A PHASE II, MULTICENTRE, DOUBLE-BLIND, RANDOMISED, PLACEBO-CONTROLLED, DOSE ESCALATION AND DOSE FINDING STUDY TO EVALUATE THE EFFICACY AND SAFETY OF DYSPORT IN VULVODYNIA PATIENTS

STUDY PROTOCOL

STUDY NUMBER: D-FR-52120-236

DYSPORT

Version 6.0: 08 October 2020

Sponsor's Medically Responsible Person:

PPD
Ipsen Bioscience Inc.,
Medical Development,
650 East Kendall Street,
Cambridge, Massachusetts 02142
United States of America (USA)
PPD

Sponsor's Co-ordinating and Monitoring Office:

PPD
Ipsen Innovation, R&D Clinical Development Program,
5 Avenue du Canada,
91940 Les Ulis,
Cedex France
PPD

Sponsor Details:

Ipsen Innovation
Z.I. de Courtaboeuf,
5 Avenue du Canada,
91940 Les Ulis,
Cedex France
PPD

Co-ordinating Investigator:

PPD
Washington, DC 20037,
USA
PPD

Pharmacovigilance/Emergency Contact:

PPD
Ipsen Innovation
ZI de Courtaboeuf - 5 avenue du Canada - 91940 Les Ulis - France
PPD

The person listed above is medically qualified and designated by the sponsor as the first point of contact for emergency situations.

For serious adverse events (SAE) reporting:

PPD

INVESTIGATOR'S AGREEMENT

Investigator Agreement and Signature:

I have read and agree to Protocol D-FR-52120-236 entitled: A Phase II, Multicentre, Double-blind, Randomised, Placebo-controlled, Dose Escalation and Dose Finding Study to Evaluate the Efficacy and Safety of Dysport in Vulvodynia Patients. 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:

DATE:
OFFICE: Ipsen Bioscience Inc.
650 East Kendall Street
Cambridge, Massachusetts 02142
United States of America
PPD

COORDINATING INVESTIGATOR'S AGREEMENT

Coordinating Investigator Agreement and Signature:

I have read and agree to Protocol D-FR-52120-236 entitled: A Phase II, Multicentre, Double-blind, Randomised, Placebo-controlled, Dose Escalation and Dose Finding Study to Evaluate the Efficacy and Safety of Dysport in Vulvodynia Patients. 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: PPD

TITLE: PRINCIPAL/COORDINATING INVESTIGATOR SIGNATURE:

DATE:

OFFICE: PPD

Washington DC 20037
USA

SUMMARY OF CHANGES

The initial version of the protocol dated 09 February 2018 was subsequently amended as below:

Table 1 List of Protocol Amendments

Amendment	Release Date	Amendment Form
Version 2.0	15 May 2018	Appendix 6
Version 3.0	04 November 2018	Appendix 7
Version 4.0	08 April 2019	Appendix 8
Version 5.0	23 January 2020	Appendix 9
Version 6.0	08 October 2020	Appendix 10

SYNOPSIS

Name of Sponsor/Company: Ipsen Innovation

Name of Finished Product: Dysport

Name of Active Ingredient(s): Botulinum toxin-A Hemagglutinin Complex (BTX-A-HAC)

Title of Study: A phase II, multicentre, double-blind, randomised, placebo-controlled, dose escalation and dose finding study to evaluate the efficacy and safety of Dysport in vulvodynia patients

Study Number: D-FR-52120-236

Number of Planned Centres: Approximately 25 centres are planned to recruit subjects.

Planned Study Period:	**Phase of Development:**
Approximately 4 years	Phase II

Study Type: interventional, dose finding safety and efficacy study

Objectives:

Primary Study Objective:

Stage 1:

- To assess the safety of increasing doses of Dysport in vulvodynia subjects with provoked vestibulodynia (PVD).

Stage 2:

- To assess the efficacy of Dysport compared to placebo in vulvodynia subjects with PVD.

Secondary Study Objectives:

Stage 1:

- To assess the efficacy of increasing doses of Dysport compared to placebo in vulvodynia subjects with PVD
- To determine the doses of Dysport to be administered in Stage 2
- To assess the sensitivity of the endpoints used in Stage 1.

Stage 2:

- To define the optimal doses of Dysport with an acceptable benefit/risk profile for the treatment of vulvodynia with PVD
- To assess effect of Dysport on:
  - Vulvar pain
  - Use of pain rescue medication (type, dose and frequency)
- To determine if primary and secondary PVD subjects benefit from Dysport administration
- To assess the time to retreatment
- To assess the safety of Dysport.

Exploratory Objectives:

- To assess effect of Dysport on:
  - Clinical Global Impression (CGI) of the treatment effect (assessed by the investigator)
  - Patient Global Impression of severity of the pain (PGI-S) and Patient Global Impression of change in pain (PGI-C)
- Emotional response, cognitive response and associated life interference as assessed on modified vulvar pain assessment questionnaire (mVPAQ) subscales
- Sexual function

- To assess the efficacy of Dysport on the pelvic floor muscles pressure
- To assess the efficacy of Dysport on depression
- To assess the efficacy of Dysport on the quality of life.

Methodology:

This is a Phase II multicentre, double-blind, randomised, placebo-controlled, dose finding study to define the optimal doses of Dysport and evaluate its efficacy and safety compared to placebo in vulvodynia subjects with PVD. The study will consist of a dose escalation stage (Stage 1) and a dose expansion stage (Stage 2). Both Stage 1 and Stage 2 will consist of a double-blind period (with treatment cycle 1; Dysport or placebo) followed by an open-label treatment period (treatment cycles 2 to 4 in which all subjects receive Dysport). Two optimally safe and effective doses of Dysport selected from Stage 1 (ranging from 100 U up to a maximum of 800 U) will be further investigated in the Stage 2.

Stage 1 (Dose Escalation) Double-Blind Period:

It is intended to enrol up to seven dose level cohorts of secondary PVD subjects (i.e. having a past history of pain-free intercourse or insertion of any object >1 cm diameter; hereafter referred to as PVD2 subjects). Each cohort will include 10 unique evaluable PVD2 subjects. Subjects in these cohorts will be randomised in a ratio of 4:1 (Dysport: 8 + Placebo: 2) in a dose-escalation manner starting with a total Dysport dose of 100 U, then 300 U, and thereafter increasing up to a maximum of 800 U by increments of 100 U.

For Dysport doses equal to or above 400 U, cohorts of primary PVD subjects (i.e. having life-long provoked vestibular pain; hereafter referred to as PVD1 subjects), will be recruited in parallel with PVD2 cohorts and at the same Dysport dose as for the PVD2 cohorts. The first PVD1 cohort at 400 U will include eight unique evaluable subjects who will be randomised in a ratio of 3:1 (Dysport: 6 + Placebo: 2). Further PVD1 cohorts (i.e. above 400 U) will include 10 unique evaluable subjects randomised in a ratio of 4:1 (Dysport: 8 + Placebo 2).

The recommendation for dose escalation/de-escalation and the staggering scheme for the subsequent cohort will be agreed at data review committee (DRC) meetings upon review of efficacy and safety data from the previous cohort(s).

Subjects who discontinue prior to Week 6 for reasons unrelated to occurrence of dose limiting events (DLEs) may be replaced at the discretion of the investigator and sponsor. When all subjects in Stage 1 have completed 6 weeks of follow-up of treatment cycle 1, the DRC will meet again to enable selection of dose(s) to be assessed. PVD1 subjects will be recruited in Stage 2 based on the DRC review of efficacy and safety data obtained from PVD1 cohort(s) in Stage 1.

Following evaluation of study eligibility at the Screening Visit (Day -14), subjects will receive study treatment injections in the pelvic floor muscles on Day 1 (Baseline Visit). Follow-up visits will be performed at:

- Week 2 (telephone contact)
- Week 6
- Week 12 and
- Every 6 weeks up until eligible for retreatment or up to a maximum of 48 weeks of follow-up.

An intermediate analysis will be performed to review the unblinded data from all cohorts in Stage 1 up to Cycle 1-Week 12 in an effort to select the two doses for Stage 2 taking into account the dosing recommendations from the DRC.

Stage 2 (Dose Expansion):

As for Stage 1, the maximum permitted dose in Stage 2 will be 800 U. Two dose levels identified from Stage 1, recommended by the DRC based on efficacy and safety data, will be investigated further and compared to placebo. It is intended to enrol 63 subjects in Stage 2 in the randomisation

ratio of 1:1:1 (Dysport high dose: 21; Dysport low dose: 21 and Placebo: 21). Following the review of data available from Stage 1, the sample size may be formally recalculated for Stage 2 after the intermediate analysis.

Following evaluation of study eligibility during a 14-day screening period, subjects will receive study treatment injections in the pelvic floor muscles on Day 1 (Baseline Visit). Treatment paradigm and follow-up visits will be the same as in Stage 1.

Open-Label Period (Stage 1 and Stage 2):

From Week 12 onwards of the double-blind period, subjects will be assessed for the need for retreatment at each visit. Subjects who require retreatment will be provided subsequent treatment with Dysport in the open-label period of the study and can receive up to three treatment cycles with Dysport administered at least 12 weeks apart. Dysport dose levels, that are approved by the DRC will be used for retreatment and will not exceed 800 U. Retreatment with Dysport will be provided to subjects when this is in the best interest of the subject based on investigator's judgement, the subject has not experienced any unacceptable adverse event (AE) as judged by the investigator and at least 12 weeks have elapsed since the last treatment received.

Study Duration (Stage 1 and Stage 2):

Individual subject participation in this study will be for a maximum of 54 weeks:

- Screening: 2 weeks (plus 2 weeks window)
- Follow-up: a maximum of 48 weeks follow-up plus 2 weeks window period for the EOS Visit depending on the number of treatments administered and the treatment intervals.

The subject's participation in the study will be considered to have ended 36 to 48 weeks after the first dose, but not before 12 weeks have elapsed after the last dose.

The number of treatment cycles will depend on the duration of each treatment cycle. A subject can receive a maximum of four treatment cycles of Dysport including the one received in the double-blind period. The minimum follow-up duration will be 36 weeks and the maximum follow-up duration will be 48 weeks plus a 2-week window period for the EOS Visit, (the end of the study will not occur before 12 weeks have elapsed from the last treatment cycle), as calculated from Cycle 1-Day 1.

Number of Subjects Planned:

The study will include approximately 180 female subjects (up to 118 in Stage 1 if all cohorts are reached, and 63 in Stage 2).

Diagnosis and Criteria for Inclusion:

Note: Lettered inclusion and exclusion criteria indicate an update or deletion following an amendment to the protocol (e.g. a=criterion amended once, b=criterion amended twice, c=criterion amended three times).

Inclusion Criteria:

(1a) Female subjects aged 18 years or above.

(2) Willing to provide a written informed consent prior to any study related procedures.

(3) Criterion 3 is removed by protocol amendment.

(4) Are premenopausal, as evidenced by a serum follicle stimulating hormone (FSH) level of <35 mIU/mL as assessed at the Screening Visit.

(5) Have a negative pregnancy test at screening.

(6) Willing to practice a highly effective form of contraception method at the beginning of the study, for the duration of the study and for a minimum of 12 weeks following last administration of study drug. Highly effective methods of contraception are defined as methods of birth control which result in a low failure rate (i.e. less than 1% per year) when used consistently and correctly such as implants, injectables, combined oral contraceptives,

intrauterine devices, or vasectomised partner. The double barrier method (condom and spermicide) may be considered an acceptable form of birth control if determined appropriate for the subject by the investigator.

(7) Have vulvodynia with provoked vestibular pain for at least 6 months and for no more than 15 years.

(8a) Have provoked pain at the posterior vestibule on a Q-tip test, with pain at positions 5, 6 and 7 o'clock (must be bilateral pain) at the Screening Visit.

(9a) Are able to tolerate the smallest dilator size (diameter 0.5 inches) at the Screening Visit, i.e. agree to the next successive dilator size to be tested for pain response (i.e. the two smallest sized dilators (#1 and 2) are to be tested).

(10a) Pain score ≥5 on an 11-point Numeric Rating Scale (NRS) for the Dilator Maximum Tested Size (DMTS) at the Baseline Visit.

(11a) Willing to abstain from sex therapy (defined as a therapy primarily focused on the management of vulvar pain) for the duration of screening and up to at least Week 6 of the first treatment cycle.

(12b) In Stage 1, Cohorts 1, 2, 3, 5, 7, 9 and 11 will include subjects with secondary vulvodynia (i.e. having a past history of pain-free intercourse or insertion of any object >1 cm diameter). In Stage 1, Cohorts 4, 6, 8, 10 and 12 will include subjects with primary vulvodynia (having life-long provoked vestibular pain). In Stage 2, subjects with either primary or secondary vulvodynia may be enrolled as approved by the DRC.

(13) Willing and able to comply with study restrictions, able to attend the clinic for the required duration of assessments during the study period and willing to return to the clinic for the follow-up evaluation as specified in the protocol.

(14) If the subject has received oral antidepressants, anxiolytics or anti-epileptics, then the dose of these medications should have been stable for at least 6 months prior to the Screening Visit and expected to remain stable throughout the first treatment cycle.

Exclusion Criteria:

(1a) Have provoked pain on a Q-tip test at the anterior vestibule (anywhere between 9 and 3 o'clock or more anteriorly) at the Screening Visit.

(2b) Able to tolerate the 6th (diameter 1¼ inches) dilator size (i.e. agree to the next successive dilator size to be tested for pain response) at the Baseline Visit (i.e. at least one of the two largest sized dilators (#7 and/or 8) is tested).

(3a) Any non-provoked (i.e. spontaneous) vulvar pain in the past 6 months prior to the Screening Visit. Note: pain provoked by any vestibular pressure (including but not limited to sitting, bicycling or tight clothing) is considered provoked pain.

(4a) Deep pain during intercourse in the past 6 months prior to the Screening Visit.

(5a) Score of 4 or 5 on any of the 3 pain questions (questions #17, 18 or 19) of the modified Female Sexual Function Index (mFSFI) questionnaire.

(6) Criterion 6 is removed by previous protocol amendment.

(7a) Significant depressive disorder, e.g. having a score ≥20/27 on the Patient Health Questionnaire (PHQ-9) scale at the Baseline Visit.

(8b) Genitourinary or gastrointestinal conditions/history including:

- Skin disease at the vestibule such as lichen sclerosus, lichen planus, vaginal or vulvar atrophy, desquamative inflammatory vaginitis and allergic vulvitis.
- Severe endometriosis (severe defined as requiring regular medications to manage the endometriosis symptoms).
- Severe bladder and bowel symptoms e.g. diagnosed interstitial cystitis/Bladder Pain Syndrome, severe urinary incontinence, faecal incontinence, inflammatory bowel

disease.
- Genitourinary or rectal cancer.
- Congenital urogenital abnormalities (e.g. vaginal septa, imperforate hymen, urethral diverticulum).
- Pain in urethra (diagnosis based on subject's interview and physical examination).
- Symptomatic urogenital prolapse at physical examination.
- History of traumatic or post radiotherapy vulvar lesions.
- Pudendal neuralgia.
- Other conditions that according to the investigator's judgement may interfere with treatment or impact the study outcome.

(9a) Previous surgery/conditions including:
- Hysterectomy
- Vestibulectomy
- Urologic surgery
- Perianal surgery
- Genital trauma or mutilation/cutting
- Other surgery/conditions that according to the investigator's judgement may impact on the study outcome.

(10) Vaginal infections (bacterial vaginosis, presence of candidiasis or trichomoniasis) at Screening Visit.

(11) Current infection at the injection site(s).

(12) Unable to receive intramuscular injections.

(13) History of hypersensitivity to Dysport or drugs with a similar structure or any excipient used in the formulation.

(14) Clinically significant history of alcohol/drug abuse the last 24 weeks prior to screening or clinically significant alcohol/drug dependence within 2 years prior to screening. Exceptions include caffeine or nicotine abuse/dependence.

(15a) Positive urine test for illicit drugs (drugs of abuse) at screening. In the event a subject tests positive for cannabinoids (tetrahydrocannabinol), the investigator will evaluate the subject's ability to abstain from cannabis during the study. If in the investigator's clinical judgement, the subject will abstain, the subject may be enrolled after consultation with the Medical Monitor. Note: at the discretion of the investigator, positive drug screens for prescribed medications will not be considered exclusionary.

(16c) Has received any of the following:
- Pelvic floor physical therapy initiated, stopped or modified (frequency or type of physical therapy) during the last 12 weeks prior to Baseline (physical therapy includes but is not limited to: internal/external myofascial release by physiotherapist, biofeedback, home pelvic floor exercises, self-taught exercises, use of vaginal dilators, etc.).
- Sex therapy in the past 6 weeks prior to Baseline.
- Previous treatment with any botulinum toxin (BTX) for any indication within the last 1 year.
- Treatment for vestibular pain, with hormonal creams, in the last 1 week prior to Screening unless continued at the same dosing regimen throughout the study.
- Currently receiving treatment for stress or urge urinary incontinence.
- Treatment with any of the following drugs that could affect neuromuscular function:

curare-like nondepolarising agents, lincosamides, polymyxins, anticholinesterases, aminoglycoside antibiotics (topical use is permitted except at the vulvar vestibular region), tizanidine and baclofen, within the last 4 weeks prior to Baseline or during the study.

- Injections of steroids in the vulva within the last 4 weeks prior to the Screening Visit or planned use during the study.
- Treatment with an investigational drug within the last 4 weeks prior to Baseline or scheduled treatment with such a drug during the study period.
- Is likely to require treatment during the study with drugs that are not permitted by the study protocol.

(17) Any mental condition rendering the subject unable to understand the nature, scope and possible consequences of the study, and/or evidence of an uncooperative attitude, as judged by the investigator.

(18) Abnormal baseline findings, any other medical condition(s) or laboratory findings that, in the opinion of the investigator, might jeopardise the subject's safety or compromise compliance with the objectives and/or procedures of this protocol or preclude the administration of BTX.

(19) Female subject who is pregnant or planning to become pregnant during the study, or is currently lactating (breastfeeding).

Test Product, Dose and Mode of Administration:

Study treatment kits will be designed to maintain the blind (for the subject, investigator and delegated person reconstituting the product) during the double-blind period.

The investigational medicinal product (IMP), Dysport, will be provided as a white, lyophilised powder in glass vials containing 300 U or 500 U of BTX-A-HAC.

Before each administration, the powder will be reconstituted at the study site with 0.9% sterile (preservative free) sodium chloride for injection.

A total volume of 2.5 mL of the reconstituted treatment will be injected intramuscularly at five needle insertion points at 10 injection sites (5 mm (superficial) and 10 mm (deep) depths at each needle insertion point) across the four pelvic floor muscles: pubococcygeus, bulbospongiosus, superficial transverse perineal muscle and deep transverse perineal muscle.

Injection procedures are described in the 'Study Treatment Administration - Training Manual' (included in the Study Manual). Training on injection procedures will be provided to each investigator performing IMP administration.

Duration of Treatment:

Each subject will receive one IMP administration during the double-blind period followed by one to three treatments with Dysport in the open-label period (if clinically indicated) at least 12 weeks apart. The maximum total follow-up duration will be for up to 48 weeks, plus a 2-week window period for the EOS Visit, from the first IMP dose administered and not before 12 weeks have elapsed since the last treatment dose.

Reference Therapy, Dose and Mode of Administration:

Study treatment kits will be designed to maintain the blind (for the subject, investigator and delegated person reconstituting the product) during the double-blind period.

The comparator will be a matching placebo, i.e. undistinguishable from the active IMP (Dysport), which will be injected during the double-blind period (i.e. treatment cycle 1 of Stage 1 and Stage 2) of the study.

Placebo will be provided as a white, lyophilised powder in glass vials, and will be similar in size, colour and appearance to the active IMP (Dysport). It will be composed of only the excipients contained within Dysport, without the addition of the active substance.

A total volume of 2.5 mL of the reconstituted treatment will be injected intramuscularly at five needle insertion points at 10 injection sites (5 mm (superficial) and 10 mm (deep) depths at each needle insertion point) across the four pelvic floor muscles: pubococcygeus, bulbospongiosus, superficial transverse perineal muscle and deep transverse perineal muscle.

Injection procedures are described in the 'Study Treatment Administration - Training Manual' (included in the Study Manual). Training on injection procedures will be provided to each investigator performing IMP administration.

Criteria for Evaluation (Endpoints):

Primary Endpoint and Evaluation:

Stage 1:

- Safety endpoints between Baseline and Cycle 1-Week 6, including the incidence of any DLE.

Stage 2:

- Mean change from Baseline to Cycle 1-Week 6 in the vaginal dilator induced pain as reported on an 11-point NRS (using the DMTS reported at Baseline).

Secondary Endpoints and Evaluations:

- Mean change from Baseline to each post-treatment visit in the vaginal dilator induced pain as reported on the 11-point NRS (using the DMTS reported at Baseline).
- Proportion of subjects who reported at least a 30% decrease in vaginal dilator induced pain as reported on the 11-point NRS (using the DMTS reported at Baseline) at each post-treatment visit.
- Proportion of subjects who reported at least 2-point decrease in vaginal dilator induced pain as reported on the 11-point NRS (using the DMTS reported at baseline) at each post-treatment visit.
- Mean change from Baseline to each post-treatment visit in the dilator size that provokes maximum tolerated pain.
- Mean change from Baseline to each post-treatment visit in the composite score for the vaginal dilator induced pain and dilator size.
- Mean change from Baseline to each post-treatment visit in pain during insertion of vaginal dilator number 6 size as reported on the 11-point NRS.
- Mean change from Baseline to each post-treatment visit in the pain during intercourse as reported on the 11-point NRS.
- Mean change from Baseline to each post-treatment visit in the number of intercourse instances in subjects with partners.
- Use of pain rescue medication (type, dose, number of pills taken and frequency).
- Proportion of subjects who reported at least a 50% decrease in vaginal dilator induced pain as reported on the 11-point NRS (using the DMTS reported at Baseline) at each post-treatment visit.
- Proportion of subjects having reported at least a 30% decrease in pain during insertion of vaginal dilator number 6 size on the mean of the NRS values at each post treatment visit.
- Proportion of subjects having reported at least 2-point decrease in pain during insertion of vaginal dilator number 6 size on the mean of the NRS values at each post treatment visit.
- Proportion of subjects having reported at least a 50% decrease in pain during insertion of vaginal dilator number 6 size on the mean of the NRS values at each post-treatment visit.

Safety Endpoints and Evaluations:

The safety and tolerability of Dysport will be assessed throughout the study by evaluating:

- Incidence of treatment emergent adverse events (TEAEs), serious AEs (SAEs), clinically

significant AEs, DLEs, AEs (or SAEs) leading to discontinuations and AEs of special interest (AESIs).

- Absolute values, values classified as abnormal/normal and change from Baseline in the clinical laboratory test results (including nonfasting clinical biochemistry and haematology parameters).
- Number of subjects who seroconvert for BTX antibodies following treatment with Dysport.
- Clinical evaluation of concomitant medication usage (except rescue medication) and therapies.

Exploratory Endpoints:

- Mean CGI (as assessed by the investigator) of the treatment effect at each post treatment visit.
- Mean PGI-C (as assessed by the subject) at each post-treatment visit.
- Mean change from baseline in PGI-S (as assessed by the subject) at each visit.
- Mean change from Baseline to each post-treatment visit in each of the mVPAQ subscales.
- Mean change from Baseline to each post-treatment visit in the mFSFI total score and domain scores.
- Mean change from Baseline in the pelvic floor muscle pressure as measured by perineometry in all subjects in Stage 1 up to 400 U and in a subset of subjects in Stage 2.

  (Note: in Stage 2, this endpoint will be evaluated in subjects who have never had a vaginal delivery (including an attempted vaginal delivery), and at study sites that were provided a perineometer to assess pelvic floor muscle pressure)
- Resting vaginal pressure
- Maximal 'squeeze' pressure.
- Mean change from Baseline in the depression score using PHQ-9 scale.
- Mean change from Baseline in quality of life (QoL) using 36-item Short Form Survey (SF-36).

Statistical Methods:

Method of Randomisation:

Stage 1: For the PVD2 cohorts, subjects will be randomised with a 4:1 (Dysport: placebo) ratio. For the PVD1 cohort(s), subjects will be randomised with a 3:1 (Dysport: placebo) ratio for Dysport 400 U and then randomised at 4:1 for Dysport 500 U and up to a maximum of 800 U.

Stage 2: Subjects will be randomised to Dysport high dose, Dysport low dose, or placebo with a 1:1:1 allocation. Randomisation will be stratified by pain onset subtype (two levels: primary, i.e. having life-long PVD, secondary, i.e. having acquired PVD after period of pain-free penetrative activities).

Sample Size and Power Considerations:

Stage 1: With 8 evaluable subjects on active treatment per PVD2 dose cohort and if there are 0 DLEs in a cohort, there is at least 80% probability that the true incidence of DLEs at the corresponding dose will not be greater than 18%. With 16 evaluable subjects on active treatment in PVD2 and PVD1 dose cohorts, and if there are 0 DLEs in the two cohorts, there is at least 80% probability that the true DLEs at the corresponding dose will not be greater than 9%. The ability to confidently rule out smaller true DLE incidence at a dose level will come from observations on subjects in Stage 2.

Stage 2: The study sample size required to have at least 80% power to detect a 2-point improvement between Dysport and the placebo group on mean change from baseline to Week 6 in the vaginal dilator induced pain as reported on a numeric pain rating scale (using the DMTS), assuming a common standard deviation of 3-point and using a one-sided 0.10 level test is 21 subjects per arm.

At the end of Stage 2, if the true DLE rate is 6% or greater, there is at least 80% probability to observe at least 1 DLE in 29 subjects (8 in Stage 1 and 21 in Stage 2). Therefore, if there are no observed DLEs in both Stage 1 and Stage 2 at a dose level, then there is good confidence that the true DLE rate is no more than 6%. If the dose chosen in Stage 2 has been tested on two cohorts (PVD1 and PVD2) in Stage 1, at the end of Stage 2, if the true DLE rate is 5% or greater, there is at least 80% probability to observe at least one DLE in 37 subjects (16 in Stage 1 and 21 in Stage 2). Therefore, if there are no observed DLEs in both Stage 1 and Stage 2 at a dose level, then there is good confidence that the true DLE rate is no more than 5%.

Following the review of data available from Stage 1, the sample size may be formally recalculated for Stage 2 after the intermediate analysis.

Statistical Procedure for the Efficacy Testing:

Change from baseline to Week 6 in pain measurement at the DTMS will be analysed using analysis of covariance adjusting for baseline pain at the DTMS and pain onset subtype (primary and secondary PVD).

Hypothesis tests will be one-sided. The planned statistical comparisons at one-sided 0.10 level do not adjust for two treatment comparisons and consequently the experiment-wise type I error rate may be up to 20%. Non-parametric tests may also be carried out to evaluate robustness of results.

Subject who discontinue prior to Week 6 for reasons unrelated to safety may be replaced at the discretion of the investigator and sponsor. Sensitivity analyses will be carried out to evaluate the impact of missing data where appropriate.

Data Review Committee (DRC) Meetings:

A DRC will be established to make recommendations for dose escalation and dose de-escalation (within the Dysport dose range of 100 U up to a maximum of 800 U) or study termination in Stage 1. If no subject reports a clinically significant AE in a cohort, the DRC will meet once all evaluable subjects have reached Week 6 of a cohort to review the efficacy and safety data and recommend the dose for the next cohort or proceed to Stage 2.

If any subject reports a clinically significant AE, then further enrolment into the cohort, as well as retreatment in open label cycles at the current dose, will be suspended and an ad hoc DRC meeting will be scheduled to review the safety data and make a recommendation with regards to further conduct of the cohort and of Stage 1. At the end of Cycle 1-Week 6 for all subjects in Stage 1, the DRC will meet to review efficacy and safety data and recommend the two doses of Dysport to be assessed in the Stage 2 of the study. The DRC will also recommend if further PVD1 cohort(s) are required or if PVD1 subjects should be removed from Stage 2.

In Stage 2 of the study, ad hoc DRC meetings will be scheduled to review efficacy and safety data in the event of an emergency safety issue.

Primary Analysis:

A primary unblinded analysis will be conducted once all Stage 2 subjects have reached the Cycle 1-Week 12 visit; this will include all available safety and efficacy data from subjects in Stage 1 and Stage 2 subjects until the cut-off date.

A final analysis will be carried out once all subjects have completed end of study evaluation.

Intermediate Analysis:

At the point when the DRC recommends moving to Stage 2 of the study, an intermediate unblinded analysis will be performed. Available data from all double-blind periods of all cohorts from Stage 1 until the last subject has completed their Cycle 1-Week 12 visit will be considered in the analysis. Descriptive statistics of the TEAEs and selected efficacy endpoints will be carried out.

Following the review of data available from Stage 1, the sample size may be formally recalculated for Stage 2 after the intermediate analysis.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ABBREVIATION	Wording Definition
AE	Adverse Event
AESI	Adverse Event of Special Interest
ANCOVA	Analysis of Covariance
BTX	Botulinum Toxin
BTX-A	Botulinum Toxin-A
BTX-A-HAC	Botulinum Toxin-A Hemagglutinin Complex
CA	Competent Authorities
CFR	Code of Federal Regulations (United States of America)
CGI	Clinical Global Impression
CRO	Contract Research Organisation
DLE	Dose Limiting Event
DTMS	Dilator Maximum Tested Size
DRC	Data Review Committee
EDC	Electronic Data Capture
EOS	End of Study
eCRF	Electronic Case Report Form
ePRO	Electronic Patient-Reported Outcome
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GPS	Global Patient Safety
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
i.m.	Intramuscular
IRB	Institutional Review Board
IRT	Interactive Response Technology
MedDRA	Medical Dictionary for Regulatory Activities
mFSFI	modified Female Sexual Function Index
mITT	modified Intent to Treat
mVPAQ	modified Vulvar Pain Assessment Questionnaire

ABBREVIATION	Wording Definition
NSAIDS	Nonsteroidal Anti-inflammatory Drugs
NRS	Numeric Rating Scale
OTC	Over the Counter
PD	Pharmacodynamics
PGI-C	Patient Global Impression of Change in Pain
PGI-S	Patient Global Impression of Severity of Pain
PHQ-9	Patient Health Questionnaire-9
PP	Per Protocol
PRN	As per Need
PVD	Provoked Vestibulodynia
QoL	Quality of Life
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SF-36	36-item Short Form Survey
SD	Standard Deviation
TEAE	Treatment Emergent Adverse Event
TFLs	Tables, Figures and Listings
TMF	Trial Master File
USA	United States (of America)
WHO	World Health Organisation

1 BACKGROUND INFORMATION

1.1 Introduction

Vulvodynia is defined as vulvar pain of at least 3 months' duration, without a clear identifiable cause, and which may have potential associated factors. The vulvar pain can be either localised, generalised or mixed; it could be either provoked (insertional or contact) or spontaneous or both; the onset vulvodynia can be primary or secondary [1]. The chronic vulvar pain is often associated with sexual dysfunction and affective distress [2]. Vulvodynia is a fairly prevalent condition with lifetime estimates ranging from 8% to 28% based on the prevalence studies in women of reproductive age group in the general population [3, 4, 5]. Vulvodynia affects young women [6], with the average age of occurrence being approximately 40 years, although a high prevalence is observed in all decades of life until age of 70 years [2, 3].

Provoked vestibulodynia (PVD), previously known as vulvar vestibulitis, is the most common form of vulvodynia and occurs when pain is localised in the vulvar vestibule and triggered by any vestibular contact (sexual or otherwise). In a population-based study, 64.8% of vulvodynia patients had provoked pain only [3].

There is currently no approved drug for the treatment of vulvodynia. A typical treatment plan for a woman with vulvodynia starts with treatments that are considered non-pharmacological (e.g. psychological treatments, physiotherapy) and, depending on her response to treatment, can progress to multiple different medication treatments, that are used as off label treatment for the condition without any established proof of benefit (e.g. tricyclic antidepressants, local anaesthetic agents, topical hormones, anti-inflammatory agents, pain modulators, local nerve block and anticonvulsant medications). If these treatments fail, then surgical intervention (e.g. vestibulectomy for localised provoked vestibulodynia) is recommended [7], however only a minority of patients may be suitable for vestibulectomy [8]. Although surgical treatment may be successful, it is associated with postoperative complications such as decreased vaginal lubrication and worsening of pain, hence is best reserved for refractory cases [2].

There are relevant and convincing medical observations and arguments to suggest that neuromuscular disorder of the pelvic floor muscles may be responsible for PVD characterised by localised provoked pain at the vaginal vestibule. Several studies provide significant evidence that patients with PVD have greater muscular hypertonia in the muscles in the superficial area of the perineum, which become painful and that the hypertonic pelvic musculature plays a role in the etiology, maintenance, and exacerbation of PVD [9]. Eighty percent of patients of PVD have muscular hypertonia of the pelvic floor muscles demonstrable by electromyography, and 90% of these patients tend to have associated vulvar allodynia [10]. Bohm-Starke found that an intraepithelial hyperplasia of the C-nerve fibres was present in the vestibular tissue, along with the presence of various pain neurotransmitters such as glutamate or substance P [6, 11]. All these factors support the neuromuscular hypothesis of the disease with an abnormal pain transmission [10]. Other treatment approaches for the condition, like physiotherapy are also aimed at the rehabilitation of the pelvic floor musculature to normalize the muscle tone, to increase elasticity of tissues at the vaginal opening, to desensitize the vulvo-vestibular area and decrease the patient’s protective guarding reactions to vaginal penetration by exercises, manual techniques, biofeedback, and electrical stimulation [9].

Botulinum toxin (BTX) is a neurotoxin that acts on the presynaptic motor neuron, cleaves the SNARE proteins thereby inhibiting the release of acetylcholine and thus leading to a reduction in muscle tone [12]. Aligned with the known pharmacological and pharmacodynamic action of Dysport® on the injected muscles, there is strong evidence to suggest its effectiveness in the treatment of vulvodynia by causing muscle relaxation of the affected pelvic floor muscles, and by inhibiting the release of neuropeptides and neurotransmitters involved in chronic pain and inflammation (Substance P and calcitonin gene related peptide) [6, 10, 13]. As a consequence, local treatment with Dysport in patients with vulvodynia is expected to provide relief from vulvar pain, subsequently improving the sexual function of women and their quality of life.

Considering the unmet need for an effective treatment for vulvodynia patients and the suggested efficacy of botulinum toxin-A (BTX-A) in the various published studies for this indication, Ipsen proposes to conduct a randomised, double-blind, placebo-controlled study designed to define optimal doses of Dysport and evaluate its efficacy and safety compared with placebo for the treatment of vulvodynia.

1.2 Name and Description of Investigational Medicinal Product(s)

Botulinum toxin-A is a potent neurotoxin isolated from the bacterium Clostridium botulinum, a gram-positive, spore-forming anaerobe. Botulinum toxin-A, a single chain protein with a molecular weight of approximately 150000 Daltons (Da), is one of seven different serotypes (classed A through G) of BTX produced by this organism. Proteins endogenous to the bacterium cleave the single chain protein, resulting in a di-chain neurotoxin containing a light chain (molecular weight of approximately 50000 Da) and a heavy chain (molecular weight ca. 100000 Da) that remain linked by inter-chain disulfide and noncovalent bonds.

Dysport is a freeze-dried preparation of Clostridium BTX-A-haemagglutinin complex (BTX-A-HAC) formulated with lactose (bulking agent) and human serum albumin.

A more detailed description of the product is given in Section 6.2.1.1.

Further details can also be found in the Dysport IB.

1.3 Findings from Nonclinical and Clinical Studies

1.3.1 Summary of Nonclinical Studies

An extensive nonclinical development program for Dysport exists, including pharmacology, distribution, and toxicology studies (including repeat use). In this program, animals (both males and females) have been treated by intramuscular administration of Dysport in striated muscles (gluteus and gastrocnemius muscles). Dysport was also studied nonclinically in the detrusor muscle.

In vivo pharmacodynamic (PD) studies conducted in rats (rat muscle force test and muscle glycogen depletion) showed significant decreased mass and force of intramuscular injection in the gastrocnemius muscle and inhibition of glycogen depletion in injected rat muscles.

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.

The results of the single or repeat dose (up to 6 months) toxicity studies demonstrated that BTX-A administered in striated muscle has been locally well tolerated by the animal species used and that it possesses no potential for producing nonpharmacologically related toxicity or specific target organ effects. 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 PD rat muscle force test. They were reversible and appeared to cause no

long term impairment of neuromuscular junction. When administered by the intradetrusor route, no histopathological modification of the bladder or adjacent reproductive organs was detected. The effects seen in the single dose intradetrusor studies in rats were consistent with the ones observed in previous striated muscle studies after single and repeated administrations on rats. Dysport was locally well tolerated by both routes of administration.

The drug was not teratogenic in rats and rabbits and no effects were observed in the pre and postnatal study on the F1 generation in rats (male and females). The drug did not alter male or female rat fertility except at doses inducing localised muscle paralysis and alteration of general conditions (severe decreased body weight and food consumption). Given in 21-day old rats (corresponding to children of 2 years old), Dysport did not affect postnatal growth, reproductive, neurological and neurobehavioral development.

The existing nonclinical development program for Dysport conducted in striated and in detrusor muscles provides a robust and adequate safety and efficacy data set to support the use of Dysport as a treatment option in female patients with vulvodynia when injected in the pelvic floor striated muscles.

Further details can also be found in the Dysport IB.

1.3.2 Summary of Clinical Studies

No previous clinical studies have been conducted by Ipsen with Dysport in this indication of vulvodynia. This is the first study that will be conducted by Ipsen in this indication. The body of clinical evidence mostly consists of data from several small scale published studies in the treatment of vulvodynia and other related conditions (e.g. vaginismus) conducted either with Dysport [14, 15] or with other BTX-A formulations [6, 10, 12, 13, 16, 17, 18, 19, 20].

1.4 Known and Potential Risks and Benefits to Human Subjects

Dysport was first approved for the treatment of blepharospasm and hemifacial spasm in the United Kingdom in 1990. Since then Dysport® has been approved in over 85 countries for a range of indications. The posology and safety of Dysport has been established in numerous clinical studies and there is over 25 years of postmarketing experience.

Dysport is generally well-tolerated, although temporary paralysis of nontargeted muscle groups may occur. Adverse events (AEs) resulting from a possible remote spread of the toxin from its site of injection have been reported (including excessive muscle weakness and aspiration pneumonia resulting from dysphagia). 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. Most AEs are of mild or moderate severity and of limited duration. 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.

Adverse reactions that are considered expected in patients treated across a variety of indications can be found in the current Dysport IB and in the Dysport Company Core Safety Information.

Based on published data in the treatment of vulvodynia and other related conditions (e.g. vaginismus) with Dysport or other BTX-A formulations and the mechanism of action of Dysport, urinary incontinence and faecal incontinence may also be observed in patients injected in pelvic floor muscles.

Treatment with Dysport in female patients with vulvodynia is expected to provide an improvement in the provoked pain (at intercourse or from any kind of vestibular pressure) and

therefore potentially an improvement in the associated sexual function, depression and quality of life.

Based on clinical evidence available from published data supporting the efficacy of BTX-A in adult female patients with vulvodynia, the known mechanism of action of Dysport and the proposed range of Dysport doses to be tested (100 U up to a maximum of 800 U) that fall within the range of approved doses for Dysport (up to 1500 U in adult patients), the benefit/risk balance is expected to be favourable for evaluation in this patient population.

Additional information regarding potential risks and benefits may be found in the current Dysport IB.

1.5 Selection of Investigational Medicinal Products and Dosages

The selection of Dysport doses to be evaluated in the dose escalation stage of the study are based on the clinical evidence from published studies with Dysport and other BTXs in the literature as well as the sponsor's clinical experience with Dysport in various indications involving targeted treatment of hypertonic muscles at several anatomical sites.

In a study by Bertolasi 2009 [15] injection of the levator ani muscle with low mean doses of Dysport (24 U±12 U) led to some reduction in vulvar pain in patients with PVD with vaginismus and no major AEs were reported with Dysport administration. Amongst the approved indications in the US, for the treatment of glabellar lines, Dysport 50 U achieves a clinical effect (i.e. causes muscle relaxation) when administered at 5 injection sites in three muscles in the glabellar area (two corrugators and one procerus) that have a relatively small muscle mass and no events suggestive of remote distribution of toxin have been reported in this indication at this dose. In this study, Dysport is to be injected at 5 sites across 6 muscles of the pelvic floor: bulbospongiosus (left and right), pubococcygeus (left and right), deep transverse muscle and superficial transverse muscle. Based on sponsor experience, a total Dysport dose of 100 U distributed between 6 muscles of the pelvic floor should be a safe starting dose, which may show some degree of muscle relaxation.

Ipsen proposes to progressively escalate Dysport doses from 100 U and 300 U, and then increasing up to a maximum dose of 800 U by increments of 100 U. Dysport doses up to 400 U are supported by data from the study by Ghazizadeh 2004 [14], in which the starting dose of 150 U Dysport injected into the levator ani (puborectalis) muscles in patients with vaginismus did not provide sufficient clinical improvement in some patients, following which the dose was gradually increased to 400 U for subsequent patients that lead to satisfactory relief from vaginismus in 95.8% of patients. No adverse effects were reported in this study with Dysport doses of 150 U to 400 U. Administration of Dysport doses above 400 U and up to a maximum of 800 U during the study will be based on recommendation by the DRC following review of safety and efficacy data from previous cohorts.

A more detailed description of administration procedures is given in Section 6.2.2.

1.6 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, Food and Drug Administration (FDA), 21 Code of Federal Regulation (CFR) Part 11, Electronic Records, Electronic Signatures, and FDA, Guidance for Industry: Computerized Systems Used in Clinical Trials. 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.

1.7 Population to be Studied

The study will recruit premenopausal adult female subjects aged 18 years or above.

In order to establish the preliminary efficacy of Dysport in this dose finding study, a subset of vulvodynia subjects suffering from provoked vestibular pain is selected. It is hypothesised that pelvic floor muscle hypertonicity underpins the posterior vestibular pain experienced and consequently these subjects are likely to respond to treatment with Dysport. This will ensure enrolment of a homogenous target population and limit intersubject variability.

Subjects suffering from PVD for at least 6 months duration but no more than 15 years, having pain at the posterior vestibule will be enrolled into the study. The subjects should have taken a stable physiotherapy (if any) for at least 12 weeks prior to the entry into the study and not have received any BTX for any indication within the last 1 year.

2 PURPOSE OF THE STUDY AND STUDY OBJECTIVES

2.1 Purpose of the Study

Dysport, a BTX-A-HAC, is already approved in the US and in many other countries worldwide for the treatment of a variety of clinical conditions in adult patients like cervical dystonia, upper and lower limb spasticity, that are associated with muscular hypertonicity, and pain in several patients.

The therapeutic value of BTX-A is derived from its ability to specifically and potently decrease muscular overactivity, thereby reducing the muscle tone for an extended duration and ameliorating the associated pain.

Based on the known mode of action of Dysport, Ipsen proposes to expand the treatment profile of Dysport and potentially add a new indication for the treatment of vulvodynia.

This study is a double-blind, randomised, parallel group, placebo-controlled study designed to define optimal doses of Dysport and evaluate its efficacy and safety compared with placebo for the treatment of vulvodynia. Treatment of vulvodynia patients with PVD with Dysport is expected to provide not only an improvement in the provoked pain (at intercourse or from any kind of vestibular pressure) but also potentially an improvement in the associated sexual function, depression and quality of life.

2.2 Study Objectives

2.2.1 Primary Study Objective

Stage 1

The primary objective of the study is to assess the safety of increasing doses of Dysport in vulvodynia subjects with PVD.

Stage 2

The primary objective of the study is to assess the efficacy of Dysport compared to placebo in vulvodynia subjects with PVD.

2.2.2 Secondary Study Objectives

The secondary objectives of the study are as follows:

Stage 1

- To assess the efficacy of increasing doses of Dysport compared to placebo in vulvodynia subjects with PVD
- To determine the doses of Dysport to be administered in Stage 2
- To assess the sensitivity of the endpoints used in Stage 1.

Stage 2

- To define the optimal doses of Dysport with an acceptable benefit/risk profile for the treatment of vulvodynia with PVD
- To assess effect of Dysport on:
  - Vulvar pain
  - Use of pain rescue medication (type, dose and frequency)
- To determine if primary and secondary PVD subjects benefit from Dysport administration
- To assess the time to retreatment
- To assess the safety of Dysport.

2.2.3 Exploratory Objectives

The exploratory objectives of the study are as follows:

- To assess effect of Dysport on:
  - Clinical Global Impression (CGI) of the treatment effect (assessed by the investigator)
  - Patient Global Impression of severity of the pain (PGI-S) and Patient Global Impression of change in pain (PGI-C)
- Emotional response, cognitive response and associated life interference as assessed on modified Vulvar Pain Assessment Questionnaire (mVPAQ) subscales
- Sexual function
- To assess the efficacy of Dysport on the pelvic floor muscles pressure
- To assess the efficacy of Dysport on depression
- To assess the efficacy of Dysport on the quality of life.

3 STUDY DESIGN

3.1 General Design and Study Schema

This is a Phase II multicentre, double-blind, randomised, placebo-controlled, dose finding study to define the optimal doses of Dysport and evaluate its efficacy and safety compared to placebo in vulvodynia patients with PVD. Study treatment will be injected at 5 needle insertion points at 10 injection sites in the vestibular area. The study will consist of a dose escalation stage (Stage 1) and a dose expansion stage (Stage 2). The purpose of the dose escalation will be to determine the Dysport doses to be further investigated in Stage 2. The study will include approximately 180 premenopausal female subjects (up to 118 in Stage 1 if all cohorts are reached, and 63 in Stage 2) aged 18 years or above with a diagnosis of PVD associated with provoked pain at the posterior vestibule. Both Stage 1 and Stage 2 will consist of a double-blind period (treatment cycle 1; Dysport or placebo) followed by an open-label treatment period (treatment cycles 2 to 4; all subjects receive Dysport). Overall study duration and period for individual subject participation are provided in Section 3.8.

An overview of the study design is presented in Figure 1.

3.1.1 Stage 1 (Dose Escalation)

It is intended to enrol up to seven dose level cohorts of secondary PVD subjects (i.e. having a past history of pain-free intercourse or insertion of any object >1 cm diameter; hereafter referred to as PVD2 subjects) evaluating Dysport doses ranging from 100 U up to a maximum of 800 U (total dose administered) to find two optimally safe and effective doses of Dysport that will be further investigated in the Stage 2. Additional dose level cohorts within this dose range (100 U and up to a maximum 800 U) may potentially be added based on the recommendations from the DRC.

Each PVD2 cohort will include 10 unique evaluable PVD2 subjects who will be randomised via the interactive response system (IRS) to the two double-blind parallel treatment arms in 4:1 ratio:

- Dysport (N=8) or
- Placebo (N=2).

Cohort 4 will include 8 unique evaluable primary PVD subjects (i.e. having life-long provoked vestibular pain; hereafter referred to as PVD1 subjects), at the same Dysport dose as for the PVD2 Cohort 3, who will be randomised via the IRT to the two double-blind parallel treatment arms in 3:1 ratio:

- Dysport (N=6) or
- Placebo (N=2).

Further PVD1 cohorts (i.e. above 400 U) will include 10 unique evaluable subjects randomised in a ratio of 4:1 (Dysport N=8 and Placebo N=2).

In an event, when the last subject in a cohort is being randomised, if an additional subject has been screened, this subject may be accepted in the cohort and be randomised.

At Screening, all subjects will be allocated a subject number. Subjects will be evaluated for eligibility during a Screening Visit at Day -14. Following confirmation of eligibility for the study, subjects will be allocated to one of the above two treatment groups. Subjects will receive study treatment injections in the pelvic floor muscles on Day 1 (Baseline Visit). Follow-up visits will be performed at:

- Week 2 (telephone contact)

- Week 6
- Week 12 and
- Every 6 weeks up to a maximum of 48 weeks of follow-up.

The screening and postbaseline assessments to be performed at each visit are discussed in Section 5.2. Assessments to be performed at the End of Study (EOS) or Early Withdrawal (EWD) visit are presented in Section 5.2.4.

Once all PVD2 and PVD1 evaluable subjects in a dose level have reached the Week 6 visit, the dose escalation for the subsequent cohort will be agreed at the DRC meeting upon review of the available efficacy and safety data. The maximum dose to which escalation is permitted will be 800 U. The definitions for clinically significant AEs and dose limiting events (DLEs) is provided in Section 3.1.1.1. The assessments to be performed by the Data Review Committee (DRC) and their timings are discussed in Section 3.1.1.2. Subject who withdraw or discontinue prior to Week 6 in the double-blind period for reasons unrelated to occurrence of DLEs may be replaced at the discretion of the investigator and sponsor. Replacement subjects will receive the same treatment as the subject they replace. Stage 1 will be stopped as soon as the dose of 800 U has been tested or otherwise recommended by the DRC.

At the end of Cycle 1 – Week 6 for all PVD2 subjects in Stage 1, the DRC will meet to review efficacy and safety data and recommend the two doses of Dysport to be assessed in the Stage 2 of the study. PVD1 subjects will be recruited in Stage 2 following DRC review of the efficacy and safety data of PVD1 cohort(s) in Stage 1.

An intermediate analysis will be performed to review the unblinded data from all cohorts in Stage 1 up to Cycle 1-Week 12 in an effort to select the two doses for Stage 2 taking into account the dosing recommendations from the DRC.

From Week 12 onwards of the double-blind period, subjects will be assessed for the need for retreatment at each visit. Subjects who require retreatment will be provided subsequent treatment with Dysport in the open-label period of the study. Dysport dose levels, that are approved by the DRC will be used for retreatment and will not exceed 800 U. Subjects not requiring or not eligible for retreatment will be evaluated every 6 weeks ±2 weeks (Additional Visit(s)) until they need retreatment or they complete at least 36 weeks of follow-up. The number of treatment cycles will depend on the duration of each treatment cycle, and thus the minimum follow-up duration will be 36 weeks and the maximum follow-up duration will be 48 weeks (the end of the study will not occur before 12 weeks have elapsed from the last treatment cycle), as calculated from Cycle 1-Day 1.

The screening and postbaseline assessments to be performed at each visit are discussed in Section 5.2. Assessments to be performed at the EOS or EWD visit are presented in Section 5.2.4.

Retreatment criteria are presented in Section 3.7.3. Retreatment dose schedule for Stage 1 is presented in Section 3.7.2.1.

3.1.1.1 Definitions of Clinically Significant Adverse Event and Dose Limiting Event

A clinically significant AE is defined as:

- Drug-related severe AE or drug related serious AE
- Treatment emergent faecal incontinence, defined as new onset faecal incontinence that lasts for more than 4 days and that in the investigator's opinion is not due to any other cause e.g. diarrhoea

- Treatment emergent urinary incontinence, defined as: new onset, or a significant and sudden deterioration in any pre-existing urinary incontinence in the investigator's opinion, that lasts for more than 4 days and that in the investigator's opinion is not due to any other cause.

A DLE for the purpose of this study is defined as a clinically significant AE that would preclude another drug administration at the same dose level in a given subject.

3.1.1.2 DRC Meetings

A DRC will be established to make recommendations for dose escalation, dose de-escalation, progression from Stage 1 to Stage 2 or study termination in Stage 1 of the clinical study (see Section 13.3.1 for the composition and operation of the DRC). The maximum dose to which escalation will be permitted will be 800 U.

If no subject reports a clinically significant AE in a cohort, the DRC will meet once all PVD2 and PVD1 evaluable subjects of a dose level have reached Week 6 to review the unblinded efficacy and safety data and recommend the dose for the next cohort. The DRC may recommend to reassess the previously used dose level based on the review of efficacy and safety data from the cohort(s).

If any subject reports a clinically significant AE (as defined in Section 3.1.1.1), then further enrolment into the cohort, as well as retreatment in open label cycles at current dose, will be suspended and an ad hoc DRC meeting will be scheduled.

During the ad-hoc meeting, the DRC will review blinded data of the subject(s) with clinically significant AE and all available efficacy and safety data from the cohort. The DRC may request to break the blind to confirm if the significant AE is a DLE, and based on this assessment, if enrolment in the cohort may continue.

At the end of Cycle 1-Week 6 visit for all subjects in Stage 1, the DRC will meet to review all safety and efficacy data from the cohort(s) and recommend the two doses to be assessed in Stage 2. The DRC will also recommend if further PVD1 cohort(s) are required or if PVD1 subjects should be removed from Stage 2.

In Stage 2 of the study, ad hoc DRC meetings will be scheduled to review efficacy and safety data in the event of an emergency safety issue.

3.1.2 Stage 2 (Dose Expansion)

Two dose levels identified from Stage 1, recommended by the DRC based on efficacy and safety data, will be investigated further and compared to placebo in Stage 2. As for Stage 1, 800 U will be the maximum permitted dose in Stage 2. It is intended to enrol 63 subjects in the randomisation ratio of 1:1:1:

- Dysport high dose (optimal highest safe and efficacious dose): 21 subjects
- Dysport low dose (selected based on safety and efficacy considerations observed in Stage 1): 21 subjects, and
- Placebo: 21 subjects.

Following the review of data available from Stage 1, the sample size may be formally recalculated for Stage 2 after the intermediate analysis.

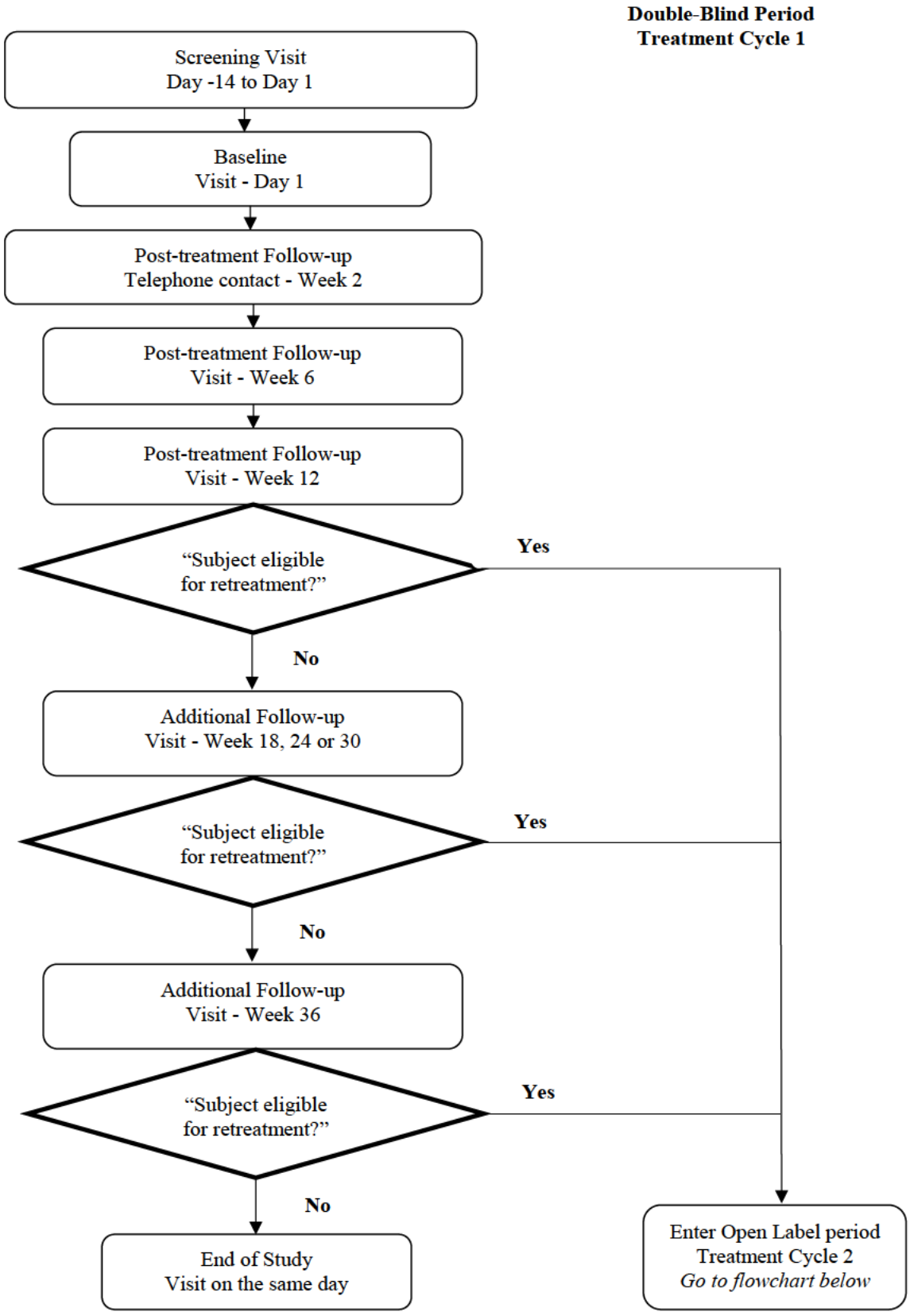
Subjects will be evaluated for eligibility during a Screening Visit at Day -14. Subjects will receive study treatment in the pelvic floor muscles on Day 1. Treatment paradigm and follow-up visits will be the same as in Stage 1. From Week 12 visit onwards, the need for retreatment will be assessed at each visit.

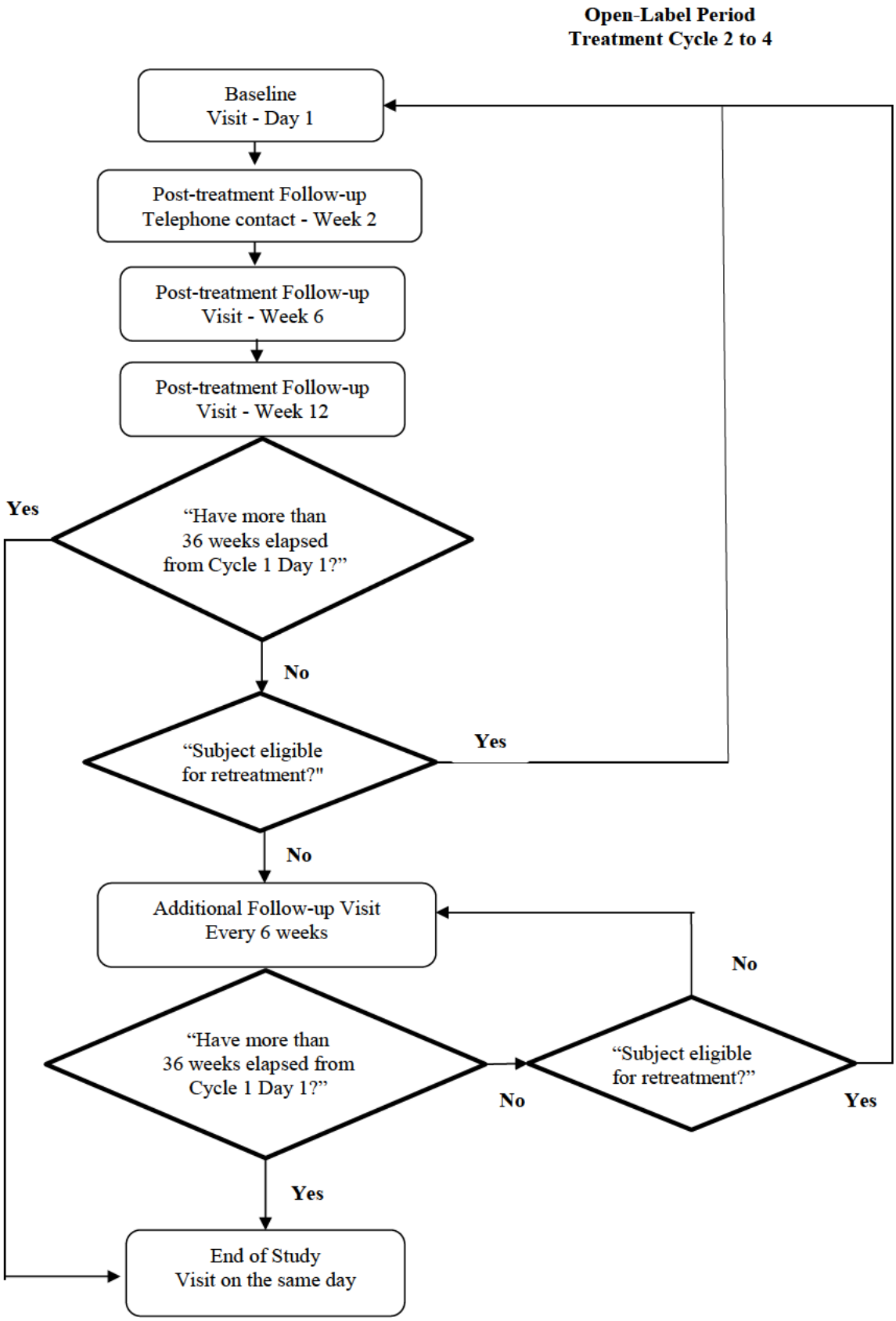
The screening and postbaseline assessments to be performed at each visit are discussed in Section 5.2.

Retreatment criteria are presented in Section 3.7.3. Retreatment dose for Stage 2 is presented in Section 3.7.2.2.

The number of treatment cycles will depend on the duration of each treatment cycle, and thus the minimum follow-up duration will be 36 weeks and the maximum follow-up duration will be 48 weeks (the end of the study will not occur before 12 weeks have elapsed from the last treatment cycle), as calculated from Cycle 1-Day 1.

Figure 1 Study Design





Each subject included in a cohort is unique and will continue to remain in the same cohort until the EOS.

3.2 Primary and Secondary Endpoints and Evaluations

3.2.1 Primary Endpoints and Evaluations

Stage 1

- Safety endpoints between Baseline and Cycle 1-Week 6, including the incidence of any DLE.

Stage 2

- Mean change from Baseline to Cycle 1-Week 6 in the vaginal dilator induced pain as reported on an 11-point numeric rating scale (NRS) (using the dilator maximum tested size (DMTS) reported at Baseline).

3.2.2 Secondary Efficacy Endpoints and Evaluations

The following secondary evaluations will be performed for Stage 1 and Stage 2:

- Mean change from Baseline to each post-treatment visit in the vaginal dilator induced pain as reported on the 11-point NRS (using the DMTS reported at Baseline).
- Proportion of subjects who reported at least a 30% decrease in vaginal dilator induced pain as reported on the 11-point NRS (using the DMTS reported at Baseline) at each post-treatment visit.
- Proportion of subjects who reported at least 2-point decrease in vaginal dilator induced pain as reported on the 11-point NRS (using the DMTS reported at baseline) at each post-treatment visit.
- Mean change from Baseline to each post-treatment visit in the dilator size that provokes maximum tolerated pain.
- Mean change from Baseline to each post-treatment visit in the composite score for the vaginal dilator induced pain and dilator size.
- Mean change from Baseline to each post-treatment visit in pain during insertion of vaginal dilator number 6 size as reported on the 11-point NRS.
- Mean change from Baseline to each post-treatment visit in the pain during intercourse as reported on the 11-point NRS.
- Mean change from Baseline to each post-treatment visit in the number of intercourse instances in subjects with partners.
- Use of pain rescue medication (type, dose, number of pills taken and frequency).
- Proportion of subjects who reported at least a 50% decrease in vaginal dilator induced pain as reported on the 11-point NRS (using the DMTS reported at Baseline) at each post-treatment visit.
- Proportion of subjects having reported at least a 50% decrease in pain during insertion of vaginal dilator number 6 size on the mean of the NRS values at each post-treatment visit.
- Proportion of subjects having reported at least a 30% decrease in pain during insertion of vaginal dilator number 6 size on the mean of the NRS values at each post-treatment visit.
- Proportion of subjects having reported at least 2-point decrease in pain during insertion of vaginal dilator number 6 size on the mean of the NRS values at each post-treatment visit.

3.2.3 Safety Endpoints and Evaluations

The safety and tolerability of Dysport will be assessed throughout the study by evaluating:

- Incidence of treatment emergent AEs (TEAEs), serious AEs (SAEs), clinically significant AEs, DLEs, AEs (or SAEs) leading to discontinuations and AEs of special interest (AESIs).
- Absolute values, values classified as abnormal/normal and change from Baseline in the clinical laboratory test results (including nonfasting clinical biochemistry and haematology parameters).
- Number of subjects who seroconvert for BTX antibodies following treatment with Dysport.
- Clinical evaluation of concomitant medication usage (except rescue medication) and therapies.

3.3 Exploratory Endpoints

- Mean CGI (as assessed by the investigator) of the treatment effect at each post-treatment visit.
- Mean PGI-C (as assessed by the subject) at each post-treatment visit.
- Mean change from Baseline in PGI-S (as assessed by the subject) at each visit.
- Mean change from Baseline to each post-treatment visit in each of the mVPAQ subscales.
- Mean change from Baseline to each post-treatment visit in the modified Female Sexual Function Index (mFSFI) total score and domain scores.
- Mean change from Baseline in the pelvic floor muscles pressure as measured by perineometry in all subjects in Stage 1 up to 400 U and in a subset of subjects in Stage 2)

  (Note: in Stage 2 this endpoint will be evaluated in subjects who have never had a vaginal delivery (including an attempted vaginal delivery), and at study sites that were provided a perineometer to assess pelvic floor muscle pressure)

  - Resting vaginal pressure
  - Maximal ‘squeeze’ pressure.
- Mean change from Baseline in the depression score using Patient Health Questionnaire (PHQ-9) scale.
- Mean change from Baseline in quality of life (QoL) using 36-item Short Form Survey (SF-36).

3.4 Biobanking

No biobanking of sample will be performed for this study.

3.5 Randomisation and Blinding

All of the investigational medicinal product (IMP) will be similar in size, colour and appearance allowing the blinded conditions of the first cycle of the study to be maintained (Stage 1 and Stage 2).

During the double-blind period of Stage 1 and Stage 2, subjects and investigators will be blinded to treatment assignment (i.e. Dysport/placebo).

During the double-blind period of Stage 2 subjects and investigators will also be blinded to the dose received.

For Stage 1, the sponsor's randomisation manager who is a statistician, independent from the study, will prepare:

- A list of randomisation numbers (List A1). It will be produced in blocks, on an unbalanced ratio (4 Dysport: 1 placebo) and will be stratified by cohort. For Cohort 4, Dysport randomisation numbers will be deactivated randomly to get an unbalanced ratio (3 Dysport: 1 placebo).
- A list of treatment numbers/treatment which will be dispatched to the sites (List B1). It will be produced in blocks, on an unbalanced ratio (3 Dysport: 2 placebo).

For Stage 2, the sponsor's randomisation manager will prepare:

- A list of randomisation numbers (List A2). It will be produced in blocks, on a balanced ratio (1 placebo: 1 Dysport low dose: 1 Dysport high dose) and will be stratified by pain onset subtype (primary and secondary PVD).
- A list of treatment numbers/treatment which will be dispatched to the sites (list B2). It will be produced in blocks, on a balanced ratio (1 placebo: 1 Dysport low dose: 1 Dysport high dose).

Mirror lists of randomisation numbers will also be produced to randomise the replacement subjects, so that the subject to be replaced and her replacement are assigned to the same treatment arm.

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 (V2), subjects will be assigned to a randomisation number and to the associated treatment arm, in sequential order within each study centre and within each level of strata. In Stage 1, from Cohort 3 onwards, the IRT will also consider the subject pain-onset subtype for cohort/randomisation number assignation.

Subjects meeting the eligibility 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. 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 site staff 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 –supporting information is provided in the investigator site file.

Recruitment will stop in each cohort of Stage 1 (and respectively in Stage 2) once 10 (or 8 in Cohort 4 only) and respectively 63 evaluable subjects have been randomised with the expected ratio.

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 she should receive the same treatment. Non-evaluable subjects will be replaced with a mirror list, so that the replacement subject is assigned to the same treatment arm as the replaced subject.

The sponsor's randomisation manager will keep the master lists. A copy of lists of treatment numbers (lists B1 and B2) will be confidentially supplied to the Ipsen PharmSciences, CCI [redacted]. Similarly, a copy of lists of randomisation/treatment numbers (lists A1, B1, A2 and B2) will be also confidentially supplied to the Contract

Research Organisation (CRO) in charge of IRT. Finally, a copy of lists concerning stage 1 (lists A1 and B1) will be also confidentially supplied to the independent statistician in charge of tables, figures and listings (TFLs) for the DRC. The master lists and the copies supplied to Ipsen PharmSciences, CRO in charge of IRT and to the independent statistician in charge of TFLs for DRC 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.

3.6 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 (GPS) at Ipsen, in case of IRT failure (this set will be prepared by 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 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 electronic case report form (eCRF).

Finally, if needed, DRC will be able to unblind any subject of Stage 1, with the hard copy sealed code break envelope of her randomisation number (this set of envelopes will be prepared by Ipsen randomisation manager) or using the IRT.

3.7 Study Treatments and Dosage

3.7.1 Study Treatments

The test product, Dysport, will be provided in glass vials containing 300 U or 500 U (nominal) of BTX-A-HAC as white lyophilised powder for reconstitution with preservative free 0.9% sodium chloride for injection. Detailed description of Dysport composition is provided in Section 6.2.1.1.

The reference therapy for the double-blind period in this study (Stage 1 and Stage 2) is a matching placebo. Detailed description of the placebo composition is provided in Section 6.2.1.2

Details on the injection sites and injection procedure are presented in Section 6.2.2.

The IMPs will be packaged by Ipsen PharmSciences, CCI [redacted] and delivered to an interim storage facility. A sufficient quantity of IMP will be supplied as well as an acknowledgement of receipt form.

The sponsor's representative will receive a Certificate of Analysis for each batch of IMP used in the study and Material Data Safety Sheet for both active and placebo IMP.

The core label texts for all packaging units will be translated or adjusted, to follow applicable regulatory requirements, national laws in force and in accordance with the local languages. A description of the core text of the IMP labels is displayed below:

- Name, address and telephone number of the sponsor (the main contact for information on the product, clinical study and emergency unblinding),
- Study Number,

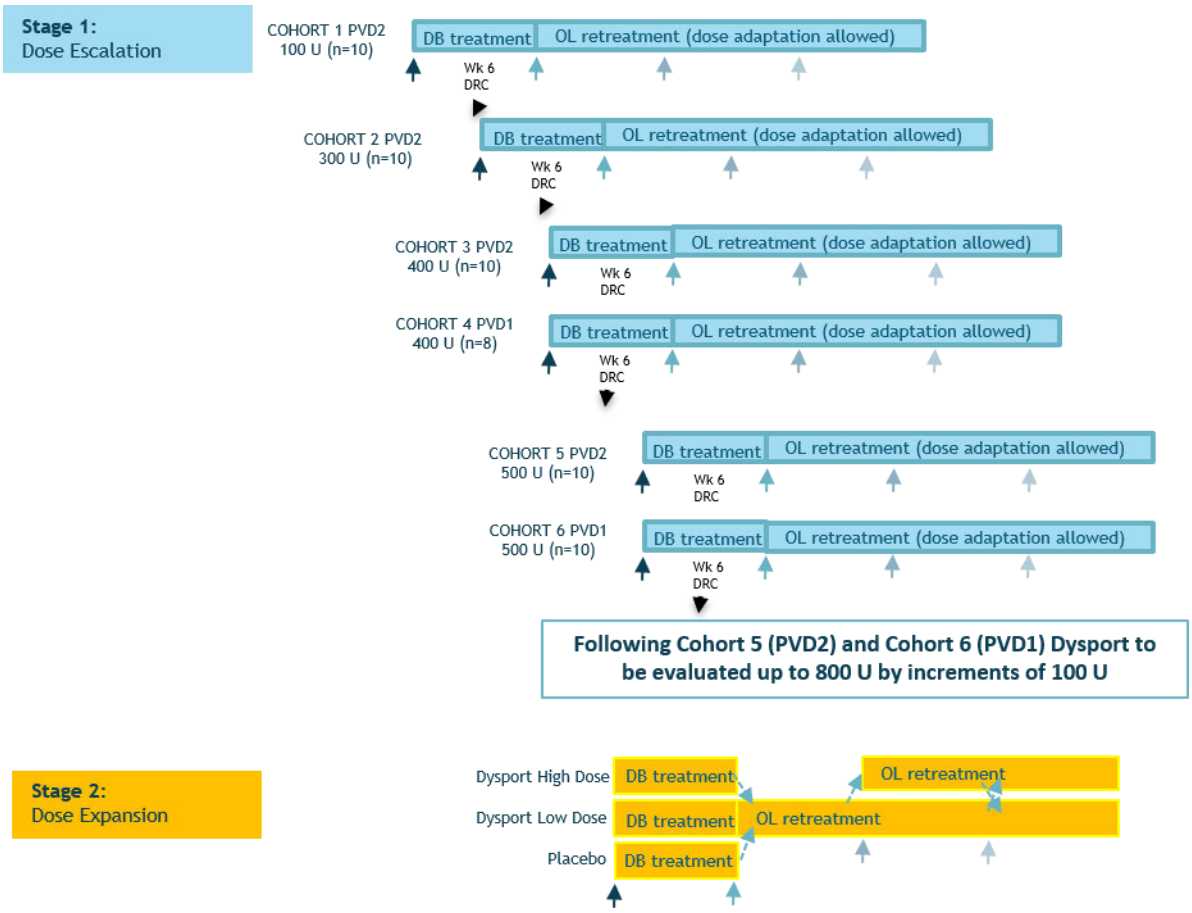
- Pharmaceutical dosage form,
- Route of administration,
- Directions for use (reference may be made to a leaflet),
- Quantity of dose units,
- Batch number,
- A specific blank space to enter the visit number (to be completed on site),
- "Caution: new drug limited by Federal Law to investigational use,"
- Investigational drug to be used by qualified investigators only,
- "For clinical trial use only,"
- Specific blank space to enter the investigator's name (to be completed on site),
- Storage conditions,
- Expiry date,
- Treatment number,
- A specific blank space to enter the subject ID (to be completed on site)
- A specific blank space to enter the site number (to be completed on site).

The investigator, or designee, will only dispense IMPs to subjects included in this study. Each subject will only be given the IMP carrying her number. The dispensing for each subject will be documented in the eCRF.

3.7.2 Study Dosage and Administration

A study flow chart for Stage 1 and Stage 2 is presented in Figure 2.

Figure 2 Study Flow Chart



DB=double-blind, OL=open-label

3.7.2.1 Stage 1

The maximum permitted dose in Stage 1 (double-blind and open-label periods) is 800 U.

Double-Blind Period (Treatment Cycle 1)

The starting dose for PVD2 Cohort 1 will be Dysport 100 U or placebo. It is anticipated that if there are no safety issues, then the predefined doses for PVD2 Cohorts 2 and 3 will be 300 U and 400 U, respectively, and doses for Cohorts 5, 7, 9 and 11 will be 500 U up to a maximum of 800 U by increments of 100 U, all with matching placebos. Subjects in PVD1 Cohorts 4, 6, 8, 10 and 12 will receive the same dose as subjects in PVD2 Cohorts 3, 5, 7, 9 and 11.The DRC may recommend to reassess the previously used dose level based on the review of efficacy and safety data from the cohorts.

Open-Label Period (Treatment Cycles 2-4)

For a given subject, the Dysport dose for treatment cycles 2, 3 and 4 will be based on the investigator's judgement (based on efficacy and safety).

- Treatment cycle 2: the Dysport dose can either be the Dysport dose assessed in the previous treatment cycle (double-blind period) for the current cohort or the Dysport dose of the following cohort (provided it has been approved by the DRC).

- Treatment cycles 3 and 4: the Dysport dose can either be the dose assessed in the previous treatment cycle, a lower dose or the dose of the following cohort (provided it has been approved by the DRC).

If any subject fulfils the retreatment criteria and needs a higher dose for treatment prior to the DRC having approved the next dose level, the subject can either accept the dose level currently on, or delay injection until the next dose level is approved by the DRC or withdraw from the study.

A subject can receive up to a maximum of 4 treatment cycles with Dysport. The last treatment cycle should last at least 12 weeks and should not be initiated after Week 36.

3.7.2.2 Stage 2

As for Stage 1, the maximum permitted dose in Stage 2 (double-blind and open-label periods) is 800 U.

Double-Blind Period (Treatment Cycle 1)

Depending upon the results from Stage 1 and the recommendation from the DRC, two doses of Dysport will be selected.

- Dysport high dose (optimal highest safe and efficacious dose) selected from Stage 1 or
- Dysport low dose selected based on safety and efficacy considerations observed in Stage 1 or
- Placebo.

Open-Label Period (Treatment Cycles 2-4)

For a given subject, the Dysport dose for treatment cycles 2, 3 and 4 will be:

- Treatment cycle 2: the Dysport dose will be the lowest of the two Dysport doses tested in the double-blind period of Stage 2.
- Treatment cycles 3 and 4: as per the investigator's judgement (based on efficacy and safety), the Dysport dose can be either the low or high dose tested during the double-blind period of Stage 2.

A subject can receive up to a maximum of 4 treatment cycles with Dysport. The last treatment cycle should last at least 12 weeks and should not be initiated after Week 36.

3.7.3 Retreatment Criteria (Stage 1 and Stage 2)

From Week 12 onwards (Stages 1 and 2), need for retreatment will be assessed at each visit. All subjects willing to continue in the study will be offered to receive Dysport (under an open-label design).

Retreatment with Dysport will only be initiated if all of the following criteria are fulfilled (retreatment criteria):

- At least 12 weeks have elapsed since the last treatment received.
- Based on investigator's judgement, this is in the best interest of the subject.
- Subject is willing to be retreated.
- The subject has not experienced any unacceptable AE as judged by the investigator.
- Negative urine pregnancy test.
- Negative drug screen test for illicit drugs.

Details on dose administration for Stage 1 are provided in Sections 3.7.2.1 and for Stage 2 in Section 3.7.2.2.

3.8 Study Duration

This study will consist of a 14-day screening period (Stage 1 and Stage 2), a double-blind treatment period including treatment administration at Day 1 and a follow-up period of 36 to 48 weeks (calculated from the dosing at Day 1). From Week 12 onwards of the double-blind period, the subject may enter an open-label treatment period and receive up to three additional treatment cycles with Dysport administered at least 12 weeks apart (a maximum of 4 treatments including the one received in the double-blind period).

Individual subject participation in this study will be for a maximum of 54 weeks (Stage 1 and Stage 2):

- Screening: 2 weeks (plus 2 weeks window)
- Follow-up: a maximum of 48 weeks follow-up plus 2 weeks window period for the EOS Visit depending on the number of treatments administered and the treatment intervals.

The subject's participation in the study will be considered to have ended 36 to 48 weeks after the first dose, but not before 12 weeks have elapsed after the last dose.

The overall duration of the study, including Stage 1 and Stage 2 with a maximum allowed dose of 800 U, will be approximately 4 years. The study will be considered to have started when the first subject has provided signed informed consent. The study will be considered to have ended after the last subject has completed the EOS visit in the study.

3.9 Stopping Rules and Discontinuation Criteria

A specific site or a given cohort can be discontinued or the entire study may be terminated if recommended by the DRC at any time during Stage 1 or if the sponsor judges it necessary for any reason any time during the study. In that case, all efforts should be made to perform the scheduled procedures and assessments for subjects who are still in the study until 12 weeks after the last dose.

The study could be stopped or discontinued due to following reasons:

- As per the DRC's decision in Stage 1:
  - Any DLE identified as a safety concern (definition provided in Section 3.1.1.1);
  - Any clinically significant AE(s) identified as a safety concern (definition provided in Section 3.1.1.1);
  - For any other safety reason.
- As per sponsor's decision anytime during the study for reasons including:
  - Failure of the site staff to comply with the protocol or with the GCP guidelines;
  - AEs or SAEs leading to safety concerns (See Section 8.1.6);
  - Inadequate subject recruitment;
  - Other reasons (decisions made by the Regulatory Authorities or Ethics Committees or any other sponsor business decision).

The subject withdrawal criteria as discussed in Section 4.4.

3.10 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, Competent Authorities (CAs). This information is included in the informed consent.

4 SELECTION AND WITHDRAWAL OF SUBJECTS

Note: Lettered inclusion and exclusion criteria indicate an update or deletion following an amendment to the protocol (e.g. a=criterion amended once, b=criterion amended twice, c=criterion amended three times).

4.1 Inclusion Criteria

All subjects must fulfil all the following criteria to be included in the study:

(1a) Female subjects aged 18 years or above.

(2) Willing to provide a written informed consent prior to any study related procedures.

(3) *Criterion 3 is removed by protocol amendment.*

(4) Are premenopausal, as evidenced by a serum follicle stimulating hormone (FSH) level of <35 mIU/mL as assessed at the Screening Visit.

(5) Have a negative pregnancy test at screening.

(6) Willing to practice a highly effective form of contraception method at the beginning of the study, for the duration of the study and for a minimum of 12 weeks following last administration of study drug. Highly effective methods of contraception are defined as methods of birth control which result in a low failure rate (i.e. less than 1% per year) when used consistently and correctly such as implants, injectables, combined oral contraceptives, intrauterine devices, or vasectomised partner. The double barrier method (condom and spermicide) may be considered an acceptable form of birth control if determined appropriate for the subject by the investigator.

(7) Have vulvodynia with provoked vestibular pain for at least 6 months and for no more than 15 years.

(8a) Have provoked pain at the posterior vestibule on a Q-tip test, with pain at positions 5, 6 and 7 o'clock (must be bilateral pain) at the Screening Visit.

(9a) Are able to tolerate the smallest dilator size (diameter 0.5 inches) at the Screening Visit, i.e. agree to the next successive dilator size to be tested for pain response (i.e. the two smallest sized dilators (#1 and 2) are to be tested).

(10a) Pain score ≥5 on an 11-point NRS for the DMTS at the Baseline Visit.

(11a) Willing to abstain from sex therapy (defined as a therapy primarily focused on the management of vulvar pain) for the duration of screening and up to at least Week 6 of the first treatment cycle.

(12b) In Stage 1, Cohorts 1, 2, 3, 5, 7, 9 and 11 will include subjects with secondary vulvodynia (i.e. having a past history of pain-free intercourse or insertion of any object >1 cm diameter). In Stage 1, Cohorts 4, 6, 8, 10 and 12 will include subjects with primary vulvodynia (having life-long provoked vestibular pain). In Stage 2, subjects with either primary or secondary vulvodynia may be enrolled as approved by the DRC.

(13) Willing and able to comply with study restrictions, able to attend the clinic for the required duration of assessments during the study period and willing to return to the clinic for the follow-up evaluation as specified in the protocol.

(14) If the subject has received oral antidepressants, anxiolytics or anti-epileptics, then the dose of these medications should have been stable for at least 6 months prior to the Screening Visit and expected to remain stable throughout the first treatment cycle.

4.2 Exclusion Criteria

Subjects will not be included in the study if they meet any of the following exclusion criteria:

(1a) Have provoked pain on a Q-tip test at the anterior vestibule (anywhere between 9 and 3 o'clock or more anteriorly) at the Screening Visit.

(2b) Able to tolerate the 6th (diameter 1¼ inches) dilator size (i.e. agree to the next successive dilator size to be tested for pain response) at the Baseline Visit (i.e. at least one of the two largest sized dilators (#7 and/or 8) is tested).

(3a) Any non-provoked (i.e. spontaneous) vulvar pain in the past 6 months prior to the Screening Visit. Note: pain provoked by any vestibular pressure (including but not limited to sitting, bicycling or tight clothing) is considered provoked pain.

(4a) Deep pain during intercourse in the past 6 months prior to the Screening Visit.

(5a) Score of 4 or 5 on any of the 3 pain questions (questions #17, 18 or 19) of the mFSFI questionnaire.

(6) *Criterion* 6 *is removed by previous protocol amendment.*

(7a) Significant depressive disorder, e.g. having a score ≥20/27 on the Patient Health Questionnaire (PHQ-9) scale at the Baseline Visit.

(8b) Genitourinary or gastrointestinal conditions/history including:

- Skin disease at the vestibule such as lichen sclerosus, lichen planus, vaginal or vulvar atrophy, desquamative inflammatory vaginitis and allergic vulvitis.
- Severe endometriosis (severe defined as requiring regular medications to manage the endometriosis symptoms).
- Severe bladder and bowel symptoms e.g. diagnosed interstitial cystitis/Bladder Pain Syndrome, severe urinary incontinence, faecal incontinence, inflammatory bowel disease.
- Genitourinary or rectal cancer.
- Congenital urogenital abnormalities (e.g. vaginal septa, imperforate hymen, urethral diverticulum).
- Pain in urethra (diagnosis based on subject's interview and physical examination).
- Symptomatic urogenital prolapse at physical examination.
- History of traumatic or post radiotherapy vulvar lesions.
- Pudendal neuralgia
- Other conditions that in accordance to the investigator's judgement may interfere with treatment or impact the study outcome.

(9) Previous surgery/conditions including:

- Hysterectomy
- Vestibulectomy
- Urologic surgery
- Perianal surgery
- Genital trauma or mutilation/cutting
- Other surgery/conditions that according to the investigator's judgement may impact the study outcome

(10) Vaginal infections (bacterial vaginosis, presence of candidiasis or trichomoniasis) at Screening Visit.

(11) Current infection at the injection site(s).

(12) Unable to receive intramuscular injections.

(13) History of hypersensitivity to Dysport or drugs with a similar structure or any excipient used in the formulation.

(14) Clinically significant history of alcohol/drug abuse the last 24 weeks prior to screening or clinically significant alcohol/drug dependence within 2 years prior to screening. Exceptions include caffeine or nicotine abuse/dependence.

(15a) Positive urine test for illicit drugs (drugs of abuse) at screening. In the event a subject tests positive for cannabinoids (tetrahydrocannabinol), the investigator will evaluate the subject's ability to abstain from cannabis during the study. If in the investigator's clinical judgement, the subject will abstain, the subject may be enrolled after consultation with the Medical Monitor. Note: at the discretion of the investigator, positive drug screens for prescribed medications will not be considered exclusionary.

(16c) Has received any of the following:

- Pelvic floor physical therapy initiated, stopped or modified (frequency or type of physical therapy) during the last 12 weeks prior to Baseline (physical therapy includes but is not limited to: internal/external myofascial release by physiotherapist, biofeedback, home pelvic floor exercises, self-taught exercises, use of vaginal dilators, etc.).
- Sex therapy in the past 6 weeks prior to Baseline.
- Previous treatment with any BTX for any indication within the last 1 year.
- Treatment for vestibular pain, with hormonal creams, in the last 1 week prior to Screening unless continued at the same dosing regimen throughout the study.
- Currently receiving treatment for stress or urge urinary incontinence.
- Treatment with any of the following drugs that could affect neuromuscular function: curare-like nondepolarising agents, lincosamides, polymyxins, anticholinesterases, aminoglycoside antibiotics (topical use is permitted except at the vulvar vestibular region), tizanidine and baclofen, within the last 4 weeks prior to Baseline or during the study.
- Injections of steroids in the vulva within the last 4 weeks prior to the Screening Visit or planned use during the study.
- Treatment with an investigational drug within the last 4 weeks prior to Baseline or scheduled treatment with such a drug during the study period.
- Is likely to require treatment during the study with drugs that are not permitted by the study protocol.

(17) Any mental condition rendering the subject unable to understand the nature, scope and possible consequences of the study, and/or evidence of an uncooperative attitude, as judged by the investigator.

(18) Abnormal baseline findings, any other medical condition(s) or laboratory findings that, in the opinion of the investigator, might jeopardise the subject's safety or compromise compliance with the objectives and/or procedures of this protocol or preclude the administration of BTX.

(19) Female subject who is pregnant or planning to become pregnant during the study or, is currently lactating (breastfeeding).

4.3 Rationale for Inclusion/Exclusion Criteria

In order to establish the preliminary efficacy of Dysport in this dose escalation and dose expansion study, a subset of vulvodynia subjects suffering from provoked vestibular pain is selected. It is hypothesised that pelvic floor muscle hypertonicity underpins the posterior vestibular pain experienced and consequently, these subjects are likely to respond to treatment with Dysport. Hence, the inclusion and exclusion criteria for this study have been tailored to ensure enrolment of female subjects with a confirmed diagnosis of PVD based on the three established criteria as per Pukall 2007 [21]: self-report of superficially-located pain during sexual intercourse; a lack of physical findings (e.g. infections) to explain the pain or the persistence of pain after conditions believed to be related to the pain have been treated; and a positive response (i.e. pain) during the cotton-swab test. This will also help target a homogenous subject population and limit intersubject variability.

4.4 Subject Withdrawal Criteria and Procedures

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 and/or sponsor can withdraw a subject at any time for any reason (e.g. protocol violation).

The investigator also has the right to withdraw a subject from the study for reasons including:

- If required by the DRC due to reasons described in Section 3.1.1.2
- Any AE that jeopardises the safety of the subjects
- Other reasons concerning the health or wellbeing of the subject
- In the event of concurrent illness, based on the benefit risk for the subject as assessed by the investigator (see concomitant medications not permitted in Section 6.3)
- Pregnancy (see Section 8.1.7)
- Lack of cooperation in completing the study visits or schedules or study assessments
- Study is stopped or discontinued (See Section 3.9 for further details)
- Death (see Section 8.1.8)
- Any other reason as judged by the investigator to be in the best interest of the subject.

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 at least 12 weeks after the last dose or up to the time of withdrawal as thoroughly as possible. A complete assessment should be made and final evaluations be done at the time of the subject's withdrawal as described in Section 5.2.4 with 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.

5 STUDY PROCEDURES

5.1 Study Schedule

The schedule of procedures and assessments during the study for the double-blind treatment period is summarised in Table 2 and for the open-label treatment period in Table 3.

Subjects enrolled prior to implementation of Version 3.0 (dated 04 November 2018), i.e. subjects included in Cohort 1, will continue to follow the study assessments and procedures as per the protocol Version 2.0 (dated 15 May 2018).

If the COVID-19 pandemic prevents subjects from coming to the site, subjects can have their study visit assessments performed remotely as judged appropriate by the investigator; the medical monitor/sponsor must be informed before implementing this. In such a case, the investigator will perform a telemedicine visit and will make every effort, where applicable, to contact the subject's general practitioner or equivalent to ensure all important medical information and safety event(s) occurring since the last visit are collected. Guidance on how to collect protocol-planned assessments will be provided to the investigator in a separate document. Such document will be filed in the Trial Master File (TMF). IECs/IRBs will be notified of the changes as applicable locally. Of note, as the adapted visit deviates from the regular protocol plan, the changes will be recorded as protocol deviations related to COVID-19.

Table 2 Study Procedures and Assessments – Double-Blind Treatment Period

Study Procedures and Assessments	Pretreatment		Double-Blind Treatment Period Cycle 1						End of Cycle 1/ EOS or EWD [b]
	V1	V2	V3	V4	V5 [a]	Additional Visits [a]			
						V6	V7	V8	
Visit Day/Week No.	**Screening (Day -14) [m]**	**Baseline (Day 1)**	**Week 2 (Day 15)**	**Week 6 (Day 43)**	**Week 12 (Day 85)**	**Week 18 (Day 127)**	**Week 24 (Day 169)**	**Week 30 (Day 211)**	**Week 36 (Day 253)**
Type of visit	**Clinic**	**Clinic**	**Telephone**	**Clinic**	**Clinic**	**Clinic**	**Clinic**	**Clinic**	**Clinic**
Visit Window	**-14 days/ +3 days**		**±3 days**	**±5 days**	**+14 days**	**±14 days**	**±14 days**	**±14 days**	**±14 days**
Informed consent [c]	X								
Inclusion/exclusion criteria	X	X							
Demographic data	X								
Height, weight, BP, HR	X								
Physical examination	X								
Significant medical/ surgical/ vulvodynia history	X								
Prior/concomitant medications and non-drug therapies (incl. BTX, sex therapy, physiotherapy, pain rescue medication)*	X	X	X	X	X	X	X	X	X
Adverse events*	X	X	X	X	X	X	X	X	X
Urine pregnancy test	X								X
Urine test for illicit drugs	X			X					X
PCS	X								
PGI-S [e]*	X	X		X	X	X	X	X	X
PGI-C [e]*				X	X	X	X	X	X
eDiary mVPAQ pain subscale [e]*	X	X		X	X	X	X	X	X
eDiary mVPAQ life interference subscale [e]*	X	X		X	X	X	X	X	X
eDiary mFSFI pain domain [e]	X	X		X	X	X	X	X	X
mVPAQ subscales (except pain and life interference) [f]*	X	X		X	X		X		X
mFSFI domains (except pain) [f]*	X	X		X	X	X	X	X	X
eDiary relationship/partner status [g]*	X	X		X	X	X	X	X	X
eDiary dilator insertion [k]*	X	X		X	X	X	X	X	X
PHQ-9*		X			X				X

Study Procedures and Assessments	Pretreatment		Double-Blind Treatment Period Cycle 1						End of Cycle 1/ EOS or EWD [b]
	V1	V2	V3	V4	V5 [a]	Additional Visits [a]			
						V6	V7	V8	
Visit Day/Week No.	Screening (Day -14) [m]	Baseline (Day 1)	Week 2 (Day 15)	Week 6 (Day 43)	Week 12 (Day 85)	Week 18 (Day 127)	Week 24 (Day 169)	Week 30 (Day 211)	Week 36 (Day 253)
Type of visit	Clinic	Clinic	Telephone	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic
Visit Window	-14 days/ +3 days		±3 days	±5 days	+14 days	±14 days	±14 days	±14 days	±14 days
SF-36*		X			X				X
eDiary intercourse details [h]*	X	X		X	X	X	X	X	X
Q-tip test	X								
Dilator test	X	X		X	X	X	X	X	X
Vaginal swab	X								
Measurement of pelvic floor pressure [n]		X		X	X	X	X	X	X
CGI				X	X	X	X	X	X
Clinical laboratory tests (nonfasting biochemistry, haematology, FSH [i])**	X				X				X [d]
Blood sample for antibodies**	X								X [d]
Randomisation		X							
Study drug administration		X [j]							
Assessment for retreatment					X	X	X	X	
Subject Interviews				X [l]					

BP=blood pressure, BTX=botulinum toxin, CGI=clinical global impression, EOS=end of study, EWD=early withdrawal, FSH=follicle stimulating hormone, HR=heart rate, ICF=informed consent form, mFSFI=modified female sexual function index, incl.=inclusive, mVPAQ=modified vulvar pain assessment questionnaire, NRS=numeric rating scale, PGI=patient global impression, PHQ-9=patient health questionnaire, SF-36=36-item short form survey, V=visit.

a From Week 12 onwards, if no retreatment is required, the subject will attend Additional Visits every 6 weeks until retreatment is required or Week 36 (EOS) is reached. When subject is eligible and all retreatment criteria all are fulfilled at any visit, the subject will complete all the assessments planned at this visit, all assessments planned at End of Cycle 1 (if not already performed at the visit) and will enter Cycle 2 Day 1 (which will be on the same day as End of Cycle 1).

b This visit (Week 36) is the End of Study if the subject is still not eligible for retreatment at the End of Cycle 1.

c ICF to be signed prior to any screening assessment.

d To be performed only if this visit is the End of Study or Early Withdrawal.

e To be assessed at Screening Visit, then 1 week prior to the next planned visit and at the visit. PGI-C will be assessed Week 6 onwards only.

f To be assessed at the site during the visit.

g To be assessed at Screening Visit, then 2 weeks prior and 1 week prior to the next planned visit and at the visit.

h To be assessed at Screening Visit, and then from 2 weeks prior to the next planned visit, subjects need to record daily if they had intercourse, the number of intercourse instances, corresponding pain during each intercourse instance on an 11-point NRS, and details of pain rescue medication if taken to prevent or treat vestibular pain.

Study Procedures and Assessments	Pretreatment		Double-Blind Treatment Period Cycle 1						End of Cycle 1/ EOS or EWD [b]
	V1	V2	V3	V4	V5 [a]	Additional Visits [a]			
						V6	V7	V8	
Visit Day/Week No.	Screening (Day -14) [m]	Baseline (Day 1)	Week 2 (Day 15)	Week 6 (Day 43)	Week 12 (Day 85)	Week 18 (Day 127)	Week 24 (Day 169)	Week 30 (Day 211)	Week 36 (Day 253)
Type of visit	Clinic	Clinic	Telephone	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic
Visit Window	-14 days/ +3 days		±3 days	±5 days	+14 days	±14 days	±14 days	±14 days	±14 days

i FSH only at Screening Visit.

j Performed after all the other procedures and assessments. Subjects to remain at the clinic for at least 30 minutes after the study drug administration.

k To be assessed weekly from 2 weeks prior to the next planned visit (assessment on the day of the visit should be avoided). Subjects need to rate the level of the corresponding pain following insertion of vaginal dilator (number 6 size) on an 11-point NRS and record details of associated pain medication if consumed.

l Subject interviews on the dilator test to be conducted in Stage 2 by invitation until the target sample of 20 subjects is achieved. Every effort should be made to conduct the interview within 2 weeks of the subject's Cycle 1-Week 6 visit.

m The visit window will be from Day -28 to Day -11.

n To be performed in all subjects in Stage 1 up to 400 U and in a subset of subjects in Stage 2 (i.e. subjects who have never had a vaginal delivery (included attempted vaginal delivery), and at study sites that were provided a perineometer to assess pelvic floor muscle pressure).

* Study assessments that can be performed remotely if a subject is unable to attend a site visit due to the COVID-19 pandemic, except for the Screening, Baseline and EOS/EWD visits.

** In the event of a remote visit being required, blood sampling should be performed as soon as onsite visit resume and prior to the Week 18 Visit (as much as possible) and recorded as an unscheduled visit.

Table 3 Study Procedures and Assessments – Open-Label Treatment Period

Study Procedures and Assessments	Open-Label Treatment Period Cycles 2 to 4						EOS / EWD
	V9, V13, V17	V10, V14, V18	V11, V15, V19	V12, V16, V20	Additional Visits [b]		
Visit Day/Week No.	Day 1 [a]	Week 2 (Day 15)	Week 6 (Day 43)	Week 12 [b] (Day 85)	Week 18 (Day 127)	Week 24 (Day 169)	Week 48 from Cycle 1 Day 1 (Day 337 from Cycle 1 Day 1) or Early withdrawal
Type of visit	Clinic	Telephone	Clinic	Clinic	Clinic	Clinic	Clinic
Visit Window		±3 days	±5 days	+14 days	±14 days	±14 days	±14 days
Prior/concomitant medication and non-drug therapies (incl. BTX and physiotherapy)*	X [c]	X	X	X	X	X	X
Adverse events*	X [c]	X	X	X	X	X	X
Urine pregnancy test	X [c]						X
Urine test for illicit drugs	X [c]		X				X
Clinical laboratory tests (non-fasting chemistry, haematology)**							X
Blood sample for antibodies**							X
PGI-S [i, j]*	X [d]		X	X	X	X	X
PGI-C [i, j]*	X [d]		X	X	X	X	X
eDiary relationship/partner status [e]*	X [d]		X	X	X	X	X
eDiary dilator insertion [k]*	X [d]		X	X	X	X	X
eDiary intercourse details [f]*	X [d]		X	X	X	X	X
Dilator test	X [d]		X	X	X	X	X
CGI	X [d]		X	X	X	X	X
Study drug administration	X [g]						
Assessment for retreatment				X [h]	X [h]	X [h]	

AE=adverse event, BTX=botulinum toxin, CGI=clinical global impression, DRC=data review committee, EOS=end of study, EWD=early withdrawal, ICF=informed consent form, incl.=inclusive, NRS=numeric rating scale, PGI=patient global impression, SF-36=36-item short form survey, V=visit.

a Day 1 should be done on the same day as last visit of previous cycle. During Stage 1, Day 1 can be delayed until the DRC has confirmed the dose for the next cohort.

b From Week 12 onwards, if no retreatment is required, the subject will attend Additional Visits every 6 weeks until retreatment is required, or EOS is reached. When subject is eligible and all retreatment criteria all are fulfilled at any visit, the subject will complete the assessments planned at this visit and will enter Day 1 of the next Cycle on the same day and once the DRC has confirmed moving to next cohort for Stage 1.

c Not to be performed if already done on the same day. AEs are assessed on a continual basis from signing of the ICF.

d To be performed only if Day 1 is not on the same day as the last visit of previous cycle and the assessment was performed more than 2 weeks prior to Day 1.

e To be assessed 2 weeks prior and 1 week prior to the next planned visit, and at the visit.

Study Procedures and Assessments	Open-Label Treatment Period Cycles 2 to 4						EOS / EWD
	V9, V13, V17	V10, V14, V18	V11, V15, V19	V12, V16, V20	Additional Visits [b]		
Visit Day/Week No.	Day 1 [a]	Week 2 (Day 15)	Week 6 (Day 43)	Week 12 [b] (Day 85)	Week 18 (Day 127)	Week 24 (Day 169)	Week 48 from Cycle 1 Day 1 (Day 337 from Cycle 1 Day 1) or Early withdrawal
Type of visit	Clinic	Telephone	Clinic	Clinic	Clinic	Clinic	Clinic
Visit Window		±3 days	±5 days	+14 days	±14 days	±14 days	±14 days

f To be recorded daily from 2 weeks prior to the next planned visit. Subjects need to record daily if they had intercourse, the number of intercourse instances, corresponding pain during each intercourse instance on an 11-point NRS and details of pain rescue medication if taken to prevent or treat vestibular pain.

g Performed after all the other procedures and assessments. Subjects to remain at the clinic for at least 30 minutes after the study drug administration.

h No assessment for retreatment if the visit occurs >36 weeks from Cycle 1 Day 1.

i To be assessed only in Cycle 2 (i.e. the first cycle of the open-label treatment period).

j To be assessed 1 week prior to the next planned visit and at the visit.

k To be assessed weekly from 2 weeks prior to the next planned visit (assessment on the day of the visit should be avoided). Subjects need to rate the level of the corresponding pain following insertion of vaginal dilator (number 6 size) on an 11-point NRS and record details of associated pain medication if consumed.

* Study assessments that can be performed remotely if a subject is unable to attend a site visit due to the COVID-19 pandemic, except for the Screening, Baseline and EOS/EWD visits.

** In the event of a remote visit being required, blood sampling should be performed as soon as onsite visit resume and prior to the Week 18 Visit (as much as possible) and recorded as an unscheduled visit.

The total volume of blood drawn for all evaluations throughout this study is approximately 46 mL for each subject (Table 4).

Table 4 Blood Volume for Collection

Purpose	Maximum Blood Volume per Sample (mL)	Maximum Number of Blood Samples	Maximum Total Blood Volume (mL)
Haematology	3	3	9
Serum Chemistry	4	3	12
FSH	1	1	1
Putative antibodies	12	2	24
Total volume for all tests			46

FSH=follicle stimulating hormone

5.2 Study Visits

For the purpose of study visits and procedures, the duration of 1 month=4 weeks=28 days. For assessments done at the Screening Visit, but not repeated at the Baseline Visit, the Screening values will be considered as Baseline.

Subjects are required to remain at the clinic for the required duration of study assessments and for at least 30 minutes after study drug administration.

The priority order for performing the assessments is discussed in Section 6.6.

If the COVID-19 pandemic prevents subjects from coming to the site, study assessments planned in the protocol will be limited to the ones possible remotely, denoted with an asterisk (*) in Table 2, Table 3, Section 5.2.2, Section 5.2.3 and Section 5.2.4; of note no study assessments should be performed remotely for the Screening, Baseline and EOS/EWD visits. Completion of questionnaires on the subjects' own device will be performed provided that the site staff can access the ePRO system to record the visit date.

5.2.1 Procedures for Screening and Enrolment - Visit 1 (Day -14 (-14 days/ +3 days))

A signed and dated informed consent form will be obtained before screening procedures. 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.

5.2.1.1 Screening – Visit 1 - Day -14 (-14 days/ +3 days)

The Screening Visit (Visit 1) will take place on Day -14 of the study. The visit window will be from Day -28 to Day -11.

The following assessments will be performed:

- Eligibility check (inclusion/exclusion criteria)
- Demographic data (year of birth, age, sex, ethnicity, and race)
- Medical history, including significant ongoing medical history, surgical history and vulvodynia history
- Vital signs (supine or sitting blood pressure and heart rate)
- Body height and weight
- Physical examination
- Blood sampling (nonfasting) for haematology, biochemistry, putative antibodies and FSH

- Urine pregnancy test
- Urine test for illicit drugs
- Vaginal culture/polymerase chain reaction for yeast, parasitic and bacterial infections
- PCS
- mFSFI (pain to be recorded at the visit, and 1 week prior to the Baseline Visit; other domains to be recorded only at the visit)
- Relationship/partner status (to be recorded at the visit and then weekly during the screening period)
- mVPAQ (pain and life interference to be recorded at the visit, and 1 week prior to the Baseline Visit; other subscales to be recorded only at the visit)
- Intercourse details (to be recorded daily during the screening period)
- Dilator size 6 insertion details (to be recorded weekly during the screening period)
- PGI-S (to be recorded at the visit, and 1 week prior to the Baseline Visit)
- Q-tip test
- Dilator test
- Record:
  - Prior and concomitant medications/therapies (including pain rescue medication) administered within 28 days before the Screening Visit
  - Prior pelvic floor physical therapy or sex therapy received in the past 2 years prior to the planned Baseline
  - Treatment for anterior vestibular pain
  - Prior treatment with any BTX within the last 1 year
  - Prior and concomitant nondrug therapies and surgical procedures administered within 28 days before the Screening Visit
  - Use of any experimental new drug or device within past 4 weeks prior to the planned Baseline.
- Collection of AEs (since the signature of the informed consent)
- Instructions on patient diary completion.

Following confirmation of eligibility of the subject for the study and confirmation that the recruitment is still open in the cohort/group, subjects will be randomised and allocated to one of the dosing groups specified in Section 3.7.2.

A subject can be rescreened once, if all eligibility criteria were met but the subject was not enrolled due to any of the following, and twice due to ANY of the following conditions if they had to stop the first screening period due to COVID-19:

- Cohort recruitment being complete by the time the subject was eligible,
- If the subject had a UTI or vaginal infection at first screening and has received adequate treatment leading to complete resolution of the infection,
- If the subject failed screening due to a selection criterion that was removed from the previous version of the protocol. If the subject failed screening due to a selection criterion that was modified, she should have fulfilled the new criterion at the time of the first screening to be able to be rescreened. In these situations, the subject may only be rescreened once the new amended protocol has been approved by the IRB.

Rescreened subjects will sign a new informed consent form and a new subject number will be allocated. All screening assessments need to be repeated for the rescreened subject.

Each investigator will maintain a record of all subjects screened (i.e. who signed the informed consent form) and enrolled (i.e. who was given a randomisation number) into the study. 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 Procedures During Double-Blind Period – Treatment Cycle 1 (Stage 1 + Stage 2)

5.2.2.1 Baseline Visit (Day 1)

The following procedures will be performed prior to the administration of study treatment:

- Eligibility check (inclusion/exclusion criteria)
- PGI-S (to be recorded 1 week prior to the visit and at the visit)
- mFSFI (pain to be recorded 1 week prior to the visit and at the visit; other domains to be recorded only at the visit)
- Relationship/partner status (to be recorded weekly from 2 weeks prior to the visit and at the visit)
- mVPAQ (pain and life interference to be recorded 1 week prior to the visit and at the visit; other subscales to be recorded only at the visit)
- PHQ-9
- SF-36
- Intercourse details (to be recorded daily from 2 weeks prior to the visit)
- Dilator size 6 insertion details (to be recorded weekly from 2 weeks preceding the visit; assessment on the day of the visit should be avoided)
- Dilator test
- Measurement of pelvic floor muscle pressure (in all subjects in Stage 1 up to 400 U and in a subset of subjects in Stage 2 (i.e. in subjects who have never had a vaginal delivery (including attempted vaginal delivery), and at study sites that were provided a perineometer))
- Review of AEs
- New or changed concomitant medications/nondrug therapies
- Randomisation.

Once these procedures have been performed, the study treatment will be injected as described in Section 6.2.2.

Following injection, subjects will be observed at the study centre for at least 30 minutes.

5.2.2.2 Week 2 – Telephone Contact (Day 15 ±3 days)

The following procedures will be performed at this telephonic contact:

- Review of AEs
- New or changed concomitant medications/nondrug therapies.

5.2.2.3 Week 6 Visit (Day 43 ±5 days)

The following procedures will be performed:

- PGI-S (to be recorded 1 week prior to the visit and at the visit)*
- PGI-C (to be recorded 1 week prior to the visit and at the visit)*

- mFSFI (pain to be recorded 1 week prior to the visit and at the visit; other domains to be recorded only at the visit)*
- Relationship/partner status (to be recorded weekly from 2 weeks prior to the visit and at the visit)*
- mVPAQ (pain and life interference to be recorded 1 week prior to the visit and at the visit; other subscales to be recorded only at the visit)*
- Intercourse details (to be recorded daily from 2 weeks prior to the visit)*
- Dilator size 6 insertion details (to be recorded weekly from 2 weeks preceding the visit; assessment on the day of the visit should be avoided)*
- Urine test for illicit drugs
- Dilator test
- Measurement of pelvic floor muscle pressure (in all subjects in Stage 1 up to 400 U and in a subset of subjects in Stage 2 (i.e. in subjects who have never had a vaginal delivery (included attempted vaginal delivery), and at study sites that were provided a perineometer to assess pelvic floor muscle pressure))
- CGI
- Review of AEs*
- New or changed concomitant medications/nondrug therapies*
- Subject interviews (every effort should be made to conduct the interview within 2 weeks of the subject's Cycle 1-Week 6 visit in Stage 2).

5.2.2.4 Week 12 Visit (Day 85 +14 days)

The following procedures will be performed:

- mFSFI (pain to be recorded 1 week prior to the visit and at the visit; other domains to be recorded only at the visit)*
- Relationship/partner status (to be recorded weekly from 2 weeks prior to the visit and at the visit)*
- mVPAQ (pain and life interference to be recorded 1 week prior to the visit and at the visit: other subscales to be recorded only at the visit)*
- PHQ-9*
- SF-36*
- PGI-S (to be recorded 1 week prior to the visit and at the visit)*
- PGI-C (to be recorded 1 week prior to the visit and at the visit)*
- Intercourse details (to be recorded daily from 2 weeks prior to the visit)*
- Dilator size 6 insertion details (to be recorded weekly from 2 weeks preceding the visit; assessment on the day of the visit should be avoided)*
- Blood sampling (nonfasting) for haematology and biochemistry**
- Dilator test
- Measurement of pelvic floor muscle pressure (in all subjects in Stage 1 up to 400 U and in a subject of subjects in Stage 2 (i.e. in subjects who have never had a vaginal delivery (included attempted vaginal delivery), and at study sites that were provided a perineometer to assess pelvic floor muscle pressure))
- CGI

- Review of AEs*
- New or changed concomitant medications/nondrug therapies*.

**In the event of a remote visit being required, blood sampling should be performed as soon as onsite visit resume and prior to the Week 18 Visit (as much as possible) and recorded as an unscheduled visit.

Once these procedures have been performed, the need for retreatment will be assessed as described in Section 3.7.3:

- Subjects eligible for retreatment will complete the remaining End of Cycle 1 assessments and enter the treatment cycle 2 (open-label, see Section 5.2.3.1) on the same day or once the DRC has confirmed the dose of the next cohort;
- Subjects not eligible for retreatment will perform an Additional Visit 6 weeks later (see Section 5.2.2.5).

In the event of a remote visit being required, subjects should not receive re-treatment with Dysport until onsite visits resume.

5.2.2.5 Weeks 18, 24, 30 and/or 36 – Additional Visits (Day 127, 169, 211 and/or 253 ±14 days)

The following procedures will be performed:

- PGI-S (to be recorded 1 week prior to the visit and at the visit)*
- PGI-C (to be recorded 1 week prior to the visit and at the visit)*
- mFSFI (pain to be recorded 1 week prior to the visit and at the visit; other domains to be recorded only at the visit)*
- Relationship/partner status (to be recorded weekly from 2 weeks prior to the visit and at the visit)*
- mVPAQ pain and life interference subscales (to be recorded 1 week prior to the visit and at the visit)*
- mVPAQ other subscales (at Week 24 and Week 36 only)*
- PHQ-9 (at Week 36 only)*
- SF-36 (at Week 36 only)*
- Intercourse details (to be recorded daily from 2 weeks prior to the visit)*
- Dilator size 6 insertion details (to be recorded weekly from 2 weeks preceding the visit; assessment on the day of the visit should be avoided)*
- Dilator test
- Measurement of pelvic floor muscle pressure (in all subjects in Stage 1 up to 400 U and in a subset of subjects in Stage 2 (i.e. in subjects who have never had a vaginal delivery (included attempted vaginal delivery), and at study sites that were provided a perineometer to assess pelvic floor muscle pressure))
- CGI
- Review of AEs*
- New or changed concomitant medications/nondrug therapies*.

Once these procedures have been performed, the need for retreatment will be assessed as described in Section 3.7.3:

- Subjects eligible for retreatment will complete the remaining End of Cycle 1 assessments and enter the treatment cycle 2 (open-label, see Section 5.2.3.1) on the same day or once the DRC has confirmed the dose of the next cohort;
- Subjects not eligible for retreatment will perform an Additional Visit, every 6 weeks until they are eligible for retreatment or until they reach Week 36 visit. If eligible for retreatment at Week 36, subjects will perform the same assessments as described above for retreatment. If not eligible for retreatment at Week 36, subjects will perform the EOS Visit on the same day and complete the remaining EOS evaluations (see Section 5.2.4).

In the event of a remote visit being required, subjects should not receive re-treatment with Dysport until onsite visits resume.

5.2.3 Procedures During Open-Label Period – Treatment Cycles 2 to 4 (Stage 1 + Stage 2)

5.2.3.1 Day 1 Visit (Treatment Visit)

The following procedures will be performed prior to the administration of study treatment:

- Urine pregnancy test
- Urine test for illicit drugs
- Review of AEs (only if the visit is not on the same day as the last visit of the previous cycle)
- New or changed concomitant medications/nondrug therapies (only if Day 1 is not on the same day as the last visit of the previous cycle).

If the visit occurs more than 2 weeks after the last visit of the previous treatment cycle, the following procedures will be done:

- PGI-S (to be recorded 1 week prior to the visit and at the visit)
- PGI-C (to be recorded 1 week prior to the visit and at the visit)
- Relationship/partner status (to be recorded weekly from 2 weeks prior to the visit and at the visit)
- Intercourse details (to be recorded daily from 2 weeks prior to the visit)
- Dilator size 6 insertion details (to be recorded weekly from 2 weeks preceding the visit; assessment on the day of the visit should be avoided)
- Dilator test
- CGI.

Once these procedures have been performed, the study treatment will be injected as described in Section 6.2.2.

Following injection, subjects will be observed at the study centre for at least 30 minutes.

5.2.3.2 Week 2 – Telephone Contact (Day 15 ±3 days)

The following procedures will be performed at this telephonic contact:

- Review of AEs
- New or changed concomitant medications/nondrug therapies.

5.2.3.3 Week 6 Visit (Day 43 ±5 days)

The following procedures will be performed:

- PGI-S (to be recorded 1 week prior to the visit and at the visit)*

- PGI-C (to be recorded 1 week prior to the visit and at the visit)*
- Relationship/partner status (to be recorded weekly from 2 weeks prior to the visit and at the visit)*
- Intercourse details (to be recorded daily from 2 weeks prior to the visit)*
- Dilator size 6 insertion details (to be recorded weekly from 2 weeks preceding the visit; assessment on the day of the visit should be avoided)*
- Urine test for illicit drugs
- Dilator test
- CGI
- Review of AEs*
- New or changed concomitant medications/nondrug therapies*.

5.2.3.4 Week 12 Visit (Day 85 ±14 days)

The following procedures will be performed:

- PGI-S (to be recorded 1 week prior to the visit and at the visit)*
- PGI-C (to be recorded 1 week prior to the visit and at the visit)*
- Relationship/partner status (to be recorded weekly from 2 weeks prior to the visit and at the visit)*
- Intercourse details (to be recorded daily from 2 weeks prior to the visit)*
- Dilator size 6 insertion details (to be recorded weekly from 2 weeks preceding the visit; assessment on the day of the visit should be avoided)*
- Dilator test
- CGI
- Review of AEs*
- New or changed concomitant medications/nondrug therapies*.

Once these procedures have been performed:

- If this visit occurs >36 weeks from Cycle 1 Day 1, subjects will perform the EOS Visit on the same day and complete the remaining EOS evaluations (see Section 5.2.4).
- If this visit occurs ≤36 weeks from Cycle 1 Day 1, the need for retreatment will be assessed as described in Section 3.7.3:
  - Subjects eligible for retreatment will enter the next open-label treatment cycle (open-label, see Section 5.2.3.1) on the same day or once the DRC has confirmed the dose of the next cohort;
  - Subjects not eligible for retreatment will perform an Additional Visit 6 weeks later (see Section 5.2.3.5).

In the event of a remote visit being required, subjects should not receive re-treatment with Dysport until onsite visits resume.

5.2.3.5 Weeks 18 and/or 24 – Additional Visits (Day 127 or 169 ±14 days)

The following procedures will be performed:

- PGI-S (to be recorded 1 week prior to the visit and at the visit)*
- PGI-C (to be recorded 1 week prior to the visit and at the visit)*

- Relationship/partner status (to be recorded weekly from 2 weeks prior to the visit and at the visit)*
- Intercourse details (to be recorded daily from 2 weeks prior to the visit)*
- Dilator size 6 insertion details (to be recorded weekly from 2 weeks preceding the visit; assessment on the day of the visit should be avoided)*
- Dilator test
- CGI
- Review of AEs*
- New or changed concomitant medications/nondrug therapies*.

Once these procedures have been performed:

- If this visit occurs >36 weeks from Cycle 1 Day 1, subjects will perform the EOS Visit on the same day and complete the remaining EOS evaluations (see Section 5.2.4).
- If this visit occurs ≤36 weeks from Cycle 1 Day 1, the need for reinjection will be assessed as described in Section 3.7.3:
  - Subjects eligible for retreatment will enter the next open-label treatment cycle (open-label, see Section 5.2.3.1) on the same day or once the DRC has confirmed the dose of the next cohort;
  - Subjects not eligible for retreatment will perform a new Additional Visit, every 6 weeks until they are eligible for retreatment (see Section 5.2.3.1), or until they reach Week 36 visit. If not eligible for retreatment at Week 36, subjects will perform the EOS Visit on the same day and complete the remaining EOS evaluations (see Section 5.2.4).

In the event of a remote visit being required, subjects should not receive re-treatment with Dysport until onsite visits resume.

5.2.4 End of Study Visit or Early Withdrawal Visit

The procedures to be carried out at the EOS Visit or EWD Visit are identical.

The following procedures will be performed at the EOS, or EWD visit (the procedures already performed on the same day at the previous study visit do not need to be repeated):

- mFSFI (pain to be recorded 1 week prior to the visit and at the visit; other domains to be recorded only at the visit; only if the EOS/EWD visit occurs during the double-blind period)
- mVPAQ (pain and life interference to be recorded 1 week prior to the visit and at the visit; other subscales to be recorded only at the visit; only if the EOS/EWD visit occurs during the double-blind period)
- PHQ-9 only if the EOS/EWD visit occurs during the double-blind period
- SF-36 (only if the EOS/EWD visit occurs during the double-blind period)
- PGI-S (to be recorded 1 week prior to the visit and at the visit)
- PGI-C (to be recorded 1 week prior to the visit and at the visit)
- Relationship/partner status (to be recorded weekly from 2 weeks prior to the visit and at the visit)
- Intercourse details (to be recorded daily from 2 weeks prior to the visit)
- Dilator size 6 insertion details (to be recorded weekly from 2 weeks preceding the visit; assessment on the day of the visit should be avoided)

- Urine pregnancy test
- Urine test for illicit drugs
- Blood sampling (nonfasting) for haematology, biochemistry and putative antibodies
- Dilator test
- CGI
- Review of AEs
- New or changed concomitant medications/nondrug therapies.

If the COVID-19 pandemic prevents subjects from coming to the site, EOS visits should be postponed until onsite visits resume.

Subjects who attend the EOS Visit will be considered to have completed the study.

Subjects with ongoing AEs or clinically significant laboratory test abnormalities (as determined by the investigator) will be monitored as described in Section 8.1.5 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.

The IMP Dysport and the matching placebo should be stored at the recommended temperature (between 2°C and 8°C).

The IMP Dysport and the matching placebo must not be frozen and should be protected from light.

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 according to the procedure detailed in the study IMP instructions.

6.1.3 Investigational Medicinal Product Accountability

All IMP is to be accounted for on the IMP accountability log agreed with the sponsor.

Any reconstituted unused IMP has to be discarded in accordance with local regulations (e.g. inactivation with sodium hypochlorite or autoclave, etc.). All disposal ancillary materials (e.g. needles and syringes) must be discarded in suitable containers intended for incineration after use at the site. Used/partly used and unused supplies must be retained for verification and accountability by the sponsor or sponsor's representative prior to destruction. If used/partly used vials must be destroyed after use at the site as per local regulations, labelled empty boxes must be retained for verification and accountability. Supplies will be destroyed preferably at the site; if not, returned to the interim storage facility for destruction.

6.2 Study Drugs Administered

6.2.1 Treatments Administered

6.2.1.1 Dysport

Dysport will be provided in glass vials containing 300 U or 500 U (nominal) of BTX-A-HAC as white lyophilised powder for reconstitution (Table 5).

Table 5 Composition of Dysport

Constituents	**Quantity**	
	Per 300 U Vial	**Per 500 U vial**
Active Substance		
Clostridium BTX-A-HAC	300 U*	500 U*
Excipients		
Human serum albumin	125 µg	125 µg
Lactose monohydrate	2.5 mg	2.5 mg

BTX-A-HAC=botulinum toxin-A-haemagglutinin complex, U=units
*One unit (U) is defined as the median lethal intraperitoneal dose in mice.

The product does not contain any antimicrobial agent.

6.2.1.2 Placebo

Placebo will be provided in glass vials and will be undistinguishable from the active product. The placebo will contain only the excipients described in Dysport, without the addition of toxin, as a white lyophilised powder for reconstitution. There will be two matching placebo vials: one matching the 300 U Dysport vial, and one matching the 500 U Dysport vial (Table 6). The constituents in both placebo vials are identical:

Table 6 Composition of Matching Placebo

Constituents	Quantity	
	Placebo 300 (Per Vial)	Placebo 500 (Per Vial)
Human serum albumin	125 µg	125 µg
Lactose monohydrate	2.5 mg	2.5 mg

The placebo product does not contain any antimicrobial agent.

6.2.2 Reconstitution and Administration Procedure

The study treatment will be reconstituted at the investigational site with preservative free 0.9% sodium chloride for injection.

The study treatment will be prepared by the investigator/pharmacist/designated personnel according to the instruction leaflet allocated for that treatment. Study treatment kits will be designed to maintain the blind and the person reconstituting the treatment (investigator/pharmacist/delegated personnel) as well as the subject will remain blinded to the treatment during the double-blind period.

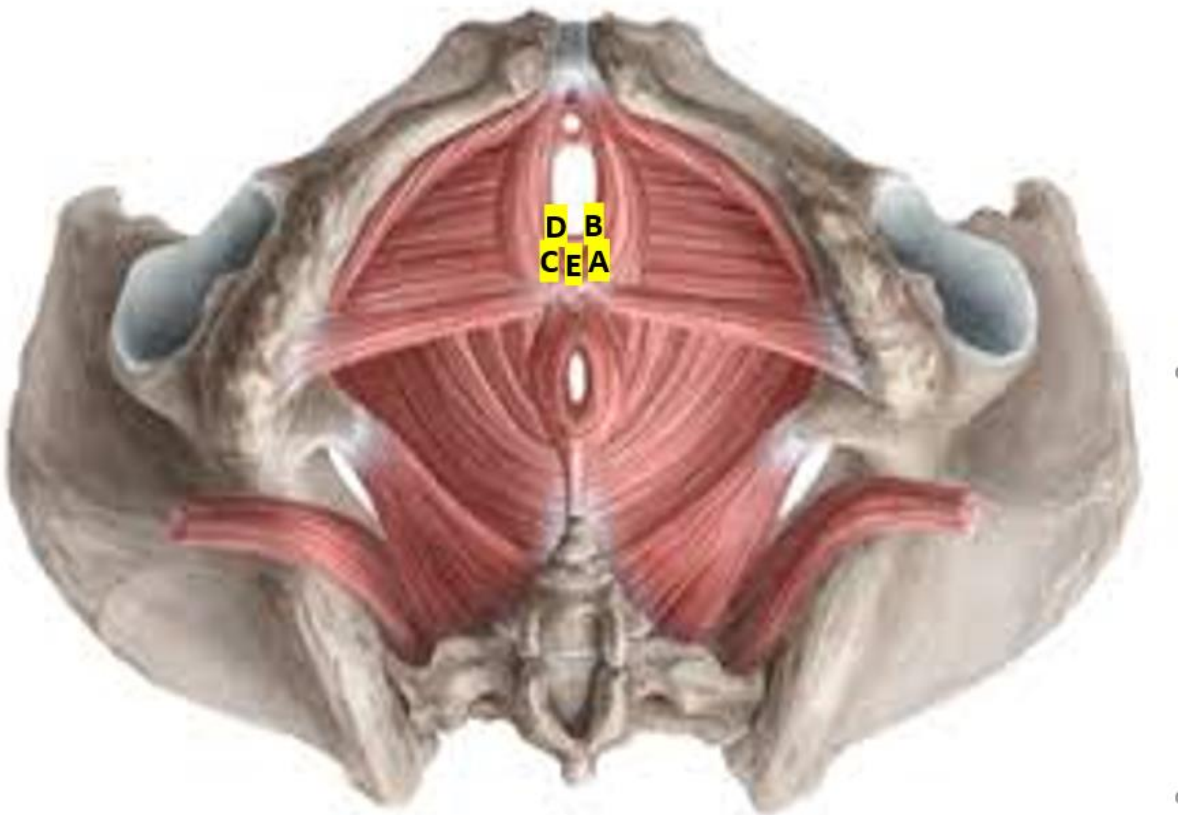
The process of reconstitution will vary based on the period of the study (double-blind or open-label) and the dose to be injected. Detailed instructions on reconstitution will be provided in the instruction leaflet.

A total of 2.5 mL of the reconstituted study treatment will be administered intramuscularly at five predefined needle insertion points (A, B, C, D, E) at 10 injection sites (5 mm (superficial) and 10 mm (deep) depths at each needle insertion point) across four pelvic floor muscles (pubococcygeus, bulbospongiosus, superficial transverse perineal muscle and deep transverse perineal muscle) in the vestibular region as described below; the injection diagram is included in Figure 3. Regardless of the study period or the treatment group to which the subject is allocated, the volume of 2.5 mL will be constant across all dose groups.

- **Insertion point - 5 o'clock anterior to hymeneal ring (0.4 mL): #A**
  - 5 mm depth: 0.2 mL → left bulbospongiosus
  - 10 mm depth: 0.2 mL → left pubococcygeus
- **Insertion point - 5 o'clock posterior to hymeneal ring (0.4 mL): #B**
  - 5 mm depth: 0.2 mL → left bulbospongiosus
  - 10 mm depth: 0.2 mL → left pubococcygeus
- **Insertion point - 7 o'clock anterior to hymeneal ring (0.4 mL): #C**
  - 5 mm depth: 0.2 mL → right bulbospongiosus
  - 10 mm depth: 0.2 mL → right pubococcygeus
- **Insertion point - 7 o'clock posterior to hymeneal ring (0.4 mL): #D**
  - 5 mm depth: 0.2 mL → right bulbospongiosus
  - 10 mm depth: 0.2 mL → right pubococcygeus
- **Insertion point - 6 o'clock perineal body (0.9 mL): #E**
  - 5 mm depth: 0.45 mL → medial aspect of right/left superficial and deep transverse perineal
  - 10 mm depth: 0.45 mL → medial aspect of right/left superficial and deep transverse perineal

Further details on the injection procedures are described in the 'Study Treatment Administration - Training Manual' (included in the Study Manual). Training on injection procedures will be provided to each investigator performing IMP administration.

Figure 3 Study Treatment – Sites of Administration



6.3 Concomitant Medication/Therapy

Any prior or concomitant medications and therapy given to a subject before screening (as described in the screening procedures in Section 5.2.1) or during the study will be indicated on the eCRF.

The following concomitant medications/therapies are not permitted during this study (see also Section 4.2):

- Sex therapy (defined as a therapy primarily focused on the management of vulvar pain) up to 6 weeks after the first treatment cycle of the double-blind period. Any sex therapy initiated after this, needs to be maintained at the same frequency/regimen throughout the study.
- Any form of BTX for administration into any other part/site of the body.
- Any experimental new drug or device.
- Illicit drugs.
- The following medications that affect neuromuscular transmission: curare-like nondepolarising agents, lincosamides, polymyxins, anticholinesterases, aminoglycoside antibiotics (topical use is permitted except at the vulvar vestibular region), tizanidine and baclofen, within the past 4 weeks prior to Baseline and during the study.
- Injections of steroids in the vulva should have been stopped 4 weeks prior to the Screening Visit and are not allowed during the study.
- Topical lidocaine, topical antidepressants, topical anti-epileptics and diazepam suppositories are not permitted during the study. Note: Immediately prior to and during study drug administration procedures, oral, topical (including lidocaine) or intravenous/injectable medications routinely used as standard of care for vaginal intramuscular injections are allowed.
- Medications that affect bleeding disorders (antiplatelet agents and/or anticoagulants) that might interfere with local injections or medications that contraindicate intramuscular injection.

The following concomitant medications/therapies are permitted during this study, but they must be monitored closely and, where applicable, their dose and dose regimen should remain constant as detailed below:

- Concomitant pelvic floor physical therapy is permitted. Subjects should maintain the dose regimen constant from 12 weeks prior to Baseline and throughout the first treatment cycle.
- Concomitant use of topical treatments for vestibular pain with topical hormonal creams are permitted if the subject has no residual anterior vestibule pain at screening and wants to continue on the same treatment regimen throughout the study to prevent recurrence of anterior vestibular pain. Note: Topical antidepressants are not permitted.
- Concomitant use of oral antidepressants, anxiolytics or anti-epileptics is permitted as long as the dose has remained stable for at least 6 months prior to the Screening Visit. Subjects should try to maintain the dose regimen constant throughout the first treatment cycle.
- Concomitant use of anticholinergic drugs (which may potentiate systemic anticholinergic effects) is permitted if the dosage has been stable for the 6 weeks prior to Baseline and is expected to remain at this stable dose throughout the study.

- If concomitantly taking other analgesics, the subjects should make their best effort to stop them at the Screening Visit. If stopping of analgesic intake is not possible or indicated, then the intake needs to be maintained at a constant dose throughout 1st treatment cycle and all details need to be captured in the eCRF.
- Pain rescue medication taken to prevent or treat provoked vestibular pain should be avoided. If needed, the subject will be allowed to take Nonsteroidal Anti-inflammatory Drugs (NSAIDS) or Acetaminophen at the recommended dose as per need (PRN). The subject should attempt to use the same pain rescue medication throughout the study. Subjects will record the dosage and count (number of pills taken) in the eDiary for the analgesic taken prior or after intercourse to prevent or treat vestibular pain (Section 7.4.2.5). However, the subject should refrain from taking any rescue medication within 24 hours of a study visit.

During Stage 2, if required, the subject will be permitted to take from the following pain rescue medications listed in Table 7 at regular strength per approved labelling (recommended dose); these medications (i.e. Aspirin, Acetaminophen, Naproxen or Ibuprofen) are available over the counter (OTC).

Table 7 Permitted Pain Rescue Medications during Stage 2

Rescue Medication	Dose per Pill	Permitted Frequency	Maximum Allowed Total Daily Dose
Acetaminophen (regular strength)	325 mg*	2 pills every 4-6 hours only while the symptoms last	4000 mg
Aspirin (regular strength)	325 mg	1-2 pills every 4 hours or 3 pills every 6 hours only while symptoms last	4000 mg
Ibuprofen	200 mg	1 pill every 4-6 hours only while symptoms last	1200 mg
Naproxen	220 mg	1 pill every 8-12 hours only while symptoms last	660 mg

mg=milligram.

*medication may also be available at 500 mg strength in some regions.

- Concomitant medications for other purposes are allowed at the investigator's discretion. It is recommended that the dosage for these medications is kept constant throughout the study. Where medically appropriate, all concomitant medications being taken by a subject at entry into the study should continue at the same dose.

6.4 Lifestyle Restrictions/Recommendations

Subjects will be requested to comply with the restriction criteria related to alcohol consumption and drugs of abuse, presented as exclusion criteria in Section 4.2.

Subjects will be instructed to avoid vulvar irritants such as perfumes, deodorants, or soaps and will be encouraged to avoid modifying hygiene habits during the study. The subject should be instructed to wear only cotton underwear.

6.5 Procedures for Monitoring Subject Compliance

The investigator will be responsible for monitoring subject compliance. Subjects can be withdrawn from the study at any time if the investigator or the sponsor determines that the subject is not in compliance with the study protocol.

Study Drug will be administered at the clinic by the investigator, thus, subject compliance with treatment is not expected to be an issue. Drug accountability records will be maintained by the investigator documenting that subject received allocated drug.

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) The subject needs to complete the questionnaires at the site (PCS, mFSFI, PHQ-9, mVPAQ, SF-36) and subsequently complete the PGI-S and PGI-C assessments prior to seeing the investigator.

(2) Interview and clinical examination by the investigator.

(3) When doing the clinical examination, the investigator needs to conduct the dilator test prior to the measurement of pelvic floor muscles pressure.

(4) For visits, other than the screening, CGI should be assessed by the investigator after all other clinical assessments have been performed.

7 ASSESSMENT OF EFFICACY

For the timing of assessments in this study, refer to the schedule for the double-blind treatment period in Table 2 and for the open-label treatment period in Table 8.

7.1 Primary Endpoint(s) and Evaluation(s)

For Stage 1, the primary endpoint is safety between baseline and Cycle 1-Week 6.

For Stage 2, the primary efficacy endpoint is the mean change from Baseline to Cycle 1-Week 6 in the vaginal dilator induced pain as reported on an 11-point numeric rating scale (NRS) (using the dilator maximum tested size (DMTS) reported at Baseline).

7.2 Secondary Efficacy Endpoints and Evaluations

Refer to Section 3.2.2 for secondary efficacy endpoints.

Secondary efficacy endpoints and evaluations are summarised in Table 8.

Table 8 Secondary Efficacy Endpoints and Evaluations

Measure	Timepoint	Variable	Endpoint
Vestibular pain using a vaginal dilator	Screening, Baseline, Week 6, Week 12 and then every 6 weeks until EOS - All TCs	11-point NRS score for each dilator size that is tolerated by the subject	Mean change from Baseline in the vaginal dilator induced pain (using the DMTS reported at baseline)
			Proportion of subjects who reported at least 30% decrease from Baseline in the vaginal dilator induced pain using DMTS at Baseline
			Proportion of subjects who reported at least 2-point decrease from Baseline in the vaginal dilator induced pain using DMTS at Baseline
			Proportion of subjects who reported at least 50% decrease in vaginal dilator induced pain using the DMTS at Baseline
Maximum tested dilator size	Screening, Baseline, Week 6, Week 12 and then every 6 weeks until EOS - All TCs	Dilator size	Mean change from Baseline in the dilator size that provokes maximum tolerated pain
Composite of vestibular pain induced by the dilator and the tolerability of the dilator size	Screening, Baseline, Week 6, Week 12 and then every 6 weeks until EOS - All TCs	Composite score of 11-point NRS score and dilator size	Mean change from Baseline in the composite score for vaginal dilator induced pain and dilator size. The composite score is the sum of all pain measurements across the full range of dilator sizes. In the construction of this endpoint, the pain score will be 10 for any dilator size that is not tested because it is beyond tolerability.
Frequency of intercourse and pain during intercourse [a]	Screening, Baseline, Week 6, Week 12 and then every 6 weeks until EOS - All TCs	11-point NRS score	Mean change from Baseline in the frequency of intercourse and pain during intercourse

Measure	Timepoint	Variable	Endpoint
Pain during insertion of vaginal dilator number 6 size [b]	Screening, Baseline, Week 6, Week 12 and then every 6 weeks until EOS - All TCs	11-point NRS score	Mean change from Baseline in pain during insertion
			Proportion of subjects having reported at least a 30% decrease in pain during insertion on the mean of the NRS values
			Proportion of subjects having reported at least a 50% decrease in pain during insertion on the mean of the NRS values
			Proportion of subjects having reported at least 2-point decrease in on the mean of the NRS values.
Use of pain rescue medications [a]	Throughout the study	Type, dose, number of pills taken and frequency of pain rescue medications	Use of pain rescue medication

DB=double-blind, DTMS=dilator tested maximum size, EOS=end of study, EWD=early withdrawal, NRS=numeric rating scale, TCs=treatment cycles.

a At the Screening Visit and then from 2 weeks prior to the next planned visit, subjects need to record daily if they had intercourse, the number of intercourse instances, corresponding pain during each intercourse instance on an 11-point NRS and details of pain rescue medication if taken to prevent or treat vestibular pain.

b From 2 weeks prior to the next planned visit, subjects need to rate weekly the level of the corresponding pain following insertion of vaginal dilator (number 6 size) on an 11-point NRS and details of associated pain medication if consumed. Assessment on the day of the visit should be avoided.

7.3 Exploratory Efficacy Endpoints and Evaluations

Refer to Section 3.3 for exploratory efficacy endpoints.

Exploratory efficacy endpoints and evaluations are summarised in Table 9.

Table 9 Exploratory Efficacy Endpoints and Evaluations

Measure	Timepoint	Variable	Endpoint
Vulvar pain and associated measures effecting life [a]	Screening, Baseline, Week 6, Week 12, and then every 6 weeks until End of TC 1 (DB period only)	mVPAQ pain and life interference subscales	Mean change from Baseline in pain and life interference subscales
	Screening, Baseline, Week 6, Week 12, Week 24, End of TC 1 (DB period only)	mVPAQ other subscale scores	Mean change from Baseline in sexual function interference, self-stimulation/ penetration interference, emotional response and cognitive response scores
Sexual function [b]	Screening, Baseline, Week 6, Week 12 and then every 6 weeks until End of TC 1 (DB period only)	mFSFI total score	Mean change from Baseline in mFSFI total score
	Screening, Baseline, Week 6, Week 12 and then every 6 weeks until End of TC 1 (DB period only)	mFSFI pain domain score	Mean change from Baseline in pain domain score
	Screening, Baseline, Week 6, Week 12 and then every 6 weeks until End of TC 1 (DB period only)	mFSFI other domain scores	Mean change from Baseline in mFSFI other domain scores
Pelvic floor muscle pressure	Baseline, Week 6, Week 12 and then every 6 weeks until End of TC 1 (DB period only)	Resting vaginal pressure	Mean change from Baseline in resting vaginal pressure of the pelvic floor muscle [c]
Pelvic floor muscle pressure	Baseline, Week 6, Week 12 and then every 6 weeks until End of TC 1 (DB period only)	Maximal squeeze pressure	Mean change from Baseline in the maximal squeeze pressure of the pelvic floor muscle [c]
Depression	Baseline, Week 12, End of TC 1 (DB period only)	PHQ-9 total score	Mean change from Baseline in the PHQ-9 total score
Quality of life	Baseline, Week 12, End of TC 1 (DB period only)	SF-36 total domain scores	Mean change from Baseline in SF-36 scores
Global impression of the treatment effect as measured by the investigator	Week 6, Week 12 and then every 6 weeks until EOS – All TCs	CGI score	Mean score
Patient Global impression of the severity of pain and change in pain as measured by the subject [d]	Screening, Baseline, Week 6, Week 12 and then every 6 weeks until EOS – All TCs	PGI-S score	Mean change from Baseline
	Week 6, Week 12 and then every 6 weeks until EOS – All TCs	PGI-C score	Mean score

CGI=clinical global impression; DB=double-blind, EOS=end of study, EWD=early withdrawal, mFSFI=modified female sexual function index, mVPAQ=modified vulvar pain assessment questionnaire, PGI=patient global impression; PHQ-9=patient health questionnaire, SF-36=36-item short form survey, TCs=treatment cycles.

a Subjects to complete the mVPAQ pain and life interference subscales at the Screening Visit, then 1 week prior to the next planned visit and at the visit; other mVPAQ subscales to be completed only at the visit.

b Subjects to complete the mFSFI pain domain at the Screening Visit, then 1 week prior to the next planned visit and at the visit; other mFSFI domains to be completed only at the visit.

c To be performed in all subjects in Stage 1 up to 400 U and in a subset of subjects in Stage 2 (i.e. in subjects who have never had a vaginal delivery (including an attempted vaginal delivery), and at study sites that were provided a perineometer to assess pelvic floor muscle pressure).

d To be assessed at Screening Visit, then 1 week prior to the next planned visit and at the visit. PGI-C will be assessed Week 6 onwards only.

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

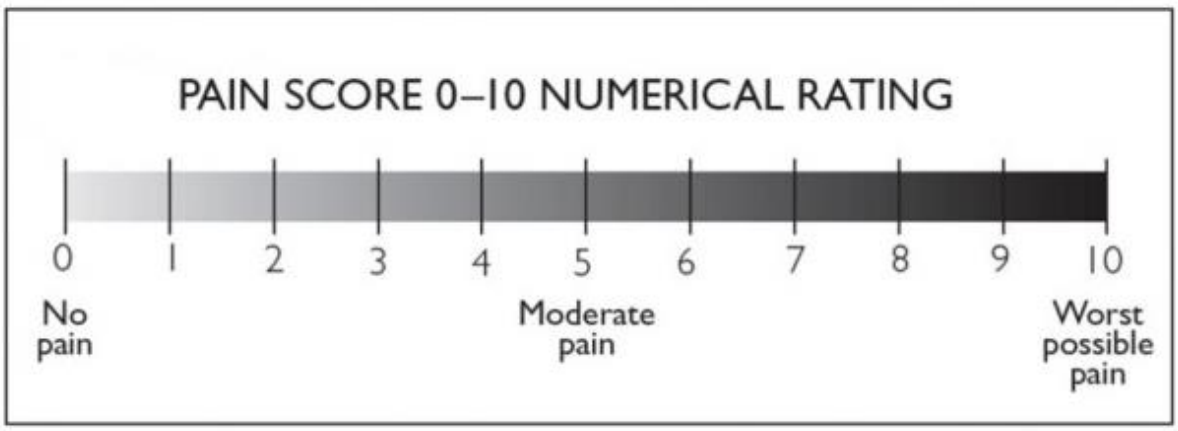
Methods for assessing efficacy data are described below. Timing of efficacy assessments are presented in Table 2 and Table 3, and discussed in Section 5.2. Procedures for recording efficacy data are discussed in Section 15.1, and methods of analyses are discussed in Section 11.4.3. The priority order for performing the assessments is discussed in Section 6.6. All efforts should be made to have the same investigator perform the clinical examinations for a given subject, at least for the Screening, Baseline, and Week 6 Visits of the first treatment cycle.

The Sponsor will provide a device to complete the e-diary questionnaires in the study 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 study.

7.4.1 Dilator Test (Vaginal Dilator Induced Pain)

A set of 8 vaginal dilators of increasing diameter (#1 being the smallest and #8 being the largest) will be used to provoke pain to allow assessment of the vestibular pain intensity in each subject. At each visit, the investigator will insert the dilator between 3 to 4 cm depth in the vagina starting with the smallest sized dilator and progressively increasing the size of the dilator. No lubricant, other than water, may be used when inserting the dilator. In order to standardise the methodology each dilator should be inserted for a period of 5 to 10 seconds and the time period between the insertion of two dilators should be 30 seconds to 1 minute. Subjects will be required to rate the pain for each dilator size on an 11-point NRS (Figure 4) at each visit. Based on the subjective pain threshold, the largest sized dilator that the subject accepts/tolerates for the test (i.e. does not agree to the next successive dilator size to be tested), will be defined as the Dilator Maximum Tested Size (DMTS) that will be established at Baseline Visit. The dilator test will be used to assess the change from Baseline in the vaginal dilator induced pain as reported on a NRS (using the DMTS reported at baseline) as well as the dilator size that provokes maximum tolerated pain.

Figure 4 Numeric Pain Rating Scale



Subject interviews to assess the content relevance of the dilator test will be performed in Stage 2. Subjects from Stage 2 will be invited to complete the interview until the target sample of 20 subjects is achieved. Every effort should be made to conduct the interview within 2 weeks of the subject's Cycle 1-Week 6 visit.

The subject interviews will be conducted by experienced interviewers trained in qualitative interview techniques. The details of the interview will be provided in the interview guide.

7.4.2 Patient Reported Questionnaires and Assessments

In order to ensure accurate and unbiased subject questionnaire completion, the following guidelines should be adhered to:

- The questionnaires should be completed by the subject (with the caregiver's assistance, if necessary), at the beginning of the site visit prior to having the interview with the investigator.
- Study site personnel should not change responses on the questionnaires.

An electronic Patient-Reported Outcome (ePRO) device will be used to complete the questionnaires (programmed in a predefined sequence) as well as to record data in the eDiary contributing towards completion of particular questionnaire subscales and efficacy endpoints. Timing of efficacy assessments are presented in Table 2 and Table 3.

7.4.2.1 Modified Vulvar Pain Assessment Questionnaire (mVPAQ)

The Vulvar Pain Assessment Questionnaire (VPAQ) is a more recently developed, self-administered, multidimensional, vulvodynia specific questionnaire, including 55 Likert-type questions and designed to capture 6 domains: pain severity, emotional response, cognitive response and interference with life, sexual function, self-stimulation/penetration [22]. The score for each question ranges from 0 to 4 and a mean score is computed for each domain.

For the purpose of the study, the VPAQ subscales will be modified as:

- mVPAQ pain subscale – The recall period will be over the past 1 week.
- mVPAQ life interference subscale – The recall period will be over the past 1 week.
- mVPAQ other subscales – The recall period will be over the past 1 month.
- The sequence of questions for reporting distress (average/ worst) on the pain severity subscale were reversed.

The mVPAQ questionnaire is included in Appendix 1.

The data to be recorded by subjects in the eDiary contributing towards the completion of the questionnaire:

- mVPAQ pain subscale – Assessed at Screening Visit, then 1 week prior to the next planned visit and at the visit.
- mVPAQ life interference subscale – Assessed at Screening Visit, then 1 week prior to the next planned visit and at the visit.
- mVPAQ other subscales – Assessed at the site during the visit (except Additional Visits at Week 18 and Week 30).

7.4.2.2 Assessment of Intercourse and Vaginal Dilator (Number 6 Size) Insertion Details

From the Screening Visit (Day -14; i.e. during the screening period), and then 2 weeks (14 days) prior to the next planned visit, subjects will record on a daily basis in the eDiary (contributing to collection of data for the corresponding endpoint):

- If they had intercourse and if yes, the number of intercourse instances in the previous 24-hour period;
- Rate the level of the corresponding pain during each intercourse instance on an 11-point NRS;

- Details of pain rescue medication consumed for each intercourse instance (yes/no; if yes - type, dose, frequency, route, duration) to prevent or treat the vestibular pain.

From 2 weeks prior to the next planned visit, all subjects are to rate in the eDiary once a week the level of the corresponding pain following insertion of the number 6 vaginal dilator into the vagina on an 11-point NRS and record details of associated pain medication if consumed. Assessment on the day of the visit should be avoided.

7.4.2.3 Modified Female Sexual Function Index (mFSFI)

The FSFI is a validated self-reported multidimensional 19-item questionnaire for assessing the sexual function in women by evaluating six key domains of sexual function: desire, arousal, lubrication, orgasm, sexual satisfaction, and pain.

A total score and domain scores will be calculated. Every item is assessed with a score from 0 or 1 to 5, the total score being 2-36.

For the purpose of the study, the recall periods for FSFI pain domain (Questions 17 to 19) will be modified as:

- mFSFI pain domain – The recall period will be over the past 1 week.
- mFSFI other domains – The recall period will be over the past 4 weeks.

From Stage 2 onwards, Question 19 of the pain domain (measuring the level of pain 'during' and 'following' vaginal penetration with a 1-week recall period) will be split into two separate questions –

- Question 19 – measuring the level of discomfort or pain during vaginal penetration.
- Question 20 – measuring the level of discomfort or pain following vaginal penetration.

The mFSFI questionnaire is included in Appendix 2.

The data to be recorded by subjects in the eDiary contributing towards the completion of the questionnaire:

- mFSFI pain domain – Assessed at Screening Visit, then 1 week prior to the next planned visit and at the visit.
- mFSFI other domains – Assessed at the site during the visit.

7.4.2.4 Patient Global Impression (PGI)

7.4.2.4.1 Patient Global Impression of Severity (PGI-S) of the Provoked Vulvar Pain

An assessment of patient global impression of severity (PGI-S) of the 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 'provoked vulvar pain' (pain specifically triggered by touching the vulvar area) over the past week?

9 = not assessable due to lack of circumstances causing provoked pain

0 = no pain

1 = mild pain

2 = moderate pain

3 = severe pain."

7.4.2.4.2 Patient Global Impression of Change (PGI-C) in the Provoked Vulvar Pain

An assessment of global impression of change in 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-C will be assessed by the subject by answering the following question: "Compared to your provoked vulvar pain at Baseline i.e. prior to the study treatment initiation, your provoked vulvar pain 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."

7.4.2.5 Use of Pain Rescue Medications

As discussed in Section 7.4.2.2 subjects will record in the eDiary the details of pain medication taken to prevent or treat the pain during intercourse and/or dilator insertion.

The type, dose and frequency of pain rescue medication intake will be analysed.

7.4.2.6 Patient Health Questionnaire (PHQ-9)

The PHQ-9 is an easy-to-use, validated questionnaire to measure the severity of depression (Appendix 3). The response to treatment is scored for each of the nine DSM-IV (Diagnostic and Statistical Manual of Mental Disorders) criteria as "0" (not at all) to "3" (nearly every day) providing a total score being 0 to 27. Scores of 5, 10, 15, and 20 represent cut-off points for mild, moderate, moderately severe and severe depression, respectively.

7.4.2.7 36-Item Short Form Health Survey (SF-36)

The SF-36 is a validated set of generic, coherent, and easily administered QoL measures (Appendix 4). These measures rely upon patient self-reporting and are now widely utilised by managed care organisations and by for routine monitoring and assessment of care outcomes in adult patients.

The SF-36 has eight scaled scores; the scores are weighted sums of the questions in eight health concepts: physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions.

The total scores range from 0 to 100. Lower scores indicate a less favourable health state and higher scores a more favourable health state.

7.4.2.8 Pain Catastrophizing Scale (PCS)

The PCS is a widely used, validated 13-item scale assessing the state of mind of subjects in pain through a comprehensive evaluation that encompassing the different perspectives on catastrophizing (Appendix 5). It is a self-administered questionnaire in which the subjects answer questions about how they feel and what they think about when they are in pain. Each item rated on a 5-point scale: 0 (not at all) to 4 (all the time). A total score, ranging from 0 to 52 (sum of the 13 items) will be calculated.

7.4.3 Investigator-Reported Assessments

7.4.3.1 Q-tip

The Q-tip test, also known as the Cotton Swab test, is a widely used standard test to diagnose PVD, i.e. to assess the vestibular pain provoked by touch. A cotton swab/ cotton-tipped applicator will be used randomly to palpate all vulvar vestibular sites and the corresponding pain will be assessed [7, 25].

The Q-tip test will be performed to screen the subjects but will not be an assessment of the efficacy of the study drug.

7.4.3.2 Clinical Global Impression (CGI)

An assessment of global impression of treatment response will be conducted by the investigator using a 7-point Likert scale (from -3: very much worse to +3: very much improved).

The CGI will be assessed by the investigator by answering the following question: 'Compared to the subject's condition at Baseline i.e. prior to the study treatment initiation, your subject's condition 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."

7.4.3.3 Measurement of Pelvic Floor Muscle Pressure

The resting vaginal pressure and maximal 'squeeze' pressure will be measured using a CE marked medical device in all subjects in Stage 1 up to 400 U and in a subset of subjects in Stage 2 who have never had vaginal delivery (included attempted vaginal delivery), and at study sites that were provided a perineometer. Three measures of resting vaginal pressure and three measures of maximal 'squeeze' vaginal pressure should be performed. The time period between each measure performed for either the resting or maximal 'squeeze' vaginal pressure should be 30 seconds to 1 minute. Each squeeze while performing the maximal 'squeeze' vaginal pressure should last for 5 seconds.

Further instructions will be provided in the Study Manual.

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 the end of study. 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 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 GPS 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 3.8).

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 safety information for assessing expectedness of AEs/event in this study will be in the current 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 (e.g. electrocardiogram changes, thyroid function disturbances) 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 Clinically Significant Adverse Events and Dose Limiting Events

Definitions for identification of a clinically significant AE and a DLE for this study is provided in Section 3.1.1.1.

Details of DRC meetings and the management of dose escalation of the cohorts by the DRC are provided in Section 3.1.1.2

8.1.4 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 the pharmacology of BTX. 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 in this study are defined as:

- Any TEAE that suggest a possible remote spread of effect of the toxin or
- Any TEAE related to urinary incontinence or faecal incontinence or
- Any TEAE assessed as a potential hypersensitivity reaction,

where there is a reasonable possibility of causal relationship with treatment with Dysport, regardless of the investigator reported causality. A list of Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) that will be used to identify potential AESIs is provided in the statistical analysis plan (SAP). The list of PTs that is used by the sponsor to identify events suggestive of remote spread of toxin includes the terms compatible with the mechanism of action of BTX-A-HAC, is based on recommendations from the US Food and Drug Administration (US FDA) (Guidance for Industry: upper facial lines botulinum toxin products (Appendix A)) and the EU Committee for Medicinal Products for Human Use (CHMP) (Joint Assessment Report on definition of toxin spread). All AE PTs retrieved using this list of MedDRA PTs will be manually reviewed and medically evaluated by the sponsor

to determine to determine if there is a plausible possibility that they represent remote spread of toxin or suggestive of hypersensitivity reaction due to Dysport treatment. In order to perform the analysis, variables including alternate aetiology (medical history, concomitant medications, or diagnosis which could account for the symptoms), location of Dysport administration, and temporal relationship to IMP administration will be considered by the sponsor.

8.1.5 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/last dose/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.

8.1.6 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 fax number or email 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 investigator considers serious should be immediately reported to the sponsor and included in the corporate SAEs database system. This includes any suspected or confirmed coronavirus COVID-19 (SARS-CoV-2) infection (seriousness criteria should be “other medically significant” if no other seriousness criteria are present (e.g. hospitalisation)).

- 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 asked for and documented in the subject’s screening records. 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 fax number or 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
- Causality
- 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.

8.1.7 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 even if this occurs after the end of the study and the subject will not receive any further administration of the IMP.

Information regarding pregnancies must be collected on the AE page of the eCRF and on the Standard Pregnancy Report Form, including pregnancies with normal progress and outcome. A Standard Pregnancy Report Form must be completed by the investigator and provided to the Sponsor's Pharmacovigilance department within 24 hours of the knowledge of the pregnancy in any study subject. 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 participation or within 12 weeks after subject's last dose of IMP must also be reported to the investigator for onward reporting to the sponsor.

8.1.8 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."

8.1.9 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 8.1.6).

In all cases, the investigator must ensure the subject receives appropriate medical follow-up (see Section 8.1.5).

In case of suspected or confirmed COVID-19 infection which is to be reported as an SAE (Section 8.1.6), the IMP administration may be temporarily postponed depending on the subject clinical presentation. In some cases, the investigator may request a subject be retested before the IMP administration.

8.1.10 Reporting to Competent Authorities (CAs)/IECs/IRBs/Other Investigators

The sponsor will ensure that processes are in place for submission of reports of Suspected Unexpected Serious Adverse Reactions occurring during the study to the CAs, 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 samples will be collected for the evaluation of haematology, serum chemistry, FSH, and putative antibodies. Full details regarding the clinical tests are provided in the Study Manual.

A vaginal swab will be taken and analysed locally to detect possible infection.

Urine samples will be collected for the evaluation of illicit drugs and pregnancy and analysed at the study site.

The schedule of assessments is detailed in Section 5.1.

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).

All clinically relevant abnormal laboratory tests occurring during the study will be repeated at appropriate intervals until they return to Baseline or to a level deemed acceptable by the investigator and the sponsor's clinical monitor (or his/her designated representative) or until the abnormality is explained by an appropriate diagnosis.

8.2.1 Haematology

Blood samples will be collected in a potassium ethylenediaminetetra-acetic acid tube to assess the following parameters: 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, basophils, and others) 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, inorganic phosphate
- alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transferase
- albumin, total protein, total cholesterol, triglycerides
- glycated haemoglobin.

8.2.3 Pregnancy Test

A human chorionic gonadotrophin urine test will be performed. 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 8.1.7.

8.2.4 Drug of Abuse

Urine drug screen (dipstick) will be performed to detect the presence of at least amphetamines, methamphetamines, cocaine, opiates and tetrahydrocannabinol.

8.2.5 Putative Antibody Testing

Blood samples will be collected for the assay of putative antitoxin-A antibodies.

After processing of the blood samples at the site, the resulting serum will be sent to the central laboratory for storage. Batch shipping to specific laboratories in charge of the analysis will be arranged by the central laboratory at appropriate intervals.

All samples will be tested for the presence of binding antibodies with a validated assay. Samples found to be positive for the presence of binding antibodies will be analysed for the presence of neutralizing antibodies using another validated assay.

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

Tests results will be provided to the study site at the end of the study.

8.2.6 Vaginal Evaluation for Yeast and Bacterial Infection

Vaginal swabs will be performed to screen the subjects but will not be an assessment of the safety of the study drug.

Vaginal swabs will be performed and analysed for identification of pathogens (including Gardnerella vaginalis, Trichomonas vaginalis and Candida albicans).

Test results need to be available during the screening period or prior to randomisation.

8.3 Physical Examination

A physical examination will be done at Screening Visit.

Any 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 Local Tolerance

Local tolerance will be part of the routine treatment assessment.

Injection sites will be examined by a physician or medical staff at the visit, and assessed for characteristics such as tenderness, erythema, bleeding, swelling, rash, pain, itching, induration, haematoma, ulceration or necrosis. If present, these will be recorded on the AE page of the eCRF.

8.5 Vital Signs

Vital signs including blood pressure and heart rate will be recorded at the Screening Visit after five minutes' rest in a supine or sitting position.

Body weight and height will also be recorded at Screening.

Any clinically significant vital sign abnormalities observed during the study will be reported as AEs.

9 ASSESSMENTS OF PHARMACOKINETICS/PHARMACODYNAMICS

Pharmacokinetics and pharmacodynamics are not assessed in this study.

10 EXPLORATORY BIOMARKERS AND BIOBANKING

Exploratory biomarker evaluation or biobanking are not being performed in 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 database lock of the intermediate analysis (described in Section 11.6). The SAP may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint and/or its analysis will be reflected either in a protocol amendment or in a dedicated CSR section.

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

The COVID-19 pandemic may have an impact on this trial and specific summaries will be provided in order to assess its impact.

11.1 Analyses Populations

The following populations will be used during statistical analyses for Stage 1 and Stage 2:

- **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).
- **Safety population**: All randomised subjects who received at least one dose of IMP administration (including only partial administration).
- **modified Intent-to-Treat (mITT) population**: All randomised subjects who received at least one IMP administration and had data for the primary endpoint at Baseline and Cycle 1-Week 6 visit (i.e. at least one pain score for one dilator size).
- **Per protocol (PP) population**: All subjects in the mITT population for whom no major protocol deviations, which may interfere with the efficacy evaluation, occurred between Screening and Cycle 1-Week 6 included.

11.1.1 Populations Analysed

In Stage 1, the primary analysis based on safety endpoints will be performed on the Safety population. Analyses of efficacy endpoints will be carried out on the mITT population.

In Stage 2, the primary efficacy analysis based on efficacy endpoints will be performed on the mITT and PP population. Secondary analyses on efficacy endpoints will be carried on the mITT population.

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. Subjects substantially affected directly or indirectly by COVID-19 will be flagged with a major protocol deviation.

The final list of protocol deviations impacting the PP population will be reviewed prior to database lock, before unblinding of treatment groups for the intermediate and primary analysis (with the exception of DRC, which may/ may not request unblinding (see Section 3.1.1.2). The list may be updated, up to the point of database lock, to include any additional major protocol deviations impacting inclusion in the PP population.

11.2 Sample Size Determination

Stage 1:

In Stage 1, the expected sample size is 10 evaluable subjects for PVD2 cohorts who will be randomised and treated in a 4:1 allocation ratio (Dysport or Placebo), and 8 evaluable subjects for PVD1 Cohort 4 treated in a 3:1 allocation ratio (Dysport or Placebo).

After Cohort 3 (PVD2) and Cohort 4 (PVD1), the expected sample size is 10 evaluable subjects for additional PVD1 and PVD2 cohorts and treated in a 4:1 allocation ratio (Dysport or Placebo).

Subject who discontinue prior to Week 6 for reasons unrelated to safety may be replaced at the discretion of the investigator and sponsor. As this is an exploratory stage, no formal power could be performed. However, with 8 active subjects per PVD2 dose cohort and if there are 0 DLEs in a cohort, there is at least 80% probability that the true incidence of DLEs at the corresponding dose will not be greater than 18%. With 16 active subjects in PVD1 and PVD2 dose cohorts and if there are 0 DLEs in a cohort, there is at least 80% probability that the true incidence of DLEs at the corresponding dose will not be greater than 9%. The ability to rule out smaller DLE rates with high confidence will come from observing additional subjects in Stage 2.

Stage 2:

The study sample size required to have at least 80% power to detect a 2-point improvement for an experimental drug arm relative to placebo on mean change from baseline to Week 6 in the vaginal dilator induced pain as reported on a numeric pain rating scale (using the DMTS) using a one-sided 0.10 level test (not corrected for multiplicity) is 21 evaluable subjects per arm (i.e. a total of 63 subjects). The following assumptions were used for the power statement:

- Expected outcome on the mean change from baseline to Week 6 in the vaginal dilator induced pain as reported on a numeric pain rating scale in the placebo group = 2-point decrease (reference approximated by VAS per speculum in Bornstein, 2010 [26])
- Expected outcome on the mean change from baseline to Week 6 in the vaginal dilator induced pain as reported on a numeric pain rating scale in a Dysport treated group = 4-point decrease
- Expected common standard deviation of the mean change from baseline to Week 6 in the vaginal dilator induced pain as reported on a numeric pain rating scale = 3-points (approximated per VAS data in Table 2 in Davis 2013 [27]).

Subject who discontinue prior to Week 6 for reasons unrelated to safety will be replaced at the discretion of the investigator and sponsor.

At the end of Stage 2, if the true DLE rate is 6% or greater, there is at least 80% probability to observe at least 1 DLE in 29 subjects (8 in Stage 1 and 21 in Stage 2). Therefore, if there are no observed DLEs in both Stage 1 and Stage 2 at a dose level, then there is good confidence that the true DLE rate is no more than 6%. If the dose chosen in Stage 2 has been tested on two cohorts (PVD1 and PVD2) in Stage 1, at the end of Stage 2, if the true DLE rate is 5% or greater, there is at least 80% probability to observe at least one DLE in 37 subjects (16 in Stage 1 and 21 in Stage 2). Therefore, if there are no observed DLEs in both Stage 1 and Stage 2 at a dose level, then there is good confidence that the true DLE rate is no more than 5%. If it is reasonable to assume that the relationship between toxicity and dose level is monotonic non-decreasing, then we may pool dose levels to obtain a higher degree of confidence for the lower dose level.

Following the review of data available from Stage 1, the sample size may be formally recalculated for Stage 2 after the intermediate analysis.

11.3 Significance Testing and Estimations

Stage 1:

As this is a descriptive safety study, no formal statistical testing will be carried out. P-values, unadjusted for multiple comparisons, may be presented, but they will be regarded as descriptive.

Stage 2:

All statistical tests will be performed at a one-sided significance level of 10%.

11.4 Statistical/Analytical Methods

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

All analyses will be provided by stages. In addition, within each stage, the double-blind and open-label periods will be separately analysed. For doses that are selected for Stage 2, safety data may be pooled and summarised.

11.4.1 Demographic and Other Baseline Characteristics

In order to evaluate 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.

In Stage 1, main demographic and baseline characteristics will be provided in patients recruited before and after the start of COVID-19 pandemic (i.e. before / after first patient randomised in Cohort 6) in order to identify a potential change in the general patients' characteristics.

11.4.2 Subject Disposition and Withdrawals

The numbers and percentages of subjects screened, randomised and included in the analysis populations will be tabulated. 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 (double-blind treatment period and open-label period) will be tabulated. Primary reasons for discontinuation of study treatment will be tabulated.

The impact of COVID-19 pandemic on the trial will be assessed through the summary of data collected in relation to COVID-19, i.e. disposition of patients including the proportion of patients impacted and withdrawn due to COVID-19 pandemic and number of patients with visits impacted by COVID-19 with the corresponding reason. Exposure to treatment will also be described before and after the start of COVID-19 pandemic (i.e. before/after first patient randomised in Cohort 6).

11.4.3 Efficacy Evaluation

Stage 1:

The primary objective and endpoint of the Stage 1 is the safety assessments.

Descriptive statistics will be performed on the safety and efficacy endpoints.

Stage 2:

The study will be considered successful if the superiority of at least 1 Dysport group relative to placebo could be demonstrated with regard to the primary efficacy endpoint.

The primary efficacy endpoint is the change from baseline to Week 6 in the vaginal dilator induced pain as reported on an 11-point NRS (using the DMTS reported at baseline).

An ANCOVA will be performed. The model will include the treatment group (2 Dysport doses and placebo) as factor, baseline pain and stratification variable (pain onset subtype (primary and secondary PVD)) as covariates. Subjects who are unable to reach the baseline maximum tested size at a postbaseline visit will have an imputed pain score of 10 at the maximum tested size for that visit.

The primary efficacy results will be presented adjusted for covariates. The following estimates will be provided:

- For each of the 3 treatment groups, the least squares means of change from baseline in vaginal dilator and 2-sided 95% confidence interval are presented.
- For each of the 2 Dysport groups, the least squares means of the difference against placebo with a 2-sided simultaneous 80% confidence intervals will be presented.

Non-parametrics tests may also be carried out to evaluate robustness of the results.

Secondary efficacy endpoints will be analysed using an ANCOVA or a logistic regression according to the endpoints scale (categorical or continuous). The treatment group will be included as factor and the baseline and stratification variable as covariates in the model.

Additional psychometric analyses will be conducted on the study data (Stage 1 and Stage 2) to validate the PROs used in the study.

The scoring of patient reported questionnaires will be detailed in the SAP. For mVPAQ, the analysis of life interference subscale will be done with and without the item 'ability to fall asleep'. The analysis of pain severity subscale will be done with and without the items 'unpleasantness' and 'distress'. The total mVPAQ will also be computed with and without these items.

11.4.4 Adjustment for Country/Centre Effect

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

11.4.5 Handling of Withdrawals, Discontinuations or Missing Data

As described in Section 11.2, for Stage 1 and Stage 2, subjects who discontinue prior to Week 6 for reasons unrelated to safety may be replaced at the discretion of the investigator and sponsor.

Sensitivity analyses will be carried out to evaluate the impact of missing data where appropriate.

11.4.6 Data Analyses Timepoints

11.4.6.1 Data Review Committee (End of Stage 1 - Cycle 1-Week 6)

When all subjects in PVD2 cohorts in Stage 1 have reached Cycle 1-Week 6 visit, the DRC will review the unblinded efficacy and safety data to enable the selection of doses.

Once all subjects in PVD1 cohorts have reached Cycle 1-Week 6 visit, the DRC will meet and based on unblinded review of all safety and efficacy data from the cohort, will recommend if further PVD1 cohort(s) are required or if PVD1 subjects should be removed from Stage 2.

11.4.6.2 Primary Analysis (End of Stage 2 Cycle 1-Week 12)

A primary unblinded analyses will be performed. The cut-off date will be when all Stage 2 subjects have completed the Cycle 1-Week 12 visit. Analyses will be performed on:

- Subjects in Stage 1 – all safety and efficacy data available at the time of the data cut-off date.
- Subjects in Stage 2 – all safety and efficacy data available up to Cycle 1-Week 12 visit.

11.4.7 Safety Evaluation

All safety data will be included in the subject data listings. Analyses and summary tables will be based upon the safety population.

All AEs will be coded according to the current version of MedDRA 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 TEAEs and SAEs will be tabulated by treatment, group, dose and overall. In addition, summary tables will be presented by maximum intensity, drug relationship and TEAEs 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, dose and by overall will be presented for 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.

The number and percentage of subjects with the presence of BTX-A antibodies (neutralising) at Baseline will be presented. The number of seroconverters (subjects who have negative results at Baseline and have at least one positive result at any one post-treatment timepoint) for neutralising antibodies will be reported.

11.5 Subgroup Analyses

Descriptive statistics for the primary efficacy endpoint and main baseline characteristics will be provided by pain onset subtype (primary and secondary PVD) for Stage 2 on the mITT population. In addition, overall adverse events summary as well as TEAEs and SAEs will be provided (by SOC and PT) by pain onset subtype.

Other subgroup analyses may be planned according to clinical interest and detailed in the SAP.

11.6 Intermediate Analyses

At the point when the DRC recommends moving to Stage 2 of the study, an intermediate unblinded analysis of data available from all double-blind periods of all cohorts in Stage 1 will be performed when all subjects from the latest cohorts have completed their Cycle 1-Week 12 visit (data cut-off date corresponding to the last Cycle 1-Week 12 visit date).

All AE data available at the time of the data cut-off date (including data from the double-blind cycle from all cohorts) will be analysed using descriptive statistics. A thorough description of TEAEs collected during the double-blind periods will be performed.

Demographic and baseline characteristics, disposition, concomitant medications and treatment exposure will be described as well.

All efficacy related secondary endpoints will be described using change from baseline and categorical analyses (as summarised in Section 7.2). In addition, descriptive statistics will also be provided for selected exploratory endpoints (mean PGI-C score, and mean changes from baseline in the following endpoints: PGI-S score, mVPAQ pain and life interference subscales scores, mFSFI total score and domain scores and PHQ-9 total score).

A detailed description of this intermediate analysis will be provided in the SAP.

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 protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol.

Major protocol deviations are a subset of protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being. (For example, major protocol deviations might include enrolling subjects in violation of key eligibility criteria designed to ensure a specific subject population or failing to collect data necessary to interpret primary endpoints, as this may compromise the scientific value of the trial.)

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 change in the study design, study conduct and/or procedures that are not in accordance with the protocol and any study materials originally approved by the IEC/IRB but do not have a major impact on the subject's rights, safety or wellbeing, or the completeness, accuracy and reliability of the study data.

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 study site personnel learn that a subject who did not meet protocol eligibility criteria was entered in a study (a protocol deviation), 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 if applicable according to the local regulatory requirement, the responsible IRB/IEC.

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 CRF 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 site 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.

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, and annotated with the subject number as identification.

13.3.1 Data Review Committee

The DRC will be composed of sponsor representatives independent from the study team, including at least a representative from neurology therapeutic area department and a statistician, a non-sponsor physician expert in the treatment of vulvodynia and a CRO representative to assist in the logistics of the meetings. A DRC charter will be developed to define roles and responsibilities and the DRC meetings will take place as defined in the charter describing the operation of this committee.

The Chair of the DRC will be responsible for communicating the committee's recommendations to the study team who will immediately inform the investigators.

The DRC charter will be available in the TMF.

Refer to Section 3.1.1.2 for details of safety assessments to be done by the DRC.

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 IEC/IRB 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 the assigned 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, ICH GCP Guidelines (Section 1), FDA 21 CFR Part 11, Electronic Records, Electronic Signatures, and FDA, Guidance for Industry: Computerized Systems Used in Clinical Trials.

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 IEC/IRB 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 IEC(s)/IRB(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 IEC/IRB 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 IEC/IRB approval or favourable opinion.

During the study, any update to the following documents will be sent to the IEC/IRB either for information, or for review and approval, depending on how substantial the modifications are: (1) IB; (2) 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 eCRFs and other documents or image material submitted to the sponsor, subjects will be identified not by their names, but by their year of birth and an identification code (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 eCRFs to appropriately qualified staff having certified user access to the eCRF.

Subject completed diaries and questionnaires will be electronic. The data will be entered by the subject directly into a separate EDC (ePRO) secured by individual and confidential access codes. Data will be accessible to the clinical site and sponsor in a read only mode.

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 (EDC) will be utilised for collecting subject data (except subject reported questionnaires and diaries entered into an ePRO). 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 group**.** 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 Study Monitoring). The CRF 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 ePRO, 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 CRO's 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 a contracted CRO, directed by the sponsor's Biometry Group, and reviewed and approved by the sponsor. Concomitant medications will be coded using WHODRUG and AEs/medical history terms will be coded using MedDRA.

Complete 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. Rescreened subjects will sign a new informed consent form and a new subject identification number will be allocated.

15.3 Record Archiving and Retention

Prior to the start of the study, 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 local 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

As indicated in Section 11.4.6, a primary analysis will be performed after all subjects in Stage 2 complete the Week 12 visit. An interim Clinical Study Report (CSR) may be prepared.

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 be prepared according to the ICH guideline on structure and contents of CSRs and will comply with any applicable regulatory requirements, national laws in force and will be in English.

18 REFERENCES

1. Bornstein J, Goldstein AT, Stockdale CK et al. 2015 ISSVD, ISSWSH, and IPPS consensus terminology and classification of persistent vulvar pain and vulvodynia. J Low Genit Tract Dis. 2016;20(2):126-130.
2. Nagandla K, Sivalingam N. Vulvodynia: integrating current knowledge into clinical practice. Review Royal College of Obstetricians and Gynaecologists 2014;16:259-267.
3. Reed BD, Harlow SD, Sen A et al. Prevalence and demographic characteristics of vulvodynia in a population-based sample. Am J Obstet Gynecol. 2012;206(2):170e1-e9.
4. Harlow BL, Kunitz CG, Nguyen RHN et al. Prevalence of symptoms consistent with a diagnosis of vulvodynia: population-based estimates from 2 geographic regions. Am J Obstet Gynecol. 2014;210:40e1-8.
5. Pukall CF, Goldstein AT, Bergeron S et al. Vulvodynia: definition, prevalence, impact, and pathophysiological factors. J Sex Med. 2016;13(3):291-304.
6. Pelletier F, Girardin M, Humbert P et al. Long-term assessment of effectiveness and quality of life of OnabotulinumtoxinA injections in provoked vestibulodynia. J Eur Acad Dermatol Venereol. 2016;30(1):106-111.
7. Goldstein AT, Pukall CF, Brown C et al. Vulvodynia: assessment and treatment. J Sex Med. 2016;13(4):572-590.
8. Mandal D, Nunns D, Byrne M et al. Guidelines for the management of vulvodynia. Br J Dermatol 2010;162:1180–1185.
9. Reissing ED, Brown C, Lord MJ et al. Pelvic floor muscle functioning in women with vulvar vestibulitis syndrome. Journal of Psychosomatic Obstetrics & Gynecology 2005;26(2):107-113.
10. Pelletier F, Parratte B, Penz S et al. Efficacy of high doses of botulinum toxin A for treating provoked vestibulodynia. Br J Dermatol. 2011 Mar;164(3):617-622.
11. Bohm-Starke N, Hilliges M, Falconer C et al. Neurochemical characterization of the vestibular nerves in women with vulvar vestibulitis syndrome. Gynecol Obstet Invest. 1999;48: 270–275.
12. Morrissey D, El-Khawand D, Ginzburg N et al. Botulinum toxin A injections into pelvic floor muscles under electromyographic guidance for women with refractory high-tone pelvic floor dysfunction: a 6-month prospective pilot study. Female Pelvic Med Reconstr Surg. 2015;21(5):277-282.
13. Dykstra DD, Presthus J. Botulinum toxin type A for the treatment of provoked vestibulodynia: an open-label, pilot study. J Reprod Med. 2006;51(6):467-470.
14. Ghazizadeh S, Nikzad M. Botulinum toxin in the treatment of refractory vaginismus. Obstet Gynecol. 2004;104:922–925.
15. Bertolasi L, Emma F, Jee Yun C. Botulinum Neurotoxin Type A injections for vaginismus secondary to Vulvar Vestibulitis Syndrome. Obstetrics & gynecology. 2009;114(5):1008-1016.
16. Abbott JA, Jarvis SK, Lyons SD et al. Botulinum toxin type A for chronic pain and pelvic floor spasm in women a randomized controlled trial. Obstetrics & Gynaecology 2006:108(4):915-923.

17. Peterson C, Giraldi A, Lundvall L et al. Botulinum toxin Type A—a novel treatment for provoked vestibulodynia? Results from a randomized, placebo controlled, double blinded study. J Sex Med 2009;6:2523–2537.
18. Shafik A and El-Sibai O. Vaginismus: results of treatment with botulin toxin. Journal of Obstetrics and Gynaecology 2000;20(3):300-302.
19. Yoon H, Chung WS. Botulinum Toxin A for the management of vulvodynia. International Journal of impotence Research 2007; 19:84-87.
20. Jeon Y, Kim Y, Yoon H et al. A retrospective study of the management of vulvodynia. Korean J Urol. 2013;54(1):48-52.
21. Pukall CF, Young RA, Roberts MJ et al. The vulvalgesiometer as a device to measure genital pressure-pain threshold. Physiol. Meas. 2007:28;1543–1550.
22. Dargie E, Holden RR, Pukall CF. The Vulvar Pain Assessment Questionnaire inventory. Pain 2016; 157(12):2672-2686.
23. Rosen R, Brown C, Heiman J et al. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. J Sex Marital Ther. 2000;26(2):191-208.
24. Wiegel M, Meston C, Rosen R. The Female Sexual Function Index (FSFI): cross-validation and development of clinical cutoff scores. J Sex Marital Ther. 2005;31(1):1-20.
25. Aerts L, Bergeron S, Pukall CF et al. Provoked Vestibulodynia: does pain intensity correlate with sexual dysfunction and dissatisfaction?. J Sex Med 2016; 1-8.
26. Bornstein J, Tuma R, Farajun Y et al. Topical nifedipine for the treatment of localized provoked vulvodynia: a placebo-controlled study. J Pain. 2010;11(12):1403-1409.
27. Davis SNP, Bergeron S, Binik YM et al. Women with provoked vestibulodynia experience clinically significant reductions in pain regardless of treatment: Results from a 2-year follow-up study. J Sex Med 2013;10:3080–3087.

19 LIST OF APPENDICES

Appendix 1 mVPAQ (Version 1.2)

VPAQfull Subscales

Pain Severity

Please rate the following about your vulvar pain (in the past 1 week)

	None	Mild	Moderate	Severe	Worst Possible
Intensity: In the past 1 week, how strong the pain sensation is					
Average pain intensity					
Worst pain intensity					
Unpleasantness: In the past 1 week, how much the pain bothers you					
Average pain unpleasantness					
Worst pain unpleasantness					
Distress: In the past 1 week, how upset the pain makes you feel					
Average distress about pain					
Worst distress about pain					

Emotional Response

In the past 1 month, how much do you experience **feeling** the following related to your vulvar pain?

	Not at all	A Little	Somewhat	A Lot	Very Much
Sad					
Unable to make changes in my life					
Bad about myself because of the pain					
Emotionally exhausted because of the pain					
Anger towards my pain					
Depressed					
That the pain will never stop					
Like my body has let me down					
Physically tense					
Like giving up					
That I am not a worthwhile person					
Distracted					
Hateful things about myself as a person					
Stressed about the pain					
That it is unfair that I have pain					

Cognitive Response
In the past 1 month, how much do you experience **thinking/worrying** about the following related to your vulvar pain?

	Not at all	A Little	Somewhat	A Lot	Very Much
That people might think I'm a bad sexual partner					
That my partner(s) might think I'm frigid (i.e., sexually unresponsive)					
That my partner(s) will leave me					
That people (would) think less of me because of my pain					
That other people are better sexual partners than me					
That I am a bad sexual partner					
That I will not be able to find [a] future partner(s)					
That my pelvic muscles will be too tight					

Life Interference
In the past 1 week, how much does your vulvar pain negatively interfere with the following?

	Not at all	A Little	Somewhat	A Lot	Very Much	I avoid because of pain
Sitting						
Walking						
Wearing tight-fitting clothing						
Taking part in recreational activities						
Ability to work						
Going out with friends						
Fulfilling responsibilities to your family						
Ability to perform tasks at work						
Activities involving direct or indirect pressure (e.g., bike riding)						
Using sanitary pads						
Ability to fall asleep						

Sexual Function Interference

In the past 1 month, how much does your vulvar pain negatively interfere with the following?

	Not at all	A Little	Somewhat	A Lot	Very Much	I avoid because of pain
My response to sexual advances made by my partner						
Desire for sexual activity						
Feeling sexual pleasure						
Orgasm frequency						
Taking part in non-penetrative sexual activity						
Taking part in penetrative sexual activity						
Worrying about sexual satisfaction no longer being possible						
Worrying that any sensation in your genitals will lead to pain						
Taking off your clothes around your partner						
Worrying about the next time your partner(s) will want sexual activity						

Self-Stimulation/Penetration Interference

In the past 1 month, how often do the following situations/activities cause vulvar pain?

	Never	Rarely	Sometimes	Often	Always	I avoid because of pain
Using tampons						
Solitary sexual stimulation of my vulva (i.e., masturbation)						
Masturbation when partner is present						
Self penetration with fingers (partner absent)						
Self penetration with sex toy (partner absent)						

Appendix 2 mFSFI (Version 1.3)

FEMALE SEXUAL FUNCTION INDEX (FSFI)©

Subject Identifier _____ Date _____/_____/_____
Month Day Year

INSTRUCTIONS: These questions ask about your sexual feelings and responses. Please answer the following questions as honestly and clearly as possible. Your responses will be kept completely confidential. In answering these questions, the following definitions apply:

Sexual activity can include caressing, foreplay, masturbation, and vaginal intercourse.

Sexual intercourse is defined as penile penetration (entry) of the vagina.

Sexual stimulation includes situations like foreplay with a partner, self-stimulation (masturbation), or sexual fantasy.

CHECK ONLY ONE BOX PER QUESTION

Sexual desire or interest is a feeling that includes wanting to have a sexual experience, feeling receptive to a partner's sexual initiation, and thinking or fantasizing about having sex.

1. Over the past 4 weeks, how **often** did you feel sexual desire or interest?

   □ = Almost always or always
   □ = Most times (more than half the time)
   □ = Sometimes (about half the time)
   □ = A few times (less than half the time)
   □ = Almost never or never

2. Over the past 4 weeks, how would you rate your **level** (degree) of sexual desire or interest?

   □ = Very high
   □ = High
   □ = Moderate
   □ = Low
   □ = Very low or none at all

FSFI - United States/English - Mapi Institute.
ID6589 / FSFI_AU1.0_eng-USori.doc
Modified version 1.3

Sexual arousal is a feeling that includes both physical and mental aspects of sexual excitement. It may include feelings of warmth or tingling in the genitals, lubrication (wetness), or muscle contractions.

3. Over the past 4 weeks, how **often** did you feel sexually aroused ("turned on") during sexual activity or intercourse?

- ☐ = No sexual activity
- ☐ = Almost always or always
- ☐ = Most times (more than half the time)
- ☐ = Sometimes (about half the time)
- ☐ = A few times (less than half the time)
- ☐ = Almost never or never

4. Over the past 4 weeks, how would you rate your **level** of sexual arousal ("turn on") during sexual activity or intercourse?

- ☐ = No sexual activity
- ☐ = Very high
- ☐ = High
- ☐ = Moderate
- ☐ = Low
- ☐ = Very low or none at all

5. Over the past 4 weeks, how **confident** were you about becoming sexually aroused during sexual activity or intercourse?

- ☐ = No sexual activity
- ☐ = Very high confidence
- ☐ = High confidence
- ☐ = Moderate confidence
- ☐ = Low confidence
- ☐ = Very low or no confidence

FSFI - United States/English - Mapi Institute.
ID6589 / FSFI_AU1.0_eng-USori.doc
Modified version 1.3

6. Over the past 4 weeks, how **often** have you been satisfied with your arousal (excitement) during sexual activity or intercourse?

□ = No sexual activity
□ = Almost always or always
□ = Most times (more than half the time)
□ = Sometimes (about half the time)
□ = A few times (less than half the time)
□ = Almost never or never

7. Over the past 4 weeks, how **often** did you become lubricated ("wet") during sexual activity or intercourse?

□ = No sexual activity
□ = Almost always or always
□ = Most times (more than half the time)
□ = Sometimes (about half the time)
□ = A few times (less than half the time)
□ = Almost never or never

8. Over the past 4 weeks, how **difficult** was it to become lubricated ("wet") during sexual activity or intercourse?

□ = No sexual activity
□ = Extremely difficult or impossible
□ = Very difficult
□ = Difficult
□ = Slightly difficult
□ = Not difficult

9. Over the past 4 weeks, how often did you **maintain** your lubrication ("wetness") until completion of sexual activity or intercourse?

□ = No sexual activity
□ = Almost always or always
□ = Most times (more than half the time)
□ = Sometimes (about half the time)
□ = A few times (less than half the time)
□ = Almost never or never

FSFI - United States/English - Mapi Institute.
ID6589 / FSFI_AU1.0_eng-USori.doc
Modified version 1.3

10. Over the past 4 weeks, how **difficult** was it to maintain your lubrication ("wetness") until completion of sexual activity or intercourse?

- □ = No sexual activity
- □ = Extremely difficult or impossible
- □ = Very difficult
- □ = Difficult
- □ = Slightly difficult
- □ = Not difficult

11. Over the past 4 weeks, when you had sexual stimulation or intercourse, how **often** did you reach orgasm (climax)?

- □ = No sexual activity
- □ = Almost always or always
- □ = Most times (more than half the time)
- □ = Sometimes (about half the time)
- □ = A few times (less than half the time)
- □ = Almost never or never

12. Over the past 4 weeks, when you had sexual stimulation or intercourse, how **difficult** was it for you to reach orgasm (climax)?

- □ = No sexual activity
- □ = Extremely difficult or impossible
- □ = Very difficult
- □ = Difficult
- □ = Slightly difficult
- □ = Not difficult

13. Over the past 4 weeks, how **satisfied** were you with your ability to reach orgasm (climax) during sexual activity or intercourse?

- □ = No sexual activity
- □ = Very satisfied
- □ = Moderately satisfied
- □ = About equally satisfied and dissatisfied
- □ = Moderately dissatisfied
- □ = Very dissatisfied

FSFI - United States/English - Mapi Institute.
ID6589 / FSFI_AU1.0_eng-USori.doc
Modified version 1.3

14. Over the past 4 weeks, how **satisfied** have you been with the amount of emotional closeness during sexual activity between you and your partner?

- □ = No sexual activity
- □ = Very satisfied
- □ = Moderately satisfied
- □ = About equally satisfied and dissatisfied
- □ = Moderately dissatisfied
- □ = Very dissatisfied

15. Over the past 4 weeks, how **satisfied** have you been with your sexual relationship with your partner?

- □ = Very satisfied
- □ = Moderately satisfied
- □ = About equally satisfied and dissatisfied
- □ = Moderately dissatisfied
- □ = Very dissatisfied

16. Over the past 4 weeks, how **satisfied** have you been with your overall sexual life?

- □ = Very satisfied
- □ = Moderately satisfied
- □ = About equally satisfied and dissatisfied
- □ = Moderately dissatisfied
- □ = Very dissatisfied

17. Over the past 1 week, how **often** did you experience discomfort or pain **during** vaginal penetration?

- □ = Did not attempt intercourse
- □ = Almost always or always
- □ = Most times (more than half the time)
- □ = Sometimes (about half the time)
- □ = A few times (less than half the time)
- □ = Almost never or never

FSFI - United States/English - Mapi Institute.
ID6589 / FSFI_AU1.0_eng-USen.doc
Modified version 1.3

18. Over the past 1 week, how **often** did you experience discomfort or pain **following** vaginal penetration?

□ = Did not attempt intercourse
□ = Almost always or always
□ = Most times (more than half the time)
□ = Sometimes (about half the time)
□ = A few times (less than half the time)
□ = Almost never or never

19. Over the past 1 week, how would you rate your **level** (degree) of discomfort or pain **during** vaginal penetration?

□ = Did not attempt intercourse
□ = Very high
□ = High
□ = Moderate
□ = Low
□ = Very low or none at all

20. Over the past 1 week, how would you rate your **level** (degree) of discomfort or pain **following** vaginal penetration?

□ = Did not attempt intercourse
□ = Very high
□ = High
□ = Moderate
□ = Low
□ = Very low or none at all

Thank you for completing this questionnaire.

FSFI - United States/English - Mapi Institute.
ID6589 / FSFI_AU1.0_eng-USori.doc
Modified version 1.3

Appendix 3 PHQ-9

PATIENT HEALTH QUESTIONNAIRE-9 (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems? *(Use "✔" to indicate your answer)*	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

FOR OFFICE CODING 0 + _____ + _____ + _____

=Total Score: _____

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

Developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke and colleagues, with an educational grant from Pfizer Inc. No permission required to reproduce, translate, display or distribute.

Appendix 4 SF-36

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. *Thank you for completing this survey!*

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. Compared to one year ago, how would you rate your health in general now?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c. Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d. Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e. Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f. Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g. Walking more than a mile	☐ 1	☐ 2	☐ 3
h. Walking several hundred yards	☐ 1	☐ 2	☐ 3
i. Walking one hundred yards	☐ 1	☐ 2	☐ 3
j. Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

4. **During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. **During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. **During the <u>past 4 weeks</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?**

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. **How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?**

None	Very mild	Mild	Moderate	Severe	Very severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. **During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?**

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

9. **These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks…**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e. Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f. Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g. Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h. Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i. Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. **During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?**

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

Appendix 5 PCS

PCS

Age:_____ Sex: M(__) F(__)

Everyone experiences painful situations at some point in their lives. These experiences may include headaches, tooth pain, joint or muscle pain. People are often exposed to situations that may cause pain such as illness, injury, dental procedures or surgery.

We are interested in the types of thoughts and feelings that you have when you are in pain. Thirteen statements are listed below describing different thoughts and feelings that may be associated with pain. Using the following scale, please indicate the degree to which you have these thoughts and feelings when you are experiencing pain.

0 – not at all 1 – to a slight degree 2 – to a moderate degree 3 – to a great degree 4 – all the time

When I'm in pain...

1. ☐ I worry all the time about whether the pain will end.
2. ☐ I feel I can't go on.
3. ☐ It's terrible and I think it's never going to get any better.
4. ☐ It's awful and I feel that it overwhelms me.
5. ☐ I feel I can't stand it anymore.
6. ☐ I become afraid that the pain will get worse.
7. ☐ I keep thinking of other painful events.
8. ☐ I anxiously want the pain to go away.
9. ☐ I can't seem to keep it out of my mind.
10. ☐ I keep thinking about how much it hurts.
11. ☐ I keep thinking about how badly I want the pain to stop.
12. ☐ There's nothing I can do to reduce the intensity of the pain.
13. ☐ I wonder whether something serious may happen.

...Total

PCS - United States/English - Version of 24 April 17 - Mapi.
ID068127 / PCS_AU1.0_eng-US.doc

Appendix 6 Protocol Amendment: Version 2.0 (15 May 2018)

STUDY NUMBER:	D-FR-52120-236
PROTOCOL TITLE:	A phase II, multicentre, double-blind, randomised, placebo-controlled, dose escalation and dose finding study to evaluate the efficacy and safety of Dysport in vulvodynia patients
AMENDED PROTOCOL VERSION NUMBER & DATE	Protocol Version 2.0: 15 May 2018

THE FOLLOWING AMENDMENT IS PROPOSED:

Version Date		**09 FEBRUARY 2018**	**15 MAY 2018**
Page	**Section**	**WAS**	**IS**
1	Title Page	Pharmacovigilance/Emergency Contact: PPD	Pharmacovigilance/Emergency Contact: PPD **The person listed above is medically qualified and designated by the sponsor as the first point of contact for emergency situations.**
8	Synopsis		**(14) If the subject has received oral antidepressants, anxiolytics or anti-epileptics, then the dose of these medications should have been stable for at least 6 months prior to the Screening Visit and expected to remain stable throughout the first treatment cycle.**
9	Synopsis	(10) Vaginal infections (bacterial vaginosis, presence of candidiasis or trichomoniasis) at screening visit (based on vaginal culture).	(10) Vaginal infections (bacterial vaginosis, presence of candidiasis or trichomoniasis) at Screening Visit.
11	Synopsis		**Mean change from Baseline to each post-treatment visit in pain during insertion of vaginal dilator number 6 size (average of weekly pain score over the previous month) as reported on the 11-point NRS.**

Version Date		09 FEBRUARY 2018	15 MAY 2018
Page	**Section**	**WAS**	**IS**
11	Synopsis	Mean change from Baseline to each post-treatment visit in the pain during intercourse (average of daily pain score over the previous month) as reported on the 11-point NRS. For women who do not have intercourse in the last 1 week, change in pain will be assessed after the insertion of vaginal dilator (number 6 size).	Mean change from Baseline to each post-treatment visit in the pain during intercourse (average of daily pain score over the previous month) as reported on the 11-point NRS.
34	3.2.2		**Mean change from Baseline to each post-treatment visit in pain during insertion of vaginal dilator number 6 size (average of weekly pain score over the previous month) as reported on the 11-point NRS.**
34	3.2.2	Mean change from Baseline to each post-treatment visit in the pain during intercourse (average of daily pain score over the previous month) as reported on the 11-point NRS. For women who do not have intercourse in the last 1 week, change in pain will be assessed after the insertion of vaginal dilator (number 6 size).	Mean change from Baseline to each post-treatment visit in the pain during intercourse (average of daily pain score over the previous month) as reported on the 11-point NRS.
35	3.5	Subjects and investigators will remain blinded to treatment assignment during the double blind period of Stage 1 and Stage 2 of the study, i.e. to the dose received in the 1st treatment cycle in each Stage. Subjects and investigators will continue to remain blinded to the dose received during the 1st treatment cycle of treatment throughout the study.	**During the double blind period of Stage 1 and Stage 2,** subjects and investigators will **be** blinded to treatment assignment **(i.e. Dysport/placebo).** **During the double-blind period of Stage 2, if 2 doses are tested,** subjects and investigators will **also be** blinded to the dose received.
42	4.1		**(14) If the subject has received oral antidepressants, anxiolytics or anti-epileptics, then the dose of these medications should have been stable for at least 6 months prior to the Screening Visit and expected to remain stable throughout the first treatment cycle.**

Version Date		09 FEBRUARY 2018	15 MAY 2018
Page	Section	WAS	IS
43	4.2	(10) Vaginal infections (bacterial vaginosis, presence of candidiasis or trichomoniasis) at screening visit (based on vaginal culture).	(10) Vaginal infections (bacterial vaginosis, presence of candidiasis or trichomoniasis) at **S**creening **V**isit.
47	Table 2	Urine pregnancy test End of Cycle 1/EOS or EWD [b] X [d]	Urine pregnancy test End of Cycle 1/EOS or EWD [b] X
48	Table 2	Swab for vaginal culture	**Vaginal Swab**
49	Table 2	h From the Screening Visit until Baseline Visit (14 days in Stage 1 and 28 days in Stage 2), and then from one month prior to the next planned visit, subjects need to record daily if they had an intercourse, the number of intercourse instances, corresponding pain during each intercourse instance on an 11-point NRS and details of pain rescue medication if taken to prevent or treat vestibular pain. If no intercourse performed in the last 7 days, subjects need to rate the level of the corresponding pain following insertion of vaginal dilator (number 6 size) on an 11-point NRS and details of associated pain medication if consumed.	h From the Screening Visit until Baseline Visit (14 days in Stage 1 and 28 days in Stage 2), and then from one month prior to the next planned visit, subjects need to record daily if they had intercourse, the number of intercourse instances, corresponding pain during each intercourse instance on an 11-point NRS and details of pain rescue medication if taken to prevent or treat vestibular pain. **S**ubjects need **also** to rate **weekly** the level of the corresponding pain following insertion of vaginal dilator (number 6 size) on an 11-point NRS and details of associated pain medication if consumed.
50	Table 3	c To be performed only if Day 1 is not on the same day as the last visit of the previous cycle.	**c Not t**o be performed if **already done** on the same day.
51	Table 3	f To be recorded daily from one month prior to the next planned visit. Subjects need to record daily if they had an intercourse, the number of intercourse instances, corresponding pain during each intercourse instance on an 11-point NRS and details of pain rescue medication if taken to prevent or treat vestibular pain. If no intercourse performed in the last 7 days, subjects need to rate the level of the corresponding pain following insertion of vaginal dilator (number 6 size) on an 11-point NRS and details of associated pain medication if consumed.	f To be recorded daily from one month prior to the next planned visit. Subjects need to record daily if they had intercourse, the number of intercourse instances, corresponding pain during each intercourse instance on an 11-point NRS and details of pain rescue medication if taken to prevent or treat vestibular pain. **S**ubjects need **also** to rate **weekly** the level of the corresponding pain following insertion of vaginal dilator (number 6 size) on an 11-point NRS and details of associated pain medication if consumed.

Version Date		09 FEBRUARY 2018	15 MAY 2018
Page	**Section**	**WAS**	**IS**
52	5.2.1.1	Vital signs (supine and standing blood pressure and heart rate)	Vital signs (supine **or sitting** blood pressure and heart rate)
62	6.3		**Topical lidocaine, topical antidepressants, topical anti-epileptics and diazepam suppositories are not permitted during the study. Note: Immediately prior to and during study drug administration procedures, oral, topical (other than lidocaine) or intravenous medications routinely used as standard of care for vaginal intramuscular injections are allowed.**
62	6.3	Concomitant use of treatments for anterior vestibular pain e.g. topical hormonal creams are permitted, if the subject has no residual anterior vestibule pain at screening and wants to continue on the same treatment regimen throughout the study to prevent recurrence of anterior vestibular pain.	Concomitant use of **topical** treatments for anterior vestibular pain e.g. topical hormonal creams are permitted if the subject has no residual anterior vestibule pain at screening and wants to continue on the same treatment regimen throughout the study to prevent recurrence of anterior vestibular pain. **Note: Topical antidepressants are not permitted.**
62	6.3	Concomitant use of antidepressant, anxiolytics or anti-epileptics to treat vulvar pain is permitted, if the subjects try to maintain the dose regimen constant throughout 1st treatment cycle.	Concomitant use of **oral** antidepressant**s**, anxiolytics or anti-epileptics to treat vulvar pain is permitted **as long as the dose has remained stable for at least 6 months prior to the Screening Visit. Subjects should** try to maintain the dose regimen constant throughout **the** 1st treatment cycle.

Version Date		09 FEBRUARY 2018	15 MAY 2018
Page	**Section**	**WAS**	**IS**
63	6.3	Pain rescue medication taken to prevent or treat provoked vestibular pain should be avoided but can be taken by the subject as per need (PRN). The subject should attempt to use the same pain rescue medication., subjects will record in the eDiary the analgesic taken prior or after intercourse to prevent or cure vestibular pain (Section 7.4.2.5).	Pain rescue medication taken to prevent or treat provoked vestibular pain should be avoided. **If needed, the subject will be allowed to take Nonsteroidal Anti-inflammatory Drugs (NSAIDS) or Acetaminophen at the recommended dose as per need (PRN).** The subject should attempt to use the same pain rescue medication **throughout the study**. Subjects will record **the dosage and count (number of pills taken)** in the eDiary **of** the analgesic taken prior or after intercourse to prevent or cure vestibular pain (Section 7.4.2.5). **However, the subject should refrain from taking any rescue medication within 24 hours of a study visit.**
65	Table 7	a Subjects to record daily if they had an intercourse, the number of intercourse instances, corresponding pain during each intercourse instance on an 11-point NRS and details of pain rescue medication if taken to prevent or treat vestibular pain. If no intercourse performed in the last 7 days, subjects need to rate the level of the corresponding pain following insertion of vaginal dilator (number 6 size) on an 11-point NRS and details of associated pain medication if consumed.	a Subjects to record daily if they had intercourse, the number of intercourse instances, corresponding pain during each intercourse instance on an 11-point NRS and details of pain rescue medication if taken to prevent or treat vestibular pain. **Subjects need to rate weekly** the level of the corresponding pain following insertion of vaginal dilator (number 6 size) on an 11-point NRS and details of associated pain medication if consumed.
66	7.4.1	A set of 8 vaginal dilators of increasing diameter will be used to provoke pain to allow assessment of the vestibular pain intensity in each subject. At each visit, the investigator will insert the dilator between 3 to 4 cm depth in the vagina starting with the smallest sized dilator and progressively increasing the size of the dilator. In order to standardise the methodology each dilator should be inserted for a period of 5 to 10 seconds and the time period between the insertion of	A set of 8 vaginal dilators of increasing diameter will be used to provoke pain to allow assessment of the vestibular pain intensity in each subject. At each visit, the investigator will insert the dilator between 3 to 4 cm depth in the vagina starting with the smallest sized dilator and progressively increasing the size of the dilator. **No lubricant, other than water, may be used when inserting the dilator.** In order to standardise the methodology each dilator should be

Version Date		09 FEBRUARY 2018	15 MAY 2018
Page	Section	WAS	IS
		two dilators should be 30 seconds to 1 minute. Subjects will be required to rate the pain for each dilator size on a 11-point NRS (Figure 4) at each visit. Based on the subjective pain threshold, the largest sized dilator that the subject accepts/tolerates for the test (i.e., does not agree to the next successive dilator size to be tested), will be defined as the Dilator Maximum Tolerated Size (DMTS) that will be established at Baseline Visit. The dilator test will be used to assess the change from Baseline in the vaginal dilator induced pain as reported on a NRS (using the DMTS reported at baseline) as well as the dilator size that provokes maximum tolerated pain.	inserted for a period of 5 to 10 seconds and the time period between the insertion of two dilators should be 30 seconds to 1 minute. Subjects will be required to rate the pain for each dilator size on a**n** 11-point NRS (Figure 4) at each visit. Based on the subjective pain threshold, the largest sized dilator that the subject accepts/tolerates for the test (i.e. does not agree to the next successive dilator size to be tested), will be defined as the Dilator Maximum Tolerated Size (DMTS) that will be established at Baseline Visit. The dilator test will be used to assess the change from Baseline in the vaginal dilator induced pain as reported on a NRS (using the DMTS reported at baseline) as well as the dilator size that provokes maximum tolerated pain.
68	7.4.2.2	If no intercourse performed in the last seven days (assessed weekly), to rate the level of the corresponding pain following insertion of vaginal dilator (number 6 size) on an 11-point NRS and details of associated pain medication if consumed.	**All subjects are** to rate the level of the corresponding pain following insertion of **the number 6** vaginal dilator **into the vagina** on an 11-point NRS and **record** details of associated pain medication if consumed.
75	8.2	Blood samples will be collected for the evaluation of haematology, serum chemistry, FSH, and putative antibodies. A swab for vaginal cultures will also be collected. Analysis will be performed by a central laboratory. Full details regarding the clinical tests are provided in the Study Manual.	Blood samples will be collected for the evaluation of haematology, serum chemistry, FSH, and putative antibodies. Full details regarding the clinical tests are provided in the Study Manual. **A vaginal swab will be taken and analysed locally to detect possible infection.**

Version Date		09 FEBRUARY 2018	15 MAY 2018
Page	**Section**	**WAS**	**IS**
77	8.2.6	Vaginal Cultures for Yeast and Bacterial infection Vaginal cultures will be performed to screen the subjects, but will not be an assessment of the safety of the study drug. Vaginal swabs will be performed and sent to a central laboratory for culture and identification of pathogens (including Gardnerella vaginalis, Trichomonas vaginalis and Candida albicans (and other morphological subtypes)). Antimicrobial susceptibility testing will be done on identified pathogens. Test results will be provided to the study site during the screening period.	Vaginal **Evaluation** for Yeast and Bacterial **I**nfection Vaginal **swabs** will be performed to screen the subjects, but will not be an assessment of the safety of the study drug. Vaginal swabs will be performed and **analysed** for identification of pathogens (including Gardnerella vaginalis, Trichomonas vaginalis and Candida albicans). Test results **need to be available** during the screening period **or prior to randomisation**.

SUMMARY & OUTCOME OF CHANGES:

STUDY NUMBER	D-FR-52120-236	
AMENDED PROTOCOL VERSION NUMBER & DATE	Protocol Version 2.0: 15 May 2018	
SUBSTANTIAL ☐	**NON-SUBSTANTIAL** ☒	
REASON(S) FOR CHANGES	The protocol was updated to address comments received from the Food and Drug Administration, reflect a change in process (analysis of potential vaginal infection done locally instead of centrally), add weekly insertion of dilator number 6, update an administrative change (Pharmacovigilance contact), and correct any inconsistencies (vital signs, blinding description).	
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)

Appendix 7 Protocol Amendment: Version 3.0 (04 November 2018)

STUDY NUMBER:	D-FR-52120-236
PROTOCOL TITLE:	A phase II, multicentre, double-blind, randomised, placebo-controlled, dose escalation and dose finding study to evaluate the efficacy and safety of Dysport in vulvodynia patients
PREVIOUS PROTOCOL VERSION NUMBER & DATE	Protocol Version 2.0: 15 May 2018
AMENDED PROTOCOL VERSION NUMBER & DATE	Protocol Version 3.0: 04 November 2018

The updated text in the amendment is reflected in bold. Minor formatting edits and correction of typos have not been recorded.

THE FOLLOWING AMENDMENT(S) ARE PROPOSED:

Version Date		**15 MAY 2018**	**04 NOVEMBER 2018**
Page	**Section**	**WAS**	**IS**
6 and 29	Synopsis and 2.2.3 (Exploratory Objectives)	Emotional response, cognitive response and associated life interference as assessed on vulvar pain assessment questionnaire (VPAQ) subscales To assess the efficacy of Dysport on the quality of life (only in Stage 2).	Emotional response, cognitive response and associated life interference as assessed on **modified** vulvar pain assessment questionnaire (**m**VPAQ) subscales To assess the efficacy of Dysport on the quality of life.
7	Synopsis (Stage 2 (Dose Expansion))	Following evaluation of study eligibility during a 28-day screening period, subjects will receive study treatment injections in the pelvic floor muscles on Day 1 (Baseline visit). Treatment paradigm and follow-up visits will be the same as in Stage 1.	Following evaluation of study eligibility during a **14-day** screening period, subjects will receive study treatment injections in the pelvic floor muscles on Day 1 (Baseline **V**isit). Treatment paradigm and follow-up visits will be the same as in Stage 1.

Version Date		15 MAY 2018	04 NOVEMBER 2018
Page	**Section**	**WAS**	**IS**
7	Synopsis (Study Duration)	Study Duration The minimum follow-up duration will be 36 weeks and the maximum follow-up duration will be 48 weeks (but not before 12 weeks have elapsed from the last treatment cycle), as calculated from Cycle 1-Day 1.	Study Duration **(Stage 1 and Stage 2)** **Individual subject participation in this study will be for a maximum of 54 weeks:** • **Screening: 2 weeks (plus 2 weeks window)** • **Follow-up: a maximum of 48 weeks follow-up plus 2 weeks window period for the EOS Visit depending on the number of treatments administered and the treatment intervals.** **The subject's participation in the study will be considered to have ended 36 to 48 weeks after the first dose, but not before 12 weeks have elapsed after the last dose.** **The number of treatment cycles will depend on the duration of each treatment cycle. A subject can receive a maximum of four treatment cycles of Dysport including the one received in the double-blind period.** The minimum follow-up duration will be 36 weeks and the maximum follow-up duration will be 48 weeks **plus a 2-week window period for the EOS Visit, (the end of the study will not occur** before 12 weeks have elapsed from the last treatment cycle), as calculated from Cycle 1-Day 1.
7, 8 and 43	Synopsis and 4.1 (Inclusion Criteria)	(1) Female subjects aged between 18 and 45 years (inclusive). (8) Have provoked pain at the posterior vestibule on a Q -tip test, with pain at positions 5, 6 and 7 o'clock (must be bilateral pain). (10) Pain score ≥5 on an 11-point Numeric Rating Scale (NRS) for the Dilator Maximum Tolerated Size (DMTS).	(1**a**) Female subjects aged 18 years **or above**. (8**a**) Have provoked pain at the posterior vestibule on a Q -tip test, with pain at positions 5, 6 and 7 o'clock (must be bilateral pain) **at the Screening Visit**. (10**a**) Pain score ≥5 on an 11-point Numeric Rating Scale (NRS) for the Dilator Maximum **Tested** Size (DMTS) **at the Baseline Visit**.
8, 9, 10 and 44, 45	Synopsis and 4.2 (Exclusion Criteria)	(1) Have provoked pain on a Q-tip test at the anterior vestibule (anywhere between 9 and 3 o'clock or more anteriorly).	(1**a**) Have provoked pain on a Q-tip test at the anterior vestibule (anywhere between 9 and 3 o'clock or more anteriorly) **at the Screening Visit**.

Version Date		15 MAY 2018	04 NOVEMBER 2018
Page	**Section**	**WAS**	**IS**
8, 9, 10 and 44, 45	Synopsis and 4.2 (Exclusion Criteria)	(2) Able to tolerate the 6th (diameter 1¼ inches) dilator size (i.e. agree to the next successive dilator size to be tested for pain response).	(2**a**) Able to tolerate the 6th (diameter 1¼ inches) dilator size (i.e. agree to the next successive dilator size to be tested for pain response) **at the Baseline Visit**.
		(3) Any non-provoked (i.e. spontaneous) vulvar pain. Note: pain provoked by any vestibular pressure (including but not limited to sitting, bicycling or tight clothing) is considered provoked pain.	(3**a**) Any non-provoked (i.e. spontaneous) vulvar pain **in the past 6 months prior to the Screening Visit**. Note: pain provoked by any vestibular pressure (including but not limited to sitting, bicycling or tight clothing) is considered provoked pain.
		(4) Deep pain during intercourse.	(4**a**) Deep pain during intercourse **in the past 6 months prior to the Screening Visit**.
		(5) Score >26.55 on the Female Sexual Function Index (FSFI).	(5**a**) Score **of 4 or 5 on any of the 3 pain questions (questions #17, 18 or 19) of** the modified Female Sexual Function Index (**m**FSFI) **questionnaire**.
		(6) Score >30 on the Pain Catastrophizing Scale (PCS).	
		(7) Significant depression disorder, e.g. having a score ≥20/27 on the depression subscale of the Patient Health Questionnaire (PHQ-9) scale.	(7**a**) Significant ~~depression~~ **depressive** disorder, e.g. having a score ≥20/27 on the Patient Health Questionnaire (PHQ-9) scale **at the Baseline Visit**.
		(8) Genitourinary conditions/history which, according to the investigator's judgement may interfere with treatment or impact outcome assessment, including but not limited to:	(8**a**) Genitourinary **or gastrointestinal** conditions/history which, according to the investigator's judgement may interfere with treatment or impact outcome assessment, including but not limited to:

Version Date		15 MAY 2018	04 NOVEMBER 2018
Page	**Section**	**WAS**	**IS**
8, 9, 10 and 44, 45	Synopsis and 4.2 (Exclusion Criteria)	(16) Has received any of the following: - Pelvic floor physical therapy or sex therapy received in the past 6 weeks prior to Baseline. - Previous treatment with any botulinum toxin (BTX) for any indication within the last 1 year. - Treatment for anterior vestibular pain, e.g. hormonal creams, in the last 1 week prior to Screening unless continued at the same dosing regimen throughout the study. - Currently receiving treatment for stress or urge urinary incontinence. - Current or planned treatment with any drug that interferes either directly or indirectly with neuromuscular function (e.g. aminoglycosides) within the last 4 weeks prior to Baseline. - Treatment with an investigational drug within the last 4 weeks prior to Baseline or scheduled treatment with such a drug during the study period. - Is likely to require treatment during the study with drugs that are not permitted by the study protocol.	(16**a**) Has received any of the following: - Pelvic floor physical therapy or sex therapy received in the past 6 weeks prior to Baseline. - Previous treatment with any BTX for any indication within the last 1 year. - Treatment for anterior vestibular pain, e.g. hormonal creams, in the last 1 week prior to Screening unless continued at the same dosing regimen throughout the study. - Currently receiving treatment for stress or urge urinary incontinence. - **Treatment** with any **of the following drugs** that **could affect** neuromuscular function**: curare-like nondepolarising agents, lincosamides, polymyxins, anticholinesterases,** aminoglycoside **antibiotics (topical use is permitted except at the vulvar vestibular region), tizanidine and baclofen,** within the last 4 weeks prior to Baseline **or during the study**. - **Injections of steroids in the vulva within the last 4 weeks prior to the Screening Visit or planned use during the study.** - Treatment with an investigational drug within the last 4 weeks prior to Baseline or scheduled treatment with such a drug during the study period. - Is likely to require treatment during the study with drugs that are not permitted by the study protocol.
10	Synopsis (Test Product, Dose and Mode of Administration)	Injection procedures are described in the 'Study Treatment Administration - Training Manual' (included in the Study Manual). Training on injection procedures will be provided at the investigator meeting.	Injection procedures are described in the 'Study Treatment Administration - Training Manual' (included in the Study Manual). Training on injection procedures will be provided **to each investigator performing IMP administration**.

Version Date		15 MAY 2018	04 NOVEMBER 2018
Page	**Section**	**WAS**	**IS**
11	Synopsis (Duration of Treatment)	The maximum total follow-up duration will be for up to 48 Weeks from the first IMP dose administered and not before 12 weeks have elapsed since the last treatment dose.	The maximum total follow-up duration will be for up to 48 weeks, **plus a 2-week window period for the EOS Visit,** from the first IMP dose administered and not before 12 weeks have elapsed since the last treatment dose.
12 and 35	Synopsis and 3.2.2 (Secondary Endpoints)	• Mean change from Baseline to each post treatment visit in pain during insertion of vaginal dilator number 6 size (average of weekly pain score over the previous month) as reported on the 11-point NRS. • Mean change from Baseline to each post treatment visit in the pain during intercourse (average of daily pain score over the previous month) as reported on the 11-point NRS. • Mean PGI-S (as assessed by the subject) at each visit.	• Mean change from Baseline to each post-treatment visit in pain during insertion of vaginal dilator number 6 size as reported on the 11-point NRS. • Mean change from Baseline to each post-treatment visit in the pain during intercourse as reported on the 11-point NRS. • Mean **change from Baseline in** PGI-S (as assessed by the subject) at each visit.
12 and 36	Synopsis and 3.3 (Exploratory Endpoints)	• Mean change from Baseline to each post-treatment visit in each of the VPAQ subscales (with modified recall periods). • Mean change from Baseline to each post-treatment visit in the Female Sexual Function Index (FSFI) total score and domain scores. • Mean change from Baseline in quality of life (QoL) using 36-item Short Form Survey (SF-36) (only in Stage 2).	• Mean change from Baseline to each post-treatment visit in each of the **m**VPAQ subscales. • Mean change from Baseline to each post-treatment visit in the **modifie**d Female Sexual Function Index (**m**FSFI) total score and domain scores. • Mean change from Baseline in quality of life (QoL) using 36-item Short Form Survey (SF-36).
21, 22	List of Abbreviations	DMTS Dilated maximum tolerated size FSFI Female Sexual Function Index VPAQ Vulvar Pain Assessment Questionnaire max Maximum min Minimum	DMTS Dilated maximum **tested** size **m**FSFI **modified** Female Sexual Function Index **m**VPAQ **modified** Vulvar Pain Assessment Questionnaire

Version Date		15 MAY 2018	04 NOVEMBER 2018
Page	**Section**	**WAS**	**IS**
23, 24	1.1 (Introduction)	A typical treatment plan for a woman with vulvodynia starts with treatments that are considered non-pharmacological (e.g. psychological treatments, physiotherapy) and, depending on her response to treatment, can progress to multiple different medication treatments, that are used as off label treatment for the condition without any established proof of benefit (e.g. tricyclic antidepressants, local anesthetic agent, topical hormones, anti-inflammatory agents, pain modulators, local nerve block and anticonvulsant medications). If these treatments fail, then surgical intervention (for e.g. vestibulectomy for localised provoked vestibulodynia) is recommended [7], however only a minority of patients may be suitable for vestibulectomy [8]. Considering the unmet need of an effective treatment for vulvodynia patients and the suggested efficacy of botulinum toxin-A (BTX-A) in the various published studies for this indication, Ipsen proposes to conduct a randomised, double-blind, placebo-controlled study designed to define optimal doses of Dysport and evaluate its efficacy and safety compared with placebo for the treatment of vulvodynia.	A typical treatment plan for a woman with vulvodynia starts with treatments that are considered non-pharmacological (e.g. psychological treatments, physiotherapy) and, depending on her response to treatment, can progress to multiple different medication treatments, that are used as off label treatment for the condition without any established proof of benefit (e.g. tricyclic antidepressants, local an**a**esthetic agents, topical hormones, anti-inflammatory agents, pain modulators, local nerve block and anticonvulsant medications). If these treatments fail, then surgical intervention (e.g. vestibulectomy for localised provoked vestibulodynia) is recommended [7], however only a minority of patients may be suitable for vestibulectomy [8]. Considering the unmet need **for** an effective treatment for vulvodynia patients and the suggested efficacy of botulinum toxin-A (BTX-A) in the various published studies for this indication, Ipsen proposes to conduct a randomised, double-blind, placebo-controlled study designed to define optimal doses of Dysport and evaluate its efficacy and safety compared with placebo for the treatment of vulvodynia.

Version Date		15 MAY 2018	04 NOVEMBER 2018
Page	**Section**	**WAS**	**IS**
31	3.1.1 (Stage 1 (Dose Escalation))	From Week 12 onwards of the double-blind period, subjects will be assessed for the need for retreatment at each visit. Subjects who require retreatment will be provided subsequent treatment with Dysport in the open-label period of the study. Dysport dose levels, that are approved by the DRC will be used for retreatment and will not exceed 400 U. Subjects not requiring or not eligible for retreatment will be evaluated every 6 weeks ±2 weeks (Additional Visit(s)) until they need retreatment or they complete at least 36 weeks of follow-up. The number of treatment cycles will depend on the duration of each treatment cycle, and thus the minimum follow-up duration will be 36 weeks and the maximum follow-up duration will be 48 weeks (but not before 12 weeks have elapsed from the last treatment cycle), as calculated from Cycle 1-Day 1.	From Week 12 onwards of the double-blind period, subjects will be assessed for the need for retreatment at each visit. Subjects who require retreatment will be provided subsequent treatment with Dysport in the open-label period of the study. Dysport dose levels, that are approved by the DRC will be used for retreatment and will not exceed 400 U. Subjects not requiring or not eligible for retreatment will be evaluated every 6 weeks ±2 weeks (Additional Visit(s)) until they need retreatment or they complete at least 36 weeks of follow-up. The number of treatment cycles will depend on the duration of each treatment cycle, and thus the minimum follow-up duration will be 36 weeks and the maximum follow-up duration will be 48 weeks (**the end of the study will not occur** before 12 weeks have elapsed from the last treatment cycle), as calculated from Cycle 1-Day 1.
32	3.1.2 (Stage 2 (Dose Expansion))	Subjects will be evaluated for eligibility during a Screening Visit at Day -28. Individual subject participation in this study will be for a minimum of 36 weeks and up to 52 weeks (but not before 12 weeks have elapsed after the last dose; Section 3.8) depending on the number of treatment cycles administered and the treatment intervals.	Subjects will be evaluated for eligibility during a Screening Visit at Day **-14**. **The number of treatment cycles will depend on the duration of each treatment cycle, and thus the minimum follow-up duration will be 36 weeks and the maximum follow-up duration will be 48 weeks (the end of the study will not occur** before 12 weeks have elapsed **from the last treatment cycle), as calculated from Cycle 1-Day 1.**
33	Figure 1 (Study Design)	Screening Visit Day -14 (Stage 1)/ Day -28 (Stage 2) to Day 1	Screening Visit Day -14 to Day 1

Version Date		15 MAY 2018	04 NOVEMBER 2018
Page	**Section**	**WAS**	**IS**
41	3.8 (Study Duration)	This study will consist of a 14-day screening period in Stage 1 (28 days in Stage 2), a double-blind treatment period including treatment administration at Day 1 and a follow-up period of 36 to 48 weeks (calculated from the dosing at Day 1). Individual subject participation in this study will be for a minimum of 36 weeks and up to 52 weeks in Stage 1 and 54 weeks in Stage 2 (2 weeks screening (4 weeks in Stage 2) + a maximum of 48 weeks follow-up + 2 weeks window period for the EOS visit) depending on the number of treatments administered and the treatment intervals.	This study will consist of a 14-day screening period (Stage 1 **and** Stage 2), a double-blind treatment period including treatment administration at Day 1 and a follow-up period of 36 to 48 weeks (calculated from the dosing at Day 1). Individual subject participation in this study will be for a **maximum of 54** weeks (Stage 1 and Stage 2): • **Screening: 2 weeks (plus 2 weeks window)** • **Follow-up: a maximum of 48 weeks follow-up plus 2 weeks window period for the EOS Visit depending on the number of treatments administered and the treatment intervals.**
47	5.1 (Study Schedule)		**Subjects enrolled after the implementation of protocol Version 3.0 (dated 04 November 2018), i.e. subjects included in Cohort 2 onwards, will follow the study assessments and procedures outlined in Version 3.0, while subjects enrolled prior to implementation of Version 3.0, i.e. subjects included in Cohort 1, will continue to follow the study assessments and procedures as per the protocol Version 2.0 (dated 15 May 2018).**
48, 49, 50	Table 2 (Study Procedures and Assessments – Double-blind Treatment Period)	Visit Day - V1 Screening (Day -14/Day -28)	Visit Day - V1 Screening (Day -14)
		Visit Window - V1 -3 days	Visit Window - V1 +3 days/-**14 days**
		PGI-S V1, V2, V4	PGI-S **[e]** V1, V2, V4**, V5 [a], V6, V7, V8, EOS or EWD [b]**
		PGI-C	PGI-C **[e]**
		eDiary VPAQ pain subscale [e]	eDiary **m**VPAQ pain subscale [e]
			eDiary mVPAQ life interference subscale [e] V1, V2, V4, V5 [a], V6, V7, V8, EOS or EWD [b]
48, 49, 50	Table 2		**eDiary mFSFI pain domain [e] V1, V2, V4, V5 [a], V6, V7, V8, EOS or EWD [b]**
		VPAQ subscales (except pain) [f]	**m**VPAQ subscales (except pain **and life interference**) [f]

Version Date		15 MAY 2018	04 NOVEMBER 2018
Page	**Section**	**WAS**	**IS**
	(Study Procedures and Assessments – Double-blind Treatment Period) Table 2	FSFI	**m**FSFI **domains (except pain) [f]**
		eDiary relationship/partner status [e]	eDiary relationship/partner status [**g**]
		SF-36 [g]	SF-36
		eDiary intercourse and/or dilator insertion details [h]	eDiary intercourse **details** [h]
			eDiary dilator insertion [k]
			Subject interviews V4 [l]
		e To be assessed at Screening Visit, then weekly during the screening period (14 days in Stage 1 and 28 days in Stage 2) until Baseline Visit, and then weekly from one month prior to the next planned visit.	e To be assessed at Screening Visit, then **1** week prior to the next planned visit **and at the visit**. **PGI-C will be assessed Week 6 onwards only.**
		g In Stage 2 only	g **To be assessed at Screening Visit, and then 2 weeks prior and 1 week prior to the next planned visit and at the visit**.
48, 49, 50		h From the Screening Visit until Baseline Visit (14 days in Stage 1 and 28 days in Stage 2), and then from one month prior to the next planned visit, subjects need to record daily if they had an intercourse, the number of intercourse instances, corresponding pain during each intercourse instance on an 11-point NRS and details of pain rescue medication if taken to prevent or treat vestibular pain. Subjects need also to rate weekly the level of the corresponding pain following insertion of vaginal dilator (number 6 size) on an 11-point NRS and details of associated pain medication if consumed.	h **To be assessed at** Screening Visit and then from **2 weeks** prior to the next planned visit, subjects need to record daily if they had intercourse, the number of intercourse instances, corresponding pain during each intercourse instance on an 11-point NRS and details of pain rescue medication if taken to prevent or treat vestibular pain.

Version Date		15 MAY 2018	04 NOVEMBER 2018
Page	**Section**	**WAS**	**IS**
	(Study Procedures and Assessments – Double-blind Treatment Period)		**k To be assessed weekly from 2 weeks prior to the next planned visit (assessment on the day of the visit should be avoided). Subjects need to rate the level of the corresponding pain following insertion of vaginal dilator (number 6 size) on an 11-point NRS and record details of associated pain medication if consumed.**
			l Subject interviews on the dilator test to be conducted in Stage 2 by invitation until the target sample of 20 subjects is achieved. Every effort should be made to conduct the interview within 2 weeks of subject's Cycle 1-Week 6 visit.
			m The visit window will be from Day -28 to Day -11.
	Table 2 Abbreviations	FSFI=female sexual function index VPAQ=vulvar pain assessment questionnaire	**ICF=informed consent form** **m**FSFI=**modified** female sexual function index **m**VPAQ=**modified** vulvar pain assessment questionnaire **NRS=numeric rating scale**
51, 52	Table 3 (Study Procedures and Assessments – Open-label Treatment Period)		**PGI-S [i, j] V9 [d], V13 [d], V17 [d]; V11, V15, V19; V12, V16, V20; Additional Visits [b]; EOS / EWD**
		PGI-C	PGI-C **[i, j]**
		eDiary intercourse and/or dilator insertion details [f]	eDiary intercourse details [f]
			eDiary dilator insertion [k] V9, V13, V17; V11, V15, V19; V12, V16, V20; Additional Visits [b]; EOS / EWD
		e To be assessed weekly from one month prior to the planned visit.	e To be assessed **2** weeks **prior** and **1 week** prior to the planned visit, **and at the visit**.

Version Date		15 MAY 2018	04 NOVEMBER 2018
Page	**Section**	**WAS**	**IS**
51, 52	Table 3 (Study Procedures and Assessments – Open-label Treatment Period)	f To be recorded daily from one month prior to the next planned visit. Subjects need to record daily if they had an intercourse, the number of intercourse instances, corresponding pain during each intercourse instance on an 11-point NRS and details of pain rescue medication if taken to prevent or treat vestibular pain. Subjects need also to rate weekly the level of the corresponding pain following insertion of vaginal dilator (number 6 size) on an 11-point NRS and details of associated pain medication if consumed.	f To be recorded daily from **2 weeks** prior to the next planned visit. Subjects need to record daily if they had intercourse, the number of intercourse instances, corresponding pain during each intercourse instance on an 11-point NRS and details of pain rescue medication if taken to prevent or treat vestibular pain.
			i To be assessed only in Cycle 2 (i.e. the first cycle of the open-label treatment period).
			j To be assessed 1 week prior to the next planned visit and at the visit.
			k To be assessed weekly from 2 weeks prior to the next planned visit (assessment on the day of the visit should be avoided). Subjects need to rate the level of the corresponding pain following insertion of vaginal dilator (number 6 size) on an 11-point NRS and record details of associated pain medication if consumed.
	Table 3 Abbreviations	FSFI= female sexual function index VPAQ= vulvar pain assessment questionnaire	**AE=adverse event** **DRC=data review committee** **ICF=informed consent form** **NRS=numeric rating scale**
53	Table 4 Abbreviation (Blood Volume for Collection)		**FSH=follicle stimulating hormone**
53	5.2 (Study Visits)		**The priority order for performing the assessments is discussed in Section 6.6.**

Version Date		15 MAY 2018	04 NOVEMBER 2018
Page	**Section**	**WAS**	**IS**
53	5.2.1 (Procedures for Screening and Enrolment)	5.2.1 Procedures for Screening and Enrolment (Visit 1; Day -14 (-3 days) in Stage 1; Day -28 (-3 days) in Stage 2)	5.2.1 Procedures for Screening and Enrolment - Visit 1 (Day -14 (-**14 days**/ +3 days))
53, 54	5.2.1.1 (Screening - Visit 1)	5.2.1.1 Screening – Visit 1 (Day -14 (-3 days) in Stage 1; Day -28 (-3 days) in Stage 2) The Screening Visit (Visit 1) will take place on Day –14 and during Stage 1 and on Day -28 in Stage 2 of the study.	5.2.1.1 Screening – Visit 1 - Day -14 (-**14 days**/ +3 days) The Screening Visit (Visit 1) will take place on Day -14 of the study. The visit window will be from Day -28 to Day -11.
		• Vaginal culture for yeast and bacterial infections	• Vaginal culture/**polymerase chain reaction** for yeast, **parasitic** and bacterial infections
		• FSFI	• **m**FSFI **(pain to be recorded at the visit, and 1 week prior to the Baseline Visit; other domains to be recorded only at the visit)**
		• Relationship/partner status	• Relationship/partner status **(to be recorded at the visit and then weekly during the screening period)**
		• VPAQ (pain and other subscales)	• **m**VPAQ (pain **and life interference to be recorded at the visit, and 1 week prior to the Baseline Visit;** and other subscales **to be recorded only at the visit)**
		• Intercourse and/or dilator insertion details (to be recorded daily during the screening period)	• Intercourse details **(to be recorded daily during the screening period)** • **D**ilator **size 6** insertion details (to be recorded **weekly** during the screening period)
		• PGI-S	• PGI-S **(to be recorded at the visit, and 1 week prior to the Baseline Visit)**
		- Prior pelvic floor physical therapy or sex therapy received in the past 6 weeks prior to Baseline	- Prior pelvic floor physical therapy or sex therapy received in the past **2 years** prior to **the planned Baseline**
		- Use of any experimental new drug or device within past 4 weeks prior to Baseline before the start of treatment.	- Use of any experimental new drug or device within past 4 weeks prior to **the planned Baseline**.

Version Date		15 MAY 2018	04 NOVEMBER 2018
Page	**Section**	**WAS**	**IS**
53, 54	5.2.1.1 (Screening - Visit 1)	A subject can be rescreened once, if all eligibility criteria were met but the subject was not enrolled either due to cohort recruitment being complete by the time the subject was eligible, or if the subject had a UTI or vaginal infection at first screening and has received adequate treatment leading to complete resolution of the infection.	A subject can be rescreened once, if all eligibility criteria were met but the subject was not enrolled due to any of the following: • Cohort recruitment being complete by the time the subject was eligible, • If the subject had a UTI or vaginal infection at first screening and has received adequate treatment leading to complete resolution of the infection, • If the subject failed screening due to a selection criterion that was removed from the previous version of the protocol. If the subject failed screening due to a selection criterion that was modified, she should have fulfilled the new criterion at the time of the first screening to be able to be rescreened. In these situations, the subject may only be rescreened once the new amended protocol has been approved by the IRB.
55, 56, 57, 60	5.2.2.1, 5.2.2.4, 5.2.2.5 (Week 36 only), 5.2.4 (Study Visits)	• SF-36 (in Stage 2 only)	• SF-36
56	5.2.2.3 (Week 6 Visit)		• **Subject interviews (every effort should be made to conduct the interview within 2 weeks of the subject's Cycle 1-Week 6 visit in Stage 2).**
55 to 60	5.2.2.1, 5.2.2.3, 5.2.2.4, 5.2.2.5. 5.2.3.1, 5.2.3.3, 5.2.3.4, 5.2.3.5, 5.2.4 (Study Visits)	• PGI-S	• PGI-S **(to be recorded 1 week prior to the visit and at the visit)**
55 to 60	5.2.2.3, 5.2.2.4, 5.2.2.5. 5.2.3.1, 5.2.3.3, 5.2.3.4, 5.2.3.5, 5.2.4 (Study Visits)	• PGI-C	• PGI-C **(to be recorded 1 week prior to the visit and at the visit)**

Version Date		15 MAY 2018	04 NOVEMBER 2018
Page	**Section**	**WAS**	**IS**
55 to 60	5.2.2.1, 5.2.2.3, 5.2.2.4, 5.2.2.5. 5.2.3.1, 5.2.3.3, 5.2.3.4, 5.2.3.5, 5.2.4 (Study Visits)	• Relationship/partner status	• Relationship/partner status **(to be recorded weekly from 2 weeks prior to the visit and at the visit)**
55 to 60	5.2.2.1, 5.2.2.3, 5.2.2.4, 5.2.2.5. 5.2.3.1, 5.2.3.3, 5.2.3.4, 5.2.3.5, 5.2.4 (Study Visits)	• Intercourse and/or dilator insertion details recorded over a 14-day period in Stage 1 and 28-day period in Stage 2 preceding the visit	• Intercourse details **(to be** recorded **daily from 2 weeks prior to the visit)** • **Dilator size 6** insertion details **(to be recorded weekly from 2 weeks** preceding the visit**; assessment on the day of the visit should be avoided)**
55, 56, 67, 60	5.2.2.1, 5.2.2.3, 5.2.2.4, 5.2.2.5, 5.2.4 (only if the EOS/EWD visit occurs during the double-blind period) (Study Visits)	• FSFI	• **m**FSFI **(pain to be recorded 1 week prior to the visit and at the visit; other domains to be recorded only at the visit)**
55, 56, 67, 60	5.2.2.1, 5.2.2.3, 5.2.2.4, 5.2.4 (only if the EOS/EWD visit occurs during the double-blind period) (Study Visits)	• VPAQ (pain and other subscales)	• **m**VPAQ (pain **and life interference to be recorded 1 week prior to the visit and at the visit;** other subscales **to be recorded only at the visit)**
56, 57	5.2.2.5 (Additional Visits)	• VPAQ pain subscale • VPAQ other subscales (at Week 24 and Week 36 only) • PHQ-9	• **m**VPAQ pain **and life interference** subscales **(to be recorded 1 week prior to the visit and at the visit)** • **m**VPAQ other subscales (at Week 24 and Week 36 only) • PHQ-9 (Week 36 only)
62	6.2.2 (Reconstitution and Administration Procedure)	Further details on the injection procedures are described in the 'Study Treatment Administration - Training Manual' (included in the Study Manual). Training on injection procedures will be provided at the investigator meeting.	Further details on the injection procedures are described in the 'Study Treatment Administration - Training Manual' (included in the Study Manual). Training on injection procedures will be provided to **each investigator performing IMP administration**.

Version Date		15 MAY 2018	04 NOVEMBER 2018
Page	**Section**	**WAS**	**IS**
64	6.3 (Concomitant Medication/Therapy)	• Medications that affect the neuromuscular transmission directly or indirectly, such as curare-like nondepolarising agents, lincosamides, polymyxins, anticholinesterases and aminoglycoside antibiotics (topical use is permitted except at the vulvar vestibular region), within the past 30 days of Baseline and during the study.	• **The following m**edications that affect neuromuscular transmission**:** curare-like nondepolarising agents, lincosamides, polymyxins, anticholinesterases**,** aminoglycoside antibiotics (topical use is permitted except at the vulvar vestibular region), **tizanidine and baclofen,** within the past **4 weeks prior to** Baseline and during the study. • **Injections of steroids in the vulva should have been stopped 4 weeks prior to the Screening Visit and are not allowed during the study.**
		• Concomitant use of oral antidepressants, anxiolytics or anti-epileptics to treat vulvar pain is permitted as long as the dose has remained stable for at least 6 months prior to the Screening Visit. Subjects should try to maintain the dose regimen constant throughout the 1st treatment cycle.	• **Concomitant use of oral antidepressants, anxiolytics or anti-epileptics is permitted as long as the dose has remained stable for at least 6 months prior to the Screening Visit. Subjects should try to maintain the dose regimen constant throughout the first treatment cycle.**
		• Pain rescue medication taken to prevent or treat provoked vestibular pain should be avoided. If needed, the subject will be allowed to take Nonsteroidal Anti-inflammatory Drugs (NSAIDS) or Acetaminophen at the recommended dose as per need (PRN). The subject should attempt to use the same pain rescue medication throughout the study. Subjects will record the dosage and count (number of pills taken) in the eDiary of the analgesic taken prior or after intercourse to prevent or cure vestibular pain (Section 7.4.2.5). However, the subject should refrain from taking any rescue medication within 24 hours of a study visit.	• Pain rescue medication taken to prevent or treat provoked vestibular pain should be avoided. If needed, the subject will be allowed to take Nonsteroidal Anti-inflammatory Drugs (NSAIDS) or Acetaminophen at the recommended dose as per need (PRN). The subject should attempt to use the same pain rescue medication throughout the study. Subjects will record the dosage and count (number of pills taken) in the eDiary **for** the analgesic taken prior or after intercourse to prevent or **treat** vestibular pain (Section 7.4.2.5). However, the subject should refrain from taking any rescue medication within 24 hours of a study visit.
		• Concomitant use of anticholinergic drugs (which may potentiate systemic anticholinergic effects) is permitted if the dosage has been stable for the six weeks prior to Baseline and is expected to remain at this stable dose throughout the study.	• Concomitant use of anticholinergic drugs (which may potentiate systemic anticholinergic effects) is permitted if the dosage has been stable for the **6** weeks prior to Baseline and is expected to remain at this stable dose throughout the study.

Version Date		15 MAY 2018	04 NOVEMBER 2018
Page	**Section**	**WAS**	**IS**
65	6.4 (Lifestyle Restrictions/Recommendations)	Subjects will be requested to comply to the restriction criteria related to alcohol consumption and drugs of abuse, presented as exclusion criteria in Section 4.2.	Subjects will be requested to comply **with** the restriction criteria related to alcohol consumption and drugs of abuse, presented as exclusion criteria in Section 4.2.
65	6.6 (Priority Order on Study Procedures)	(1) The subject needs to complete the questionnaires at the site prior to the seeing the investigator (PCS, FSFI, PHQ-9, VPAQ, SF-36) and complete PGI-S and PGI-C scoring. The intercourse or dilator insertion details need to be recorded in the eDiary.	(1) The subject needs to complete the questionnaires at the site (PCS, **m**FSFI, PHQ-9, **m**VPAQ, SF-36) and **subsequently** complete **the** PGI-S and PGI-C assessments **prior to seeing the investigator**.
66, 67	Table 7 (Secondary Efficacy Endpoints and Evaluations)	Composite score of 11 NRS score and dilator size	Composite score of 11-**point** NRS score and dilator size
		Maximum tolerated dilator size	Maximum **tested** dilator size
		Frequency of intercourse and pain during intercourse and/ or pain during size 6 dilator insertion [a] a Subjects to record daily if they had an intercourse, the number of intercourse instances, corresponding pain during each intercourse instance on an 11-point NRS and details of pain rescue medication if taken to prevent or treat vestibular pain. Subjects need to rate weekly the level of the corresponding pain following insertion of vaginal dilator (number 6 size) on an 11-point NRS and details of associated pain medication if consumed.	Frequency of intercourse and pain during intercourse [a] a **At the Screening Visit and then from 2 weeks prior to the next planned visit,** subjects **need** to record daily if they had intercourse, the number of intercourse instances, corresponding pain during each intercourse instance on an 11 point NRS and details of pain rescue medication if taken to prevent or treat vestibular pain.
		Mean change from Baseline in the frequency of intercourse and pain during intercourse or dilator insertion	Mean change from Baseline in the frequency of intercourse and pain during intercourse

Version Date		15 MAY 2018	04 NOVEMBER 2018
Page	**Section**	**WAS**	**IS**
66, 67	Table 7 (Secondary Efficacy Endpoints and Evaluations)		**Pain during insertion of vaginal dilator number 6 size [b]; Screening, Baseline, Week 6, Week 12 and then every 6 weeks until EOS - All TCs; 11-point NRS score; Mean change from Baseline in pain during insertion** **b From 2 weeks prior to the next planned visit, subjects need to rate weekly the level of the corresponding pain following insertion of vaginal dilator (number 6 size) on an 11-point NRS and details of associated pain medication if consumed. Assessment on the day of the visit should be avoided.**
		Patient Global impression of the severity of pain and change in pain as measured by the subject	Patient Global impression of the severity of pain and change in pain as measured by the subject **[c]** **c To be assessed at Screening Visit, then 1 week prior to the next planned visit and at the visit. PGI-C will be assessed Week 6 onwards only.**
		Screening, Baseline and Week 6 - All TCs	Screening, Baseline, Week 6**, Week 12 and then every 6 weeks until EOS** – All TCs
		Mean score	Mean **change from Baseline**
	Table 7 Abbreviations	DTMS=dilator tolerated maximum size	DTMS=dilator **tested** maximum size
68	Table 8 (Exploratory Efficacy Endpoints and Evaluations)	VPAQ pain subscale	**m**VPAQ pain **and life interference** subscales
		Mean change from Baseline in pain	Mean change from Baseline in pain **and life interference subscales**
		VPAQ other subscale scores	**m**VPAQ other subscale scores
		Mean change from Baseline in life interference, sexual function interference, self-stimulation/ penetration interference, emotional response and cognitive response scores	Mean change from Baseline in sexual function interference, self-stimulation/ penetration interference, emotional response and cognitive response scores

Version Date		15 MAY 2018	04 NOVEMBER 2018
Page	**Section**	**WAS**	**IS**
68	Table 8 (Exploratory Efficacy Endpoints and Evaluations)	a Subjects to complete the VPAQ pain questionnaire weekly during the screening period (14 days in Stage 1 and 28 days in Stage 2) until Baseline Visit, and then weekly from one month prior to the next planned visit.	a Subjects to complete the mVPAQ pain and life interference **subscales at the Screening Visit**, then **1 week** prior to the next planned visit **and at the visit; other mVPAQ subscales to be completed only at the visit**.
		Sexual function	Sexual function **[b]** **b Subjects to complete the mFSFI pain domain at the Screening Visit, then 1 week prior to the next planned visit and at the visit; other mFSFI domains to be completed only at the visit.**
		FSFI total score	**m**FSFI total score
		Baseline, Week 6, Week 12 and then every 6 weeks until End of TC 1 (DB period only)	**Screening,** Baseline, Week 6, Week 12 and then every 6 weeks until End of TC 1 (DB period only)
		Mean change from Baseline in FSFI total score	Mean change from Baseline in **m**FSFI total score **mFSFI pain domain score; Screening, Baseline, Week 6, Week 12 and then every 6 weeks until End of TC 1 (DB period only); Mean change from Baseline in pain domain score**
		FSFI domain scores	**m**FSFI **other** domain scores
		Baseline, Week 6, Week 12 and then every 6 weeks until End of TC 1 (DB period only)	**Screening,** Baseline, Week 6, Week 12 and then every 6 weeks until End of TC 1 (DB period only)
		Mean change from Baseline in FSFI domain scores	Mean change from Baseline in **m**FSFI **other** domain scores
		Quality of life (Only in Stage 2)	Quality of life
		SF-36 total score	SF-36 total **domain** scores
	Table 8 Abbreviations	FSFI= female sexual function index	**m**FSFI=**modified** female sexual function index
		VPAQ=vulvar pain assessment questionnaire	**m**VPAQ=**modified** vulvar pain assessment questionnaire

Version Date		15 MAY 2018	04 NOVEMBER 2018
Page	Section	WAS	IS
68	7.4 (Methods and Timing of Assessing, Recording and Analysing Efficacy data)	Methods for assessing efficacy data are described below. Timing of efficacy assessments are presented in Table 2 and Table 3, and discussed in Section 5.2. Procedures for recording efficacy data are discussed in Section 15.1, and methods of analyses are discussed in Section 11.4.3. The priority order for performing the assessments is discussed in Section 6.6.	Methods for assessing efficacy data are described below. Timing of efficacy assessments are presented in Table 2 and Table 3, and discussed in Section 5.2. Procedures for recording efficacy data are discussed in Section 15.1, and methods of analyses are discussed in Section 11.4.3. The priority order for performing the assessments is discussed in Section 6.6. **All efforts should be made to have the same investigator perform the clinical examinations for a given patient, at least for the Screening, Baseline, and Week 6 Visits of the first treatment cycle.**
69	7.4.1 (Dilator Test (Vaginal Dilator Induced Pain))	Based on the subjective pain threshold, the largest sized dilator that the subject accepts/tolerates for the test (i.e. does not agree to the next successive dilator size to be tested), will be defined as the Dilator Maximum Tolerated Size (DMTS) that will be established at Baseline Visit.	Based on the subjective pain threshold, the largest sized dilator that the subject accepts/tolerates for the test (i.e. does not agree to the next successive dilator size to be tested), will be defined as the Dilator Maximum T**ested** Size (DMTS) that will be established at Baseline Visit. **Subject interviews to assess the content relevance of the dilator test will be performed in Stage 2. Subjects from Stage 2 will be invited to complete the interview until the target sample of 20 subjects is achieved. Every effort should be made to conduct the interview within 2 weeks of the subject's Cycle 1-Week 6 visit.** **The subject interviews will be conducted by experienced interviewers trained in qualitative interview techniques. The details of the interview will be provided in the interview guide.**

Version Date		15 MAY 2018	04 NOVEMBER 2018
Page	**Section**	**WAS**	**IS**
70	7.4.2.1 (Modified Vulvar Pain Assessment Questionnaire)	7.4.2.1 Vulvar Pain Assessment Questionnaire (VPAQ) The VPAQ is a more recently developed, self-administered, multidimensional, vulvodynia specific questionnaire, including 55 Likert-type questions and designed to capture 6 domains (VPAQfull): pain severity, emotional response, cognitive response and interference with life, sexual function, self-stimulation/penetration [22]. The score for each question ranges from 0 to 4 and a mean score is computed for each domain. For the purpose of the study, the recall periods for VPAQ subscales will be modified as: • VPAQ pain subscale – The recall period will be over the past 1 week. • VPAQ other subscales - The recall period will be over the past 1 month. The VPAQ questionnaire (with modified recall periods) is included in Appendix 1. The data to be recorded by subjects in the eDiary contributing towards the completion of the questionnaire: • VPAQ pain subscale – Assessed at Screening Visit, then weekly during the screening period (14 days in Stage 1 and 28 days in Stage 2) until Baseline Visit, and then weekly from one month prior to the next planned visit. • VPAQ other subscales - Assessed at the site during the visit (except Additional Visits at Week 18 and Week 30).	7.4.2.1 **Modified** Vulvar Pain Assessment Questionnaire (**m**VPAQ) The Vulvar Pain Assessment Questionnaire (VPAQ) is a more recently developed, self-administered, multidimensional, vulvodynia specific questionnaire, including 55 Likert-type questions and designed to capture 6 domains: pain severity, emotional response, cognitive response and interference with life, sexual function, self-stimulation/penetration [22]. The score for each question ranges from 0 to 4 and a mean score is computed for each domain. For the purpose of the study, the VPAQ subscales will be modified as: • **m**VPAQ pain subscale – The recall period will be over the past 1 week. • **mVPAQ life interference subscale – The recall period will be over the past 1 week.** • **m**VPAQ other subscales – The recall period will be over the past 1 month. • **The sequence of questions for reporting distress (average/ worst) on the pain severity subscale were reversed.** The **m**VPAQ questionnaire is included in Appendix 1. The data to be recorded by subjects in the eDiary contributing towards the completion of the questionnaire: • VPAQ pain subscale – Assessed at Screening Visit, then **1** week prior to the next planned visit **and at the visit**. • **mVPAQ life interference subscale – Assessed at Screening Visit, then 1 week prior to the next planned visit and at the visit.** • VPAQ other subscales - Assessed at the site during the visit (except Additional Visits at Week 18 and Week 30).

Version Date		15 MAY 2018	04 NOVEMBER 2018
Page	**Section**	**WAS**	**IS**
70	7.4.2.2 (Assessment of Intercourse and Vaginal Dilator (Number 6 Size) Insertion Details)	7.4.2.2 Assessment of Intercourse and/or Vaginal Dilator (Number 6 Size) Insertion Details From the Screening Visit during Stage 1 (Day -14) and Stage 2 (Day -28) (i.e. during the screening period), and then one month (28 days) prior to the next planned visit, subjects will record on a daily basis in the eDiary (contributing to collection of data for the corresponding endpoint): All subjects are to rate the level of the corresponding pain following insertion of the number 6 vaginal dilator into the vagina on an 11-point NRS and record details of associated pain medication if consumed.	7.4.2.2 Assessment of Intercourse and Vaginal Dilator (Number 6 Size) Insertion Details From the Screening Visit (Day -14**;** i.e. during the screening period), and then **2 weeks** (**14** days) prior to the next planned visit, subjects will record on a daily basis in the eDiary (contributing to collection of data for the corresponding endpoint): **From 2 weeks prior to the next planned visit, a**ll subjects are to rate **in the eDiary once a week** the level of the corresponding pain following insertion of the number 6 vaginal dilator into the vagina on an 11-point NRS and record details of associated pain medication if consumed. **Assessment on the day of the visit should be avoided.**

Version Date		15 MAY 2018	04 NOVEMBER 2018
Page	**Section**	**WAS**	**IS**
70, 71	7.4.2.3 (Modified Female Sexual Function Index)	7.4.2.3 Female Sexual Function Index (FSFI) The FSFI is a validated self-reported multidimensional 19-item questionnaire for assessing the sexual function in women by evaluating six key domains of sexual function: desire, arousal, lubrication, orgasm, sexual satisfaction, and pain (Appendix 2). A total score and domain scores will be calculated. Every item is assessed with a score from 0 or 1 to 5, the total score being 2-36. Higher scores indicate better sexual function. Sexual function is considered pathological when the total score is ≤26.55 and hence subjects with a baseline score above this value are excluded from the study [23, 24].	7.4.2.3 **Modified** Female Sexual Function Index (**m**FSFI) The FSFI is a validated self-reported multidimensional 19-item questionnaire for assessing the sexual function in women by evaluating six key domains of sexual function: desire, arousal, lubrication, orgasm, sexual satisfaction, and pain. A total score and domain scores will be calculated. Every item is assessed with a score from 0 or 1 to 5, the total score being 2-36. **For the purpose of the study, the recall periods for FSFI pain domain (Questions 17 to 19) will be modified as:** • **mFSFI pain domain – The recall period will be over the past 1 week.** • **mFSFI other domains – The recall period will be over the past 4 weeks.** **The mFSFI questionnaire is included in Appendix 2.** **The data to be recorded by subjects in the eDiary contributing towards the completion of the questionnaire:** • **mFSFI pain domain – Assessed at Screening Visit, then 1 week prior to the next planned visit and at the visit.** • **mFSFI other domains – Assessed at the site during the visit.**
72	7.4.2.7 (36-Item Short Form Health Survey)	7.4.2.7 36-Item Short Form Health Survey (SF-36) (Stage 2 only) The total scores range from 0 to 100. Lower scores indicate more disability and higher scores less disability.	7.4.2.7 36-Item Short Form Health Survey (SF-36) The total scores range from 0 to 100. Lower scores indicate **a less favourable health state** and higher scores **a more favourable health state**.
72	7.4.2.8 (Pain Catastrophizing Scale)	A total score, ranging from 0 to 53 (sum of the 13 items) will be calculated. The PCS will be performed to screen the subjects, but will not be an assessment of the efficacy of the study drug. Subjects with baseline PCS scores of >30 will be excluded from the study.	A total score, ranging from 0 to **52** (sum of the 13 items) will be calculated.

Version Date		15 MAY 2018	04 NOVEMBER 2018
Page	**Section**	**WAS**	**IS**
77	8.1.6 (Reporting of Serious Adverse Events)	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 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 • **Causality** • Investigator's name and contact details
78	8.1.7 (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 and **on the Standard Pregnancy Report Form, including pregnancies with normal progress and outcome. A Standard Pregnancy Report Form must be completed by the investigator and provided to the Sponsor's Pharmacovigilance department within 24 hours of the knowledge of the pregnancy in any study subject.** 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.
83	11.1 (Analyses Populations)	• modified intention to treat (mITT) population: All randomised subjects who received at least one IMP administration and had performed the Cycle1-Week 6 visit.	• modified **Intent-to-Treat** (mITT) population: All randomised subjects who received at least one IMP administration and had **data for the primary endpoint at** Cycle1-Week 6 visit (i.e. at least one pain score for one dilator size).
83	11.1.1 (Populations Analysed)	In Stage 1, the primary analysis based on safety endpoints will be performed on the Safety population. Analyses of efficacy endpoints will be carried out on the mITT and PP populations.	In Stage 1, the primary analysis based on safety endpoints will be performed on the Safety population. Analyses of efficacy endpoints will be carried out on the mITT population.

Version Date		15 MAY 2018	04 NOVEMBER 2018
Page	**Section**	**WAS**	**IS**
83, 84	11.2 (Sample Size Determination)	Subject who discontinue prior to Week 6 for reasons unrelated to safety may be replaced at the discretion of the investigator and sponsor. Subjects who prematurely discontinue after receiving the dose of Dysport or Placebo, will be not replaced. As this is an exploratory stage, no formal power could be performed. However, with 8 active subjects per dose cohort and if there are 0 DLEs in a cohort, there is at least 80% probability that the true incidence of DLEs at the corresponding dose will not be greater than 18%. The ability to rule out smaller DLE rates with high confidence will come from observing additional subjects in Stage 2.	Subject who discontinue prior to Week 6 for reasons unrelated to safety may be replaced at the discretion of the investigator and sponsor. As this is an exploratory stage, no formal power could be performed. However, with 8 active subjects per dose cohort and if there are 0 DLEs in a cohort, there is at least 80% probability that the true incidence of DLEs at the corresponding dose will not be greater than 18%. The ability to rule out smaller DLE rates with high confidence will come from observing additional subjects in Stage 2.
84	11.3 (Significance Testing and Estimations)	As this is a descriptive safety study, no formal statistical testing will be carried out. All statistical tests performed using a two-sided significance level of 5% will be considered as exploratory. No adjustment for multiple comparisons will be applied.	As this is a descriptive safety study, no formal statistical testing will be carried out. **P-values, unadjusted** for multiple comparisons**, may be presented, but they will be regarded as descriptive.**

Version Date		15 MAY 2018	04 NOVEMBER 2018
Page	**Section**	**WAS**	**IS**
85	11.4.3 (Efficacy Evaluation)	Stage 1: The primary objective and endpoint of the stage 1 is the safety assessments. However, as indicated in Section 7.1, the main secondary efficacy endpoint is the change from baseline to Week 6 in the vaginal dilator induced pain as reported on an 11-point NRS (using the DMTS reported at baseline). Change from baseline to Week 6 will be assessed by analysis of covariance (ANCOVA) with treatment group (4 Dysport doses and placebo) included as a factor and baseline pain value as covariate. The primary efficacy results will be presented adjusted for covariate in the model. Dose trend analysis will also be carried out. The secondary efficacy endpoints (as indicated in Section 7.2) will be analysed using an ANCOVA or a logistic regression according to the endpoints scale (continuous or categorical). Cohort and treatment group will be included as factor and baseline value as covariate. Stage 2: Subjects who are unable to reach the baseline maximum tolerated size at a postbaseline will have an imputed pain score of 10 at the maximum tolerated size for that visit.	Stage 1: The primary objective and endpoint of the stage 1 is the safety assessments. **Descriptive statistics will be performed on the safety and efficacy endpoints**. Stage 2: Subjects who are unable to reach the baseline maximum **tested** size at a postbaseline **visit** will have an imputed pain score of 10 at the maximum **tested** size for that visit. **Additional psychometric analyses will be conducted on the study data (Stage 1 and Stage 2) to validate the PROs used in the study.**

Version Date		15 MAY 2018	04 NOVEMBER 2018
Page	**Section**	**WAS**	**IS**
88	13.1.2 (Protocol Deviations and Exceptions)	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.	A protocol deviation is any **change,** divergence**, or departure from the study design or procedures defined in the protocol.** **Major protocol deviations are a subset of protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being. (For example, major protocol deviations might include enrolling subjects in violation of key eligibility criteria designed to ensure a specific subject population or failing to collect data necessary to interpret primary endpoints, as this may compromise the scientific value of the trial.)**
		A minor protocol deviation is any significant divergence from the protocol that does not impact the study results or subject rights.	A minor protocol deviation is any **change in the study design, study conduct and/or procedures that are not in accordance with** the protocol **and any study materials originally approved by the IEC/IRB but do** not **have a major** impact **on** the subject's rights**, safety or wellbeing, or the completeness, accuracy and reliability of the study data**.
100	Appendix 1	VPAQ (with modified recall periods)	**m**VPAQ **Version 1.1**
103	Appendix 2	FSFI	**m**FSFI **Version 1.1**

SUMMARY & OUTCOME OF CHANGES:

STUDY NUMBER	D-FR-52120-236	
AMENDED PROTOCOL VERSION NUMBER & DATE	Protocol Version 3.0: 04 November 2018	
SUBSTANTIAL ☒	**NON-SUBSTANTIAL** ☐	
REASON(S) FOR CHANGES	The protocol was updated to add more flexibility in the duration of the screening period, to make the screening period consistent between Stage 1 and Stage 2, remove the upper age limit of subjects, clarify the timing of assessments performed as part of inclusion/exclusion criteria, revise the scoring requirement of the mFSFI questionnaire exclusion criterion, remove the PCS exclusion criterion, clarify the concomitant medications exclusion criterion, update the rescreening criteria, specify the PGI-S secondary endpoint as mean change from baseline, modify the mITT population to be consistent with the SAP, and correct any inconsistencies. Additionally, in response to the FDA agency feedback: • The recall periods for some subscales/domains of patient reported outcomes were modified and questionnaires updated (mFSFI and mVPAQ) which were appended to the protocol • The schedule of assessments was updated with regards to the frequency and timing of collection of some parameters to align with the recommendations • Subject interviews to assess the content relevance of the dilator test (primary endpoint) were added.	
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)*

Appendix 8 Protocol Amendment: Version 4.0 (08 April 2019)

STUDY NUMBER:	D-FR-52120-236
PROTOCOL TITLE:	A phase II, multicentre, double-blind, randomised, placebo-controlled, dose escalation and dose finding study to evaluate the efficacy and safety of Dysport in vulvodynia patients
PREVIOUS PROTOCOL VERSION NUMBER & DATE	Protocol Version 3.0: 04 November 2018
AMENDED PROTOCOL VERSION NUMBER & DATE	Protocol Version 4.0: 08 April 2019

The updated text in the amendment is reflected in bold and deletions are marked in strikeout text.

THE FOLLOWING AMENDMENT(S) ARE PROPOSED:

Version Date		**04 NOVEMBER 2018**	**08 APRIL 2019**
Page	**Section**	**WAS**	**IS**
6	**Synopsis** Stage 1 (Dose Escalation) Double-Blind Period	It is intended to enroll up to three dose level cohorts. Each cohort will include 10 unique evaluable subjects. Subjects will be randomised in a ratio of 4:1 (Dysport: 8 + Placebo: 2) in a dose-escalation manner starting with a total Dysport dose of 100 U, 300 U and 400 U, however doses will be adapted as necessary within this dose range (100 U to 400 U), based on results observed.	It is intended to enroll up to three dose level cohorts **of secondary PVD subjects (i.e. having a past history of pain-free intercourse or insertion of any object >1 cm diameter; hereafter referred to as PVD2 subjects)**. Each cohort will include 10 unique evaluable **PVD2** subjects. Subjects **in these cohorts** will be randomised in a ratio of 4:1 (Dysport: 8 + Placebo: 2) in a dose-escalation manner starting with a total Dysport dose of 100 U, 300 U and 400 U, however doses will be adapted as necessary within this dose range (100 U to 400 U), based on results observed.

Version Date		04 NOVEMBER 2018	08 APRIL 2019
Page	**Section**	**WAS**	**IS**
6	**Synopsis** (Stage 1 (Dose Escalation) Double-Blind Period)	When all subjects in Stage 1 have completed 6 weeks of follow-up of treatment cycle 1, the DRC will meet again to enable selection of dose(s) to be assessed and confirm the sample size for Stage 2.	When all subjects in **the PVD2 cohorts of** Stage 1 have completed 6 weeks of follow-up of treatment cycle 1, the DRC will meet again to enable selection of dose(s) to be assessed and confirm the sample size for Stage 2. **In parallel with the PVD2 Cohort 3, an additional cohort (Cohort 4) of primary PVD subjects (i.e. having life-long provoked vestibular pain; hereafter referred to as PVD1 subjects), will be recruited, at the same Dysport dose as for the PVD2 Cohort 3. This Cohort 4 will include 8 unique evaluable PVD1 subjects who will be randomised in a ratio of 3:1 (Dysport: 6 + Placebo: 2). PVD1 subjects will be recruited in Stage 2 based on the DRC review of efficacy and safety data obtained from PVD1 cohort(s) in Stage 1.**
7	**Synopsis** (Number of Subjects Planned)	The study will include approximately a total of 93 female subjects (approximately 30 in Stage 1 and 63 in Stage 2).	The study will include approximately ~~a total of 93~~**100** female subjects (approximately 3~~0~~ in Stage 1 and 63 in Stage 2).

Version Date		04 NOVEMBER 2018	08 APRIL 2019
Page	**Section**	**WAS**	**IS**
8 and 44	**Synopsis and Section 4.1** (Inclusion Criteria)	(9) Are able to tolerate the smallest dilator size (diameter 0.5 inches) at the Screening Visit, i.e. agree to the next successive dilator size to be tested for pain response. (11) Willing to abstain from physical therapy and sex therapy (defined as a therapy primarily focused on the management of vulvar pain) for the duration of screening and up to at least Week 6 of the first treatment cycle (physical therapy includes but is not limited to: internal/external myofascial release by physiotherapist, biofeedback, home pelvic floor exercises, self-taught exercises, etc.). (12) In Stage 1, only subjects with secondary vulvodynia (i.e. having a past history of pain-free intercourse or insertion of any object >1 cm diameter) will be enrolled. In Stage 2, subjects with either primary (having life-long provoked vestibular pain) or secondary vulvodynia ~~can~~ be enrolled.	(9**a**) Are able to tolerate the smallest dilator size (diameter 0.5 inches) at the Screening Visit, i.e. agree to the next successive dilator size to be tested for pain response **(i.e. the two smallest sized dilators (#1 and 2) are to be tested)** (11**a**) Willing to abstain from ~~physical therapy and~~ sex therapy (defined as a therapy primarily focused on the management of vulvar pain) for the duration of screening and up to at least Week 6 of the first treatment cycle ~~(physical therapy includes but is not limited to: internal/external myofascial release by physiotherapist, biofeedback, home pelvic floor exercises, self-taught exercises, etc.)~~. (12**a**) In Stage 1, ~~only~~ **in all cohorts except Cohort 4,** ~~only~~ subjects with secondary vulvodynia (i.e. having a past history of pain-free intercourse or insertion of any object >1 cm diameter) will be enrolled. ~~In~~ **Stage 1** ~~2~~**, Cohort 4 will only include subjects with** ~~either~~ **primary vulvodynia (having life-long provoked vestibular pain).** In Stage 2, subjects with either primary ~~(having life-long provoked vestibular pain)~~ or secondary vulvodynia **may** be enrolled **as approved by the DRC.**

Version Date		04 NOVEMBER 2018	08 APRIL 2019
Page	**Section**	**WAS**	**IS**
9, 10 and 45, 46	**Synopsis and Section 4.2** (Exclusion Criteria)	(2a) Able to tolerate the 6th (diameter 1¼ inches) dilator size (i.e. agree to the next successive dilator size to be tested for pain response) at the Baseline Visit. (7a) Significant depression disorder, e.g. having a score ≥20/27 on the depression subscale of on the Patient Health Questionnaire (PHQ-9) scale at the Baseline Visit. (15) Positive urine test for illicit drugs (drugs of abuse) at screening. In the event a subject tests positive for cannabinoids (tetrahydrocannabinol), the investigator will evaluate the subject's ability to abstain from cannabis during the study. If in the investigator's clinical judgement, the subject will abstain, the subject may be enrolled after consultation with the Medical Monitor. (16a) Has received any of the following: - Pelvic floor physical therapy or sex therapy received in the past 6 weeks prior to Baseline. - Previous treatment with any botulinum toxin (BTX) for any indication within the last 1 year. - Treatment for anterior vestibular pain, e.g. hormonal creams, in the last 1 week prior to Screening unless continued at the same dosing regimen throughout the study.	(2b~~a~~) Able to tolerate the 6th (diameter 1¼ inches) dilator size (i.e. agree to the next successive dilator size to be tested for pain response) at the Baseline Visit **(i.e. at least one of the two largest sized dilators (#7 and/or 8) is tested)**. (7a) Significant ~~depression~~ depressive disorder, e.g. having a score ≥20/27 ~~on the depression subscale of~~ on the Patient Health Questionnaire (PHQ-9) scale at the Baseline Visit. (15**a**) Positive urine test for illicit drugs (drugs of abuse) at screening. In the event a subject tests positive for cannabinoids (tetrahydrocannabinol), the investigator will evaluate the subject's ability to abstain from cannabis during the study. If in the investigator's clinical judgement, the subject will abstain, the subject may be enrolled after consultation with the Medical Monitor. **Note: at the discretion of the investigator, positive drug screens for prescribed medications will not be considered exclusionary**. (16b~~a~~) Has received any of the following: - Pelvic floor physical therapy ~~or sex therapy received in the past 6 weeks~~**initiated, stopped or modified (frequency or type of physical therapy) during the last 12 weeks** prior to Baseline **(physical therapy includes but is not limited to: internal/external myofascial release by physiotherapist, biofeedback, home pelvic floor exercises, self-taught exercises, use of vaginal dilators, etc.).** - **Sex therapy in the past 6 weeks prior to Baseline.** - Previous treatment with any botulinum toxin (BTX) for any indication within the last 1 year. - Treatment for anterior vestibular pain, ~~e.g.~~**with** hormonal creams, in the last 1 week prior to Screening unless continued at the same dosing regimen throughout the study.

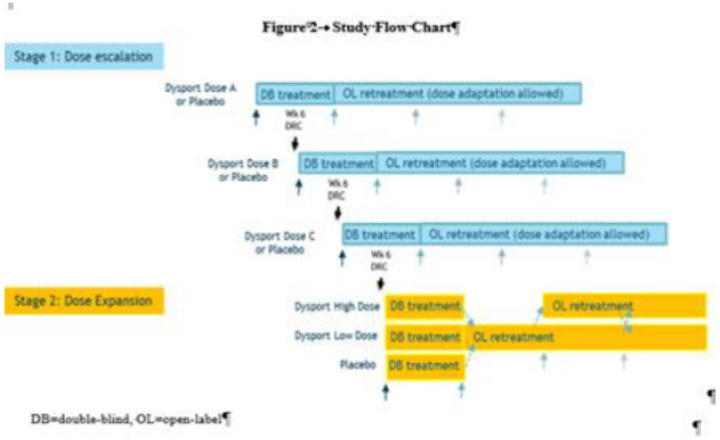
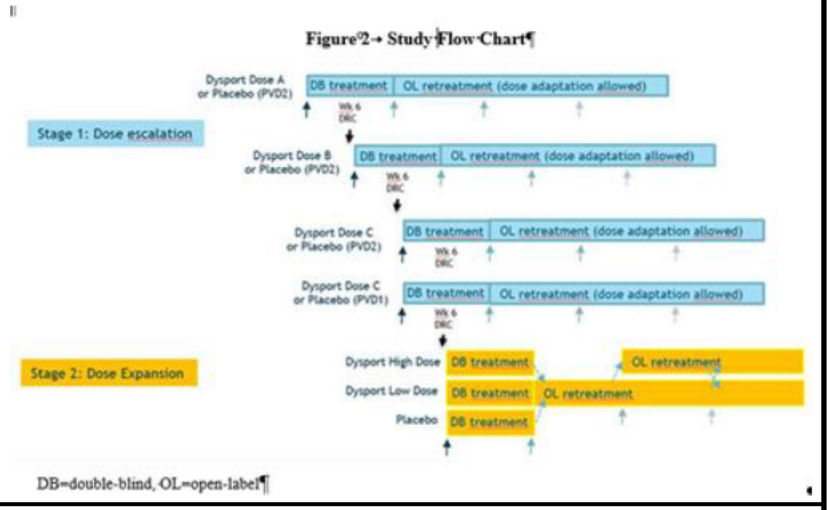
Version Date		04 NOVEMBER 2018	08 APRIL 2019
Page	**Section**	**WAS**	**IS**
13	**Synopsis** (Method of Randomisation)	Stage 1: For each cohort, subjects will be randomised with a 4:1 (Dysport: placebo) ratio.	Stage 1: For ~~each~~ **the PVD2** cohorts, subjects will be randomised with a 4:1 (Dysport: placebo) ratio. **For the PVD1 cohort, subjects will be randomised with a 3:1 (Dysport: placebo) ratio.**
13	**Synopsis** (Sample Size and Power Considerations)	Stage 1: With 8 evaluable subjects on active treatment per dose cohort and if there are 0 DLEs in a cohort, there is at least 80% probability that the true incidence of DLEs at the corresponding dose will not be greater than 18%.	Stage 1: With 8 evaluable subjects on active treatment per **PVD2** dose cohort and if there are 0 DLEs in a cohort, there is at least 80% probability that the true incidence of DLEs at the corresponding dose will not be greater than 18%.
14	**Synopsis** (Data Review Committee (DRC) Meetings)	If no subject reports a clinically significant AE up to Week 6 in a cohort, the DRC will meet once all 10 evaluable subjects have reached Week 6 of a cohort to review the efficacy and safety data and decide the dose for the next cohort. At the end of Cycle 1–Week 6 for all subjects in Stage 1, the DRC will meet to review efficacy and safety data and decide on the one or two doses of Dysport to be assessed in the Stage 2 of the study and the sample size for Stage 2 will be recalculated.	If no subject reports a clinically significant AE up to Week 6 in a cohort, the DRC will meet once all 10 **PVD2 (or 8 PVD1)** evaluable subjects have reached Week 6 of a cohort to review the efficacy and safety data and decide the dose for the next cohort. At the end of Cycle 1–Week 6 for all subjects in **PVD2 cohorts in** Stage 1, the DRC will meet to review efficacy and safety data and decide on the one or two doses of Dysport to be assessed in the Stage 2 of the study and the sample size for Stage 2 will be recalculated. **Once all PVD1 subjects in Cohort 4 have reached Cycle 1-Week 6 visit, the DRC will meet and based on review of all safety and efficacy data from the cohort, will decide if further PVD1 cohort(s) are required or if PVD1 subjects should be removed from Stage 2.**
22	**List of abbreviations**	CMC Chemistry, Manufacturing and Control	~~CMC Chemistry, Manufacturing and Control~~
25	**Section 1.4** (Known and Potential Risks and Benefits to Human Subjects)	Adverse events (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).	Adverse events (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 **resulting from dysphagia**).

Version Date		04 NOVEMBER 2018	08 APRIL 2019
Page	**Section**	**WAS**	**IS**
26, 27	**Section 1.7** (Population to be Studied)	The study will recruit premenopausal adult female subjects aged between 18 and 45 years. The subjects should not have taken physiotherapy for at least 6 weeks prior to the entry into the study and not have received any BTX for any indication within the last 1 year. In the dose escalation stage of the study, only subjects with secondary PVD (having acquired PVD, i.e. developing pain after a period of pain-free penetrative activities) will be enrolled. In the dose expansion stage of the study, the subject population will be expanded to include subjects with both primary (having life-long PVD) and secondary vulvodynia to assess the efficacy and safety of Dysport in both subpopulations.	The study will recruit premenopausal adult female subjects aged ~~between~~ 18 ~~and 45~~ years **or above.** The subjects should ~~not~~ have taken **a stable** physiotherapy **(if any)** for at least ~~6~~**12** weeks prior to the entry into the study and not have received any BTX for any indication within the last 1 year. ~~In the dose escalation stage of the study, only subjects with secondary PVD (having acquired PVD, i.e. developing pain after a period of pain-free penetrative activities) will be enrolled. In the dose expansion stage of the study, the subject population will be expanded to include subjects with both primary (having life-long PVD) and secondary vulvodynia to assess the efficacy and safety of Dysport in both subpopulations.~~
30	**Section 3.1** (Study Design)	The study will include approximately a total of 93 premenopausal female subjects (approximately 30 in Stage 1 and 63 in Stage 2) aged between 18 and 45 years with a diagnosis of PVD associated with provoked pain at the posterior vestibule.	The study will include approximately ~~a total of 93~~**100** premenopausal female subjects (approximately 38~~0~~ in Stage 1 and 63 in Stage 2) aged ~~between~~ 18 ~~and 45~~ years **or above** with a diagnosis of PVD associated with provoked pain at the posterior vestibule.

Version Date		04 NOVEMBER 2018	08 APRIL 2019
Page	**Section**	**WAS**	**IS**
30, 31	**Section 3.1.1** (Stage 1 (Dose Escalation))	It is intended to enroll up to three dose level cohorts evaluating Dysport doses ranging from 100 U to 400 U (total dose administered) to find one or two optimally safe and effective doses of Dysport that will be further investigated in the Stage 2. Additional dose level cohorts within this dose range (100 to 400 U) may potentially be added based on the recommendations from the DRC. Each cohort will include 10 unique evaluable subjects who will be randomised via the interactive response system (IRS) to the two double-blind parallel treatment arms in 4:1 ratio: • Dysport (N=8) or • Placebo (N=2). Once 10 evaluable subjects in a cohort have reached the Week 6 visit, decision for dose escalation for the subsequent cohort will be agreed at the DRC meeting upon review of the available efficacy and safety data. At the end of Cycle 1 – Week 6 for all subjects in Stage 1, the DRC will meet to review efficacy and safety data and decide on the one or two doses of Dysport to be assessed in the Stage 2 of the study and the sample size for Stage 2 will be recalculated.	It is intended to enroll up to three dose level cohorts **of secondary PVD subjects (i.e. having a past history of pain free intercourse or insertion of any object >1 cm diameter; hereafter referred to as PVD2 subjects)** evaluating Dysport doses ranging from 100 U to 400 U (total dose administered) to find one or two optimally safe and effective doses of Dysport that will be further investigated in the Stage 2. Additional dose level cohorts within this dose range (100 **U** to 400 U) may potentially be added based on the recommendations from the DRC. Each **PVD2** cohort will include 10 unique evaluable **PVD2** subjects who will be randomised via the interactive response system (IRS) to the two double-blind parallel treatment arms in 4:1 ratio: • Dysport (N=8) or • Placebo (N=2). **An additional Cohort 4 will include 8 unique evaluable primary PVD subjects (i.e. having life-long provoked vestibular pain; hereafter referred to as PVD1 subjects), at the same Dysport dose as for the PVD2 Cohort 3, who will be randomised via the IRT to the two double-blind parallel treatment arms in 3:1 ratio:** • **Dysport (N=6) or** • **Placebo (N=2).** **In an event, when the 10th subject (or 8th in Cohort 4) is being randomised, if an additional subject (11th (or 9th in Cohort 4)) has been screened, this subject may be accepted in the cohort and be randomised.** Once 10 **PVD2 (or 8 PVD1)** evaluable subjects in a cohort have reached the Week 6 visit, decision for dose escalation for the subsequent cohort will be agreed at the DRC meeting upon review of the available efficacy and safety data. At the end of Cycle 1 – Week 6 for all **PVD2** subjects in Stage 1, the DRC will meet to review efficacy and safety data and decide on the one or two doses of Dysport to be assessed in the Stage 2 of the study and the sample size for Stage 2 will be recalculated. **PVD1 subjects will be recruited in Stage 2 following DRC review of the efficacy and safety data of PVD1 cohort(s) in Stage 1.**

Version Date		04 NOVEMBER 2018	08 APRIL 2019
Page	**Section**	**WAS**	**IS**
32	**Section 3.1.1.2** (DRC Meetings)	If no subject reports a clinically significant AE up to Week 6 in a cohort, the DRC will meet once all 10 evaluable subjects of a cohort have reached Week 6 to review the unblinded efficacy and safety data and decide the dose for the next cohort. Once all subjects in Stage 1 have reached Cycle 1-Week 6 visit, the DRC will meet and, based on the unblinded review of all safety and efficacy data from the cohort(s), will decide the one or two dose(s) to be assessed in Stage 2 and the sample size for Stage 2 will be formally recalculated.	If no subject reports a clinically significant AE up to Week 6 in a cohort, the DRC will meet once all 10 **PVD2 (or 8 PVD1)** evaluable subjects of a cohort have reached Week 6 to review the unblinded efficacy and safety data and decide the dose for the next cohort. Once all subjects in **PVD2 cohorts in** Stage 1 have reached Cycle 1-Week 6 visit, the DRC will meet and, based on the unblinded review of all safety and efficacy data from the cohort(s), will decide the one or two dose(s) to be assessed in Stage 2 and the sample size for Stage 2 will be formally recalculated. **Once all PVD1 subjects in Cohort 4 have reached Cycle1-Week6 visit, the DRC will meet and based on unblinded review of all safety and efficacy data from the cohort, will decide if further PVD1 cohort(s) are required or if PVD1 subjects should be removed from Stage 2.**

Version Date		04 NOVEMBER 2018	08 APRIL 2019
Page	**Section**	**WAS**	**IS**
37, 38	**Section 3.5** (Randomisation and Blinding)	For Stage 1, the sponsor's randomisation manager who is a statistician, independent from the study, will prepare: • A list of randomisation numbers (List A1). It will be produced in blocks, on an unbalanced ratio (4 Dysport: 1 placebo) and will be stratified by cohort. After eligibility is confirmed, at Baseline (V2), subjects will be assigned to a randomisation number and to the associated treatment arm, in sequential order within each study centre and within each level of strata. Recruitment will stop in each cohort of Stage 1 (and respectively in Stage 2) once 10 (**(or 8 in Cohort 4)** and respectively 63) evaluable subjects have been randomised with the expected ratio. The sponsor's randomisation manager will keep the master lists. A copy of lists of treatment numbers (lists B1 and B2) will be confidentially supplied to the Chemistry Manufacturing and Control (CMC) Supply Chain CCI [redacted] The master lists and the copies supplied to the CMC Supply Chain, CRO in charge of IRT and to the independent statistician in charge of TFLs for DRC will be kept confidential in a secure location.	For Stage 1, the sponsor's randomisation manager who is a statistician, independent from the study, will prepare: • A list of randomisation numbers (List A1). It will be produced in blocks, on an unbalanced ratio (4 Dysport: 1 placebo) and will be stratified by cohort. **For Cohort 4, Dysport randomisation numbers will be deactivated randomly to get an unbalanced ratio (3 Dysport: 1 placebo).** After eligibility is confirmed, at Baseline (V2), subjects will be assigned to a randomisation number and to the associated treatment arm, in sequential order within each study centre and within each level of strata. **In Stage 1, from Cohort 3 onwards, the IRT will also consider the subject pain-onset subtype for cohort/randomisation number assignation.** Recruitment will stop in each cohort of Stage 1 (and respectively in Stage 2) once 10 (**(or 8 in Cohort 4)** and respectively 63) evaluable subjects have been randomised with the expected ratio. The sponsor's randomisation manager will keep the master lists. A copy of lists of treatment numbers (lists B1 and B2) will be confidentially supplied to the ~~Chemistry Manufacturing and Control (CMC) Supply Chain~~ CCI [redacted] The master lists and the copies supplied to ~~the~~ **Ipsen PharmSciences**~~CMC Supply Chain~~, CRO in charge of IRT and to the independent statistician in charge of TFLs for DRC will be kept confidential in a secure location.
39	**Section 3.6** (Management of Randomisation and Blinding)	Finally, if needed, DRC will be able to unblind any subject of Stage 1, with the hard copy sealed code break envelope of her randomisation number (this set of envelopes will be prepared by Ipsen randomisation manager).	Finally, if needed, DRC will be able to unblind any subject of Stage 1, with the hard copy sealed code break envelope of her randomisation number (this set of envelopes will be prepared by Ipsen randomisation manager) **or using the IRT**.

Version Date		04 NOVEMBER 2018	08 APRIL 2019
Page	**Section**	**WAS**	**IS**
39	**Section 3.7.1** (Study Treatments)	The IMPs will be packaged by CMC Supply Chain CCI [redacted] and delivered to an interim storage facility.	The IMPs will be packaged by ~~CMC Supply Chain~~ CCI [redacted] and delivered to an interim storage facility.
40	**Section 3.7.2** (Figure 2 – Study Flow Chart)		
40	**Section 3.7.2.1** (Stage 1)	<u>Double-Blind Period (Treatment Cycle 1)</u> The starting dose for Cohort 1 will be Dysport 100 U or placebo. It is anticipated that if there are no safety issues then the pre-defined doses for Cohorts 2 and 3 will be 300 U and 400 U, respectively, with matching placebos. However, the DRC may decide to assess intermediate dose(s) within the dose range of 100 U to 400 U or to reassess the previously used dose level based on the review of efficacy and safety data from the cohort(s). An additional dose level cohort (Cohort 4) may also potentially be added with 10 evaluable subjects based on the recommendations from the DRC.	<u>Double-Blind Period (Treatment Cycle 1)</u> The starting dose for **PVD2** Cohort 1 will be Dysport 100 U or placebo. It is anticipated that if there are no safety issues then the pre-defined doses for **PVD2** Cohorts 2 and 3 will be 300 U and 400 U, respectively, with matching placebos. **Subjects in PVD1 Cohort 4 will receive the same dose as subjects in PVD2 Cohort 3.** However, the DRC may decide to assess intermediate dose(s) within the dose range of 100 U to 400 U or to reassess the previously used dose level based on the review of efficacy and safety data from the cohort(s). ~~An a~~**A**dditional dose level cohort**(s)** ~~(Cohort 4)~~ may also potentially be added ~~with 10 evaluable subjects~~ based on the recommendations from the DRC **(the requirement for primary and/or secondary PVD subjects will be specified by the DRC)**.

Version Date		04 NOVEMBER 2018	08 APRIL 2019
Page	**Section**	**WAS**	**IS**
41	**Section 3.7.2.1** (Stage 1)	Open-Label Period (Treatment Cycles 2-4) For a given subject, the Dysport dose for treatment cycles 2, 3 and 4 will be based on the investigator's judgement (based on efficacy and safety). • Treatment cycle 2: the Dysport dose can either be the Dysport dose assessed in the previous treatment cycle (double-blind period) for the current cohort or the Dysport dose of the following cohort (provided it has been approved by the DRC). Subjects who received placebo in the treatment cycle 1, will receive the previous dose approved by the DRC.	Open-Label Period (Treatment Cycles 2-4) For a given subject, the Dysport dose for treatment cycles 2, 3 and 4 will be based on the investigator's judgement (based on efficacy and safety). • Treatment cycle 2: the Dysport dose can either be the Dysport dose assessed in the previous treatment cycle (double-blind period) for the current cohort or the Dysport dose of the following cohort (provided it has been approved by the DRC). ~~Subjects who received placebo in the treatment cycle 1, will receive the previous dose approved by the DRC.~~
65	**Section 6.3** (Concomitant Medication/ Therapy)	The following concomitant medications/therapies are not permitted during this study (see also Section 4.2): • Pelvic floor physical therapy and sex therapy (defined as a therapy primarily focused on the management of vulvar pain) up to 6 weeks after the first treatment cycle of the double-blind period. Any pelvic floor physical therapy or sex therapy initiated after this, needs to be maintained at the same frequency/regimen throughout the study. • Topical lidocaine, topical antidepressants, topical anti-epileptics and diazepam suppositories are not permitted during the study. Note: Immediately prior to and during study drug administration procedures, oral, topical (other than lidocaine) or intravenous medications routinely used as standard of care for vaginal intramuscular injections are allowed.	The following concomitant medications/therapies are not permitted during this study (see also Section 4.2): • ~~Pelvic floor physical therapy and s~~Sex therapy (defined as a therapy primarily focused on the management of vulvar pain) up to 6 weeks after the first treatment cycle of the double-blind period. Any ~~pelvic floor physical therapy or~~ sex therapy initiated after this, needs to be maintained at the same frequency/regimen throughout the study. • Topical lidocaine, topical antidepressants, topical anti-epileptics and diazepam suppositories are not permitted during the study. Note: Immediately prior to and during study drug administration procedures, oral, topical (~~other than~~**including** lidocaine) or intravenous medications routinely used as standard of care for vaginal intramuscular injections are allowed.

Version Date		04 NOVEMBER 2018	08 APRIL 2019
Page	**Section**	**WAS**	**IS**
65	**Section 6.3** (Concomitant Medication/ Therapy)	The following concomitant medications are permitted during this study, but they must be monitored closely and, where applicable, every effort should be made to keep their dose and dose regimen constant: • Concomitant use of topical treatments for anterior vestibular pain e.g. topical hormonal creams are permitted if the subject has no residual anterior vestibule pain at screening and wants to continue on the same treatment regimen throughout the study to prevent recurrence of anterior vestibular pain. Note: Topical antidepressants are not permitted.	The following concomitant medications/**therapies** are permitted during this study, but they must be monitored closely and, where applicable, every effort should be made to keep their dose and dose regimen constant: • **Concomitant pelvic floor physical therapy is permitted. Subjects should maintain the dose regimen constant from 12 weeks prior to Baseline and throughout the first treatment cycle.** • Concomitant use of topical treatments for anterior vestibular pain ~~e.g.~~**with** topical hormonal creams are permitted if the subject has no residual anterior vestibule pain at screening and wants to continue on the same treatment regimen throughout the study to prevent recurrence of anterior vestibular pain. Note: Topical antidepressants are not permitted.
70	**Section 7.4.1** (Dilator Test (Vaginal Dilator Induced Pain))	A set of 8 vaginal dilators of increasing diameter will be used to provoke pain to allow assessment of the vestibular pain intensity in each subject.	A set of 8 vaginal dilators of increasing diameter **(#1 being the smallest and #8 being the largest)** will be used to provoke pain to allow assessment of the vestibular pain intensity in each subject.
84	**Section 11.1** (Analyses Populations)	The following populations will be used during statistical analyses for Stage 1 and Stage 2: • modified Intent-to-Treat (mITT) population: All randomised subjects who received at least one IMP administration and had data for the primary endpoint at Cycle 1-Week 6 visit (i.e. at least one pain score for one dilator size). • Per protocol (PP) population: All subjects in the mITT population for whom no major protocol deviations, which may interfere with the efficacy evaluation, occurred until Cycle 1-Week 6.	The following populations will be used during statistical analyses for Stage 1 and Stage 2: • modified Intent-to-Treat (mITT) population: All randomised subjects who received at least one IMP administration and had data for the primary endpoint at **Baseline and** Cycle 1-Week 6 visit (i.e. at least one pain score for one dilator size). • Per protocol (PP) population: All subjects in the mITT population for whom no major protocol deviations, which may interfere with the efficacy evaluation, occurred ~~until~~**between Screening and** Cycle 1-Week 6 **included**.

Version Date		04 NOVEMBER 2018	08 APRIL 2019
Page	**Section**	**WAS**	**IS**
84, 85	**Section 11.2** (Sample Size Determination)	Stage 1: In Stage 1, the expected sample size is 10 evaluable subjects per cohort who will be randomised and treated in a 4:1 allocation ratio (Dysport or Placebo). Subject who discontinue prior to Week 6 for reasons unrelated to safety may be replaced at the discretion of the investigator and sponsor. As this is an exploratory stage, no formal power could be performed. However, with 8 active subjects per dose cohort and if there are 0 DLEs in a cohort, there is at least 80% probability that the true incidence of DLEs at the corresponding dose will not be greater than 18%.	Stage 1: In Stage 1, the expected sample size is 10 evaluable subjects ~~per~~ **for PVD2** cohorts who will be randomised and treated in a 4:1 allocation ratio (Dysport or Placebo)**, and 8 evaluable subjects for PVD1 Cohort 4 treated in a 3:1 allocation ratio (Dysport or Placebo).** Subject who discontinue prior to Week 6 for reasons unrelated to safety may be replaced at the discretion of the investigator and sponsor. As this is an exploratory stage, no formal power could be performed. However, with 8 active subjects per **PVD2** dose cohort and if there are 0 DLEs in a cohort, there is at least 80% probability that the true incidence of DLEs at the corresponding dose will not be greater than 18%.
87	**Section 11.4.6.1** (Data Review Committee (End of Stage 1 – Cycle 1-Week 6))	When all subjects in Stage 1 have reached Cycle 1-Week 6 visit, the DRC will review the unblinded efficacy and safety data to enable: • Selection of doses • Confirm the sample size for Stage 2 • Confirm the list of endpoints to be used in Stage 2.	When all subjects in **PVD2 cohorts in** Stage 1 have reached Cycle 1-Week 6 visit, the DRC will review the unblinded efficacy and safety data to enable: • Selection of doses • Confirm the sample size for Stage 2 • Confirm the list of endpoints to be used in Stage 2. **Once all PVD1 subjects in Cohort 4 have reached Cycle 1-Week 6 visit, the DRC will meet and based on unblinded review of all safety and efficacy data from the cohort, will decide if further PVD1 cohort(s) are required or if PVD1 subjects should be removed from Stage 2.**

SUMMARY & OUTCOME OF CHANGES:

STUDY NUMBER	D-FR-52120-236	
AMENDED PROTOCOL VERSION NUMBER & DATE	Protocol Version 4.0: 08 April 2019	
SUBSTANTIAL ☒	**NON-SUBSTANTIAL** ☐	
REASON(S) FOR CHANGES	The protocol was updated to: • Include an additional Cohort 4 in Stage 1 enrolling 8 subjects with primary vulvodynia (PVD1 subjects) in parallel to the Cohort 3 enrolling subjects with secondary vulvodynia (PVD2 subjects), thus impacting the overall sample size. • Further clarify the inclusion and exclusion criteria to facilitate subject recruitment. • Further clarify the concomitant medications exclusion criterion. • Update the name of the sponsor's Chemistry, Manufacturing and Control Supply Chain department. • Update the definition used to define the mITT and PP populations.	
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)*

Appendix 9 Protocol Amendment Version 5.0 (23 January 2020)

STUDY NUMBER:	D-FR-52120-236
PROTOCOL TITLE:	A phase II, multicentre, double-blind, randomised, placebo-controlled, dose escalation and dose finding study to evaluate the efficacy and safety of Dysport in vulvodynia patients
PREVIOUS PROTOCOL VERSION NUMBER & DATE	Protocol Version 4.0: 08 April 2019
AMENDED PROTOCOL VERSION NUMBER & DATE	Protocol Version 5.0: 23 January 2020

The updated text in the amendment is reflected in bold and deletions are marked in strikeout text.

THE FOLLOWING AMENDMENT(S) ARE PROPOSED:

Version Date		**08 APRIL 2019**	**23 JANUARY 2020**
Page	**Section**	**WAS**	**IS**
1	**Title Page**	**Sponsor's Medically Responsible Person:** PPD	**Sponsor's Medically Responsible Person:** PPD
1	**Title Page**	**Sponsor's Co-ordinating and Monitoring Office:** PPD	**Sponsor's Co-ordinating and Monitoring Office:** PPD

Version Date		08 APRIL 2019	23 JANUARY 2020
Page	**Section**	**WAS**	**IS**
		Ipsen Innovation, R&D Clinical Development Program, 5 Avenue du Canada, 91940 Les Ulis, Cedex France PP D	Ipsen Innovation, R&D Clinical Development Program, 5 Avenue du Canada, 91940 Les Ulis, Cedex France PP D
1	**Title Page**	For serious adverse events (SAE) reporting: PPD	For serious adverse events (SAE) reporting: PPD
2	**Investigator's Agreement**	**Sponsor's Representative Signature:** PPD	**Sponsor's Representative Signature:** PPD

Version Date		08 APRIL 2019	23 JANUARY 2020
Page	**Section**	**WAS**	**IS**
			PPD
5	**Synopsis** (Number of Planned Centres)	Approximately 10 to 20 centres are planned to recruit subjects.	Approximately ~~10 to 20~~ **25** centres are planned to recruit subjects.
5	**Synopsis** (Planned Study Period)	Approximately 3 years	Approximately ~~3~~ **4** years
6	**Synopsis** (Methodology)	One or two optimally safe and effective doses of Dysport selected from Stage 1 (ranging from 100 U to 400 U) will be further investigated in the Stage 2. **Stage 1 (Dose Escalation) Double-Blind Period:** It is intended to enroll up to three dose level cohorts of secondary PVD subjects (i.e. having a past history of pain free intercourse or insertion of any object >1 cm diameter; hereafter referred to as PVD2 subjects). Each cohort will include 10 unique evaluable PVD2 subjects. Subjects in these cohorts will be randomised in a ratio of 4:1 (Dysport: 8 + Placebo: 2) in a dose-escalation manner starting with a total Dysport dose of 100 U, 300 U and 400 U, however doses will be adapted as necessary within this dose range (100 U to 400 U), based on results observed. Once 10 evaluable subjects in a cohort have completed Week 6 visit of treatment cycle 1, the decision for dose escalation/de escalation and the staggering scheme for the subsequent cohort will be agreed at the data review committee (DRC) meetings upon review of efficacy and safety data from the previous cohort(s). Additional dose level cohorts may potentially be added based on the recommendations from the DRC. The maximum dose to which escalation will be permitted will be 400 U. Subject who discontinue prior to Week 6 for reasons unrelated to occurrence of dose limiting events (DLEs) may be replaced at the discretion of the investigator and sponsor. When all subjects in the PVD2 cohorts of Stage 1 have completed 6 weeks of follow-up of treatment cycle 1, the DRC will meet again to enable selection of dose(s) to be assessed and	One or two optimally safe and effective doses of Dysport selected from Stage 1 (ranging from 100 U **up** to **a maximum of** ~~4~~800 U) will be further investigated in the Stage 2. **Stage 1 (Dose Escalation) Double-Blind Period:** It is intended to enrol~~l~~ up to ~~three~~ **seven** dose level cohorts of secondary PVD subjects (i.e. having a past history of pain free intercourse or insertion of any object >1 cm diameter; hereafter referred to as PVD2 subjects). Each cohort will include 10 unique evaluable PVD2 subjects. Subjects in these cohorts will be randomised in a ratio of 4:1 (Dysport: 8 + Placebo: 2) in a dose-escalation manner starting with a total Dysport dose of 100 U~~,~~ **then** 300 U**, and thereafter increasing up to a maximum of 800 U by increments of 100 U**. ~~and 400 U, however doses will be adapted as necessary within this dose range (100 U to 400 U), based on results observed. Once 10 evaluable subjects in a cohort have completed Week 6 visit of treatment cycle 1, the decision for dose escalation/de escalation and the staggering scheme for the subsequent cohort will be agreed at the data review committee (DRC) meetings upon review of efficacy and safety data from the previous cohort(s). Additional dose level cohorts may potentially be added based on the recommendations from the DRC. The maximum dose to which escalation will be permitted will be 400 U.~~ **For Dysport doses equal to or above 400 U, cohorts of primary PVD subjects (i.e. having life long provoked vestibular pain; hereafter referred to as PVD1 subjects), will be recruited in parallel with PVD2 cohorts and at the same Dysport dose as for the PVD2 cohorts. The first PVD1 cohort at 400 U will include eight unique evaluable subjects who will be randomised in a ratio of 3:1 (Dysport: 6 + Placebo: 2). Further PVD1 cohorts (i.e. above 400 U) will include 10**

Version Date		08 APRIL 2019	23 JANUARY 2020
Page	**Section**	**WAS**	**IS**
		confirm the sample size for Stage 2. In parallel with the PVD2 Cohort 3, an additional cohort (Cohort 4) of primary PVD subjects (i.e. having life-long provoked vestibular pain; hereafter referred to as PVD1 subjects), will be recruited, at the same Dysport dose as for the PVD2 Cohort 3. This Cohort 4 will include 8 unique evaluable PVD1 subjects who will be randomised in a ratio of 3:1 (Dysport: 6 + Placebo: 2). PVD1 subjects will be recruited in Stage 2 based on the DRC review of efficacy and safety data obtained from PVD1 cohort(s) in Stage 1.	**unique evaluable subjects randomised in a ratio of 4:1 (Dysport: 8 + Placebo 2).** **The decision for dose escalation/de-escalation and the staggering scheme for the subsequent cohort will be agreed at data review committee (DRC) meetings upon review of efficacy and safety data from the previous cohort(s).** Subject who discontinue prior to Week 6 for reasons unrelated to occurrence of dose limiting events (DLEs) may be replaced at the discretion of the investigator and sponsor. When all subjects in ~~the PVD2 cohorts of~~ Stage 1 have completed 6 weeks of follow-up of treatment cycle 1, the DRC will meet again to enable selection of dose(s) to be assessed and confirm the sample size for Stage 2. ~~In parallel with the PVD2 Cohort 3, an additional cohort (Cohort 4) of primary PVD subjects (i.e. having life-long provoked vestibular pain; hereafter referred to as PVD1 subjects), will be recruited, at the same Dysport dose as for the PVD2 Cohort 3. This Cohort 4 will include 8 unique evaluable PVD1 subjects who will be randomised in a ratio of 3:1 (Dysport: 6 + Placebo: 2).~~ PVD1 subjects will be recruited in Stage 2 based on the DRC review of efficacy and safety data obtained from PVD1 cohort(s) in Stage 1.
7	**Synopsis** (Stage 2 (Dose Expansion))	As for Stage 1, the maximum permitted dose in Stage 2 will be 400 U. One or two dose levels identified from Stage 1, defined by the DRC based on efficacy and safety data, will be investigated further and compared to placebo. It is intended to enroll 63 subjects in Stage 2 in the randomisation ratio of 1:1:1 (Dysport high dose: 21; Dysport low dose: 21 and Placebo: 21).	As for Stage 1, the maximum permitted dose in Stage 2 will be ~~4~~800 U. One or two dose levels identified from Stage 1, defined by the DRC based on efficacy and safety data, will be investigated further and compared to placebo. It is intended to enroll~~l~~ 63 subjects in Stage 2 in the randomisation ratio of 1:1:1 (Dysport high dose: 21; Dysport low dose: 21 and Placebo: 21).
7	**Synopsis** (Open-Label Period (Stage 1 and Stage 2))	Dysport dose levels, that are approved by the DRC will be used for retreatment and will not exceed 400 U.	Dysport dose levels, that are approved by the DRC will be used for retreatment and will not exceed ~~4~~800 U.
8	**Synopsis** (Number of Subjects Planned)	The study will include approximately 100 female subjects (approximately 38 in Stage 1 and 63 in Stage 2).	The study will include approximately ~~100~~ **180** female subjects (~~approximately 38~~ **up to 118** in Stage 1 **if all cohorts are reached,** and 63 in Stage 2).
8	**Synopsis** (Diagnosis and	**Diagnosis and Criteria for Inclusion:**	**Diagnosis and Criteria for Inclusion:**

Version Date		08 APRIL 2019	23 JANUARY 2020
Page	**Section**	**WAS**	**IS**
& 45	Criteria for Inclusion) & **Section 4.1** (Inclusion Criteria)	Inclusion Criteria: (1a) Female subjects aged 18 years or above. (2) Willing to provide a written informed consent prior to any study related procedures. (3) Who have never had a vaginal delivery including attempted vaginal delivery. (4) Are premenopausal, as evidenced by a serum follicle stimulating hormone (FSH) level of <35 mIU/mL as assessed at the Screening Visit.	**Note: Lettered inclusion and exclusion criteria indicate an update or deletion following an amendment to the protocol (e.g. a=criterion amended once, b=criterion amended twice, c=criterion amended three times).** Inclusion Criteria: (1a) Female subjects aged 18 years or above. (2) Willing to provide a written informed consent prior to any study related procedures. (3) ~~Who have never had a vaginal delivery including attempted vaginal delivery.~~ ***Criterion 3 is removed by protocol amendment.*** (4) Are premenopausal, as evidenced by a serum follicle stimulating hormone (FSH) level of <35 mIU/mL as assessed at the Screening Visit.
9 & 46 and 47	**Synopsis** (Diagnosis and Criteria for Inclusion – Exclusion Criteria) & **Section 4.2** (Exclusion Criteria)	Exclusion Criteria: (1a) Have provoked pain on a Q-tip test at the anterior vestibule (anywhere between 9 and 3 o'clock or more anteriorly) at the Screening Visit. (2b) Able to tolerate the 6th (diameter 1¼ inches) dilator size (i.e. agree to the next successive dilator size to be tested for pain response) at the Baseline Visit (i.e. at least one of the two largest sized dilators (#7 and/or 8) is tested). (3a) Any non-provoked (i.e. spontaneous) vulvar pain in the past 6 months prior to the Screening Visit. Note: pain provoked by any vestibular pressure (including but not limited to sitting, bicycling or tight clothing) is considered provoked pain. (4a) Deep pain during intercourse in the past 6 months prior to the Screening Visit. (5a) Score of 4 or 5 on any of the 3 pain questions (questions #17, 18 or 19) of the modified Female Sexual Function Index (mFSFI) questionnaire.	Exclusion Criteria: (1a) Have provoked pain on a Q-tip test at the anterior vestibule (anywhere between 9 and 3 o'clock or more anteriorly) at the Screening Visit. (2b) Able to tolerate the 6th (diameter 1¼ inches) dilator size (i.e. agree to the next successive dilator size to be tested for pain response) at the Baseline Visit (i.e. at least one of the two largest sized dilators (#7 and/or 8) is tested). (3a) Any non-provoked (i.e. spontaneous) vulvar pain in the past 6 months prior to the Screening Visit. Note: pain provoked by any vestibular pressure (including but not limited to sitting, bicycling or tight clothing) is considered provoked pain. (4a) Deep pain during intercourse in the past 6 months prior to the Screening Visit. (5a) Score of 4 or 5 on any of the 3 pain questions (questions #17, 18 or 19) of the modified Female Sexual Function Index (mFSFI) questionnaire. ***(6) Criterion 6 is removed by previous protocol amendment.***

Version Date		08 APRIL 2019	23 JANUARY 2020
Page	Section	WAS	IS
		(7a) Significant depressive disorder, e.g. having a score ≥20/27 on the Patient Health Questionnaire (PHQ-9) scale at the Baseline Visit. (8a) Genitourinary or gastrointestinal conditions/history which, according to the investigator's judgement may interfere with treatment or impact outcome assessment, including but not limited to: - Skin disease at the vestibule such as lichen sclerosus, lichen planus, vaginal or vulvar atrophy, desquamative inflammatory vaginitis, allergic vulvitis etc. - Severe endometriosis (severe defined as requiring regular medications to manage the endometriosis symptoms). - Severe bladder and bowel symptoms e.g. diagnosed interstitial cystitis/Bladder Pain Syndrome, severe urinary incontinence, faecal incontinence, inflammatory bowel disease. - Genitourinary or rectal cancer. - Congenital urogenital abnormalities (e.g. vaginal septa, imperforate hymen, urethral diverticulum). - Pain in urethra (diagnosis based on subject's interview and physical examination). - Symptomatic urogenital prolapse at physical examination. - History of traumatic or post radiotherapy vulvar lesions. (9) Previous surgery that according to investigator's judgement may impact on study outcome (including but not limited to hysterectomy, vestibulectomy, urologic surgery, perianal surgery) or genital trauma or	(7a) Significant depressive disorder, e.g. having a score ≥20/27 on the Patient Health Questionnaire (PHQ-9) scale at the Baseline Visit. (8~~a~~**ab**) Genitourinary or gastrointestinal conditions/history ~~which, according to the investigator's judgement may interfere with treatment or impact outcome assessment,~~ including ~~but not limited to~~: - Skin disease at the vestibule such as lichen sclerosus, lichen planus, vaginal or vulvar atrophy, desquamative inflammatory vaginitis, **and** allergic vulvitis ~~etc~~. - Severe endometriosis (severe defined as requiring regular medications to manage the endometriosis symptoms). - Severe bladder and bowel symptoms e.g. diagnosed interstitial cystitis/Bladder Pain Syndrome, severe urinary incontinence, faecal incontinence, inflammatory bowel disease. - Genitourinary or rectal cancer. - Congenital urogenital abnormalities (e.g. vaginal septa, imperforate hymen, urethral diverticulum). - Pain in urethra (diagnosis based on subject's interview and physical examination). - Symptomatic urogenital prolapse at physical examination. - History of traumatic or post radiotherapy vulvar lesions. - **Pudendal neuralgia** - **Other conditions that according to the investigator's judgement may interfere with treatment or impact the study outcome.** (9**a**) Previous surgery/**conditions** ~~that according to investigator's judgement may impact on study outcome~~ (including**:** ~~but not limited to hysterectomy, vestibulectomy, urologic surgery, perianal surgery) or genital trauma or mutilation/cutting~~. - **Hysterectomy**

Version Date		08 APRIL 2019	23 JANUARY 2020
Page	Section	WAS	IS
		mutilation/cutting. (10) Vaginal infections (bacterial vaginosis, presence of candidiasis or trichomoniasis) at Screening Visit. (11) Current infection at the injection site(s). (12) Unable to receive intramuscular injections. (13) History of hypersensitivity to Dysport or drugs with a similar structure or any excipient used in the formulation. (14) Clinically significant history of alcohol/drug abuse the last 24 weeks prior to screening or clinically significant alcohol/drug dependence within 2 years prior to screening. Exceptions include caffeine or nicotine abuse/dependence. (15a) Positive urine test for illicit drugs (drugs of abuse) at screening. In the event a subject tests positive for cannabinoids (tetrahydrocannabinol), the investigator will evaluate the subject's ability to abstain from cannabis during the study. If in the investigator's clinical judgement, the subject will abstain, the subject may be enrolled after consultation with the Medical Monitor. Note: at the discretion of the investigator, positive drug screens for prescribed medications will not be considered exclusionary. (16b) Has received any of the following: - Pelvic floor physical therapy initiated, stopped or modified (frequency or type of physical therapy) during the last 12 weeks prior to Baseline (physical therapy includes but is not limited to: internal/external myofascial release by physiotherapist, biofeedback, home pelvic floor exercises, self-taught exercises, use of vaginal dilators, etc.).	- **Vestibulectomy** - **Urologic surgery** - **Perianal surgery** - **Genital trauma or mutilation/cutting** - **Other surgery/conditions that according to the investigator's judgement may impact on the study outcome.** (10) Vaginal infections (bacterial vaginosis, presence of candidiasis or trichomoniasis) at Screening Visit. (11) Current infection at the injection site(s). (12) Unable to receive intramuscular injections. (13) History of hypersensitivity to Dysport or drugs with a similar structure or any excipient used in the formulation. (14) Clinically significant history of alcohol/drug abuse the last 24 weeks prior to screening or clinically significant alcohol/drug dependence within 2 years prior to screening. Exceptions include caffeine or nicotine abuse/dependence. (15a) Positive urine test for illicit drugs (drugs of abuse) at screening. In the event a subject tests positive for cannabinoids (tetrahydrocannabinol), the investigator will evaluate the subject's ability to abstain from cannabis during the study. If in the investigator's clinical judgement, the subject will abstain, the subject may be enrolled after consultation with the Medical Monitor. Note: at the discretion of the investigator, positive drug screens for prescribed medications will not be considered exclusionary. (16~~b~~**c**) Has received any of the following: - Pelvic floor physical therapy initiated, stopped or modified (frequency or type of physical therapy) during the last 12 weeks prior to Baseline (physical therapy includes but is not limited to: internal/external myofascial release by

Version Date		08 APRIL 2019	23 JANUARY 2020
Page	**Section**	**WAS**	**IS**
		- Sex therapy in the past 6 weeks prior to Baseline. - Previous treatment with any botulinum toxin (BTX) for any indication within the last 1 year. - Treatment for anterior vestibular pain, with hormonal creams, in the last 1 week prior to Screening unless continued at the same dosing regimen throughout the study.	physiotherapist, biofeedback, home pelvic floor exercises, self-taught exercises, use of vaginal dilators, etc.). - Sex therapy in the past 6 weeks prior to Baseline. - Previous treatment with any botulinum toxin (BTX) for any indication within the last 1 year. - Treatment for ~~anterior~~ vestibular pain, with hormonal creams, in the last 1 week prior to Screening unless continued at the same dosing regimen throughout the study.
13 & 38	**Synopsis** (Exploratory Endpoints) & **Section 3.3** (Exploratory Endpoints)	Exploratory Endpoints: • Mean change from Baseline to each post-treatment visit in each of the mVPAQ subscales. • Mean change from Baseline to each post-treatment visit in the mFSFI total score and domain scores. • Mean change from Baseline in the pelvic floor muscles pressure - Resting vaginal pressure - Maximal 'squeeze' pressure. • Mean change from Baseline in the depression score using PHQ-9 scale. • Mean change from Baseline in quality of life (QoL) using 36-item Short Form Survey (SF-36).	Exploratory Endpoints: • Mean change from Baseline to each post-treatment visit in each of the mVPAQ subscales. • Mean change from Baseline to each post-treatment visit in the mFSFI total score and domain scores. • Mean change from Baseline in the pelvic floor muscles pressure **as measured by perineometry in all subjects in Stage 1 up to 400 U and in a subset of subjects in Stage 2.** • **(Note: in Stage 2, this endpoint will be evaluated in subjects who have never had a vaginal delivery (including an attempted vaginal delivery), and at study sites that were provided a perineometer to assess pelvic floor muscle pressure)** - Resting vaginal pressure - Maximal 'squeeze' pressure. • Mean change from Baseline in the depression score using PHQ-9 scale. • Mean change from Baseline in quality of life (QoL) using 36-item Short Form Survey (SF-36).
13 & 14	**Synopsis** (Statistical Methods)	**Method of Randomisation:** Stage 1: For the PVD2 cohorts, subjects will be randomised with a 4:1 (Dysport: placebo) ratio. For the PVD1 cohort,	**Method of Randomisation:** Stage 1: For the PVD2 cohorts, subjects will be randomised with a 4:1 (Dysport: placebo) ratio. For the PVD1 cohort**(s)**, subjects will be

Version Date		08 APRIL 2019	23 JANUARY 2020
Page	Section	WAS	IS
		subjects will be randomised with a 3:1 (Dysport: placebo) ratio. Stage 2: Subjects will be randomised to Dysport high dose, Dysport low dose, or placebo with a 1:1:1 allocation. Randomisation will be stratified by pain onset subtype (two levels: primary, i.e. having life-long PVD, secondary, i.e. having acquired PVD after period of pain-free penetrative activities). If only one Dysport dose is selected, it is intended to randomise subjects in the ratio of 2:1. **Sample Size and Power Considerations:** Stage 1: With 8 evaluable subjects on active treatment per PVD2 dose cohort and if there are 0 DLEs in a cohort, there is at least 80% probability that the true incidence of DLEs at the corresponding dose will not be greater than 18%. The ability to confidently rule out smaller true DLE incidence at a dose level will come from observations on subjects in Stage 2. Stage 2: The study sample size required to have at least 80% power to detect a 2-point improvement between Dysport and the placebo group on mean change from baseline to Week 6 in the vaginal dilator induced pain as reported on a numeric pain rating scale (using the DMTS), assuming a common standard deviation of 3-point and using a one-sided 0.10 level test is 21 subjects per arm. At the end of Stage 2, if the true DLE rate is 6% or greater, there is at least 80% probability to observe at least 1 DLE in 29 subjects (8 in Stage 1 and 21 in Stage 2). Therefore, if there are no observed DLEs in both Stage 1 and Stage 2 at a dose level, then there is good confidence that the true DLE rate is no more than 6%. If only one Dysport dose is selected, it is intended to randomise subjects in the ratio of 2:1. Sample size will be formally recalculated using data from Stage 1.	randomised with a 3:1 (Dysport: placebo) ratio **for Dysport 400 U and then randomised at 4:1 for Dysport 500 U and up to a maximum of 800 U**. Stage 2: Subjects will be randomised to Dysport high dose, Dysport low dose, or placebo with a 1:1:1 allocation. Randomisation will be stratified by pain onset subtype (two levels: primary, i.e. having life-long PVD, secondary, i.e. having acquired PVD after period of pain-free penetrative activities). If only one Dysport dose is selected, it is intended to randomise subjects in the ratio of 2:1. **Sample Size and Power Considerations:** Stage 1: With 8 evaluable subjects on active treatment per PVD2 dose cohort and if there are 0 DLEs in a cohort, there is at least 80% probability that the true incidence of DLEs at the corresponding dose will not be greater than 18%. **With 16 evaluable subjects on active treatment in PVD2 and PVD1 dose cohorts, and if there are 0 DLEs in the two cohorts, there is at least 80% probability that the true DLEs at the corresponding dose will not be greater than 9%.** The ability to confidently rule out smaller true DLE incidence at a dose level will come from observations on subjects in Stage 2. Stage 2: The study sample size required to have at least 80% power to detect a 2-point improvement between Dysport and the placebo group on mean change from baseline to Week 6 in the vaginal dilator induced pain as reported on a numeric pain rating scale (using the DMTS), assuming a common standard deviation of 3-point and using a one-sided 0.10 level test is 21 subjects per arm. At the end of Stage 2, if the true DLE rate is 6% or greater, there is at least 80% probability to observe at least 1 DLE in 29 subjects (8 in Stage 1 and 21 in Stage 2). Therefore, if there are no observed DLEs in both Stage 1 and Stage 2 at a dose level, then there is good confidence that the true DLE rate is no more than 6%. **If the dose chosen in Stage 2 has been tested on two cohorts (PVD1 and PVD2) in Stage 1, at the end of Stage 2, if the true DLE rate is 5% or greater, there is at least 80% probability to observe at least one DLE in 37 subjects (16 in Stage 1**

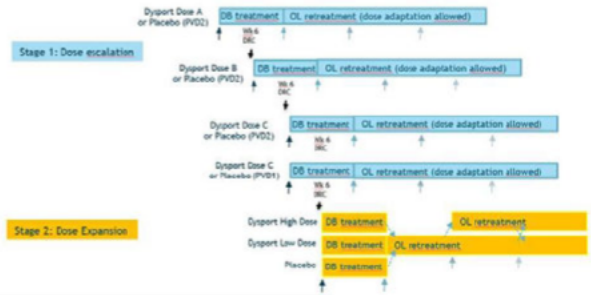
Version Date		08 APRIL 2019	23 JANUARY 2020
Page	**Section**	**WAS**	**IS**
			and 21 in Stage 2). Therefore, if there are no observed DLEs in both Stage 1 and Stage 2 at a dose level, then there is good confidence that the true DLE rate is no more than 5%. If only one Dysport dose is selected, it is intended to randomise subjects in the ratio of 2:1. Sample size will be formally recalculated using data from Stage 1.
14	**Synopsis** (Data Review Committee (DRC) Meetings)	A DRC will be established to take decisions for dose escalation and dose de-escalation (within the Dysport dose range of 100 U to 400 U) or study termination decisions in Stage 1. If no subject reports a clinically significant AE up to Week 6 in a cohort, the DRC will meet once all 10 PVD2 (or 8 PVD1) evaluable subjects have reached Week 6 of a cohort to review the efficacy and safety data and decide the dose for the next cohort. If any subject reports a clinically significant AE up to Week 6, then further enrolment into the cohort will be suspended and an ad hoc DRC meeting will be scheduled to review the safety data and make a decision with regards to further conduct of the cohort and of Stage 1. At the end of Cycle 1–Week 6 for all subjects in PVD2 cohorts in Stage 1, the DRC will meet to review efficacy and safety data and decide on the one or two doses of Dysport to be assessed in the Stage 2 of the study and the sample size for Stage 2 will be recalculated. Once all PVD1 subjects in Cohort 4 have reached Cycle 1-Week 6 visit, the DRC will meet and based on review of all safety and efficacy data from the cohort, will decide if further PVD1 cohort(s) are required or if PVD1 subjects should be removed from Stage 2.	A DRC will be established to take decisions for dose escalation and dose de-escalation (within the Dysport dose range of 100 U **up** to **a maximum of 4**800 U) or study termination decisions in Stage 1. If no subject reports a clinically significant AE up to Week 6 in a cohort, the DRC will meet once all ~~10 PVD2 (or 8 PVD1)~~ evaluable subjects have reached Week 6 of a cohort to review the efficacy and safety data and decide the dose for the next cohort. If any subject reports a clinically significant AE ~~up to Week 6~~, then further enrolment into the cohort will be suspended and an ad hoc DRC meeting will be scheduled to review the safety data and make a decision with regards to further conduct of the cohort and of Stage 1. At the end of Cycle 1–Week 6 for all subjects in ~~PVD2 cohorts in~~ Stage 1, the DRC will meet to review efficacy and safety data and decide on the one or two doses of Dysport to be assessed in the Stage 2 of the study and the sample size for Stage 2 will be recalculated. ~~Once all PVD1 subjects in Cohort 4 have reached Cycle 1 Week 6 visit, the~~ **The** DRC ~~will meet and based on review of all safety and efficacy data from the cohort,~~ will **also** decide if further PVD1 cohort(s) are required or if PVD1 subjects should be removed from Stage 2. **In Stage 2 of the study, ad hoc DRC meetings will be scheduled to review efficacy and safety data in the event of an emergency safety issue.**
26	**Section 1.4** (Known and Potential Risks and Benefits to Human Subjects)	Based on clinical evidence available from published data supporting the efficacy of BTX-A in adult female patients with vulvodynia, the known mechanism of action of Dysport and the proposed range of Dysport doses to be tested (100 U to 400 U) that fall within the range of approved doses for Dysport (up to	Based on clinical evidence available from published data supporting the efficacy of BTX-A in adult female patients with vulvodynia, the known mechanism of action of Dysport and the proposed range of Dysport doses to be tested (100 U **up** to **a maximum of 4**800 U) that fall within the range of approved doses for Dysport (up to 1500 U in adult patients), the

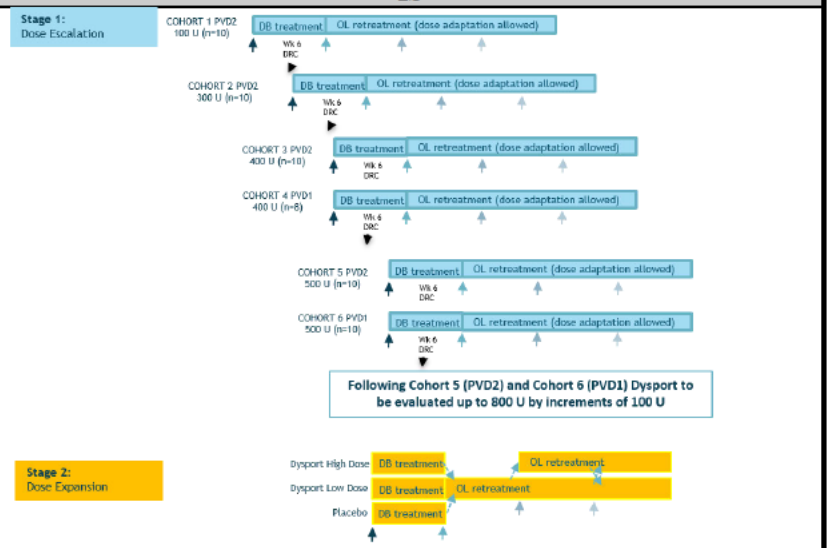
Version Date		08 APRIL 2019	23 JANUARY 2020
Page	**Section**	**WAS**	**IS**
		1500 U in adult patients), the benefit/risk balance is expected to be favourable for evaluation in this patient population.	benefit/risk balance is expected to be favourable for evaluation in this patient population.
27	**Section 1.5** (Selection of Investigational Medicinal Product)	Ipsen proposes to progressively escalate Dysport doses from 100 U to 300 U, and up to a maximum dose of 400 U. This recommendation is supported by data from the study by Ghazizadeh 2004 [14], in which the starting dose of 150 U Dysport injected into the levator ani (puborectalis) muscles in patients with vaginismus did not provide sufficient clinical improvement in some patients, following which the dose was gradually increased to 400 U for subsequent patients that lead to satisfactory relief from vaginismus in 95.8% of patients. No adverse effects were reported in this study with Dysport doses of 150 U to 400 U.	Ipsen proposes to progressively escalate Dysport doses from 100 U ~~to~~ **and** 300 U, **and then increasing** up to a maximum dose of ~~4~~800 U **by increments of 100 U**. ~~This recommendation is~~ **Dysport doses up to 400 U** are supported by data from the study by Ghazizadeh 2004 [14], in which the starting dose of 150 U Dysport injected into the levator ani (puborectalis) muscles in patients with vaginismus did not provide sufficient clinical improvement in some patients, following which the dose was gradually increased to 400 U for subsequent patients that lead to satisfactory relief from vaginismus in 95.8% of patients. No adverse effects were reported in this study with Dysport doses of 150 U to 400 U. **Administration of Dysport doses above 400 U and up to a maximum of 800 U during the study will be based on recommendation by the DRC following review of safety and efficacy data from previous cohorts.**
31	**Section 3.1** (General Design and Study Schema)	This is a Phase II multicentre, double-blind, randomised, placebo-controlled, dose finding study to define the optimal doses of Dysport and evaluate its efficacy and safety compared to placebo in vulvodynia patients with PVD. Study treatment will be injected at 5 needle insertion points at 10 injection sites in the vestibular area. The study will consist of a dose escalation stage (Stage 1) and a dose expansion stage (Stage 2). The purpose of the dose escalation will be to determine the Dysport dose(s) to be further investigated in Stage 2. The study will include approximately 100 premenopausal female subjects (approximately 38 in Stage 1 and 63 in Stage 2) aged 18 years or above with a diagnosis of PVD associated with provoked pain at the posterior vestibule. Both Stage 1 and Stage 2 will consist of a double-blind period (treatment cycle 1; Dysport or placebo) followed by an open-label treatment period (treatment cycles 2 to 4; all subjects receive Dysport).	This is a Phase II multicentre, double-blind, randomised, placebo-controlled, dose finding study to define the optimal doses of Dysport and evaluate its efficacy and safety compared to placebo in vulvodynia patients with PVD. Study treatment will be injected at 5 needle insertion points at 10 injection sites in the vestibular area. The study will consist of a dose escalation stage (Stage 1) and a dose expansion stage (Stage 2). The purpose of the dose escalation will be to determine the Dysport dose(s) to be further investigated in Stage 2. The study will include approximately ~~100~~ **180** premenopausal female subjects (~~approximately 38~~ **up to 118** in Stage 1 **if all cohorts are reached,** and 63 in Stage 2) aged 18 years or above with a diagnosis of PVD associated with provoked pain at the posterior vestibule. Both Stage 1 and Stage 2 will consist of a double-blind period (treatment cycle 1; Dysport or placebo) followed by an open-label treatment period (treatment cycles 2 to 4; all subjects receive Dysport).
31	**Section 3.1.1** (Stage	It is intended to enroll up to three dose level cohorts of	It is intended to enrol~~l~~ up to ~~three~~ **seven** dose level cohorts of secondary

Version Date		08 APRIL 2019	23 JANUARY 2020
Page	Section	WAS	IS
	1 (Dose Escalation))	secondary PVD subjects (i.e. having a past history of pain-free intercourse or insertion of any object >1 cm diameter; hereafter referred to as PVD2 subjects) evaluating Dysport doses ranging from 100 U to 400 U (total dose administered) to find one or two optimally safe and effective doses of Dysport that will be further investigated in the Stage 2. Additional dose level cohorts within this dose range (100 U to 400 U) may potentially be added based on the recommendations from the DRC. Each PVD2 cohort will include 10 unique evaluable PVD2 subjects who will be randomised via the interactive response system (IRS) to the two double-blind parallel treatment arms in 4:1 ratio: • Dysport (N=8) or • Placebo (N=2). An additional Cohort 4 will include 8 unique evaluable primary PVD subjects (i.e. having life-long provoked vestibular pain; hereafter referred to as PVD1 subjects), at the same Dysport dose as for the PVD2 Cohort 3, who will be randomised via the IRT to the two double-blind parallel treatment arms in 3:1 ratio: • Dysport (N=6) or • Placebo (N=2). In an event, when the 10th subject (or 8th in Cohort 4) is being randomised, if an additional subject (11th (or 9th in Cohort 4)) has been screened, this subject may be accepted in the cohort and be randomised. At Screening, all subjects will be allocated a subject number. Subjects will be evaluated for eligibility during a Screening Visit at Day -14. Following confirmation of eligibility for the study, subjects will be allocated to one of the above two treatment groups. Subjects will receive study treatment injections in the pelvic floor muscles on Day 1 (Baseline Visit). Follow-up visits will be performed at:	PVD subjects (i.e. having a past history of pain-free intercourse or insertion of any object >1 cm diameter; hereafter referred to as PVD2 subjects) evaluating Dysport doses ranging from 100 U **up** to **a maximum of 48**00 U (total dose administered) to find one or two optimally safe and effective doses of Dysport that will be further investigated in the Stage 2. Additional dose level cohorts within this dose range (100 U **and up** to **a maximum of 48**00 U) may potentially be added based on the recommendations from the DRC. Each PVD2 cohort will include 10 unique evaluable PVD2 subjects who will be randomised via the interactive response system (IRS) to the two double-blind parallel treatment arms in 4:1 ratio: • Dysport (N=8) or • Placebo (N=2). ~~An additional~~ Cohort 4 will include 8 unique evaluable primary PVD subjects (i.e. having life-long provoked vestibular pain; hereafter referred to as PVD1 subjects), at the same Dysport dose as for the PVD2 Cohort 3, who will be randomised via the IRT to the two double-blind parallel treatment arms in 3:1 ratio: • Dysport (N=6) or • Placebo (N=2). **Further PVD1 cohorts (i.e. above 400 U) will include 10 unique evaluable subjects randomised in a ratio of 4:1 (Dysport N=8 and Placebo N=2).** In an event, when the ~~10th~~ **last** subject ~~(or 8th in Cohort 4)~~ **in a cohort** is being randomised, if an additional subject ~~(11th (or 9th in Cohort 4))~~ has been screened, this subject may be accepted in the cohort and be randomised. At Screening, all subjects will be allocated a subject number. Subjects will be evaluated for eligibility during a Screening Visit at Day -14. Following confirmation of eligibility for the study, subjects will be allocated to one of the above two treatment groups. Subjects will receive study treatment injections in the pelvic floor muscles on Day 1 (Baseline Visit). Follow-up

Version Date		08 APRIL 2019	23 JANUARY 2020
Page	Section	WAS	IS
		• Week 2 (telephone contact) • Week 6 • Week 12 and • Every 6 weeks up to a maximum of 48 weeks of follow-up. The screening and postbaseline assessments to be performed at each visit are discussed in Section 5.2. Assessments to be performed at the End of Study (EOS) or Early Withdrawal (EWD) visit are presented in Section 5.2.4. Once 10 PVD2 (or 8 PVD1) evaluable subjects in a cohort have reached the Week 6 visit, decision for dose escalation for the subsequent cohort will be agreed at the DRC meeting upon review of the available efficacy and safety data. The maximum dose to which escalation is permitted will be 400 U. The definitions for clinically significant AEs and dose limiting events (DLEs) is provided in Section 3.1.1.1. The assessments to be performed by the Data Review Committee (DRC) and their timings are discussed in Section 3.1.1.2. Subject who withdraw or discontinue prior to Week 6 in the double-blind period for reasons unrelated to occurrence of DLEs may be replaced at the discretion of the investigator and sponsor. Replacement subjects will receive the same treatment as the subject they replace. Stage 1 will be stopped as soon as the dose of 400 U has been tested or otherwise decided by the DRC. At the end of Cycle 1 – Week 6 for all PVD2 subjects in Stage 1, the DRC will meet to review efficacy and safety data and decide on the one or two doses of Dysport to be assessed in the Stage 2 of the study and the sample size for Stage 2 will be recalculated. PVD1 subjects will be recruited in Stage 2 following DRC review of the efficacy and safety data of PVD1 cohort(s) in Stage 1. From Week 12 onwards of the double-blind period, subjects will be assessed for the need for retreatment at each visit.	visits will be performed at: • Week 2 (telephone contact) • Week 6 • Week 12 and • Every 6 weeks up to a maximum of 48 weeks of follow-up. The screening and postbaseline assessments to be performed at each visit are discussed in Section 5.2. Assessments to be performed at the End of Study (EOS) or Early Withdrawal (EWD) visit are presented in Section 5.2.4. Once **all** ~~10~~ PVD2 ~~(or 8~~ **and** PVD1~~)~~ evaluable subjects in a ~~cohort~~ **dose level** have reached the Week 6 visit, decision for dose escalation for the subsequent cohort will be agreed at the DRC meeting upon review of the available efficacy and safety data. The maximum dose to which escalation is permitted will be ~~4~~**8**00 U. The definitions for clinically significant AEs and dose limiting events (DLEs) is provided in Section 3.1.1.1. The assessments to be performed by the Data Review Committee (DRC) and their timings are discussed in Section 3.1.1.2. Subject who withdraw or discontinue prior to Week 6 in the double-blind period for reasons unrelated to occurrence of DLEs may be replaced at the discretion of the investigator and sponsor. Replacement subjects will receive the same treatment as the subject they replace. Stage 1 will be stopped as soon as the dose of ~~4~~**8**00 U has been tested or otherwise decided by the DRC. At the end of Cycle 1 – Week 6 for all PVD2 subjects in Stage 1, the DRC will meet to review efficacy and safety data and decide on the one or two doses of Dysport to be assessed in the Stage 2 of the study and the sample size for Stage 2 will be recalculated. PVD1 subjects will be recruited in Stage 2 following DRC review of the efficacy and safety data of PVD1 cohort(s) in Stage 1. From Week 12 onwards of the double-blind period, subjects will be assessed for the need for retreatment at each visit. Subjects who require retreatment will be provided subsequent treatment with Dysport in the open-label period of the study. Dysport dose levels, that are approved by

Version Date		08 APRIL 2019	23 JANUARY 2020
Page	**Section**	**WAS**	**IS**
		Subjects who require retreatment will be provided subsequent treatment with Dysport in the open-label period of the study. Dysport dose levels, that are approved by the DRC will be used for retreatment and will not exceed 400 U. Subjects not requiring or not eligible for retreatment will be evaluated every 6 weeks ±2 weeks (Additional Visit(s)) until they need retreatment or they complete at least 36 weeks of follow-up. The number of treatment cycles will depend on the duration of each treatment cycle, and thus the minimum follow-up duration will be 36 weeks and the maximum follow-up duration will be 48 weeks (the end of the study will not occur before 12 weeks have elapsed from the last treatment cycle), as calculated from Cycle 1-Day 1.	the DRC will be used for retreatment and will not exceed ~~4~~**8**00 U. Subjects not requiring or not eligible for retreatment will be evaluated every 6 weeks ±2 weeks (Additional Visit(s)) until they need retreatment or they complete at least 36 weeks of follow-up. The number of treatment cycles will depend on the duration of each treatment cycle, and thus the minimum follow-up duration will be 36 weeks and the maximum follow-up duration will be 48 weeks (the end of the study will not occur before 12 weeks have elapsed from the last treatment cycle), as calculated from Cycle 1-Day 1.
33	**Section 3.1.1.2** (DRC Meetings)	A DRC will be established to take decisions for dose escalation, dose de escalation or study termination decisions in Stage 1 of the clinical study (see Section 13.3.1 for the composition and operation of the DRC). The maximum dose to which escalation will be permitted will be 400 U. If no subject reports a clinically significant AE up to Week 6 in a cohort, the DRC will meet once all 10 PVD2 (or 8 PVD1) evaluable subjects of a cohort have reached Week 6 to review the unblinded efficacy and safety data and decide the dose for the next cohort. The DRC may decide to assess intermediate dose(s) or to reassess the previously used dose level based on the review of efficacy and safety data from the cohort(s). If any subject reports a clinically significant AE (as defined in Section 3.1.1.1) up to Week 6, then further enrolment into the cohort will be suspended and an ad hoc DRC meeting will be scheduled. During the ad hoc meeting, the DRC will review blinded data of the subject(s) with clinically significant AE and all available efficacy and safety data from the cohort. The DRC may request to break the blind to confirm if the significant AE is a DLE, and	A DRC will be established to take decisions for dose escalation, dose de escalation or study termination decisions in Stage 1 of the clinical study (see Section 13.3.1 for the composition and operation of the DRC). The maximum dose to which escalation will be permitted will be ~~4~~**8**00 U. If no subject reports a clinically significant AE ~~up to Week 6~~ in a cohort, the DRC will meet once all ~~10~~ PVD2 ~~(or 8~~ and PVD1~~)~~ evaluable subjects of a ~~cohort~~ **dose level** have reached Week 6 to review the unblinded efficacy and safety data and decide the dose for the next cohort. The DRC may decide to assess intermediate dose(s) or to reassess the previously used dose level based on the review of efficacy and safety data from the cohort(s). If any subject reports a clinically significant AE (as defined in Section 3.1.1.1) ~~up to Week 6~~, then further enrolment into the cohort will be suspended and an ad hoc DRC meeting will be scheduled. During the ad hoc meeting, the DRC will review blinded data of the subject(s) with clinically significant AE and all available efficacy and safety data from the cohort. The DRC may request to break the blind to confirm if the significant AE is a DLE, and based on this assessment, if enrolment in the cohort may continue. ~~Once all subjects in PVD2 cohorts in Stage 1 have reached~~ **At the end of**

Version Date		08 APRIL 2019	23 JANUARY 2020
Page	**Section**	**WAS**	**IS**
		based on this assessment, if enrolment in the cohort may continue. Once all subjects in PVD2 cohorts in Stage 1 have reached Cycle 1-Week 6 visit, the DRC will meet and, based on the unblinded review of all safety and efficacy data from the cohort(s), will decide the one or two dose(s) to be assessed in Stage 2 and the sample size for Stage 2 will be formally recalculated. Once all PVD1 subjects in Cohort 4 have reached Cycle 1-Week 6 visit, the DRC will meet and based on unblinded review of all safety and efficacy data from the cohort, will decide if further PVD1 cohort(s) are required or if PVD1 subjects should be removed from Stage 2.	Cycle 1-Week 6 visit **for all subjects in Stage 1**, the DRC will meet **to** ~~and, based on the unblinded review of~~ all safety and efficacy data from the cohort(s), ~~will~~ **and** decide the one or two dose(s) to be assessed in Stage 2 and the sample size for Stage 2 will be formally recalculated. ~~Once all PVD1 subjects in Cohort 4 have reached Cycle 1 Week 6 visit, the~~ **The** DRC will ~~meet and based on unblinded review of all safety and efficacy data from the cohort,~~ will **also** decide if further PVD1 cohort(s) are required or if PVD1 subjects should be removed from Stage 2. **In Stage 2 of the study, ad hoc DRC meetings will be scheduled to review efficacy and safety data in the event of an emergency safety issue.**
33	**Section 3.1.2** (Stage 2 (Dose Expansion)	One or two dose levels identified from Stage 1, defined by the DRC based on efficacy and safety data, will be investigated further and compared to placebo in Stage 2. As for Stage 1, 400 U will be the maximum permitted dose in Stage 2. It is intended to enroll 63 subjects in the randomisation ratio of 1:1:1:	One or two dose levels identified from Stage 1, defined by the DRC based on efficacy and safety data, will be investigated further and compared to placebo in Stage 2. As for Stage 1, ~~4~~800 U will be the maximum permitted dose in Stage 2. It is intended to enroll~~l~~ 63 subjects in the randomisation ratio of 1:1:1:
39	**Section 3.5** (Randomisation and Blinding)	Recruitment will stop in each cohort of Stage 1 (and respectively in Stage 2) once 10 ((or 8 in Cohort 4) and respectively 63) evaluable subjects have been randomised with the expected ratio.	Recruitment will stop in each cohort of Stage 1 (and respectively in Stage 2) once 10 ((or 8 in Cohort 4 **only**) and respectively 63~~)~~ evaluable subjects have been randomised with the expected ratio.
41	**Section 3.7.2** (Study Dosage and Administration)	Figure 2 Study Flow Chart 	Figure 2 Study Flow Chart

Version Date		08 APRIL 2019	23 JANUARY 2020
Page	**Section**	**WAS**	**IS**
			
41 & 42	**Section 3.7.2.1** (Stage 1)	The maximum permitted dose in Stage 1 (double-blind and open-label periods) is 400 U. **Double-Blind Period (Treatment Cycle 1)** The starting dose for PVD2 Cohort 1 will be Dysport 100 U or placebo. It is anticipated that if there are no safety issues then the pre-defined doses for PVD2 Cohorts 2 and 3 will be 300 U and 400 U, respectively, with matching placebos. Subjects in PVD1 Cohort 4 will receive the same dose as subjects in PVD2 Cohort 3. However, the DRC may decide to assess intermediate dose(s) within the dose range of 100 U to 400 U or to reassess the previously used dose level based on the review of efficacy and safety data from the cohort(s). Additional dose level cohort(s) may also potentially be added based on the recommendations from the DRC (the requirement for primary and/or secondary PVD subjects will be specified by the DRC).	The maximum permitted dose in Stage 1 (double-blind and open-label periods) is ~~4~~800 U. **Double-Blind Period (Treatment Cycle 1)** The starting dose for PVD2 Cohort 1 will be Dysport 100 U or placebo. It is anticipated that if there are no safety issues then the pre-defined doses for PVD2 Cohorts 2 and 3 will be 300 U and 400 U, respectively, **and doses for Cohorts 5, 7, 9 and 11 will be 500 U up to a maximum of 800 U by increments of 100 U, all** with matching placebos. Subjects in PVD1 Cohorts 4**, 6, 8, 10 and 12** will receive the same dose as subjects in PVD2 Cohorts 3**, 5, 7, 9 and 11**. However, the DRC may decide to assess intermediate dose(s) within the dose range of 100 U **up** to **a maximum of** ~~4~~800 U or to reassess the previously used dose level based on the review of efficacy and safety data from the cohort(s). ~~Additional dose level cohort(s) may also potentially be added based on the recommendations from the DRC (the requirement for primary and/or secondary PVD subjects will be specified by the DRC).~~

Version Date		08 APRIL 2019	23 JANUARY 2020
Page	**Section**	**WAS**	**IS**
42	**Section 3.7.2.2** (Stage 2)	As for Stage 1, the maximum permitted dose in Stage 2 (double-blind and open-label periods) is 400 U.	As for Stage 1, the maximum permitted dose in Stage 2 (double-blind and open-label periods) is ~~4~~800 U.
43	**Section 3.8** (Study Duration)	The overall duration of the study, including Stage 1 and Stage 2 with a maximum allowed dose of 400 U, will be approximately 3 years. The study will be considered to have started when the first subject has provided signed informed consent. The study will be considered to have ended after the last subject has completed the EOS visit in the study.	The overall duration of the study, including Stage 1 and Stage 2 with a maximum allowed dose of ~~4~~800 U, will be approximately ~~3~~ **4** years. The study will be considered to have started when the first subject has provided signed informed consent. The study will be considered to have ended after the last subject has completed the EOS visit in the study.
48	**Section 4.3** (Rationale for Inclusion/ Exclusion Criteria)	In order to establish the preliminary efficacy of Dysport in this dose escalation and dose expansion study, a subset of vulvodynia subjects suffering from provoked vestibular pain is selected. It is hypothesised that pelvic floor muscle hypertonicity underpins the posterior vestibular pain experienced and consequently, these subjects are likely to respond to treatment with Dysport. Hence, the inclusion and exclusion criteria for this study have been tailored to ensure enrolment of female subjects with a confirmed diagnosis of PVD based on the three established criteria as per Pukall 2007 [21]: self-report of superficially-located pain during sexual intercourse; a lack of physical findings (e.g. infections) to explain the pain or the persistence of pain after conditions believed to be related to the pain have been treated; and a positive response (i.e. pain) during the cotton-swab test. This will also help target a homogenous subject population and limit intersubject variability. In Stage 2, female subjects with primary PVD will also be included (i.e. having lifelong PVD) to assess the efficacy of Dysport in this subject population.	In order to establish the preliminary efficacy of Dysport in this dose escalation and dose expansion study, a subset of vulvodynia subjects suffering from provoked vestibular pain is selected. It is hypothesised that pelvic floor muscle hypertonicity underpins the posterior vestibular pain experienced and consequently, these subjects are likely to respond to treatment with Dysport. Hence, the inclusion and exclusion criteria for this study have been tailored to ensure enrolment of female subjects with a confirmed diagnosis of PVD based on the three established criteria as per Pukall 2007 [21]: self-report of superficially-located pain during sexual intercourse; a lack of physical findings (e.g. infections) to explain the pain or the persistence of pain after conditions believed to be related to the pain have been treated; and a positive response (i.e. pain) during the cotton-swab test. This will also help target a homogenous subject population and limit intersubject variability. ~~In Stage 2, female subjects with primary PVD will also be included (i.e. having lifelong PVD) to assess the efficacy of Dysport in this subject population.~~
49	**Section 5.1** (Study Schedule)	The schedule of procedures and assessments during the study for the double blind treatment period is summarised in Table 2 and for the open-label treatment period in Table 3. Subjects enrolled after the implementation of protocol Version 3.0 (dated 04 November 2018), i.e. subjects included in Cohort	The schedule of procedures and assessments during the study for the double blind treatment period is summarised in Table 2 and for the open-label treatment period in Table 3. Subjects enrolled after the implementation of protocol Version 3.0 (dated 04 November 2018), i.e. ~~subjects included in Cohort 2 onwards, will~~

Version Date		08 APRIL 2019	23 JANUARY 2020
Page	**Section**	**WAS**	**IS**
		2 onwards, will follow the study assessments and procedures outlined in Version 3.0, while subjects enrolled prior to implementation of Version 3.0, i.e. subjects included in Cohort 1, will continue to follow the study assessments and procedures as per the protocol Version 2.0 (dated 15 May 2018).	~~follow the study assessments and procedures outlined in Version 3.0, while subjects enrolled prior to implementation of Version 3.0, i.e.~~ subjects included in Cohort 1, will continue to follow the study assessments and procedures as per the protocol Version 2.0 (dated 15 May 2018).
51 & 52	**Section 5.1** (Study Schedule; Table 2)	Measurement of pelvic floor pressure m The visit window will be from Day -28 to Day -11.	Measurement of pelvic floor pressure **[n]** m The visit window will be from Day -28 to Day -11. **n To be performed in all subjects in Stage 1 up to 400 U and in a subset of subjects in Stage 2 (i.e. subjects who have never had a vaginal delivery (included attempted vaginal delivery), and at study sites that were provided a perineometer to assess pelvic floor muscle pressure).**
57, 58 & 59	**Sections 5.2.2.1, 5.2.2.3, 5.2.2.4 & 5.2.2.5**	• Dilator test • Measurement of pelvic floor muscle pressure	• Dilator test • Measurement of pelvic floor muscle pressure **(in all subjects in Stage 1 up to 400 U and in a subset of subjects in Stage 2 (i.e. in subjects who have never had a vaginal delivery (including attempted vaginal delivery), and at study sites that were provided a perineometer))**
66	**Section 6.3** (Concomitant Medication/ Therapy)	• Topical lidocaine, topical antidepressants, topical anti-epileptics and diazepam suppositories are not permitted during the study. Note: Immediately prior to and during study drug administration procedures, oral, topical (including lidocaine) or intravenous medications routinely used as standard of care for vaginal intramuscular injections are allowed. • Concomitant use of topical treatments for anterior vestibular pain with topical hormonal creams are permitted if the subject has no residual anterior vestibule pain at screening and wants to continue on the	• Topical lidocaine, topical antidepressants, topical anti-epileptics and diazepam suppositories are not permitted during the study. Note: Immediately prior to and during study drug administration procedures, oral, topical (including lidocaine) or intravenous/**injectable** medications routinely used as standard of care for vaginal intramuscular injections are allowed. • Concomitant use of topical treatments for ~~anterior~~ vestibular pain with topical hormonal creams are permitted if the subject has no residual anterior vestibule pain at screening and wants to continue on the same treatment regimen throughout the study to prevent recurrence of anterior vestibular pain. Note: Topical

<table>
<tr><th colspan="2">Version Date</th><th>08 APRIL 2019</th><th>23 JANUARY 2020</th></tr>
<tr><th>Page</th><th>Section</th><th>WAS</th><th>IS</th></tr>
<tr><td></td><td></td><td>same treatment regimen throughout the study to prevent recurrence of anterior vestibular pain. Note: Topical antidepressants are not permitted.</td><td>antidepressants are not permitted.</td></tr>
<tr><td>70</td><td>Section 7.3
(Exploratory Efficacy Endpoints and Evaluations; Table 8)</td><td>
<table>
<tr><td>Pelvic floor muscle pressure</td><td>Baseline, Week 6, Week 12 and then every 6 weeks until End of TC 1 (DB period only)</td><td>Resting vaginal pressure</td><td>Mean change from Baseline in resting vaginal pressure of the pelvic floor muscle</td></tr>
<tr><td>Pelvic floor muscle pressure</td><td>Baseline, Week 6, Week 12 and then every 6 weeks until End of TC 1 (DB period only)</td><td>Maximal squeeze pressure</td><td>Mean change from Baseline in the maximal squeeze pressure of the pelvic floor muscle</td></tr>
</table>
DB=double-blind, EOS=end of study, EWD=early withdrawal, mFSFI=modified female sexual function index, mVPAQ=modified vulvar pain assessment questionnaire, PHQ-9=patient health questionnaire, SF-36=36-item short form survey, TCs=treatment cycles.
a Subjects to complete the mVPAQ pain and life interference subscales at the Screening Visit, then 1 week prior to the next planned visit and at the visit; other mVPAQ subscales to be completed only at the visit.
b Subjects to complete the mFSFI pain domain at the Screening Visit, then 1 week prior to the next planned visit and at the visit; other mFSFI domains to be completed only at the visit.
</td><td>
<table>
<tr><td>Pelvic floor muscle pressure</td><td>Baseline, Week 6, Week 12 and then every 6 weeks until End of TC 1 (DB period only)</td><td>Resting vaginal pressure</td><td>Mean change from Baseline in resting vaginal pressure of the pelvic floor muscle [c]</td></tr>
<tr><td>Pelvic floor muscle pressure</td><td>Baseline, Week 6, Week 12 and then every 6 weeks until End of TC 1 (DB period only)</td><td>Maximal squeeze pressure</td><td>Mean change from Baseline in the maximal squeeze pressure of the pelvic floor muscle [c]</td></tr>
</table>
DB=double-blind, EOS=end of study, EWD=early withdrawal, mFSFI=modified female sexual function index, mVPAQ=modified vulvar pain assessment questionnaire, PHQ-9=patient health questionnaire, SF-36=36-item short form survey, TCs=treatment cycles.
a Subjects to complete the mVPAQ pain and life interference subscales at the Screening Visit, then 1 week prior to the next planned visit and at the visit; other mVPAQ subscales to be completed only at the visit.
b Subjects to complete the mFSFI pain domain at the Screening Visit, then 1 week prior to the next planned visit and at the visit; other mFSFI domains to be completed only at the visit.
c To be performed in all subjects in Stage 1 up to 400 U and in a subset of subjects in Stage 2 (i.e. in subjects who have never had a vaginal delivery (including an attempted vaginal delivery), and at study sites that were
</td></tr>
</table>

Version Date		08 APRIL 2019	23 JANUARY 2020
Page	**Section**	**WAS**	**IS**
			provided a perineometer to assess pelvic floor muscle pressure).
70 & 71	**Section 7.4** (Methods and Timing of Assessing, Recording, and Analysing Efficacy Data)	Methods for assessing efficacy data are described below. Timing of efficacy assessments are presented in Table 2 and Table 3, and discussed in Section 5.2. Procedures for recording efficacy data are discussed in Section 15.1, and methods of analyses are discussed in Section 11.4.3. The priority order for performing the assessments is discussed in Section 6.6. All efforts should be made to have the same investigator perform the clinical examinations for a given patient, at least for the Screening, Baseline, and Week 6 Visits of the first treatment cycle.	Methods for assessing efficacy data are described below. Timing of efficacy assessments are presented in Table 2 and Table 3, and discussed in Section 5.2. Procedures for recording efficacy data are discussed in Section 15.1, and methods of analyses are discussed in Section 11.4.3. The priority order for performing the assessments is discussed in Section 6.6. All efforts should be made to have the same investigator perform the clinical examinations for a given ~~patient~~ **subject**, at least for the Screening, Baseline, and Week 6 Visits of the first treatment cycle. **The Sponsor will provide a device to complete the e-diary questionnaires in the study 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 study.**

Version Date		08 APRIL 2019	23 JANUARY 2020
Page	**Section**	**WAS**	**IS**
75	**Section 7.4.3.3** (Measurement of Pelvic Floor Muscle Pressure)	The resting vaginal pressure and maximal 'squeeze' pressure will be measured using a CE marked medical device. Three measures of resting vaginal pressure and three measures of maximal 'squeeze' vaginal pressure should be performed. The time period between each measure performed for either the resting or maximal 'squeeze' vaginal pressure should be 30 seconds to 1 minute. Each squeeze while performing the maximal 'squeeze' vaginal pressure should last for 5 seconds. Further instructions will be provided in the Study Manual.	The resting vaginal pressure and maximal 'squeeze' pressure will be measured using a CE marked medical device **in all subjects in Stage 1 up to 400 U and in a subset of subjects in Stage 2 who have never had vaginal delivery (included attempted vaginal delivery), and at study sites that were provided a perineometer**. Three measures of resting vaginal pressure and three measures of maximal 'squeeze' vaginal pressure should be performed. The time period between each measure performed for either the resting or maximal 'squeeze' vaginal pressure should be 30 seconds to 1 minute. Each squeeze while performing the maximal 'squeeze' vaginal pressure should last for 5 seconds. Further instructions will be provided in the Study Manual.
85 & 86	**Section 11.2** (Sample Size Determination)	**Stage 1:** In Stage 1, the expected sample size is 10 evaluable subjects for PVD2 cohorts who will be randomised and treated in a 4:1 allocation ratio (Dysport or Placebo), and 8 evaluable subjects for PVD1 Cohort 4 treated in a 3:1 allocation ratio (Dysport or Placebo). Subject who discontinue prior to Week 6 for reasons unrelated to safety may be replaced at the discretion of the investigator and sponsor. As this is an exploratory stage, no formal power could be performed. However, with 8 active subjects per PVD2 dose cohort and if there are 0 DLEs in a cohort, there is at least 80% probability that the true incidence of DLEs at the corresponding dose will not be greater than 18%. The ability to rule out smaller DLE rates with high confidence will come from observing additional subjects in Stage 2. **Stage 2:** The study sample size required to have at least 80% power to detect a 2-point improvement for an experimental drug arm relative to placebo on mean change from baseline to Week 6 in the vaginal dilator induced pain as reported on a numeric pain rating scale (using the DMTS) using a one-sided 0.10 level test	**Stage 1:** In Stage 1, the expected sample size is 10 evaluable subjects for PVD2 cohorts who will be randomised and treated in a 4:1 allocation ratio (Dysport or Placebo), and 8 evaluable subjects for PVD1 Cohort 4 treated in a 3:1 allocation ratio (Dysport or Placebo). **After Cohort 3 (PVD2) and Cohort 4 (PVD1), the expected sample size is 10 evaluable subjects for additional PVD1 and PVD2 cohorts and treated in a 4:1 allocation ratio (Dysport or Placebo).** Subject who discontinue prior to Week 6 for reasons unrelated to safety may be replaced at the discretion of the investigator and sponsor. As this is an exploratory stage, no formal power could be performed. However, with 8 active subjects per PVD2 dose cohort and if there are 0 DLEs in a cohort, there is at least 80% probability that the true incidence of DLEs at the corresponding dose will not be greater than 18%. **With 16 active subjects in PVD1 and PVD2 dose cohorts and if there are 0 DLEs in a cohort, there is at least 80% probability that the true incidence of DLEs at the corresponding dose will not be greater than 9%.** The ability to rule out smaller DLE rates with high confidence will come from observing additional subjects in Stage 2. **Stage 2:** The study sample size required to have at least 80% power to detect a

Version Date		08 APRIL 2019	23 JANUARY 2020
Page	Section	WAS	IS
		(not corrected for multiplicity) is 21 evaluable subjects per arm (i.e. a total of 63 subjects). The following assumptions were used for the power statement: • Expected outcome on the mean change from baseline to Week 6 in the vaginal dilator induced pain as reported on a numeric pain rating scale in the placebo group = 2-point decrease (reference approximated by VAS per speculum in Bornstein, 2010 [26]) • Expected outcome on the mean change from baseline to Week 6 in the vaginal dilator induced pain as reported on a numeric pain rating scale in a Dysport treated group = 4-point decrease • Expected common standard deviation of the mean change from baseline to Week 6 in the vaginal dilator induced pain as reported on a numeric pain rating scale = 3-points (approximated per VAS data in Table 2 in Davis 2013 [27]). Subject who discontinue prior to Week 6 for reasons unrelated to safety will be replaced at the discretion of the investigator and sponsor. At the end of Stage 2, if the true DLE rate is 6% or greater, there is at least 80% probability to observe at least 1 DLE in 29 subjects (8 in Stage 1 and 21 in Stage 2). Therefore, if there are no observed DLEs in both Stage 1 and Stage 2 at a dose level, then there is good confidence that the true DLE rate is no more than 6%. If it is reasonable to assume that the relationship between toxicity and dose level is monotonic non-decreasing, then we may pool dose levels to obtain a higher degree of confidence for the lower dose level. If only one Dysport dose is selected, it is intended to randomise subjects in the ratio of 2:1. Sample size will be formally recalculated using data from Stage 1.	2-point improvement for an experimental drug arm relative to placebo on mean change from baseline to Week 6 in the vaginal dilator induced pain as reported on a numeric pain rating scale (using the DMTS) using a one-sided 0.10 level test (not corrected for multiplicity) is 21 evaluable subjects per arm (i.e. a total of 63 subjects). The following assumptions were used for the power statement: • Expected outcome on the mean change from baseline to Week 6 in the vaginal dilator induced pain as reported on a numeric pain rating scale in the placebo group = 2-point decrease (reference approximated by VAS per speculum in Bornstein, 2010 [26]) • Expected outcome on the mean change from baseline to Week 6 in the vaginal dilator induced pain as reported on a numeric pain rating scale in a Dysport treated group = 4-point decrease • Expected common standard deviation of the mean change from baseline to Week 6 in the vaginal dilator induced pain as reported on a numeric pain rating scale = 3-points (approximated per VAS data in Table 2 in Davis 2013 [27]). Subject who discontinue prior to Week 6 for reasons unrelated to safety will be replaced at the discretion of the investigator and sponsor. At the end of Stage 2, if the true DLE rate is 6% or greater, there is at least 80% probability to observe at least 1 DLE in 29 subjects (8 in Stage 1 and 21 in Stage 2). Therefore, if there are no observed DLEs in both Stage 1 and Stage 2 at a dose level, then there is good confidence that the true DLE rate is no more than 6%. **If the dose chosen in Stage 2 has been tested on two cohorts (PVD1 and PVD2) in Stage 1, at the end of Stage 2, if the true DLE rate is 5% or greater, there is at least 80% probability to observe at least one DLE in 37 subjects (16 in Stage 1 and 21 in Stage 2). Therefore, if there are no observed DLEs in both Stage 1 and Stage 2 at a dose level, then there is good confidence that the true DLE rate is no more than 5%.** If it is reasonable to assume that the relationship between toxicity and dose level is monotonic non-decreasing, then we may pool dose levels to obtain a higher degree of confidence for the lower dose level.

Version Date		08 APRIL 2019	23 JANUARY 2020
Page	**Section**	**WAS**	**IS**
			If only one Dysport dose is selected, it is intended to randomise subjects in the ratio of 2:1. Sample size will be formally recalculated using data from Stage 1.
88	**Section 11.4.6.1** (Data Review Committee (End of Stage 1 – Cycle 1-Week 6))	When all subjects in PVD2 cohorts in Stage 1 have reached Cycle 1-Week 6 visit, the DRC will review the unblinded efficacy and safety data to enable: ▲ Selection of doses ▲ Confirm the sample size for Stage 2 ▲ Confirm the list of endpoints to be used in Stage 2. Once all PVD1 subjects in Cohort 4 have reached Cycle 1-Week 6 visit, the DRC will meet and based on unblinded review of all safety and efficacy data from the cohort, will decide if further PVD1 cohort(s) are required or if PVD1 subjects should be removed from Stage 2.	When all subjects in PVD2 cohorts in Stage 1 have reached Cycle 1-Week 6 visit, the DRC will review the unblinded efficacy and safety data to enable: ▲ Selection of doses ▲ Confirm the sample size for Stage 2 ▲ Confirm the list of endpoints to be used in Stage 2. Once all **subjects in** PVD1 ~~subjects in~~ Cohorts ~~4~~ have reached Cycle 1-Week 6 visit, the DRC will meet and based on unblinded review of all safety and efficacy data from the cohort, will decide if further PVD1 cohort(s) are required or if PVD1 subjects should be removed from Stage 2.

<table>
<tr><th colspan="2">Version Date</th><th>08 APRIL 2019</th><th>23 JANUARY 2020</th></tr>
<tr><th>Page</th><th>Section</th><th>WAS</th><th>IS</th></tr>
<tr><td>103</td><td>Appendix 1 mVPAQ</td><td>
Appendix 1 mVPAQ (Version 1.1)

VPAQfull Subscales

Pain Severity
Please rate the following about your vulvar pain (in the past 1 week)
<table>
<tr><th></th><th>None</th><th>Mild</th><th>Moderate</th><th>Severe</th><th>Worst Possible</th></tr>
<tr><td colspan="6">Intensity: In the past 1 week, how strong the pain sensation is</td></tr>
<tr><td>Average pain intensity</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Worst pain intensity</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td colspan="6">Unpleasantness: In the past 1 week, how much the pain bothers you</td></tr>
<tr><td>Average pain unpleasantness</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Worst pain unpleasantness</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td colspan="6">Distress: In the past 1 week, how upset the pain makes you feel</td></tr>
<tr><td>Average distress about pain</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Worst distress about pain</td><td></td><td></td><td></td><td></td><td></td></tr>
</table>
Emotional Response
In the past 1 month, how much do you experience feeling the following related to your vulvar
</td><td>
Appendix 1 mVPAQ (Version 1.2)

VPAQfull Subscales

Pain Severity
Please rate the following about your vulvar pain (in the past 1 week)
<table>
<tr><th></th><th>None</th><th>Mild</th><th>Moderate</th><th>Severe</th><th>Worst Possible</th></tr>
<tr><td colspan="6">Intensity: In the past 1 week, how strong the pain sensation is</td></tr>
<tr><td>Average pain intensity</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Worst pain intensity</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td colspan="6">Unpleasantness: In the past 1 week, how much the pain bothers you</td></tr>
<tr><td>Average pain unpleasantness</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Worst pain unpleasantness</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td colspan="6">Distress: In the past 1 week, how upset the pain makes you feel</td></tr>
<tr><td>Average distress about pain</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Worst distress about pain</td><td></td><td></td><td></td><td></td><td></td></tr>
</table>
Emotional Response
In the past 1 month, how much do you experience feeling the following related to your vulvar
</td></tr>
<tr><td>106, 110 &111</td><td>Appendix 2 mFSFI</td><td>
Appendix 2 mFSFI (Version 1.1)

FEMALE SEXUAL FUNCTION INDEX (FSFI)©

Subject Identifier _____ Date _____/_____/_____
Month Day Year

INSTRUCTIONS: These questions ask about your sexual feelings and responses. Please answer the following questions as honestly and clearly as possible. Your responses will be kept completely confidential. In answering these questions, the following definitions apply:

Sexual activity can include caressing, foreplay, masturbation, and vaginal intercourse.

Sexual intercourse is defined as penile penetration (entry) of the vagina.

Sexual stimulation includes situations like foreplay with a partner, self-stimulation (masturbation), or sexual fantasy.
</td><td>
Appendix 2 mFSFI (Version 1.2)

FEMALE SEXUAL FUNCTION INDEX (FSFI)©

Subject Identifier _____ Date _____/_____/_____
Month Day Year

INSTRUCTIONS: These questions ask about your sexual feelings and responses. Please answer the following questions as honestly and clearly as possible. Your responses will be kept completely confidential. In answering these questions, the following definitions apply:

Sexual activity can include caressing, foreplay, masturbation, and vaginal intercourse.

Sexual intercourse is defined as penile penetration (entry) of the vagina.

Sexual stimulation includes situations like foreplay with a partner, self-stimulation (masturbation), or sexual fantasy.
</td></tr>
</table>

Version Date		08 APRIL 2019	23 JANUARY 2020
Page	**Section**	**WAS**	**IS**
		14. Over the past 4 weeks, how **satisfied** have you been with the amount of emotional closeness during sexual activity between you and your partner? □ = No sexual activity □ = Very satisfied □ = Moderately satisfied □ = About equally satisfied and dissatisfied □ = Moderately dissatisfied □ = Very dissatisfied 15. Over the past 4 weeks, how **satisfied** have you been with your sexual relationship with your partner? □ = Very satisfied □ = Moderately satisfied □ = About equally satisfied and dissatisfied □ = Moderately dissatisfied □ = Very dissatisfied 16. Over the past 4 weeks, how **satisfied** have you been with your overall sexual life? □ = Very satisfied □ = Moderately satisfied □ = About equally satisfied and dissatisfied □ = Moderately dissatisfied □ = Very dissatisfied 17. Over the past 1 week, how **often** did you experience discomfort or pain during vaginal penetration? □ = Did not attempt intercourse □ = Almost always or always □ = Most times (more than half the time) □ = Sometimes (about half the time) □ = A few times (less than half the time) □ = Almost never or never Copyright ©2000 All Rights Reserved Page 5 (of 6) FSFI - United States/English - Mapi Institute.	14. Over the past 4 weeks, how **satisfied** have you been with the amount of emotional closeness during sexual activity between you and your partner? □ = No sexual activity □ = Very satisfied □ = Moderately satisfied □ = About equally satisfied and dissatisfied □ = Moderately dissatisfied □ = Very dissatisfied 15. Over the past 4 weeks, how **satisfied** have you been with your sexual relationship with your partner? □ = Very satisfied □ = Moderately satisfied □ = About equally satisfied and dissatisfied □ = Moderately dissatisfied □ = Very dissatisfied 16. Over the past 4 weeks, how **satisfied** have you been with your overall sexual life? □ = Very satisfied □ = Moderately satisfied □ = About equally satisfied and dissatisfied □ = Moderately dissatisfied □ = Very dissatisfied 17. Over the past 1 week, how **often** did you experience discomfort or pain **during** vaginal penetration? □ = Did not attempt intercourse □ = Almost always or always □ = Most times (more than half the time) □ = Sometimes (about half the time) □ = A few times (less than half the time) □ = Almost never or never Copyright ©2000 All Rights Reserved Page 5 (of 6) FSFI - United States/English - Mapi Institute.

Version Date		08 APRIL 2019	23 JANUARY 2020
Page	**Section**	**WAS**	**IS**
		18. Over the past 1 week, how **often** did you experience discomfort or pain following vaginal penetration? ☐ = Did not attempt intercourse ☐ = Almost always or always ☐ = Most times (more than half the time) ☐ = Sometimes (about half the time) ☐ = A few times (less than half the time) ☐ = Almost never or never 19. Over the past 1 week, how would you rate your **level** (degree) of discomfort or pain during or following vaginal penetration? ☐ = Did not attempt intercourse ☐ = Very high ☐ = High ☐ = Moderate ☐ = Low ☐ = Very low or none at all ***Thank you for completing this questionnaire.*** Copyright ©2000 All Rights Reserved Page 8 (of 8) FSFI - United States/English - Mapi Institute. [illegible]	18. Over the past 1 week, how **often** did you experience discomfort or pain **following** vaginal penetration? ☐ = Did not attempt intercourse ☐ = Almost always or always ☐ = Most times (more than half the time) ☐ = Sometimes (about half the time) ☐ = A few times (less than half the time) ☐ = Almost never or never 19. Over the past 1 week, how would you rate your **level** (degree) of discomfort or pain **during or following** vaginal penetration? ☐ = Did not attempt intercourse ☐ = Very high ☐ = High ☐ = Moderate ☐ = Low ☐ = Very low or none at all ***Thank you for completing this questionnaire.*** Copyright ©2000 All Rights Reserved Page 6 (of 6) FSFI - United States/English - Mapi Institute. [illegible]

SUMMARY & OUTCOME OF CHANGES:

STUDY NUMBER	D-FR-52120-236	
AMENDED PROTOCOL VERSION NUMBER & DATE	Protocol Version 5.0: 23 January 2020	
SUBSTANTIAL ☒	**NON-SUBSTANTIAL** ☐	
REASON(S) FOR CHANGES	The protocol was updated to: • Include additional cohorts up to a maximum of 800 U • Clarify assessment for pelvic floor muscles pressure • Update the sample size determination criteria • Clarify inclusion/exclusion criteria related to vaginal delivery and medical history • Update the names of sponsor representatives	
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)*

Appendix 10 Protocol Amendment Version 6.0 (08 October 2020)

STUDY NUMBER:	D-FR-52120-236
PROTOCOL TITLE:	A phase II, multicentre, double-blind, randomised, placebo-controlled, dose escalation and dose finding study to evaluate the efficacy and safety of Dysport in vulvodynia patients
PREVIOUS PROTOCOL VERSION NUMBER & DATE	Protocol Version 5.0: 23 January 2020
AMENDED PROTOCOL VERSION NUMBER & DATE	Protocol Version 6.0: 08 October 2020

The updated text in the amendment is reflected in bold and deletions are marked in strikeout text; general changes across sections are presented in italics and underlined text. Minor formatting edits and correction of typos have not been recorded.

THE FOLLOWING AMENDMENT(S) ARE PROPOSED:

Version Date		**23 JANUARY 2020**	**08 OCTOBER 2020**
Page	**Section**	**WAS**	**IS**
2	**Investigator's Agreement**	**Sponsor's Representative Signature:** PPD	**Sponsor's Representative Signature:** PPD

Version Date		23 JANUARY 2020	08 OCTOBER 2020
Page	**Section**	**WAS**	**IS**
5 27 28	**Synopsis** **(Study Objectives)** **Section 2.2.2** **Section 2.2.3**	Secondary Study Objectives: Stage 1: • To determine the dose(s) of Dysport to be administered in Stage 2. Stage 2: • To define the optimal dose(s) of Dysport with an acceptable benefit/risk profile for the treatment of vulvodynia with PVD • To assess effect of Dysport on: - Vulvar pain - Use of pain rescue medication (type, dose and frequency) - Clinical Global Impression (CGI) of the treatment effect (assessed by the investigator) - Patient Global Impression of severity of the pain (PGI-S) and Patient Global Impression of change in pain (PGI-C)	Secondary Study Objectives: Stage 1: • To determine the dose~~(s)~~ of Dysport to be administered in Stage 2. Stage 2: • To define the optimal dose~~(s)~~ of Dysport with an acceptable benefit/risk profile for the treatment of vulvodynia with PVD • To assess effect of Dysport on: - Vulvar pain - Use of pain rescue medication (type, dose and frequency) ~~- Clinical Global Impression (CGI) of the treatment effect (assessed by the investigator)~~ ~~- Patient Global Impression of severity of the pain (PGI-S) and Patient Global Impression of change in pain (PGI-C)~~ Exploratory Objectives: • **To assess effect of Dysport on:** - **Clinical Global Impression (CGI) of the treatment effect (assessed by the investigator)** - **Patient Global Impression of severity of the pain (PGI-S) and Patient Global Impression of change in pain (PGI-C)**
6-7 13 29-30 31	**Synopsis** **(Methodology – Stages 1 and 2)** **(Statistical Methods)** **Section 3.1.1** **Section 3.1.1.2**	*The role of the DRC is to make decision on dose escalation, dose de-escalation, progression from Stage 1 to Stage 2 or study termination decisions in Stage 1.*	*Clarify that the role of the DRC is to make recommendations on dose escalation, dose de-escalation, progression from Stage 1 to Stage 2 or study termination decisions in Stage 1.* *A provision of intermediate analysis to be performed at the point when the DRC recommends moving to Stage 2 was added. It was clarified that, following the review of data available from Stage 1, the sample size may be formally recalculated for Stage 2 after the intermediate analysis; the*

Version Date		23 JANUARY 2020	08 OCTOBER 2020
Page	**Section**	**WAS**	**IS**
31 40 41 88 89	**Section 3.1.2** **Section 3.7.2.1** **Section 3.7.2.2** **Section 11.2** **Section 11.4.6.1**		*sample size recalculation for Stage 2 was removed from DRC responsibilities.*
6 12-13 29-30 31 31 36-37 41 88	**Synopsis (Methodology-Stage 2)** **(Statistical Methods)** **Section 3.1.1** **Section 3.1.1.2** **Section 3.1.2** **Section 3.5** **Section 3.7.2.2** **Section 11.2**	*One or two optimally safe and effective doses of Dysport will be further investigated in the Stage 2.*	*The protocol was updated throughout to reflect that during Stage 2, two optimally safe and effective doses of Dysport will be further investigated; the option of testing one Dysport dose during Stage 2 was removed.*
6 30	**Synopsis (Methodology – Stage 1)** **Section 3.1.1**		**An intermediate analysis will be performed to review the unblinded data from all cohorts in Stage 1 up to Cycle 1-Week 12 in an effort to select the two doses for Stage 2 taking into account the dosing recommendations from the DRC.**
8 44	**Synopsis (Inclusion Criteria)** **Section 4.1**	(12a) In Stage 1, in all cohorts except Cohort 4, subjects with secondary vulvodynia (i.e. having a past history of pain free intercourse or insertion of any object >1 cm diameter) will be enrolled. Stage 1 Cohort 4 will only include subjects with primary vulvodynia (having life-long provoked vestibular pain). In Stage 2, subjects with either primary or secondary vulvodynia may be enrolled as approved by the DRC.	(12b~~a~~) In Stage 1, ~~in all e~~Cohorts **1, 2, 3, 5, 7, 9 and 11 will include** ~~except Cohort 4~~, subjects with secondary vulvodynia (i.e. having a past history of pain free intercourse or insertion of any object >1 cm diameter) ~~will be enrolled~~. **In** Stage 1**,** Cohorts **4, 6, 8, 10 and 12** will ~~only~~ include subjects with primary vulvodynia (having life-long provoked vestibular pain). In Stage 2, subjects with either primary or secondary vulvodynia may be enrolled as approved by the DRC.

Version Date		23 JANUARY 2020	08 OCTOBER 2020
Page	**Section**	**WAS**	**IS**
11-12 35 36 69-70 71	**Synopsis (Criteria for Evaluation) (Endpoints))** **Section 3.2.2** **Section 3.3** **Section 7.2 (Table 8)** **Section 7.3 (Table 9)**	**Criteria for Evaluation (Endpoints):** Secondary Endpoints and Evaluations: • Proportion of subjects who reported at least 2-point decrease in vaginal dilator induced pain as reported on the 11-point NRS (using the DMTS reported at baseline) at each post-treatment postbaseline visit. • Mean CGI (as assessed by the investigator) of the treatment effect at each post-treatment visit. • Mean PGI-C (as assessed by the subject) at each post-treatment visit. • Mean change from baseline in PGI-S (as assessed by the subject) at each visit. • Use of pain rescue medication (type, dose, and frequency).	**Criteria for Evaluation (Endpoints):** Secondary Endpoints and Evaluations: • Proportion of subjects who reported at least 2-point decrease in vaginal dilator induced pain as reported on the 11-point NRS (using the DMTS reported at baseline) at each **post-treatment** ~~postbaseline~~ visit. • ~~Mean CGI (as assessed by the investigator) of the treatment effect at each post-treatment visit.~~ • ~~Mean PGI-C (as assessed by the subject) at each post-treatment visit.~~ • ~~Mean change from baseline in PGI-S (as assessed by the subject) at each visit.~~ • Use of pain rescue medication (type, dose, **number of pills** taken and frequency). • **Proportion of subjects who reported at least a 50% decrease in vaginal dilator induced pain as reported on the 11-point NRS (using the DMTS reported at Baseline) at each post-treatment visit.** • **Proportion of subjects having reported at least a 50% decrease in pain during insertion of vaginal dilator number 6 size on the mean of the NRS values at each post treatment visit.** • **Proportion of subjects having reported at least a 30% decrease in pain during insertion of vaginal dilator number 6 size on the mean of the NRS values at each post treatment visit.** • **Proportion of subjects having reported at least 2-point decrease in pain during insertion of vaginal dilator number 6 size on the mean of the NRS values at each post treatment visit.** Exploratory Endpoints: • **Mean CGI (as assessed by the investigator) of the treatment effect at each post treatment visit.**

Version Date		23 JANUARY 2020	08 OCTOBER 2020
Page	**Section**	**WAS**	**IS**
			• **Mean PGI-C (as assessed by the subject) at each post-treatment visit.** • **Mean change from baseline in PGI-S (as assessed by the subject) at each visit.**
14	**Synopsis (Statistical Methods)**		**Intermediate Analysis:** **At the point when the DRC recommends moving to Stage 2 of the study, an intermediate unblinded analysis will be performed. Available data from all double-blind periods of all cohorts from Stage 1 until the last subject has completed their Cycle 1-Week 12 visit will be considered in the analysis. Descriptive statistics of the TEAEs and selected efficacy endpoints will be carried out.** **Following the review of data available from Stage 1, the sample size may be formally recalculated for Stage 2 after the intermediate analysis.**
39	**Section 3.7.1**		*The following information, specific to the Canadian regulation, was added/amended to the description of the core text of the IMP labels:* • ~~**Where relevant,**~~ **A specific blank space to enter** the visit number **(to be completed on site)**, • **Investigational drug to be used by qualified investigators only,** • A specific blank space to enter the subject ID **(to be completed on site)** • **A specific blank space to enter the site number (to be completed on site).**

Version Date		23 JANUARY 2020	08 OCTOBER 2020
Page	**Section**	**WAS**	**IS**
42	**Section 3.9**	A specific site or a given cohort can be discontinued or the entire study may be terminated if recommended by the DRC at any time during Stage 1 or if the sponsor judges it necessary for any reason any time during the study. In that case, all scheduled procedures and assessments for subjects who are still in the study will be performed. • As per sponsor's decision anytime during the study for reasons including: - Failure of the site staff to comply with the protocol or with the GCP guidelines; - AEs or SAEs leading to safety concerns (See Section 8.1.6); - Inadequate subject recruitment.	A specific site or a given cohort can be discontinued or the entire study may be terminated if recommended by the DRC at any time during Stage 1 or if the sponsor judges it necessary for any reason any time during the study. In that case, all **efforts should be made to perform the** scheduled procedures and assessments for subjects who are still in the study ~~**will be performed**~~ **until 12 weeks after the last dose**. • As per sponsor's decision anytime during the study for reasons including: - Failure of the site staff to comply with the protocol or with the GCP guidelines; - AEs or SAEs leading to safety concerns (See Section 8.1.6); - Inadequate subject recruitment**;** - **Other reasons (decisions made by the Regulatory Authorities or Ethics Committees or any other sponsor business decision)**.
55	**Section 5.2.1.1**	A subject can be rescreened once, if all eligibility criteria were met but the subject was not enrolled due to any of the following:	A subject can be rescreened once, if all eligibility criteria were met but the subject was not enrolled due to any of the following**, and twice due to ANY of the following conditions if they had to stop the first screening period due to COVID-19**:
48-53 54 56-57 57-58 58-59 59-60 60	**Section 5.1 (Tables 2 and 3)** **Section 5.2** **Section 5.2.2.3** **Section 5.2.2.4** **Section 5.2.2.5** **Section 5.2.3.3** **Section 5.2.3.4**		*If the COVID-19 pandemic prevents subjects from coming to the site, a provision was added for the subjects to have their study visit assessments performed remotely as judged appropriate by the investigator, and after having discussed with the medical monitor/sponsor before being implemented.* *It was also specified which particular planned study assessments could be possibly performed remotely for subjects unable to attend the site visit due to the COVID-19 pandemic.*

Version Date		23 JANUARY 2020	08 OCTOBER 2020
Page	**Section**	**WAS**	**IS**
60-61 62	**Section 5.2.3.5** **Section 5.2.4**		
63	**Section 6.1.3**	Any reconstituted unused IMP has to be inactivated using bleach. All disposal ancillary materials (e.g. needles and syringes) must be discarded in suitable containers intended for incineration after use at the site.	Any reconstituted unused IMP has to be **discarded in accordance with local regulations (e.g. inactivation with sodium hypochlorite or autoclave, etc.)**~~inactivated using bleach~~. All disposal ancillary materials (e.g. needles and syringes) must be discarded in suitable containers intended for incineration after use at the site.
67	**Section 6.3**	The following concomitant medications/therapies are permitted during this study, but they must be monitored closely and, where applicable, every effort should be made to keep their dose and dose regimen constant:	The following concomitant medications/therapies are permitted during this study, but they must be monitored closely and, where applicable, ~~every effort should be made to keep~~ their dose and dose regimen **should remain** constant **as detailed below**: *A list of allowed pain rescue medications available over the counter, if required during Stage 2, was added* ***(as Table 7)*** *with the corresponding recommended doses.*
74 108-113	**Section 7.4.2.3**		**From Stage 2 onwards, Question 19 of the pain domain (measuring the level of pain 'during' and 'following' vaginal penetration with a 1-week recall period) will be split into two separate questions –** • **Question 19 – measuring the level of discomfort or pain during vaginal penetration.** • **Question 20 – measuring the level of discomfort or pain following vaginal penetration.** *Appendix 2 mFSFI version 1.2 was updated with mFSFI version* ***1.3*** *reflecting the change where question 19 was split into two questions (Question 19 and Question 20) in order to align with the change outlined in Section 7.4.2.3.*
74	**Section 7.4.2.4**	The PGI-S will be assessed by the subject by answering the following question: "How severe was your 'provoked vulvar pain' over the past week?	The PGI-S will be assessed by the subject by answering the following question: "How severe was your 'provoked vulvar pain' **(pain specifically triggered by touching the vulvar area)** over the past week?

Version Date		23 JANUARY 2020	08 OCTOBER 2020
Page	**Section**	**WAS**	**IS**
80	**Section 8.1.6**		**This includes any suspected or confirmed coronavirus COVID-19 (SARS-CoV-2) infection (seriousness criteria should be "other medically significant" if no other seriousness criteria are present (e.g. hospitalisation)).**
81	**Section 8.1.9**		**In case of suspected or confirmed COVID-19 infection which is to be reported as an SAE (Section 8.1.6), the IMP administration may be temporarily postponed depending on the subject clinical presentation. In some cases, the investigator may request a subject be retested before the IMP administration.**
86	**Section 11**	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 database lock of the primary analysis (described in Section 11.4.6.2).	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 database lock of the ~~primary~~**intermediate** analysis (described in Section ~~11.4.6.2~~**11.6**). **The COVID-19 pandemic may have an impact on this trial and specific summaries will be provided in order to assess its impact.**
86	**Section 11.1.2**	Any major protocol deviation (see Section 13.1.2 for definition) will be described. The final list of protocol deviations impacting the PP population will be reviewed prior to database lock, before unblinding of treatment groups for the primary analysis (with the exception of DRC, which may/ may not request unblinding (see Section 3.1.1.2).	Any major protocol deviation (see Section 13.1.2 for definition) will be described. **Subjects substantially affected directly or indirectly by COVID-19 will be flagged with a major protocol deviation.** The final list of protocol deviations impacting the PP population will be reviewed prior to database lock, before unblinding of treatment groups for the **intermediate and** primary analysis (with the exception of DRC, which may/ may not request unblinding (see Section 3.1.1.2).
88	**Section 11.4.1**		**In Stage 1, main demographic and baseline characteristics will be provided in patients recruited before and after the start of COVID-19 pandemic (i.e. before / after Cohort 6) in order to identify a potential change in the general patients' characteristics.**
88	**Section 11.4.2**		**The impact of COVID-19 pandemic on the trial will be assessed through the summary of data collected in relation to COVID-19, i.e. disposition of patients including the proportion of patients impacted**

Version Date		23 JANUARY 2020	08 OCTOBER 2020
Page	**Section**	**WAS**	**IS**
			and withdrawn due to COVID-19 pandemic and number of patients with visits impacted by COVID-19 with the corresponding reason. Exposure to treatment will also be described before and after the start of COVID-19 pandemic (i.e. before/after Cohort 6).
89	**Section 11.4.3**		**The scoring of patient reported questionnaires will be detailed in the SAP. For mVPAQ, the analysis of life interference subscale will be done with and without the item 'ability to fall asleep'. The analysis of pain severity subscale will be done with and without the items 'unpleasantness' and 'distress'. The total mVPAQ will also be computed with and without these items.**
89	**Section 11.4.6.1**	When all subjects in PVD2 cohorts in Stage 1 have reached Cycle 1-Week 6 visit, the DRC will review the unblinded efficacy and safety data to enable: • Selection of doses • Confirm the sample size for Stage 2 • Confirm the list of endpoints to be used in Stage 2.	When all subjects in PVD2 cohorts in Stage 1 have reached Cycle 1-Week 6 visit, the DRC will review the unblinded efficacy and safety data to enable~~:~~ **S**selection of doses • ~~Confirm the sample size for Stage 2~~ • ~~Confirm the list of endpoints to be used in Stage 2~~.
90	**Section 11.5**	Descriptive statistics for the primary efficacy endpoint will be provided by pain onset subtype (primary and secondary PVD) for Stage 2 on the mITT population.	Descriptive statistics for the primary efficacy endpoint **and main baseline characteristics** will be provided by pain onset subtype (primary and secondary PVD) for Stage 2 on the mITT population. **In addition, overall adverse events summary as well as TEAEs and SAEs will be provided (by SOC and PT) by pain onset subtype.**
90-91	**Section 11.6**		**Section 11.6 Intermediate Analyses** **At the point when the DRC recommends moving to Stage 2 of the study, an intermediate unblinded analysis of data available from all double-blind periods of all cohorts in Stage 1 will be performed when all subjects from the latest cohorts have completed their Cycle 1-Week 12 visit (data cut-off date corresponding to the last Cycle 1-Week 12 visit date).** **All AE data available at the time of the data cut-off date (including data from the double-blind cycle from all cohorts) will be analysed**

Version Date		23 JANUARY 2020	08 OCTOBER 2020
Page	Section	WAS	IS
			using descriptive statistics. A thorough description of TEAEs collected during the double-blind periods will be performed. Demographic and baseline characteristics, disposition, concomitant medications and treatment exposure will be described as well. All efficacy related secondary endpoints will be described using change from baseline and categorical analyses (as summarised in Section 7.2). In addition, descriptive statistics will also be provided for selected exploratory endpoints (mean PGI-C score, and mean changes from baseline in the following endpoints: PGI-S score, mVPAQ pain and life interference subscales scores, mFSFI total score and domain scores and PHQ-9 total score). A detailed description of this intermediate analysis will be provided in the SAP.

SUMMARY & OUTCOME OF CHANGES:

STUDY NUMBER	D-FR-52120-236	
AMENDED PROTOCOL VERSION NUMBER & DATE	Protocol Version 6.0: 08 October 2020	
SUBSTANTIAL ☒	**NON-SUBSTANTIAL** ☐	
REASON(S) FOR CHANGES	The protocol was updated to: • Reflect that during Stage 2, two optimally safe and effective doses of Dysport will be further investigated; the option of testing one Dysport dose during Stage 2 was removed. • Clarify that the role of the DRC was to make recommendation on dose escalation, dose de-escalation, progression from Stage 1 to Stage 2 or study termination decisions in Stage 1. • Clarify in inclusion criteria 12b, the specific cohorts that enrolled subjects with primary vulvodynia versus secondary vulvodynia. • Shift the evaluation of CGI-C and PGI-C from secondary objectives/efficacy parameters to exploratory objectives/efficacy parameters. • Add guidance on COVID-19 infection to be reported as an SAE, and its impact on IMP administration. • Add a provision for the subjects to have their study visit assessments performed remotely, if they are unable to attend the site visit due to the COVID-19 pandemic. • Add permitted pain rescue medication during Stage 2. • Add further clarification in the statistical section on the: ➢ Doses being evaluated in Stage 2, ➢ COVID-19 specific analyses, ➢ Intermediate analyses to be performed at the point when the DRC recommends moving to Stage 2 and ➢ Potential sample size recalculation for Stage 2 following the intermediate analysis. • Update the mFSFI questionnaire to version 1.3.	
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)*