronic diary which will be accessed at the site during the visit. Site staff should not help subjects answer questions but must ensure that the subject can access the eDiary to complete the assessment while at the site**
43	6.2.3 Injection – Guided Technique	A Teflon coated, 2~~7~~ to 30-gauge, open lumen needle will be used to stimulate the targeted muscle once per second (repetitive square wave pulses, 0.25 msec in duration). Injection will be performed when either a continuous or stretch of muscle has been induced by the electrical stimulator confirming the location of the targeted muscle.	A Teflon coated, 2**2** to 30-gauge, open lumen needle will be used to stimulate the targeted muscle once per second (repetitive square wave pulses, 0.25 msec in duration). Injection will be performed when either a continuous or stretch of muscle has been induced by the electrical stimulator confirming the location of the targeted muscle.
44	6.3 Concomitant Medication/Therapy	Subjects who require treatment with antipsychotic (e.g. D2 antagonists) or antidepressant (e.g. selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors) will need to demonstrate evidence of stable dose regimen in the 30 days prior to Screening and will maintain that dose for the duration of the study.	• Subjects who require treatment with antipsychotic (e.g. D2 antagonists) or antidepressant (e.g. selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors) **medications** will need to demonstrate evidence of stable dose regimen in the 30 days prior to Screening and will maintain that dose for the duration of the study.

Version Date		25 MAY 2018	7 SEPTEMBER 2018
Page	**Section**	**WAS**	**IS**
44	6.4 Lifestyle Restrictions/Recommendations	This includes toe-spacers or any other device intended for this purpose. Over-the counter shoe will be permitted during the study only for subjects who have used these for at least 30 days prior to screening.	This includes toe-spacers or any other device intended for this purpose. Over-the counter shoe **inserts** will be permitted during the study only for subjects who have used these for at least 30 days prior to screening.
45	6.6 Priority Order on Study Procedures	The following priority order should be followed in case study procedures are scheduled at the same time point: 1. NPRS 2. mFFI 3. PGI-I and PGI-S (pain and disability) 4. SF-36 5. Weight-bearing radiographs	The following priority order should be followed in case study procedures are scheduled at the same time point: 1. NPRS* 2. mFFI* 3. PGI-I and PGI-S (pain and disability) 4. SF-36 5. Weight-bearing radiographs ***These assessments are assessed at home after baseline.**
45	7.1 Methods and Timing of Assessing, Recording, and Analysing Efficacy Data	Methods for assessing efficacy data is described below. Timing of efficacy assessments are discussed in Section 5. Procedures for recording efficacy data are discussed in Section 15.1, and methods of analyses are discussed in Section 11.4.4.	Methods for assessing efficacy data is described below. Timing of efficacy assessments are discussed in Section 5. Procedures for recording efficacy data are discussed in Section 15.1, and methods of analyses are discussed in Section 11.4.4. **For all assessments related to pain, the subject is to be instructed by the investigator to report severity specifically for his/her study foot when completing the questionnaires. Also, it is critical that investigators and site staff instruct and remind subjects to complete home-based self-assessments (eg, NPRS, mFFI) in the evening.**

Version Date		25 MAY 2018	7 SEPTEMBER 2018
Page	Section	WAS	IS
45	7.1.1 Numeric Pain Rating Scale	The NPRS is a widely used, and validated unidimensional measure of pain intensity in adults. Subjects will be asked to rate the intensity of their foot pain during physical activity (e.g. walking, standing or running) based on an 11-point scale ranging from 0 to 10, where 0 equals “no pain” and 10 equals “worst possible pain” ~~in which t~~hey will be asked to rate their daily pain intensity by responding directly to the following question: "Please rate the average intensity of the pain in your **treated** foot while performing physical activities (e.g. standing, walking or running) over the past 24 hours".	The NPRS is a widely used and validated unidimensional measure of pain intensity in adults. Subjects will be asked to rate the intensity of their foot pain during physical activity (e.g. walking, standing or running) based on an 11-point scale ranging from 0 to 10, where 0 equals “no pain” and 10 equals “worst possible pain”. **T**hey will be asked to rate their daily pain intensity by responding directly to the following question: "Please rate the average intensity of the pain in your **treated** foot while performing physical activities (e.g. standing, walking or running) over the past 24 hours".
45	7.1.1 Numeric Pain Rating Scale	Daily pain intensities will be recorded by the subject using an electronic diary for 7 consecutive days prior to the study visits as outlined in Section 5.1. The electronic diary should be completed by the subject at the same time each day, **preferably in the evening**.	Daily pain intensities will be recorded by the subject using an electronic diary for 7 consecutive days prior to the study visits as outlined in Section 5.1. The electronic diary should be completed by the subject at the same time each day, **preferably in the evening**. **The subject should be instructed by the investigator to focus on his/her study foot when completing the questionnaire. This instruction is critical in subjects with bilateral disease.**
45	7.1.2 Foot Function Index	7.1.2 Foot Function Index	7.1.2 **Modified** Foot Function Index

Version Date		25 MAY 2018	7 SEPTEMBER 2018
Page	Section	WAS	IS
46	7.1.2 Foot Function Index	The mFFI items are rated using numeric rating scales ranging from 0 to 10. The poles are labelled “no pain” and “worst pain imaginable” (pain), “no difficulty” and “so difficult unable” (disability), and “none of the time” and “all of the time” (limitations). For each item, the subject is asked to record the number value which best corresponds to the effect of the foot complaints. To obtain a subscale score, the item scores for a given subscale (i.e. pain, disability or activity limitation subscales) are totalled and divided by the maximum total possible multiplied by 100 ~~for all of the subscale items~~. Each subscale score, as well as the total score will range from 0 to 100. Daily pain intensities, disability and activity limitations will be recorded by the subject using an electronic diary for 7 consecutive days prior to the study visits as outlined in Section 5.1. The electronic diary should be completed by the subject at the same time each day, **preferably in the evening**.	The mFFI items are rated using numeric rating scales ranging from 0 to 10 **and cover a period of the ‘past’ 24 hours**. The poles are labelled “no pain” and “worst pain imaginable” (pain), “no difficulty” and “so difficult unable **to do**” (disability), and “none of the time” and “all of the time” (limitations). For each item, the subject is asked to record the number value which best corresponds to the effect of the foot complaints. To obtain a subscale score, the item scores for a given subscale (i.e. pain, disability or activity limitation subscales) are totalled and divided by the maximum total possible **and then** multiplied by 100. Each subscale score, as well as the total score, will range from 0 to 100. **If a patient did not perform the task listed in the question, they will be instructed to mark the item as not applicable (N/A).** Daily pain intensities, disability and activity limitations will be recorded by the subject using an electronic diary for 7 consecutive days prior to the study visits as outlined in Section 5.1. The electronic diary should be completed by the subject at the same time each day, **preferably in the evening**. **The subject should be instructed by the investigator to focus on his/her study foot when completing the questionnaire. This instruction is critical in subjects with bilateral disease. In addition, all subjects should be educated on the proper use of the “not applicable” option. For example, subjects that do not stand on their tiptoes in the course of their daily lives should mark “not applicable” for that particular item. However, if the subject does not stand on his or her tiptoes due to their disease, then he or she should choose the option “so difficult unable to do”.**

Version Date		25 MAY 2018	7 SEPTEMBER 2018
Page	Section	WAS	IS
46	7.1.5 Patient Global Impression of Improvement of Foot Pain	An assessment of PGI-I of foot pain will be conducted by the subject using a 7-point Likert scale (from -3: very much worse to +3: very much improved). The PGI-I will be assessed by the subject answering the following question: "Compared to your foot pain ~~at Baseline (Cycle 1 Day 1)~~ i.e. prior to the study treatment initiation, your foot pain while performing physical activities (e.g. standing, walking or running ~~over the past 24 hours~~ is: +3=very much improved; +2=much improved; +1=minimally improved; 0=no change ~~from baseline~~; -1=minimally worse; -2=much worse; -3=very much worse").# The PGI-S of foot pain will be recorded by the subject using an electronic diary ~~for 7 consecutive days prior to~~ the study visits as outlined in Section 5.1. The ~~electronic diary~~ should be ~~completed~~ by ~~the subject at~~ the ~~same time each day~~, ~~preferably in the evening~~.	An assessment of PGI-I of foot pain will be conducted by the subject using a 7-point Likert scale (from -3: very much worse to +3: very much improved). The PGI-I will be assessed by the subject answering the following question: "Compared to your foot pain prior to the study treatment initiation, your foot pain while performing physical activities (e.g. standing, walking or running) **now** is: +3=very much improved; +2=much improved; +1=minimally improved; 0=no change; -1=minimally worse; -2=much worse; -3=very much worse"). The PGI-I of foot pain will be recorded by the subject using an electronic diary **during** the study visits **at site** as outlined in Section 5.1. The **subject** should be **instructed** by the **investigator to focus on his/her study foot when completing** the **questionnaire**. **This instruction is critical in subjects with bilateral disease.**
47	Section 7.1.6 Patient Global Impression of Severity of Foot Pain	The PGI-S will be assessed by the subject by answering the following question: "How severe was your foot pain while performing physical activities (e.g. standing, walking or running) over the past ~~24 hours~~?" (0=no pain; 1=mild pain; 2=moderate pain; 3=severe pain). The PGI-S of foot pain will be recorded by the subject using an electronic diary for ~~7 consecutive days prior to the~~ study visits as outlined in Section 5.1. ~~The electronic diary should be completed by the subject at the same time each day, **preferably in the evening**.~~	The PGI-S will be assessed by the subject by answering the following question: "How severe was your foot pain while performing physical activities (e.g. standing, walking or running) over the past **week**?" (0=no pain; 1=mild pain; 2=moderate pain; 3=severe pain). The PGI-S of foot pain will be recorded by the subject using an electronic diary **during** the study visits on site as outlined in Section 5.1. **The subject should be instructed by the investigator to focus on his/her study foot when completing the questionnaire. This instruction is critical in subjects with bilateral disease.**

Version Date		25 MAY 2018	7 SEPTEMBER 2018
Page	Section	WAS	IS
47	7.1.7 Patient Global Impression of Improvement of Disability	The PGI-I will be assessed by the subject answering the following question: "Compared to your ~~disability at Baseline (Cycle 1 Day 1) i.e.~~ prior to the study treatment initiation, your disability while performing physical activities (e.g. standing, walking or running ~~over the past 24 hours~~ is: +3=very much improved; +2=much improved; +1=minimally improved; 0=no change from baseline; -1=minimally worse; -2=much worse; -3=very much worse"). The PGI-I of disability will be recorded by the subject using an electronic diary ~~for 7 consecutive days prior to~~ the study visits as outlined in Section 5.1.	The PGI-I will be assessed by the subject answering the following question: "Compared to your disability prior to the study treatment initiation, your disability while performing physical activities (e.g. standing, walking or running**) now** is: +3=very much improved; +2=much improved; +1=minimally improved; 0=no change from baseline; -1=minimally worse; -2=much worse; -3=very much worse"). The PGI-I of disability will be recorded by the subject using an electronic diary during the study visits on site as outlined in Section 5.1.
47	7.1.8 Patient Global Impression of Severity of Disability	The PGI-S will be assessed by the subject by answering the following question: "How severe was your disability while performing physical activities (e.g. standing, walking or running) over the past ~~24 hours~~?" (0=no disability; 1=mild disability; 2=moderate disability; 3=severe disability). The PGI-S of disability will be recorded by the subject using an electronic diary ~~for 7 consecutive days prior to~~ the study visits as outlined in Section 5.1. ~~The electronic diary should be completed by the subject at the same time each day, **preferably in the evening**.~~	The PGI-S will be assessed by the subject by answering the following question: "How severe was your disability while performing physical activities (e.g. standing, walking or running) over the past **week**?" (0=no disability; 1=mild disability; 2=moderate disability; 3=severe disability). The PGI-S of disability will be recorded by the subject using an electronic diary **during** the study visits on site outlined in Section 5.1.

Version Date		25 MAY 2018	7 SEPTEMBER 2018
Page	Section	WAS	IS
58	11.1 Analyses Populations	The following populations will be used during statistical analyses: • Screened population: All subjects screened (i.e. who signed the informed consent). ~~• Randomised population: All subjects randomised (i.e. who were randomly allocated to a treatment group by IRT).~~ • Safety population: All subjects who received at least one dose of IMP administration (including only partial administration). • Intention-to-treat (ITT) population: All randomised subjects. • Per protocol (PP) population: All subjects in the ITT population for whom no major protocol deviations (which may interfere with efficacy evaluation) occurred until Week 8 of the DB period. • Open-label (OL) population: All randomised subjects who received at least one dose of Dysport (including only partial administration) during the OL period.	The following populations will be used during statistical analyses: • Screened population: All subjects screened (i.e. who signed the informed consent). • Safety population: All subjects who received at least one dose of IMP administration (including only partial administration). • Intention-to-treat (ITT) population: All randomised subjects **(i.e. who were randomly allocated to a treatment group by IRT)**. • Per protocol (PP) population: All subjects in the ITT population for whom no major protocol deviations (which may interfere with efficacy evaluation) occurred until Week 8 of the DB period. • Open-label (OL) population: All randomised subjects who received at least one dose of Dysport (including only partial administration) during the OL period. • **Active Treatment population: All randomised subjects who received at least one dose of Dysport (including only partial administration) during the DB or OL period**
58	11.1.1 Populations Analysed	In addition, PP analysis will be performed as confirmatory. Secondary ~~analysis~~ based on secondary efficacy endpoints will be performed on the ITT population (for the DB period) and on the ~~OL~~ population (for ~~the OL period~~).	In addition, PP analysis will be performed as confirmatory. Secondary **analyses** based on secondary efficacy endpoints will be performed on the ITT population (for the DB period) and on the **Active Treatment** population (for **analysis by active treatment cycle**).

Version Date		25 MAY 2018	7 SEPTEMBER 2018
Page	**Section**	**WAS**	**IS**
59	11.3 Significance Testing and Estimations	For other efficacy ~~analysis~~, all statistical tests will be performed two sided with a type I error rate set at 5%. For safety ~~analysis~~, no ~~format~~ statistical will be carried out, only descriptive statistics will be provided.	For other efficacy **analyses**, all statistical tests will be performed two sided with a type I error rate set at 5%. For safety **analyses**, no **formal** statistical **analyses** will be carried out; only descriptive statistics will be provided.
59	11.4.3.1 Efficacy Evaluation	The NPRS score data collected over the 7 consecutive days prior to a visit, will be ~~retrieve~~ using an electronic diary (see Section 7.1.1). ~~No missing baseline is expected as NPRS assessment is part of the inclusion criteria. Subjects will have reminders to complete the electronic diary, and site staff will be alerted if they miss a day. Therefore, the risk of have missing days is minimised. However, as described in Table 6, any cases of possible missing data will be considered.~~	The NPRS score data collected over the 7 consecutive days prior to a visit will be **retrieved** using an electronic diary (see Section 7.3.1).

60	11.4.3 Efficacy Evaluation	(2) Surgery for HAV. No treatment switch or interruption is possible as the primary efficacy endpoint is evaluated following a single injection of study treatment. Intercurrent event (1) is unlikely to occur, as the evaluation period for the primary efficacy endpoint is up to Week 8 (short period). Intercurrent event (2) is also unlikely to occur. All subjects with this level of pain severity and angular displacement are considered surgical candidates theoretically. However, the upper limit on HV angle (30 degrees) will likely limit the need ~~of~~ a "rescue" surgery. Subjects are expected to continue follow-up assessments regardless of these two intercurrent events. NPRS scores will be used as observed. A mixed model for repeated measures (MMRM) on change from baseline in foot pain as measured by the daily NPRS score averaged over the 7 consecutive days prior to each scheduled assessment timepoint of the DB period (up to Week 12) will be used to evaluate the estimand and compare treatment groups. ~~Missing data will be considered missing at random (MAR).~~ This model will include the fixed categorical effects of treatment group, visit, treatment group-by-visit interaction, the stratification parameter as fixed categorical covariates and the baseline value as fixed continuous covariate. The treatment group factor will have three levels (Dysport 300 U, Dysport 500 U and placebo), the factor visit three levels (Week 4, Week 8 and Week 12) and the stratification parameter two ~~level~~ (unilateral and bilateral HAV). ~~No missing baseline is expected as NPRS assessment is part of the inclusion criteria. Subjects will have reminders to complete the electronic diary, and site staff will be alerted if they miss a day.~~	(2) Surgery for HAV. No treatment switch or interruption is possible as the primary efficacy endpoint is evaluated following a single injection of study treatment. Intercurrent event (1) is unlikely to occur, as the evaluation period for the primary efficacy endpoint is up to Week 8 (short period). Intercurrent event (2) is also unlikely to occur. All subjects with this level of pain severity and angular displacement are considered surgical candidates theoretically. However, the upper limit on HV angle (30 degrees) will likely limit the need **for** a "rescue" surgery. Subjects are expected to continue follow-up assessments regardless of these two intercurrent events. NPRS scores will be used as observed. A mixed model for repeated measures (MMRM) on change from baseline in foot pain as measured by the daily NPRS score averaged over the 7 consecutive days prior to each scheduled assessment timepoint of the DB period (up to Week 12) will be used to evaluate the estimand and compare treatment groups. This model will include the fixed categorical effects of treatment group, visit, treatment group-by-visit interaction, the stratification parameter as fixed categorical covariates and the baseline value as fixed continuous covariate. The treatment group factor will have three levels (Dysport 300 U, Dysport 500 U and placebo), the factor visit three levels (Week 4, Week 8 and Week 12) and the stratification parameter two **levels** (unilateral and bilateral HAV). **Average scores will be calculated if there is at least 5-day e-diary completed. No missing baseline is expected as NPRS assessment is part of the inclusion criteria. Subjects will have reminders to complete the electronic diary, and site staff will be alerted if they miss a day. Therefore, the risk of having missing days is minimised. However, if subjects have no post-baseline efficacy assessment, Week 8 score will be imputed**

Version Date		25 MAY 2018	7 SEPTEMBER 2018
Page	**Section**	**WAS**	**IS**
			(imputation method will be described in the SAP). Other missing data will be considered missing at random (MAR).
60	Table 6	1 or 2 days missing in the 7-day NPRS e-diary Average on the completed days	Subjects not withdrawn before Week 8 of the DB period with a missing NPRS at Week 8 Multiple imputation based on subject with similar characteristics within the same treatment group
62	Table 7	Difference between each Dysport ~~doses~~ and the placebo group in the mean change from baseline in the mean daily mFFI pain subscale score averaged for the 7 consecutive days prior to Week 4, Week 8 and Week 12 DB visits.	Difference between each Dysport **dose** and the placebo group in the mean change from baseline in the mean daily mFFI pain subscale score averaged for the 7 consecutive days prior to Week 4, Week 8 and Week 12 DB visits.
63	Table 7	PGI-I pain and disability scores, respectively, ~~averaged over the 7 consecutive days prior to~~ Week 4, Week 8 and Week 12 DB visits.	PGI-I pain and disability scores, respectively, **at** Week 4, Week 8 and Week 12 DB visits.
63	11.4.3.2 Analysis of Secondary Efficacy Endpoints Double-blind Period	~~A~~ MMRM model on change from baseline including each scheduled timepoint up to Week 12 will be used to evaluate the estimands and compare treatment groups. Missing data will be considered ~~at~~ MAR.	**According to the scale, an** MMRM model **or a mixed-linear-generalized model** on change from baseline including each scheduled timepoint up to Week 12 will be used to evaluate the estimands and compare treatment groups. Missing data will be considered **as** MAR.

Version Date		25 MAY 2018	7 SEPTEMBER 2018
Page	**Section**	**WAS**	**IS**
64	11.4.3.2 Analysis of Secondary Efficacy Endpoints Open label Period	Open-Label period Table 8 summarises the secondary efficacy endpoints, their associated estimates and estimands during the ~~OL period~~.	Active Treatment Cycles Table 8 summarises the secondary efficacy endpoints, their associated estimates and estimands during the **active treatment cycles**.
64	Table 8	Table 8 Analysis of Secondary Efficacy Endpoints (~~Open-label Period~~)	Table 8 Analysis of Secondary Efficacy Endpoints (**active treatment cycles**)
65	11.4.3.2 Analysis of Secondary Efficacy Endpoints	Only descriptive statistics will be performed for the ~~open-label period~~.	Only descriptive statistics will be performed for **the active treatment cycles**.
	11.5 Subgroup analysis	Descriptive statistics for the primary efficacy ~~endpoints~~ will be provided on the stratification parameter (unilateral or bilateral HAV) on the ITT population. Other subgroup analyses may be planned according to clinical interest and will be detailed in the SAP.	Descriptive statistics for the primary efficacy **endpoint** will be provided on the stratification parameter (unilateral or bilateral HAV) on the ITT population. Other subgroup analyses may be planned according to clinical interest and will be detailed in the SAP.
	Appendix 1 Modified Foot Function Index		New version appended

SUMMARY & OUTCOME OF CHANGES:

STUDY NUMBER	D-FR-52120-237	
AMENDED PROTOCOL VERSION NUMBER & DATE	**Protocol Version 4.0 (Amendment 3)** **7 September 2018**	
SUBSTANTIAL ☐	**NON-SUBSTANTIAL** ☒	

REASON(S) FOR CHANGES	**Changes:**
	After internal and external consultation the following changes were made to update the protocol:
	• Incorporate the items from the administrative letter sent in July (attached the admin letter).
	  o assessment of the PGI-S for pain and PGI-S for disability at the Screening visit need to be added back into Table 3 (they inadvertently removed in the last amendment).
	  o gauge sizes were expanded to 22 to 30.
	• adding an N/A option to the mFFI questionnaire and providing **written** guidance within protocol for administering the questionnaire to the sites. Text to be included which reminds the PI to instruct the patient on the following:
	  o Complete assessments always on study foot
	  o Complete assessments in the evening
	  o Finish assessment completely (eg, do not start then finish later)
	  o Explain the "NA" option
	• Update the IM angle minimum entry criteria from 12° to 18° to 9° to 18°.
	• modify the frequency of the PGI-I and PGI-S.
	  o change administration from performing at home to completing the assessment at the site on site computer.
	• mFFI Instrument changes:
	  o Add a "not applicable" option to the mFFI questionnaire (all items).	

	○ addition of the word "study" to three areas of the questionnaire to focus the subject's attention on their treated study foot when answering questions. ○ updating "therapist" to "clinician" in the initial instructions. • Update/add instructions to the site regarding importance of instructing subjects to focus on their treated study foot when completing modified FFI, NRS, and PGI assessments ○ additional subject take-home instructions on this topic. • Update SF-36 superscript at early termination instructing that the assessment should be done every day for seven days. Statistical Sections: • - Clarification regarding missing data handling • - Replace 'open-label' analysis by 'active treatment analysis'.	
OTHER ACTION REQUIRED?	CRF UPDATE	Yes ☒ No ☐ *(tick one)*
	LOCAL CONSENT FORM UPDATE	Yes ☐ No ☐ *(tick one)*
	DATABASE UPDATE	Yes ☒ No ☐ *(tick one)*
	STATISTICAL ANALYSIS PLAN (SAP) UPDATE	Yes ☒ No ☐ *(tick one)*

STUDY NUMBER:	D-FR-52120-237
PROTOCOL TITLE:	A MULTIPLE-DOSE, DOUBLE-BLIND, RANDOMISED, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF DYSPORT FOR THE TREATMENT OF PAIN ASSOCIATED WITH HALLUX ABDUCTO VALGUS
AMENDED PROTOCOL VERSION NUMBER & DATE	Protocol Version 3.0 (Amendment 2) 25 May 2018

THE FOLLOWING AMENDMENTS ARE PROPOSED: (deleted text is indicated with strikethrough; new text is indicated in bold)

Version Date		**22 MAY 2018**	**25 MAY 2018**
Page	**Section**	**WAS**	**IS**
2	Investigator's Agreement	PPD [redacted]	[redacted]

Version Date		22 MAY 2018	25 MAY 2018
Page	**Section**	**WAS**	**IS**
5, 25, 26, 42 & 45	Synopsis Methodology 3.1 Fig 2 footnotes 3.1.2 Open-label Period (Cycles 2 to 3) Table 4 footnotes 6.2 Study Drugs Administered	Following completion of the DB period (i.e. completion of Cycle 1), subjects who meet retreatment criteria will be eligible to participate in the OL period. All retreatment-eligible subjects will receive OL treatment with Dysport 300 U at the first retreatment cycle (Cycle 2) in the HAV study foot selected during the DB period. At the second retreatment cycle (Cycle 3), subjects will be treated with either Dysport 300 U or 500 U in the HAV study foot based on investigator judgment and following clinical evaluation at the time of retreatment. The muscles to be injected and procedures for injection are identical to those targeted in the DB period.	Following completion of the DB period (i.e. completion of Cycle 1), subjects who meet retreatment criteria will be eligible to participate in the OL period. All retreatment-eligible subjects will receive OL treatment with Dysport 300 U at the first retreatment cycle (Cycle 2) in the HAV study foot selected during the DB period. At the second retreatment cycle (Cycle 3), subjects will be treated with either Dysport 300 U or 500 U in the HAV study foot based on investigator judgment and following clinical evaluation at the time of retreatment. **The decision to increase the dose at the beginning of Cycle 3 will be based on 1) evaluation of safety and tolerability (review related AEs and consideration of any significant changes in the study foot) and 2) severity of pain (considering NPRS score) and disability (considering mFFI Disability subscale score) experienced by the subject at the time of evaluation.** The muscles to be injected and procedures for injection are identical to those targeted in the DB period.
5 & 32	Synopsis Diagnosis and criteria for inclusion 4.1 Inclusion Criteria	(2) Male or female, aged 18 years ~~**to 75,**~~ years ~~**inclusive**~~	(2) Male or female, aged 18 years **or older**

9 & 10	Synopsis Criteria for evaluation (endpoints)	Efficacy: Primary Endpoint: the change from baseline in foot pain as measured by the daily NPRS score averaged over the 7 consecutive days prior to the Week 8 DB visit. Secondary Endpoints: • The change from baseline as measured by the daily NPRS score averaged over the 7 consecutive days prior to each scheduled ~~**assessment timepoint (except at** Week **8** DB**)**~~. • The change from baseline in the daily mFFI Disability subscale score averaged over the 7 consecutive days prior each scheduled ~~**assessment timepoint.**~~ • The change from baseline in the daily mFFI Pain subscale score averaged over the 7 consecutive days prior to each scheduled ~~**assessment timepoint.**~~ • The change from baseline in the daily mFFI total score averaged over the 7 consecutive days prior to each scheduled ~~**assessment timepoint.**~~ • The change from baseline in the daily mFFI activity limitation subscale score averaged over the 7 consecutive days prior to each scheduled ~~**assessment timepoint.**~~	Efficacy: Primary Endpoint: the change from baseline in foot pain as measured by the daily NPRS score averaged over the 7 consecutive days prior to the Week 8 DB visit. Secondary Endpoints: • The change from baseline as measured by the daily NPRS score averaged over the 7 consecutive days prior to Week **4 and Week 12** DB **visits and at each scheduled visit in the OL period.** • The change from baseline in the daily mFFI Disability subscale score averaged over the 7 consecutive days prior **to Week 4, Week 8 and Week 12 DB visits and at** each scheduled **visit in the OL period.** • The change from baseline in the daily mFFI Pain subscale score averaged over the 7 consecutive days prior to **Week 4, Week 8 and Week 12 DB visits and at** each scheduled **visit in the OL period.** • The change from baseline in the daily mFFI total score averaged over the 7 consecutive days prior to **Week 4, Week 8 and Week 12 DB visits and at** each scheduled **visit in the OL period.** • The change from baseline in the daily mFFI activity limitation subscale score averaged over the 7 consecutive days prior to **Week 4, Week 8 and Week 12 DB visits and at** each scheduled **visit in the OL period.**

		• The change from baseline in quality of life as measured by the SF-36 at each scheduled ~~**assessment timepoint.**~~	• The change from baseline in quality of life as measured by the SF-36 at **Week 8 and Week 12 DB visits and at** each scheduled **visit in the OL period.**
		• The change from baseline in HV angle as measured directly by weight-bearing anterior-posterior radiographs at each scheduled ~~**assessment timepoint.**~~	• The change from baseline in HV angle as measured directly by weight-bearing anterior-posterior radiographs at **Week 4 and Week 12 DB visits and at** each scheduled **visit in the OL period**.
		• The change from baseline in intermetatarsal angle as measured directly by weight-bearing anterior-posterior radiographs at each scheduled~~ **assessment timepoint.**~~	• The change from baseline in intermetatarsal angle as measured directly by weight-bearing anterior-posterior radiographs at **Week 4, Week 8 and Week 12 DB visits and at** each scheduled **visit in the OL period.**
		• Time to retreatment	• Time to retreatment
		• Patient Global Impression of Improvement of foot pain score averaged over the 7 consecutive days prior to each scheduled ~~**assessment timepoint.**~~	• Patient Global Impression of Improvement of foot pain score averaged over the 7 consecutive days prior to **Week 4, Week 8 and Week 12 DB visits and at** each scheduled **visit in the OL period.**
		• Patient Global Impression of Improvement in disability score averaged over the 7 consecutive days prior to ~~**each scheduled assessment timepoint.**~~	• Patient Global Impression of Improvement in disability score averaged over the 7 consecutive days prior to **Week 4, Week 8 and Week 12 DB visits and at** each scheduled **visit in the OL period.**

Version Date		22 MAY 2018	25 MAY 2018
Page	**Section**	**WAS**	**IS**
		• The change from baseline in the Patient Global Impression of Severity of foot pain score averaged over the 7 consecutive days prior to each scheduled ~~**assessment timepoint**~~. • The change from baseline in the Patient Global Impression of Severity disability score averaged over the 7 consecutive days prior to each scheduled~~— **assessment timepoint**~~.	• The change from baseline in the Patient Global Impression of Severity of foot pain score averaged over the 7 consecutive days prior to **Week 4, Week 8 and Week 12 DB visits and at** each scheduled **visit in the OL period.** • The change from baseline in the Patient Global Impression of Severity disability score averaged over the 7 consecutive days prior to **Week 4, Week 8 and Week 12 DB visits and at** each scheduled **visit in the OL period.**
22	1.8 Population to be studies	The study will enrol adult male and female subjects aged 18 years ~~**to 75, inclusive,**~~ suffering from clinically significant HAV who have not undergone surgery for their condition.	The study will enrol adult male and female subjects aged 18 years **or older** suffering from clinically significant HAV who have not undergone surgery for their condition.
26	3.2.1 Primary Efficacy Endpoint	The primary efficacy endpoint is the change from baseline in the daily NPRS score averaged over the 7 consecutive days prior to the Week 8 ~~**assessment timepoint.**~~	The primary efficacy endpoint is the change from baseline in the daily NPRS score averaged over the 7 consecutive days prior to the Week 8 **DB visit.**

27 & 62	3.2.2 Secondary Efficacy Endpoints Table 2	**Secondary Efficacy Endpoints**	**Secondary Efficacy Endpoints**
		The change from baseline in the daily NPRS score averaged over the 7 consecutive days prior to each scheduled ~~**assessment timepoint (except Week 8** DB**)**~~.	The change from baseline in the daily NPRS score averaged over the 7 consecutive days prior to **Week 4 and Week 12** DB **visits and** each scheduled **visit in the OL period**.
		The change from baseline in the daily mFFI disability subscale score averaged over the 7 consecutive days prior to each scheduled ~~**assessment timepoint**~~.	The change from baseline in the daily mFFI disability subscale score averaged over the 7 consecutive days prior to **Week 4, Week 8 and Week 12 DB visits and** each scheduled **visit in the OL period.**
		The change from baseline in the daily mFFI pain subscale score averaged over the 7 consecutive days prior to each scheduled ~~**assessment timepoint.**~~	The change from baseline in the daily mFFI pain subscale score averaged over the 7 consecutive days prior to **Week 4, Week 8 and Week 12 DB visits and** each scheduled **visit in the OL period.**
		The change from baseline in the daily mFFI total score averaged over the 7 consecutive days prior to each scheduled ~~**assessment timepoint.**~~	The change from baseline in the daily mFFI total score averaged over the 7 consecutive days prior to **Week 4, Week 8 and Week 12 DB visits and** each scheduled **visit in the OL period.**
		The change from baseline in the daily mFFI activity limitation subscale score averaged over the 7 consecutive days prior to each scheduled ~~**assessment timepoint.**~~	The change from baseline in the daily mFFI activity limitation subscale score averaged over the 7 consecutive days prior to **Week 4, Week 8 and Week 12 DB visits at** each scheduled **visit in the OL period**.
		The change from baseline in HV angle as measured directly by weight-bearing anterior-posterior radiographs ~~**at**~~ each scheduled ~~**assessment timepoint.**~~	The change from baseline in HV angle as measured directly by weight-bearing anterior posterior radiographs **at Week 4, Week 8 and Week 12 DB visits and** each scheduled **visit in the OL period.**
		The change from baseline in intermetatarsal angle as measured directly by weight-bearing anterior-posterior radiographs at each scheduled ~~**assessment timepoint.**~~	The change from baseline in intermetatarsal angle as measured directly by weight bearing anterior-posterior radiographs **at Week 4, Week 8 and Week 12 DB visits and** each scheduled **visit in the OL period.**
		The time to retreatment	The time to retreatment
		The change from baseline in PGI-S of foot pain score averaged over the 7 consecutive days prior each scheduled ~~**assessment timepoint.**~~	The change from baseline in PGI-S of foot pain score averaged over the 7 consecutive days prior **to Week 4, Week 8 and Week 12 DB visits and** each scheduled **visit in the OL period**.

<table>
<tr><th colspan="2">Version Date</th><th>22 MAY 2018</th><th>25 MAY 2018</th></tr>
<tr><th>Page</th><th>Section</th><th>WAS</th><th>IS</th></tr>
<tr><td></td><td></td><td>The change from baseline in PGI-S disability score averaged over the 7 consecutive days prior each scheduled <s>assessment timepoint.</s></td><td>The change from baseline in PGI-S disability score averaged over the 7 consecutive days prior to Week 4, Week 8 and Week 12 DB visits and each scheduled visit in the OL period.</td></tr>
<tr><td></td><td></td><td>The PGI-I foot pain score averaged over the 7 consecutive days prior to each scheduled <s>assessment timepoint</s></td><td>The PGI-I foot pain score averaged over the 7 consecutive days prior to Week 4, Week 8 and Week 12 DB visits and each scheduled visit in the OL period.</td></tr>
<tr><td></td><td></td><td>The PGI-I disability score averaged over the 7 consecutive days prior to each scheduled <s>assessment timepoint</s></td><td>The PGI-I disability score averaged over the 7 consecutive days prior to Week 4, Week 8 and Week 12 DB visits and each scheduled visit in the OL period.</td></tr>
<tr><td></td><td></td><td>The change from baseline in quality of life as measured by the SF-36 at each scheduled <s>assessment timepoint.</s></td><td>The change from baseline in quality of life as measured by the SF-36 at Week 8 and Week 12 DB visits and each scheduled visit in the OL period.</td></tr>
<tr><td>27</td><td>3.2.4
Safety Endpoints and Evaluations</td><td>• The incidence of AEs, serious AEs (SAEs), AEs leading to discontinuations and AEs of special interest (AESIs) (i.e. remote effects of toxin)</td><td>• The incidence of AEs, serious AEs (SAEs), AEs leading to discontinuations and AEs of special interest (AESIs) (i.e. remote effects of toxin and hypersensitivity like reactions)</td></tr>
<tr><td>30</td><td>3.7
Stopping Rules and Discontinuation Criteria</td><td>• failure of the investigator staff to comply with the protocol or with the GCP guidelines;
• safety concerns;
• inadequate subject recruitment.</td><td>• failure of the investigator staff to comply with the protocol or with the GCP guidelines;
• New and significant safety concerns;
• inadequate subject recruitment.</td></tr>
<tr><td>38</td><td>Table 3
Study Procedures and Assessments: Double-blind Period</td><td><table><tr><td>tibial sesamoid position[a]</td><td></td><td></td></tr><tr><td>NPRS</td><td>X[i]</td><td>X</td></tr><tr><td>mFFI</td><td>X[i]</td><td>X</td></tr></table></td><td><table><tr><td></td><td></td><td></td></tr><tr><td>NPRS</td><td>X</td><td>X[i]</td></tr><tr><td>mFFI</td><td>X</td><td>X[i]</td></tr></table></td></tr>
</table>

Version Date		22 MAY 2018	25 MAY 2018
Page	**Section**	**WAS**	**IS**
43	6.2 Study Drugs Administered	A blinded kit will be used in this study to maintain the blinding of the study during the DB period. Each blinded kit will contain two vials regardless of treatment assignment~~.~~ The two vials in each kit will contain either a Dysport 300 U vial + a placebo vial, a Dysport 500 U vial + a placebo vial or two placebo vials, based on treatment assignment. Investigators will be blinded to which vial contains Dysport and which vial contains placebo.	A blinded kit will be used in this study to maintain the blinding of the study during the DB period. Each blinded kit will contain two vials regardless of treatment assignment**: one vial 300 U or placebo and one vial 500 U or placebo**. The two vials in each kit will contain either a Dysport 300 U vial + a placebo vial, a Dysport 500 U vial + a placebo vial or two placebo vials, based on treatment assignment. Investigators will be blinded to which vial contains Dysport and which vial contains placebo.
53	8.2 Clinical Laboratory Tests	Blood and urine samples will be collected during the DB and OL periods as described in the study procedures and assessments in Table 3 and Table 4 for the evaluation of haematology and serum chemistry.	Blood and urine samples will be collected during the DB and OL periods as described in the study procedures and assessments in Table 3 and Table 4 for the evaluation of haematology and serum chemistry **and urine examination.**
55	8.4.1 Dermatological examination	The investigator will evaluate and record whether these or other dermatological conditions are present in the study foot and will record ~~**any**~~ AEs that were not present at Baseline resulting from the dermatologic examination.	The investigator will evaluate and record whether these or other dermatological conditions are present in the study foot and will record **new findings as** AEs that were not present at Baseline resulting from the dermatologic examination.
55	8.42 Neurological Examination	The investigator will evaluate and record whether the neurological condition of the study foot is “normal” or “abnormal” based on their medical judgment regarding the degree of loss of sensation in the study foot and will record ~~**any**~~ AEs that were not present at Baseline resulting from the neurological examination.	The investigator will evaluate and record whether the neurological condition of the study foot is “normal” or “abnormal” based on their medical judgment regarding the degree of loss of sensation in the study foot and will record **new findings as** AEs that were not present at Baseline resulting from the neurological examination.

Version Date		22 MAY 2018	25 MAY 2018
Page	**Section**	**WAS**	**IS**
56	8.4.3 Musculoskeletal Examination	The investigator will evaluate and record whether these or other musculoskeletal conditions of the study foot are present and will record ~~any~~ AEs that were not present at Baseline resulting from the musculoskeletal examination.	The investigator will evaluate and record whether these or other musculoskeletal conditions of the study foot are present and will record **new findings as** AEs that were not present at Baseline resulting from the musculoskeletal examination.
60	11.4.3 Efficacy evaluation	Sensitivity analysis Two sensitivity analyses will be performed. First, the primary efficacy analysis will be re-run imputing missing data as described in Table 6. Then~~, the primary efficacy analysis~~ will be ~~re-run on the PP population~~.	Sensitivity analysis Two sensitivity analyses will be performed **to investigate the robustness of the primary efficacy analysis**. First, the primary efficacy analysis will be re-run imputing missing data as described in Table 6. Then**, a tipping point analysis will be performed (analysis** will be **detailed in the Statistical Analysis Plan).**
60	11.4.3 Efficacy evaluation	*Supplementary analyses* Supplementary analyses will be performed in order to complement the primary estimand ~~considering~~ two other estimands~~:~~	*Supplementary analyses* Supplementary analyses will be performed in order to complement the primary estimand. **The primary efficacy analysis will be first re-run on the PP population. In addition,** two other estimands **will be considered**:

60	11.4.3 Table 7 Column 1	Secondary Efficacy Endpoints	**Secondary Efficacy Endpoints**
		The change from baseline as measured by the daily NPRS score averaged over 7 consecutive days prior to ~~**each scheduled assessment timepoint (except at Week 8 DB)**~~.	The change from baseline in the daily NPRS score averaged over the 7 consecutive days prior to **Week 4 and Week 12 DB visits.**
		The change from baseline in the daily mFFI Disability subscale score averaged over the 7 consecutive days prior ~~**each scheduled assessment timepoint.**~~	The change from baseline in the daily mFFI disability subscale score averaged over the 7 consecutive days prior **to Week 4, Week 8 and Week 12 DB visits.**
		The change from baseline in the daily mFFI Pain subscale score averaged over the 7 consecutive days prior to ~~**each scheduled assessment timepoint.**~~	The change from baseline in the daily mFFI pain subscale score averaged over the 7 consecutive days prior **to Week 4, Week 8 and Week 12 DB visits.**
		The change from baseline in the daily mFFI total score averaged over the 7 consecutive days prior to ~~**each scheduled assessment timepoint.**~~	The change from baseline in the daily mFFI total score averaged over the 7 consecutive days prior **to Week 4, Week 8 and Week 12 DB visits.**
		The change from baseline in the daily mFFI activity limitation subscale score averaged over the 7 consecutive days prior to ~~**each scheduled assessment timepoint.**~~	The change from baseline in the daily mFFI activity limitation subscale score averaged over the 7 consecutive days prior to **Week 4, Week 8 and Week 12 DB visits**.
		The change from baseline in the PGI-S pain and disability scores, respectively, averaged over the 7 consecutive days prior to ~~**each scheduled assessment timepoint**~~.	The change from baseline in the PGI-S pain and disability scores, respectively, averaged over the 7 consecutive days prior to **Week 4, Week 8 and Week 12 DB visits.**
		PGI-I pain and disability scores, respectively, averaged over the 7 consecutive days prior to ~~**each scheduled assessment timepoint**~~.	PGI-I pain and disability scores, respectively, averaged over the 7 consecutive days prior to **Week 4, Week 8 and Week 12 DB visits**.

Version Date		22 MAY 2018	25 MAY 2018
Page	**Section**	**WAS**	**IS**
		The change from baseline in HV angle as measured directly by weight-bearing anterior-posterior radiographs at ~~**each scheduled assessment timepoint**~~.	The change from baseline in HV angle as measured directly by weight-bearing anterior-posterior radiographs at **Week 4, Week 8 and Week 12 DB visits.**
		The change from baseline in intermetatarsal angle as measured directly by weight-bearing anterior-posterior radiographs at ~~**each scheduled assessment timepoint**~~.	The change from baseline in intermetatarsal angle as measured directly by weight-bearing anterior-posterior radiographs at **Week 4, Week 8 and Week 12 DB visits**.
		The change from baseline in quality of life as measured by the SF-36 ~~**at each scheduled assessment timepoint.**~~	The change from baseline in quality of life as measured by the SF-36 at **Week 8 and Week 12 DB visits**.
		Time to retreatment	Time to retreatment

60	11.4.3 Table 7 Column 2	**Estimate of Treatment Effect**	**Estimate of Treatment Effect**
		Difference between each Dysport doses and the placebo group, in the mean change from baseline in the mean daily NPRS score averaged for the 7 consecutive days prior to each scheduled ~~**assessment timepoint.**~~	Difference between each Dysport doses and the placebo group, in the mean change from baseline in the mean daily NPRS score averaged for the 7 consecutive days prior to **Week 4 and Week 12 DB visits**.
		Difference between each Dysport doses and the placebo group in the mean change from baseline in the mean daily mFFI disability subscale score averaged for the 7 consecutive days prior to each scheduled ~~**assessment timepoint**~~	Difference between each Dysport doses and the placebo group in the mean change from baseline in the mean daily mFFI disability subscale score averaged for the 7 consecutive days prior to **Week 4 and Week 12 DB visits**.
		Difference between each Dysport doses and the placebo group in the mean change from baseline in the mean daily mFFI pain subscale score averaged for the 7 consecutive days prior to each scheduled ~~**assessment timepoint**~~	Difference between each Dysport doses and the placebo group in the mean change from baseline in the mean daily mFFI pain subscale score averaged for the 7 consecutive days prior to **Week 4 and Week 12 DB visits**.
		Difference between each Dysport doses and the placebo group in the mean change from baseline in the mean daily mFFI total score averaged for the 7 consecutive days prior to each scheduled ~~**assessment timepoint**~~	Difference between each Dysport doses and the placebo group in the mean change from baseline in the mean daily mFFI total score averaged for the 7 consecutive days prior to **Week 4 and Week 12 DB visits**.
		Difference between each Dysport doses and the placebo group in the mean change from baseline in the mean daily mFFI activity limitation subscale score averaged for the 7 consecutive days prior to each scheduled ~~**assessment timepoint**~~	Difference between each Dysport doses and the placebo group in the mean change from baseline in the mean daily mFFI activity limitation subscale score averaged for the 7 consecutive days prior to **Week 4 and Week 12 DB visits**.
		Difference between each Dysport doses and the placebo group in the change from baseline in the mean daily PGI-S pain and disability scores,	Difference between each Dysport doses and the placebo group in the change from baseline in the mean daily PGI-S pain and disability scores, respectively, averaged for the 7 consecutive days prior to **Week 4 and Week 12 DB visits**.
			Difference between each Dysport doses and the placebo group in the mean daily PGI-I pain and disability scores, respectively, averaged for the 7 consecutive days prior to ~~**Week 4 and Week 12 DB visits**~~.

Version Date		22 MAY 2018	25 MAY 2018
Page	**Section**	**WAS**	**IS**
		respectively, averaged for the 7 consecutive days prior to each scheduled ~~**assessment timepoint**~~	Difference between each Dysport doses and the placebo group in then mean change from baseline in HV angle at **Week 4 and Week 12 DB visits.**
		Difference between each Dysport doses and the placebo group in the mean daily PGI-I pain and disability scores, respectively, averaged for the 7 consecutive days prior to each scheduled ~~**assessment timepoint**~~	Difference between each Dysport doses and the placebo group in then mean change from baseline in intermetatarsal angle at **Week 4 and Week 12 DB visits**.
		Difference between each Dysport doses and the placebo group in then mean change from baseline in HV angle at **each scheduled ~~assessment timepoint~~**	~~Difference between each Dysport doses group~~ and the placebo group in the SF-36 scores to **Week 4 and Week 12 DB visits** (analysis will be detailed in the statistical analysis plan)
		Difference between each Dysport doses and the placebo group in then mean change from baseline in intermetatarsal angle at each scheduled ~~**assessment timepoint**~~	~~Difference between each Dysport doses group~~ and the placebo group in the median time to retreatment between the first and the second injection.
		Difference between each Dysport doses group and the placebo group in the SF-36 scores to each scheduled ~~**assessment timepoint**~~ (analysis will be detailed in the statistical analysis plan)	
		Difference between each Dysport doses group and the placebo group in the median time to retreatment between the first and the second injection.	

SUMMARY & OUTCOME OF CHANGES:

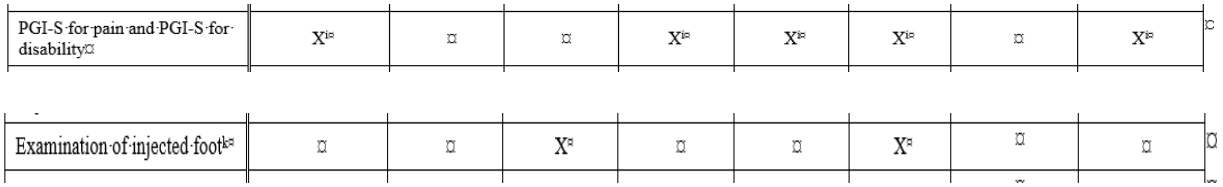
STUDY NUMBER	D-FR-52120-237	
AMENDED PROTOCOL VERSION NUMBER & DATE	Protocol Version 3.0 (Amendment 2) 25 May 2018	
SUBSTANTIAL ☐	**NON-SUBSTANTIAL** ☒	
REASON FOR CHANGES	Follow-up on FDA advice/information re: IND 136332 Dysport - Reference ID: 4259336	
OTHER ACTION REQUIRED?	CRF UPDATE	Yes ☒ No ☐ *(tick one)*
	LOCAL CONSENT FORM UPDATE	Yes ☒ No ☐ *(tick one)*
	DATABASE UPDATE	Yes ☒ No ☐ *(tick one)*
	REPORTING & ANALYSIS PLAN (RAP) UPDATE	Yes ☒ No ☐ *(tick one)*

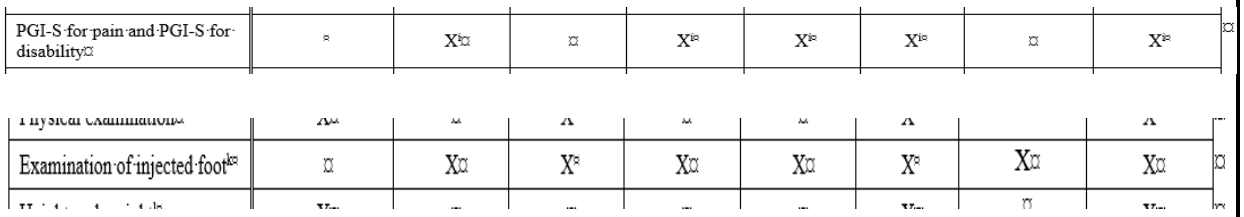
STUDY NUMBER:	D-FR-52120-237
PROTOCOL TITLE:	A MULTIPLE-DOSE, DOUBLE-BLIND, RANDOMISED, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF DYSPORT FOR THE TREATMENT OF PAIN ASSOCIATED WITH HALLUX ABDUCTO VALGUS
AMENDED PROTOCOL VERSION NUMBER & DATE	Protocol Version 2.0 (Amendment 1) 22 May 2018

THE FOLLOWING AMENDMENTS ARE PROPOSED: (deleted text is indicated with strikethrough; new text is indicated in bold)

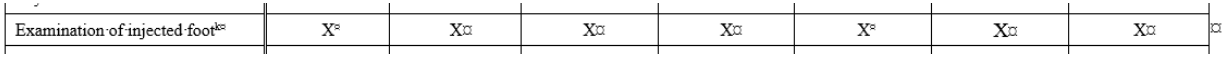
Version Date		**06 MARCH 2018**	**22 MAY 2018**
Page	**Section**	**WAS**	**IS**
7 & 33	Synopsis & 4.2	Subject presents with metatarsus primus ~~**elevates**~~ in the study foot	Subject presents with metatarsus primus **elevatus** in the study foot
7 & 33	Synopsis & 4.2	(8) Subject presents with medical history or clinical evidence of ~~**any**~~ vascular disease	(8) Subject presents with medical history or clinical evidence of **peripheral** vascular disease
7 & 33	Synopsis & 4.2	(13) Subject is using orthotic ~~**inserts**~~ ~~**or**~~ device~~**s**~~ ~~**on**~~ the study foot	(13) Subject is using **an** orthotic device **of any kind (including over-the-counter toe-spacers) which could influence the functioning of the hallux of** the study foot **in any way, or any other device intended for this purpose. Over-the-counter shoe inserts for the study foot are permitted if used for at least 30 days prior to screening**.
7 & 33	Synopsis & 4.2	(14) Subject has medical history or clinical evidence of peripheral neuropathy	(14) Subject has medical history or clinical evidence of peripheral neuropathy **or fibromyalgia**
7 & 33	Synopsis & 4.2	(19) Subject demonstrates evidence of inflammatory arthritis (including gout) or osteoarthritis based on either history or clinical evaluation	(19) Subject demonstrates evidence of inflammatory arthritis (including gout) **in the study foot** or osteoarthritis in **the study foot** based on either history or clinical evaluation

Version Date		06 MARCH 2018	22 MAY 2018
Page	**Section**	**WAS**	**IS**
8 & 34	Synopsis & 4.2	(30) Subject is medically unable to discontinue treatment with medications with anticoagulant/antiplatelet effects for at least 3 days before ~~**Screening**~~. Subjects ~~**who are medically unable to stop these medications for the duration of the study (in the opinion**~~ of the investigator)~~ **will not be eligible to participate in the study**~~.	(30) Subject is medically unable to discontinue treatment with medications with anticoagulant/antiplatelet effects **(e.g. warfarin and other coumadin derivatives, acetylsalicylic acid and clopidogrel/ticlopidine)** for at least 3 days before **randomisation/injection of study treatment.** Subjects **are permitted restart anticoagulant/antiplatelet medications one day after injection of study treatment (or longer at the discretion** of the investigator)**.**
8 & 43	Synopsis & 6.2	Investigators will inject 0.5 mL of the reconstituted solution containing study treatment into each of four specified muscles of the foot	Investigators will inject 0.5 mL of the reconstituted solution containing study treatment into each of four specified muscles of the foot **(2.0 mL total volume)**
9, 27 & 63	Throughout document	The change from baseline in ~~**functional outcome**~~ as measured by the SF-36 at each scheduled assessment timepoint.	• The change from baseline in **quality of life** as measured by the SF-36 at each scheduled assessment timepoint.
26	3.1.2.1 Retreatment Criteria	Prior to receiving retreatment with Dysport in each of the two retreatment cycles in the OL period (Cycles 2 and 3), subjects will be required to meet the following retreatment criteria: • Subject is willing to receive a new treatment cycle with Dysport • ~~**Retreatment**~~ with Dysport is in the best interest of the subject based on the investigator's clinical judgment.	Prior to receiving retreatment with Dysport in each of the two retreatment cycles in the OL period (Cycles 2 and 3), subjects will be required to meet **all** the following retreatment criteria: • Subject is willing to receive a new treatment cycle with Dysport • **Treatment** with Dysport is in the best interest of the subject based on the investigator's clinical judgment.

Version Date		06 MARCH 2018	22 MAY 2018
Page	**Section**	**WAS**	**IS**
26	3.2.1 Primary Efficacy Endpoint	The primary efficacy endpoint is the change from baseline in the daily NPRS score averaged over the 7 consecutive days prior to ~~**each scheduled**~~ assessment timepoint. The baseline is defined as the daily NPRS score averaged over the 7 consecutive days prior to the baseline visit (Day 1).	The primary efficacy endpoint is the change from baseline in the daily NPRS score averaged over the 7 consecutive days prior to **the Week 8** assessment timepoint. The baseline is defined as the daily NPRS score averaged over the 7 consecutive days prior to the baseline visit (Day 1).
38 & 39	5.1 Study Schedule Table 2	Was:  k Assessment to include ~~**examination of the injection sites on the study foot specifically evaluating the foot for the presence of injection site irritation or emergence of other foot deformities or dysfunctions (e.g. hammer toe, claw toe, neuropathy). Assessment to include evaluation of sensation of the study foot and, any the development of skin irritations or ulcerations on the study foot.**~~	

<table>
<tr><th colspan="2">Version Date</th><th>06 MARCH 2018</th><th>22 MAY 2018</th></tr>
<tr><th>Page</th><th>Section</th><th>WAS</th><th>IS</th></tr>
<tr><td></td><td></td><td colspan="2">Is:
 

k Assessment to include complete physical examination of the injection sites on the study foot specifically evaluating the foot for any dermatologic, neurologic or musculoskeletal abnormalities (see Section 8.4 for further details).</td></tr>
<tr><td>40 & 41</td><td>5.1
Study Schedule
Table 3</td><td colspan="2">Was:
 

k Assessment to include <s>examination of the injection sites on the study foot specifically evaluating the foot for the presence of injection site irritation or emergence of other foot deformities or dysfunctions (e.g. hammer toe, claw toe, neuropathy). Assessment to include evaluation of sensation of the study foot and, any the development of skin irritations or ulcerations on the study foot.</s>
Is:
 

k Assessment to include a complete physical examination of the injection sites on the study foot specifically evaluating the foot for any dermatologic, neurologic or musculoskeletal abnormalities (see Section 8.4 for further details).</td></tr>
</table>

Version Date		06 MARCH 2018	22 MAY 2018
Page	**Section**	**WAS**	**IS**
45	6.3 Concomitant Medication/ Therapy	• Opioids • ~~**Anticoagulants, with the exception of over the counter pain medications (i.e. low dose aspirin) for short-term treatment of minor ailments (e.g. common cold)**~~ • Subjects who require treatment with antipsychotic (e.g. D2 antagonists) or antidepressant (e.g. selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors) will need to demonstrate evidence of stable dose regimen in the 30 days prior to Screening and will maintain that dose for the duration of the study.	• Opioids • **Any medication not specifically permitted by the protocol which has antinociceptive (pain relieving) properties. This includes any and all narcotic pain relievers, as well as pregabalin and gabapentin.** • Subjects who require treatment with antipsychotic (e.g. D2 antagonists) or antidepressant (e.g. selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors) will need to demonstrate evidence of stable dose regimen in the 30 days prior to Screening and will maintain that dose for the duration of the study. • After consultation with prescribing physician, anticoagulant medications must be stopped 3 days prior to administration of study treatment. These medications can be restarted one day after administration of study treatment and can be stopped for a longer period if deemed necessary in the opinion of the investigator, and in compliance with standard medical practice and the manufactures' discontinuation recommendations for the medication. Anticoagulant medications permitted during the study include, but are not limited to: o warfarin and other coumadin derivatives o acetylsalicylic acid (including low-dose aspirin) o clopidogrel/ticlopidine If medically indicated, lower molecular weight heparins are permitted providing the last dose was within 24 hours prior to administration of study treatment, and may be restarted one day following administration of study treatment.

Version Date		06 MARCH 2018	22 MAY 2018
Page	**Section**	**WAS**	**IS**
46	6.4 Lifestyle Restrictions/ Recommendations	Besides restrictions already presented in the exclusion criteria, subjects should not use ~~orthotic inserts or devices on the study foot at any time during the study~~.	Besides restrictions already presented in the exclusion criteria, subjects should not use **an orthotic device or 'over-the-counter shoe-insert' of any kind which could influence the functioning of the hallux of the study foot in any way during the study. This includes toe-spacers or any other device intended for this purpose. Over-the counter shoe inserted will be permitted during the study only for subjects who have used these for at least 30 days prior to screening.**
46	7.1.2 Foot Function Index	To obtain a subscale score, the item scores for a given subscale (i.e. pain, disability or activity limitation subscales) are ~~totalled~~ and divided by the maximum total possible multiplied by 100 for all of the subscale items ~~which the subject indicated were applicable~~. Each subscale score, as well as the total score will range from 0 to 100.	To obtain a subscale score, the item scores for a given subscale (i.e. pain, disability or activity limitation subscales) are **totaled** and divided by the maximum total possible multiplied by 100 for all of the subscale items. Each subscale score, as well as the total score will range from 0 to 100.
47	7.1.3 Intermetatarsal Angle, Hallux Valgus Angle and Sesamoid Position	Intermetatarsal angle, HV angle and tibial sesamoid position will be measured directly on weight-bearing anteriorposterior radiographs, in which the X-ray beam is angled 15° towards the heel centered on the second tarsometatarsal joint with a source to image-receptor distance of 100 cm. ~~**Radiographs should be done using a foot positioner.**~~ Images should be taken by the same radiology technician. Angle measurements will be performed by a blinded central reader.	Intermetatarsal angle, HV angle and tibial sesamoid position will be measured directly on weight-bearing anteriorposterior radiographs, in which the X-ray beam is angled 15° towards the heel centered on the second tarsometatarsal joint with a source to image-receptor distance of 100 cm. **Radiographic measurements will be conducted by following the General Acquisition Guidelines document provided to sites by the Sponsor to ensure accurate reproducibility of image acquisition across sites.** Images should be taken by the same radiology technician. Angle measurements will be performed by a blinded central reader.

Version Date		06 MARCH 2018	22 MAY 2018
Page	**Section**	**WAS**	**IS**
48	7.1.8 Patient Global Impression of Severity of Disability	The PGI-S will be assessed by the subject by answering the following question: "How severe was your disability while performing physical activities (e.g. standing, walking or running) over the past 24 hours?" (0=no ~~**pain**~~; 1=mild ~~**pain**~~; 2=moderate ~~**pain**~~; 3=severe ~~**pain**~~).	The PGI-S will be assessed by the subject by answering the following question: "How severe was your disability while performing physical activities (e.g. standing, walking or running) over the past 24 hours?" (0=no **disability**; 1=mild **disability**; 2=moderate **disability**; 3=severe **disability**).
49	8.1 Adverse Events	The investigator will be responsible for a clinical assessment of the study participants during the whole participation of the subjects in the study, from informed consent up to discharge from the study, and for the setup of a discharge plan if needed.	The investigator will be responsible for a clinical **safety** assessment of the study participants during the whole participation of the subjects in the study, from informed consent up to discharge from the study, and for the setup of a discharge plan if needed.

Version Date		06 MARCH 2018	22 MAY 2018
Page	**Section**	**WAS**	**IS**
50	8.1.3 Adverse events of Special Interest	The effects of Dysport and all BTX products may spread from the area of injection to produce symptoms consistent with BTX effects. These symptoms have been reported hours to weeks after injection. Remote spread of toxin ~~that~~ affects swallowing and breathing can be life threatening, and there have been reports of death.-The risk of symptoms is increased in subjects who have underlying conditions (e.g. disorders of the neuromuscular junction) that would predispose them to these symptoms.-Dysport is contraindicated in individuals with known hypersensitivity to any BTX preparation or to any of the components in the formulation. Adverse events of special interest (AESIs) for Dysport are AEs that suggest a possible remote spread of effect of the toxin or hypersensitivity. A list of preferred terms of AESIs will be provided in the Statistical Analysis Plan (SAP). All AEs will be monitored by the sponsor to determine if they meet the criteria of AESIs. These AESIs will be further analysed to determine if there is a plausible possibility that they represent distant spread of toxin or hypersensitivity. A list of preferred terms of AESIs will be provided in the Statistical Analysis Plan (SAP). All AEs will be monitored by the sponsor to determine if they meet the criteria of AESIs. These AESIs will be further analysed to determine if there is a plausible possibility that they represent distant spread of toxin or hypersensitivity. In order to perform the analysis, variables including alternative aetiology (medical history, concomitant medication, or diagnosis which could account for the symptoms), location of Dysport administration, and temporal relationship to Dysport administration will be considered by the sponsor.	Adverse events of special interest (AESIs) for Dysport are AEs that suggest a possible remote spread of effect of the toxin or events suggestive of hypersensitivity **like reactions.** The effects of Dysport and all BTX products may spread away from the area of injection to produce symptoms consistent with remote spread of BTX effects. These symptoms have been reported hours to weeks after injection. **The events of** remote spread of toxin **maybe severe and** affects swallowing and breathing**,** can be life threatening, and there have been reports of death. The risk of symptoms is increased in subjects who have underlying conditions (e.g. disorders of the neuromuscular junction) that would predispose them to these symptoms. Dysport is contraindicated in individuals with known hypersensitivity to any BTX preparation or to any of the components in the formulation. A list of preferred terms of AESIs will be provided in the Statistical Analysis Plan (SAP). All AEs will be monitored by the sponsor to determine if they meet the criteria of AESIs. These AESIs will be further analysed to determine if there is a plausible possibility that they represent remote spread of toxin or hypersensitivity **like reactions**. In order to perform the analysis, variables including alternative aetiology (medical history, concomitant medication, or diagnosis which could account for the symptoms), location of Dysport administration, and temporal relationship to Dysport administration will be considered by the sponsor.

Version Date		06 MARCH 2018	22 MAY 2018
Page	**Section**	**WAS**	**IS**
52	8.1.6 Pregnancy	Information regarding pregnancies must be collected on the AE page of the eCRF ~~**and reported to the sponsor as an SAE**~~. The sponsor will request further information from the investigator as to the course and outcome of the pregnancy using the Standard Pregnancy Outcome Report Form.	Information regarding pregnancies must be collected on the AE page of the eCRF. The sponsor will request further information from the investigator as to the course and outcome of the pregnancy using the Standard Pregnancy Outcome Report Form.
53	8.1.9 Reporting to Competent Authorities/IECs/IRBs/Other Investigators	The sponsor will ensure that processes are in place for submission of reports of Suspected Unexpected Serious Adverse Reactions (SUSARs) occurring during the study to the Competent Authorities (CA), IECs and other investigators concerned by the IMP. Reporting will be done in accordance with the applicable regulatory requirements. ~~**The sponsor must report all SUSARs to European Medicines Agency's EudraVigilance database within 15 days. Fatal and life-threatening SUSARs should be reported within 7 calendar days, with another 8 days for completion of the report.**~~ For study centres in the USA, Investigational New Drug Application Safety Reports will be submitted directly to the investigators. It is the investigators' responsibility to notify their IRB in a timely manner.	The sponsor will ensure that processes are in place for submission of reports of Suspected Unexpected Serious Adverse Reactions (SUSARs) occurring during the study to the Competent Authorities (CA), IECs and other investigators concerned by the IMP. Reporting will be done in accordance with the applicable regulatory requirements. For study centres in the USA, Investigational New Drug Application Safety Reports will be submitted directly to the investigators. It is the investigators' responsibility to notify their IRB in a timely manner.

Version Date		06 MARCH 2018	22 MAY 2018
Page	**Section**	**WAS**	**IS**
55	8.4 Examination of the Study Foot	(8.3.1) ~~**An**~~ examination of the study foot will be conducted as outlined in Table 3 and Table 4. The examination will include ~~**assessment of the injection sites on the study foot specifically evaluating the foot for the presence of injection site irritation or emergence of other foot deformities or dysfunctions (e.g., hammer toe, claw toe, neuropathy). The assessment will also include evaluation of sensation of the study foot and any development of skin irritations or ulcerations on the study foot. Any findings will be reported as AEs.**~~	(8.4) **A complete physical** examination of the study foot will be conducted as outlined in Table 3 and Table 4 **for the DB and OL periods.** The examination will include **evaluation of the a) dermatologic, b) neurologic and c) musculoskeletal condition of the study foot. For dermatologic and musculoskeletal foot examinations, the Investigator will record whether a given abnormality or deformity is present. For neurological examinations, the Investigator will record whether the specified neurological parameters are "normal" or "abnormal" based on clinical presentation.** **Any findings that were not present at Baseline based on examination of the study will be recorded as AEs. As for all AEs reported during the study, the investigator should use his/her medical judgment to determine if treatment of the study foot is required based on an abnormal finding, and/or if the subject should be withdrawn from the study due to an abnormal finding in the study foot.** **Details for each of the study foot examination parameters required during the study are provided in the sections below.**

Version Date		06 MARCH 2018	22 MAY 2018
Page	**Section**	**WAS**	**IS**
55	8.4.1 Dermatological Examination		**The dermatologic examination will consist of a global inspection of the study foot and injection sites for injection site irritations, ulcerations, bleeding, discolorations, calluses, wounds, fissures, lesions, macerations, nail dystrophy, hyperpigmentation, erythema, oedema or paronychia. Inspection of the toes should include a search for fungal, ingrown or elongated nails, as well as areas between the toes for the presence of deeper lesions. The investigator will evaluate and record whether these or other dermatological conditions are present in the study foot and will record any AEs that were not present at Baseline resulting from the dermatologic examination.**
55	8.4.2 Neurological Examination		**The neurological examination will consist of the evaluation of protective sensation using the Ipswich Touch Test [22], as subjects who develop neuropathies with loss of sensation at are increased risk for unrecognized injury. The subject will be instructed to close their eyes while the investigator lightly rests his/her finger on each of the subject's first, third and fifth toes of the study foot for 1 to 2 seconds. Subjects will be instructed to respond "yes" when they feel the investigator's touch. The investigator will evaluate and record whether the neurological condition of the study foot is "normal" or "abnormal" based on their medical judgment regarding the degree of loss of sensation in the study foot and will record any AEs that were not present at Baseline resulting from the neurological examination.**

Version Date		06 MARCH 2018	22 MAY 2018
Page	**Section**	**WAS**	**IS**
56	8.4.3 Musculo skeletal Examination		**The musculoskeletal examination will include a visual inspection of the study foot, as well as direct evaluation via palpation, range of motion (ie, dorsiflexion, plantar flexion), motor strength and muscle tone to identify the presence of abnormalities or foot deformities (except for HAV). The investigator will specifically look for the presence of bony prominences, asymmetry, wasting, fasciculations or the presence of foot deformities (except for HAV) including but not limited to hammer toe, claw toe, Charcot's neuroarthropathy, pes planus, cavus planus, Morton's neuroma, or hallux limitus. The investigator will evaluate and record whether these or other musculoskeletal conditions of the study foot are present and will record any AEs that were not present at Baseline resulting from the musculoskeletal examination.**
65	11.4.5 Safety Evaluation		**Descriptive statistics will be provided for study foot examination (i.e. dermatological, neurological and musculoskeletal). Results of these assessments will include whether a given dermatologic or musculoskeletal deformity is present in the study foot, or whether the neurological foot evaluation domain evaluated is "normal" or "abnormal". For each of the three parameters summaries will be provided by treatment group for both the DB and OL periods.**
78	18 References		22. **Raymond G, Prashanth R, Baker N et al. The Ipswich Touch Test: a simple and novel method to identify in patients with diabetes at risk of foot ulceration. Diabetes Care. 2011;34(7):1517-8.**

SUMMARY & OUTCOME OF CHANGES:

STUDY NUMBER	D-FR-52120-237	
AMENDED PROTOCOL VERSION NUMBER & DATE	Protocol Version 2.0 (Amendment 1) 22 May 2018	
SUBSTANTIAL ☐	**NON-SUBSTANTIAL** ☒	
REASON FOR CHANGES	Changes made based on FDA recommendation to expand and clarify required examination of the study foot following injection; use of anticoagulants and pain relieving medications during the study. In addition, the IRB requested for the clarification for discontinuation of anticoagulants.	
OTHER ACTION REQUIRED?	CRF UPDATE	Yes ☒ No ☐ *(tick one)*
	LOCAL CONSENT FORM UPDATE	Yes ☒ No ☐ *(tick one)*
	DATABASE UPDATE	Yes ☒ No ☐ *(tick one)*
	REPORTING & ANALYSIS PLAN (RAP) UPDATE	Yes ☒ No ☐ *(tick one)*