(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

- 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

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	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

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	

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

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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.

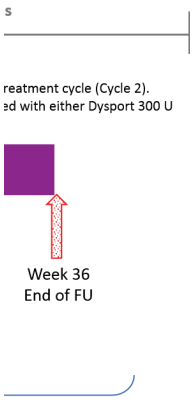
During the OL period, each treatment cycle (Cycles 2 and 3) will include the following study visits after the retreatment injection with Dysport at the beginning of each treatment cycle:

- 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

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

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

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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

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

- 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.

- 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.

10 EXPLORATORY BIOMARKERS AND BIOBANKING

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

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.

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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.

(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

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.

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

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)

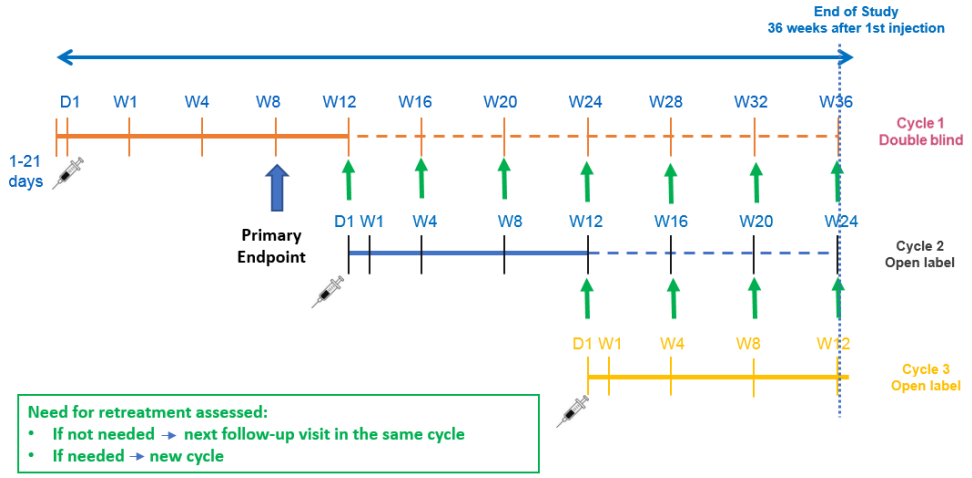
Additional follow-up visits will be performed every 4 weeks after Visit 6 during the DB period, and after Visits 11 and 16 during the OL period to determine eligibility for retreatment.

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.

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

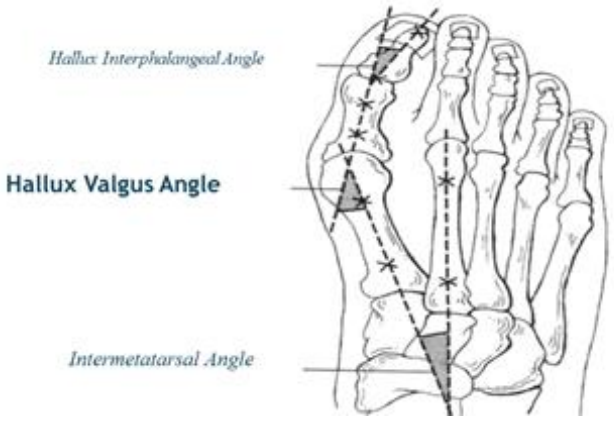
The secondary efficacy evaluations and endpoints are presented in Table 2.

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

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.

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:

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

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:

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	

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.