

A PHASE III, MULTICENTRE, RANDOMISED, DOUBLE BLIND, PARALLEL GROUP, PLACEBO CONTROLLED STUDY TO ASSESS THE EFFICACY AND SAFETY OF ONE OR MORE INTRADETRUSOR TREATMENTS OF 600 OR 800 UNITS OF DYSPORT® FOR THE TREATMENT OF URINARY INCONTINENCE IN SUBJECTS WITH NEUROGENIC DETRUSOR OVERACTIVITY DUE TO SPINAL CORD INJURY OR MULTIPLE SCLEROSIS

STUDY PROTOCOL

STUDY number: D-FR-52120-222

EudraCT number: 2015-003471-30

DYSPORT®

Final Version 2.0 Dated 16 April 2018, incorporating amendment 1**Sponsor's Medically Responsible Person:**

PPD [REDACTED]
 PPD [REDACTED],
 PPD [REDACTED]
 PPD [REDACTED]
 Tel: PPD [REDACTED]
 Email: PPD [REDACTED]

Study Sponsor:

Ipsen Innovation
 Ipsen Group
 5 Avenue du Canada
 91940 Les Ulis Cedex, France
 Tel: +33 (0)1 60 92 20 00
 Fax: PPD [REDACTED]

Monitoring Office and/or CRO:

PPD [REDACTED]
 CCI [REDACTED]
 [REDACTED]
 [REDACTED]
 PPD [REDACTED]
 PPD [REDACTED]

Co-ordinating Investigator:

PPD [REDACTED], PPD [REDACTED]
 PPD [REDACTED]
 [REDACTED]
 [REDACTED]
 [REDACTED]
 [REDACTED]
 [REDACTED]
 Tel: +PPD [REDACTED]
 Email: PPD [REDACTED]

Pharmacovigilance/Emergency Contact:

PPD [REDACTED], PPD [REDACTED]
 [REDACTED]

Phone: PPD [REDACTED] - Mobile: PPD [REDACTED]

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

Tel: PPD [REDACTED] mobile telephone for emergencies
 PPD [REDACTED] (USA only)

For serious adverse event (SAE) reporting:

Fax: +PPD [REDACTED]
 [REDACTED]

Persons supplied with this information must understand that it is strictly confidential. Information contained herein cannot be disclosed, submitted for publication or used for any purpose other than that contemplated herein without the sponsor's prior written authorisation.

INVESTIGATOR'S AGREEMENT**Investigator Agreement and Signature:**

I have read and agree to Protocol D-FR-52120-222 entitled "A phase III, multicentre, randomised, double blind, parallel group, placebo controlled study to assess the efficacy and safety of one or more intradetrusor treatments of 600 or 800 units of Dysport® for the treatment of urinary incontinence in subjects with neurogenic detrusor overactivity due to spinal cord injury or multiple sclerosis". 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:

PRINCIPAL

SIGNATURE:

INVESTIGATOR

DATE:

OFFICE:

Sponsor's Representative Signature:

NAME:

PPD

TITLE:

PPD

SIGNATURE:

DATE:

OFFICE:

Ipsen Innovation

5 Avenue du Canada

91940 Les Ulis Cedex

France

Tel: +33 (0)1 60 92 20 00

PPD

COORDINATING INVESTIGATOR'S AGREEMENT**Coordinating Investigator Agreement and Signature:**

I have read and agree to Protocol D-FR-52120-222 entitled "A phase III, multicentre, randomised, double blind, parallel group, placebo controlled study to assess the efficacy and safety of one or more intradetrusor treatments of 600 or 800 units of Dysport[®] for the treatment of urinary incontinence in subjects with neurogenic detrusor overactivity due to spinal cord injury or multiple sclerosis". I am aware of my responsibilities as a coordinating 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: COORDINATING
INVESTIGATOR

SIGNATURE:

DATE:
OFFICE:

Summary of Changes

The current version of the protocol was released on 16 April 2018 and includes Amendment 1. For all protocol amendments, amendment forms were prepared and are provided in Appendix 2.0 (see [Table 1](#)).

Table 1 List of Protocol Amendments

Amendment	Release date	Amendment form
1	16 April 2018	Appendix 2

SYNOPSIS

Name of sponsor/company: Ipsen Innovation	
Name of finished product: Dysport® for Injection	
Name of active ingredient: AbobotulinumtoxinA (Clostridium BTX-A-haemagglutinin complex)	
Title of study: A phase III, multicentre, randomised, double blind, parallel group, placebo controlled study to assess the efficacy and safety of one or more intradetrusor treatments of 600 or 800 units of Dysport® for the treatment of urinary incontinence in subjects with neurogenic detrusor overactivity due to spinal cord injury or multiple sclerosis.	
Study number: D-FR-52120-222	
Number of planned sites: Approximately 90 study sites	
Planned study period: First quarter 2016 (estimated first subject randomised) until last quarter 2020 (estimated last subject last visit)	Phase of development: Phase III
<p>Objectives:</p> <p>Target Population: Subjects with urinary incontinence (UI) caused by neurogenic detrusor overactivity (NDO) due to either spinal cord injury (SCI) or multiple sclerosis (MS), who have not been adequately managed with oral medication and who routinely require clean intermittent catheterisation (CIC) to manage their bladder function.</p> <p>Primary Study Objective:</p> <ul style="list-style-type: none"> To assess the efficacy of two Dysport® doses (600 units (U) and 800 U), compared to placebo in reducing UI from Baseline to Week 6 following the first investigational medicinal product (IMP) administration. <p>Secondary Study Objectives:</p> <ul style="list-style-type: none"> To assess the efficacy of two Dysport® doses (600 U and 800 U), compared to placebo in improving bladder diary measures, urodynamic and patient-reported efficacy endpoints following the first IMP administration, including assessing duration of effect. To assess the efficacy of two Dysport® doses (600 U and 800 U) in improving bladder diary measures and patient-reported efficacy endpoints following retreatment IMP administrations, including assessing duration of effect. To assess the safety of two Dysport® doses (600 U and 800 U) for the treatment of UI due to NDO. 	
<p>Methodology:</p> <p>Study design This is a phase III, multicentre, randomised, double blind, parallel group, placebo controlled study to assess the efficacy and safety of two Dysport® doses (600 U and 800 U) administered to the bladder of adult subjects with SCI or MS, and UI due to NDO. This study has two treatment periods:</p> <ul style="list-style-type: none"> A double blind placebo controlled period, during which subjects receive a single IMP treatment administration of either 600 U or 800 U Dysport® or placebo. 	

- A subsequent double blind active treatment period, during which subjects can receive multiple active IMP retreatment administrations of either 600 U or 800 U Dysport®.

Duration of subject participation

104 weeks (24 months) to 116 weeks depending on the timing of final IMP administration.

Screening

Screening period will last for up to 30 days (but can be extended in certain circumstances, see Section 5.2.1), during which time informed consent will be obtained and eligibility for study participation will be assessed. Subjects will complete a 7-day bladder diary, urodynamic assessment, patient-reported outcome questionnaires and have blood and urine samples taken.

Randomisation/treatment

The Treatment Visit (Day 1) should occur up to 14 days after screening period (but can be extended where a UTI has occurred, see Section 5.2.3). At the Treatment Visit (Day 1), subjects who meet all the eligibility criteria will be randomised (in a 2:2:1:1 ratio) to one of four treatment sequences:

Sequence	Subjects	Treatment 1	Subsequent retreatment(s)
1	110 subjects	600 U Dysport®	600 U Dysport®
2	110 subjects	800 U Dysport®	800 U Dysport®
3	55 subjects	Placebo	600 U Dysport®
4	55 subjects	Placebo	800 U Dysport®

During analysis of study Treatment 1, the two placebo containing sequences will be pooled into a single arm.

Randomisation will be stratified by aetiology of NDO (SCI or MS) and also by previous intradetrusor botulinum toxin type A (BTX-A) usage (BTX-A naive vs. BTX-A non-naive in the bladder).

IMP administration may be performed using local anaesthesia (if required) or a short-duration general anaesthesia (if required), and will consist of 30 cystoscopically placed injections (0.5 mL per injection point) of the IMP evenly distributed throughout the bladder (avoiding the trigone). CCI

Follow-up (after the first IMP administration):

- Week 1 (Day 8) (telephone)
- Week 2 (Day 15) (clinic visit)
- Week 4 (Day 29) (telephone)
- Week 6 (Day 43) (clinic visit; primary timepoint)
- Week 12 (Day 85) (clinic visit)
- Every 12 weeks (telephone visits; until retreatment received or end of study (EOS) at Week 104 116).

Details of the procedures performed at each visit following the first treatment are shown in [Table 2](#).

Retreatment assessment

A subject may request retreatment at any time ≥ 12 weeks after their most recent study treatment.

If the request occurs between scheduled visits or at a scheduled telephone visit then the subject will require a Retreatment Assessment Visit prior to receiving study retreatment (some retreatment criteria can be assessed prior to the Retreatment Assessment Visit).

If the request occurs at a scheduled visit then the Retreatment Assessment Visit procedures should be performed at the same visit.

Retreatment criteria

The retreatment criteria are as follows:

- 1) Retreatment requested by subject;
- 2) More than 12 weeks (84 days) since the previous IMP administration;
- 3) CCI [REDACTED]

- 5) In the investigator's opinion it is safe and appropriate to provide a retreatment.

Retreatment should ideally occur within 14 days of confirmation of eligibility for retreatment and can occur up to and including Week 104 following the first IMP administration.

Retreatment follow-up

Follow-up after each retreatment follows the same schedule as the first IMP administration:

- Week 1 (Day 8) (telephone)
- Week 2 (Day 15) (clinic visit)
- Week 4 (Day 29) (telephone)
- Week 6 (Day 43) (clinic visit)
- Week 12 (Day 85) (clinic visit)
- Every 12 weeks (telephone visits; until retreatment received or EOS at Week 104 116).

Details of the procedures performed at each Retreatment Follow-up Visit are contained in [Table 3](#).

End of Study Visit

The EOS Visit will take place between 104 and 116 weeks after the first IMP administration (Day 1). Subjects may receive study retreatment up to and including Week 104 and a minimum of 12 weeks of follow-up is required after each IMP administration. For those subjects completing the study, the EOS Visit will occur:

- 104 weeks after the first IMP administration; if it has been more than 12 weeks since the previous IMP administration
- At the Week 12 Retreatment Follow-up Visit, if the subject received their most recent IMP administration between Week 92 and Week 104 following their first IMP administration.

Early discontinuation

A subject who discontinues early should, if at all possible, be followed-up for at least 12 weeks following their most recent IMP administration and should attend the EOS Visit.

Number of subjects planned: 330 randomised subjects.

Diagnosis and criteria for inclusion:***Inclusion criteria***

The following inclusion criteria will be assessed at the beginning of the Screening process:

- 1) Written informed consent prior to any study-related procedure.
- 2) Male or female, aged 18 to 80 years inclusive.
- 3) UI for at least 3 months prior to Screening as a result of NDO due to SCI or MS.
- 4) Subjects with SCI must have a stable neurological injury at T1 level or below which occurred at least 6 months prior to Screening.
OR
Subjects with MS must be clinically stable in the investigator's opinion, with no exacerbation (relapse) of MS for at least 3 months prior to Screening.
- 5) Subjects must have had an inadequate response CCI [REDACTED] of oral medications used in the treatment of NDO (e.g. anticholinergics, beta-3 agonists) and/or have intolerable side-effects.
- 6) CCI [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
- 8) Routinely performing CIC to ensure adequate bladder emptying CCI [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
- 10) Female subjects of childbearing potential must have a negative pregnancy test result and be willing to use reliable contraceptive measures throughout study participation. Reliable forms of contraception include but are not limited to:
 - hormonal contraceptives (e.g. oral, patch, injection)
 - double barrier (e.g. male condom plus spermicide, or female diaphragm plus spermicide)
 - intrauterine device
 - male partner has had a vasectomy
 - total abstinence from intercourse with male partners (periodic abstinence is not acceptable).

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

 - postmenopausal (≥ 47 years of age and amenorrhoeic for at least 12 consecutive months)

- have been sterilised surgically (e.g. bilateral tubal ligation)
- have had a hysterectomy
- have had a bilateral oophorectomy.

11) Documented urinary tract ultrasound is available in the 6 months prior to Screening, confirming that no medical issues exist that would preclude entry to the study (e.g. bladder stones or unexplained renal mass).

- If not performed in the 6 months prior to Screening or results are not available, then a urinary tract ultrasound must be conducted during Screening.

12) Ability to complete all study requirements in the opinion of the investigator, including regularly completing the 7-day bladder diary and attending all scheduled study visits. The caregiver may assist with the completion of study documentation and procedures (including the bladder diary and questionnaires), if required.

The following inclusion criteria will be assessed following completion of screening bladder diary:

13) An average of at least two episodes per day of UI recorded on the screening bladder diary.

CC [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

Exclusion criteria

The following exclusion criteria will be assessed throughout the Screening process:

1) Any current condition (other than NDO) that may impact on bladder function,

CCI [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

2) Previous or current, tumour or malignancy affecting the spinal column or spinal cord, or any other nonstable cause of SCI.

3) Surgery less than 6 months prior to Screening for bladder stones.

4) Surgery less than 6 months prior to Screening for uterine prolapse, cystocele or rectocele.

5) Previous open surgery for NDO, e.g. augmentation cystoplasty.

6) Previous urethral stent placement or sphincterotomy.

- 7) Previous or current diagnosis of, or symptoms/signs/investigations suggestive of, significant urological or pelvic disease, CCI [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
- 8) Previous or current uninvestigated haematuria. CCI [REDACTED] [REDACTED] [REDACTED]
[REDACTED]
[REDACTED].
- 9) Any condition that will prevent cystoscopic treatment administration or CIC usage, e.g. urethral strictures.
- 10) Current indwelling bladder catheter, or removal of indwelling bladder catheter less than 4 weeks prior to Screening.
- 11) BTX-A treatment within 9 months prior to Screening for any urological condition (e.g. detrusor or urethral sphincter treatments).
- 12) BTX-A treatment within 3 months prior to Screening for any non-urological condition.
- 13) Bladder instillation with any pharmacologic agent less than 3 months prior to Screening.
- 14) Use of capsaicin or resiniferatoxin less than 6 months prior to Screening.
- 15) Any neuromodulation/electrostimulation usage for urinary symptoms/incontinence within 4 weeks prior to Screening. Any implanted neuromodulation device must be switched off at least 4 weeks prior to Screening and must remain off throughout study participation.
- 16) Any concomitant therapy usage that, in the investigator's opinion, would interfere with the evaluation of safety or efficacy of the IMP, and/or confound the study results.
- 17) History of chronic drug or alcohol abuse.
- 18) Female subject who is pregnant or planning to become pregnant during the study, or is currently lactating (breastfeeding).
- 19) Any medical condition or disease that might interfere with neuromuscular function, CCI [REDACTED]
[REDACTED]
- 20) Use of medications that affect neuromuscular transmission, CCI [REDACTED]
[REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]
[REDACTED]
- 21) CCI [REDACTED]
[REDACTED]
- 22) Known hypersensitivity to BTX-A or to any components in the IMP formulation (including cow's milk protein).
- 23) History of allergy to, or intolerance to, the anaesthetic or antibiotic agents that the investigator intends to use during the study.

- 24) Unable to stop medications with anticoagulant/antiplatelet effects for at least 3 days prior to each IMP administration and to recommence the day following each IMP administration (low molecular weight heparins may be used within 3 days of IMP administration).
- 25) Any condition that may cause excessive bleeding (e.g. haemophilia or clotting factor deficiencies).
- 26) Any condition or situation which, in the investigator’s opinion, puts the subject at significant risk, may confound the study results, or may interfere with the subject’s participation in the study.
- 27) Treatment with any new investigational drug or device in the 4 weeks prior to Screening or scheduled to be used during the study period. CCI [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Investigational medicinal product, dose, and mode of administration:

Active IMP (Dysport®) will be supplied as a white, lyophilised powder in vials containing 300 U or 500 U of BTX-A-haemagglutinin complex (abobotulinumtoxinA).

ACCI [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

CCI [REDACTED]

[REDACTED]

[REDACTED]

The mode of IMP administration will be via the urethra using either a rigid or flexible cystoscope to allow direct visualisation of the interior of the bladder. Commercially available cystoscopic bladder injection needles will be used and IMP will be delivered at 30 injection points (0.5 mL per injection point).

Duration of treatment:

Subject may receive multiple IMP retreatment administrations (if clinically indicated) for up to 104 weeks after the first IMP administration; with a minimum of 12 weeks between IMP administrations.

CCI [REDACTED]

Reference therapy, dose, and mode of administration:

During Treatment 1 the comparator will be a matching placebo, CCI [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]).

[REDACTED]

[REDACTED]

[REDACTED]

Reconstitution and administration procedures for placebo are identical to the active IMP (Dysport®).

Criteria for evaluation:***Efficacy:******Primary efficacy endpoint:***

- Mean change from study Baseline (assessed at Screening) to Week 6 after the first IMP administration in the weekly number of UI episodes:
 - measured on a 7-day bladder diary.

Secondary efficacy endpoints

Timepoints following the first and subsequent treatments for efficacy endpoint assessments are listed in [Table 2](#) and [Table 3](#):

- Bladder diary measures:
 - weekly number of UI episodes
 - daily urinary frequency (total, spontaneous void only, CIC only)
 - 24-hour voided volume (total, spontaneous void only, CIC only)
 - volume per void (total, spontaneous void only, CIC only).
- Urodynamic measures:
 - maximum cystometric capacity (MCC)
 - maximum detrusor pressure (MDP) during storage
 - volume at first involuntary detrusor contraction (Vol@1stIDC)
 - maximum detrusor pressure at first involuntary detrusor contraction (PdetMax@1stIDC)
 - end fill pressure (EFP)
 - detrusor compliance (DC).
- Patient-reported outcome questionnaires:
 - incontinence quality of life (I-QoL) total summary score
 - EuroQol 5-dimension 5-level (EQ-5D-5L)
 - modified patient global impression - improvement (mPGI-I) score.
- Proportion of subjects at post-treatment timepoints following the first and subsequent treatments with:
 - no episodes of UI (i.e. continence is achieved)
 - UI response at several levels (i.e. $\geq 30\%$ improvement, $\geq 50\%$ improvement, $\geq 75\%$ improvement, etc.)
 - no IDCs on urodynamic assessment (i.e. urodynamic cure is achieved).
- Duration of effect following the first and subsequent treatments.

A hierarchical analysis will be performed in the order listed for the following secondary efficacy measures at Week 6 after the first IMP administration:

- mean change from study Baseline in the MCC
- mean change from study Baseline in the MDP during storage
- mean change from study Baseline in the Vol@1stIDC
- proportion of subjects with no episodes of UI (i.e. continence is achieved)

- proportion of subjects with no IDCs on urodynamic assessment (i.e. urodynamic cure is achieved)
- mean change from study Baseline in the I-QoL total summary score.

Safety:

- adverse events (AEs)
- vital signs
- laboratory blood parameters (haematology and serum chemistry)
- laboratory urine parameters (laboratory urinalysis/microscopy, culture and sensitivity)
- development of BTX-A antibodies
- usage of concomitant medications and therapies.

Statistical methods:***Primary efficacy endpoint***

The primary efficacy endpoint will be analysed using a mixed model. This model will include treatment group, and stratification variables and baseline value as fixed covariates.

Secondary efficacy endpoints

Secondary efficacy endpoints will be assessed according to their scale (categorical or continuous), using a logistic regression model, mixed model, or survival analysis-type methods (e.g. Kaplan-Meier plots, log-rank statistics).

Safety endpoints

The safety analysis will be descriptive in nature; inferential assessment of treatment group differences for safety outcomes is not planned. Subject incidence of each system organ class and preferred term will be tabulated.

Antibody testing

The number and percentage of subjects with the presence of neutralising BTX-A antibodies at Screening will be described. The number of seroconverters (subjects having a negative result at Screening and at least one positive result at any post-treatment timepoint) for neutralizing antibodies will be reported for each treatment group.

Sample size considerations

The sample size is based on the desire to detect a statistically significant treatment difference in the weekly number of UI episodes at Week 6 following the first treatment in the two Dysport[®] arms compared to the placebo arm. Assuming a weekly decrease of 21 UI episodes in each Dysport[®] arm and a weekly decrease of 12 UI episodes in the placebo arm, with a common standard deviation of 20 UI episodes, 80% power, and an alpha of 0.025 (as testing of both the 600 U and 800 U doses vs. the placebo dose will be performed simultaneously), a sample size of N=96 subjects per group (a total of 288 subjects) is needed. Dropout between randomisation and Week 6 (primary efficacy timepoint) is expected to be 10%, and thus a total of 318 subjects would be needed to be enrolled. However, in order to ensure that the development program will deliver adequate Dysport exposure data to meet ICH E1 guideline recommendations, a total of 330 subjects are planned to be randomised.

Control of type one error

Experiment wise control of type one error for the primary endpoint will be performed using a conservative approach. The primary efficacy hypotheses are as follows:

- Ho: There is **no** difference between treatment with 600 U or 800 U Dysport® and treatment with placebo with respect to the change from pretreatment to Week 6 after the first study treatment in the number of UI episodes per week.
- Ha: There **is** a difference between treatment with 600 U or 800 U Dysport® and treatment with placebo with respect to the change from pretreatment to Week 6 after the first study treatment in the number of UI episodes per week.

As there are multiple primary tests being performed simultaneously (two primary tests), a Hochberg correction will be applied. If both p-values for the two primary tests (the test of 800 U vs. placebo and the test of 600 U vs. placebo) are lower than 0.05, both will be declared statistically significant. If one of the primary tests has a p-value greater than or equal to 0.05, then the other test will be declared statistically significant if its p-value is lower than 0.025.

The six ordered secondary endpoints will be tested for both doses at the 0.05 level (using a hierarchical methodology) if, for both doses, the two primary tests achieve a p-value lower than 0.05. If one of the primary tests has a p-value greater than or equal to 0.05, and the other has a p-value lower than 0.025, secondary endpoints will be assessed (using hierarchical methodology) for the dose group with p-value lower than 0.025 at the 0.025 significance level. All other secondary endpoints will be tested at a significance level of 0.05.

CCI [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Table 2 Study Procedures and Assessments for First Treatment and Follow-Up Until Retreatment or End of Study

	Screening		Treatment	Post-Treatment 1 Follow-up						End of Study/ Withdrawal
	Screening Visit 1	Screening Visit 2 [h][p]	Treatment Visit (Day 1) [h]	Week 1 Visit (Day 8)	Week 2 Visit (Day 15)	Week 4 Visit (Day 29)	Week 6 Visit (Day 43)	Week 12 Visit (Day 85)	Routine Visit every 12 weeks (84 days) until retreatment occurs	End of Study Visit (Week 104 to Week 116) [o]
	Clinic	Clinic	Clinic	Telepho ne [m]	Clinic	Telepho ne [m]	Clinic	Clinic	Telephone [m]	Clinic
Visit window (days)	-30 to -1[p]		Within 14 days of Screening Visit 2 [h]	±3 days	±3 days	±3 days	±3 days	±7 days	±14 days	±14 days
Informed consent	X									
Demographic data	X									
Medical/surgical/NDO history	X									
Prior medications and therapies	X									
Inclusion/exclusion criteria	X	X	X							
Concomitant medications and therapies	X	X	X	X	X	X	X	X	X	X
Prior and concomitant treatments for NDO [a]	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X
Physical examination (symptom-based)	X						X			X
Vital signs	X [f]		X [l]		X		X	X		X
Urinary tract ultrasound	X [g]									
Urine pregnancy test [b]	X		X							
Laboratory urinalysis/microscopy [c]	X						X	X		X
Urine culture [c]	X						X			
Dispense antibiotics		X [i]					X [n]			
Haematology and serum chemistry	X						X			X
Anti BTX-A antibodies	X						X			X
Dispense bladder diary & training [d]	X									
Bladder diary review		X [j]			X [j]		X [j]	X [j]	X [j]	X [j]
I-QoL and EQ-5D-5L			X				X	X		X
mPGI-I [e]					X		X	X	X	X
Urodynamics (filling cystometry)		X [k]					X			
Randomisation			X							
IMP administration			X							

BTX-A=botulinum toxin type A; EOS=End of Study; EQ-5D-5L=EuroQoL 5-dimension 5-level; IMP=investigational medicinal product; I-QoL=incontinence quality of life; mPGI-I=modified patient global impression - improvement; NDO=neurogenic detrusor overactivity.

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- a Concomitant treatments for NDO (e.g. anticholinergics, beta-3 agonists, clean intermittent catheterisation rate) should remain stable during the first 12 weeks after Treatment 1 (preferably for the entire duration of the study).
- b Pregnancy test to be performed only in females of childbearing potential. Must be performed prior to randomisation on the day of treatment.
- c Laboratory urinalysis/microscopy and urine culture to be performed at any follow-up visit if there is a suspicion of urinary tract infection based on subject symptoms.
- d Bladder diary device to be returned when subject completes study (e.g. in the event of screen failure, EOS Visit, Early Withdrawal Visit, etc.)
- e mPGL-I will be completed on the electronic bladder diary device and should be completed at home prior to the visit.
- f Body weight and height will be measured at Screening Visit 1 only.
- g Urinary tract ultrasound is only required if no adequate documented urinary tract ultrasound is available in the 6 months prior to Screening (see inclusion criterion #11).
- h Treatment Visit should occur within 14 days of Screening Visit 2 (where a UTI occurs and impacts the ability to perform IMP administration the time to the Treatment Visit can be extended until the UTI is resolved). Both visits may be performed on the same day, as long as all Screening Visit 2 procedures are performed prior to the Treatment Visit procedures and antibiotics were commenced 3 or more days prior to treatment.
- i Adapted antibiotics based on screening urine culture sensitivities must be provided to cover both the urodynamic procedure (at least 2-day course starting on the day of the urodynamics) and to cover the treatment administration **CCI**
- j Site should check if bladder diary has been commenced at least 8 days prior to visit. If not commenced then site should contact subject to remind subject (and/or caregiver) to commence collecting bladder diary data. Electronic bladder diary data may be reviewed by the site prior to the visit (recommended, to check if bladder diary is fully completed).
- k Screening urodynamics should only be performed if the subject is eligible based on a valid screening 7-day bladder diary.
- l At the Treatment Visit, vital signs will be recorded before and at least 30 minutes after treatment administration. In addition, blood pressure and heart rate will be monitored during the entire treatment procedure in subjects with spinal cord injury with vertebral lesions above the T6 level.
- m Telephone Visits may be conducted as clinic visits, if required in the investigator's opinion.
- n Empiric antibiotics should be provided to cover the Week 6 urodynamic procedure (at least 2-day course starting on the day of the urodynamic procedure). If there are any concerns regarding risk of infection then additional urine for culture and sensitivity should be sent to the central laboratory 1 to 2 weeks prior to the Week 6 urodynamic assessment, and adapted antibiotics based on the urine culture sensitivities should be used instead of empiric antibiotics.
- o The EOS Visit should be scheduled for Week 104 for subjects who had their most recent IMP administration at Week 92 or earlier; and at the same time as the Week 12 post-retreatment Visit for subjects who had their most recent study retreatment after Week 92.
- p The time to Screening Visit 2 can be extended to obtain an appropriately and fully completed bladder diary or to obtain a valid bladder diary. In addition, where a UTI occurs after completion of the bladder diary and impacts the ability to perform urodynamics the time to Screening Visit 2 can be extended until the UTI is resolved.

Table 3 Study Procedures and Assessments for Retreatment and Follow-Up Until Subsequent Retreatment or End Of Study

	Retreatment		Post-retreatment Follow-up						End of Study/ Withdrawal
	Retreatment Assessment Visit [d]	Retreatment Visit (Day 1 of treatment cycle)	Week 1 Visit [i] (Day 8)	Week 2 Visit [i] (Day 15)	Week 4 Visit [i] (Day 29)	Week 6 Visit [i] (Day 43)	Week 12 Visit [i] (Day 85)	Routine Visit every 12 weeks (84 days) (until retreatment occurs) [i]	End of Study Visit (Week 104 to Week 116 relative to date of first treatment) [k]
	Clinic	Clinic	Telephone [j]	Clinic	Telephone [j]	Clinic	Clinic	Telephone [j]	Clinic
Visit window (days)	Within 14 days of request	Within 14 days of confirmed eligibility	±3 days [i]	±3 days [i]	±3 days [i]	±3 days [i]	±7 days [i]	±14 days [i]	±14 days
Concomitant medications and therapies	X	X	X	X	X	X	X	X	X
Concomitant treatments for NDO	X	X	X	X	X	X	X	X	X
Retreatment criteria	X [e]	X [e]							
Adverse events	X	X	X	X	X	X	X	X	X
Physical examination (symptom based)	X					X			X
Vital signs	X	X [h]		X		X	X		X
Urine pregnancy test [a]		X							
Laboratory urinalysis/microscopy [b]	X					X	X		X
Urine culture [b]	X								
Dispense antibiotics	X [f]								
Haematology and serum chemistry	X					X			X
Anti BTX-A antibodies	X								X
Bladder diary review	X [g]			X [g]		X [g]	X [g]	X [g]	X [g]
I-QoL and EQ-5D-5L	X					X	X		X
mPGI-I [c]	X			X		X	X	X	X
IMP administration		X							

BTX-A=botulinum toxin type A; EOS=End of Study; EQ-5D-5L=EuroQol 5-dimension 5-level; IMP=investigational medicinal product; I-QoL=incontinence quality of life; mPGI-I=modified patient global impression - improvement; NDO=neurogenic detrusor overactivity.

- a Pregnancy test to be performed only in females of childbearing potential. Must be performed prior to retreatment administration on the day of retreatment.
- b Laboratory urinalysis/microscopy and urine culture to be performed at any follow-up visit if there is a suspicion of urinary tract infection based on subject symptoms.
- c mPGI-I will be completed on the electronic bladder diary device and should be completed at home prior to the visit.
- d The retreatment assessment can be performed at the same time as a scheduled visit (if a subject requests retreatment at the scheduled visit) or it can be performed as an unscheduled visit if the subject requests treatment between scheduled visits (subject should be requested to complete the 7-day bladder diary prior to attending for the unscheduled retreatment assessment visit). The Retreatment Assessment Visit may be repeated, for example, if a subject initially fails the retreatment criteria and makes a request for retreatment at a later time.

-
- e If the retreatment criteria are not met then the subject should continue on the follow-up schedule of the most recent treatment until the subject requests retreatment again.
- f Empiric antibiotics should be provided to cover the retreatment procedure (CCI [REDACTED]). However, if there are any concerns regarding risk of infection, then adapted antibiotics should be used. This will require waiting for the urine culture results to be available from the Retreatment Assessment Visit before dispensing adapted antibiotics (CCI [REDACTED]).
- g Bladder diary device to be returned when subject completes study (e.g. in the event of screen failure, EOS Visit, Early Withdrawal Visit, etc.). Site should check if bladder diary has been commenced at least 8 days prior to visit. If not commenced then site should contact subject to remind subject (and/or caregiver) to commence collecting bladder diary data. Electronic bladder diary data may be reviewed by the site prior to the visit (recommended, to check if bladder diary is fully completed).
- h At the Retreatment Visit, vital signs will be recorded before and at least 30 minutes after treatment administration. In addition, blood pressure and heart rate will be monitored during the entire treatment procedure in subjects with spinal cord injury with lesions above the T6 level.
- i Visit window and timing relative to most recent Retreatment Visit
- j Telephone Visits may be conducted as clinic visits, if required in the investigator's opinion.
- k The EOS Visit will occur at Week 104 for subjects who had their most recent IMP administration at Week 92 or earlier. The EOS Visit will occur at the same time as the Week 12 postretreatment Visit for subjects who had their most recent study retreatment after Week 92.

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LIST OF ABBREVIATIONS

<u>ABBREVIATION</u>	<u>Wording Definition</u>
AE	Adverse event
AESI	Adverse event of special interest
ASIA	American Spinal Injury Association
BP	Blood pressure
BTX	Botulinum toxin
BTX-A	Botulinum toxin type A
BTX-A-HAC	Clostridium BTX-A-haemagglutinin complex
CA	Competent Authority
CFR	Code of Federal Regulations (of the United States of America)
CIC	Clean intermittent catheterisation
CMC SC	Chemistry Manufacturing and Control Supply Chain (relates to sponsor)
CRO	Contract Research Organisation
CSR	Clinical study report
Da	Dalton
DC	Detrusor compliance
eCRF	Electronic case report form
EDC	Electronic data capture
EFP	End fill pressure
EOS	End of Study
EQ-5D-5L	EuroQol 5-dimension 5-level
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HR	Heart rate
IB	Investigator's brochure
ICH	International Conference on Harmonisation
IDC	Involuntary detrusor contraction
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
I-QoL	Incontinence quality of life
IRB	Institutional Review Board

<u>ABBREVIATION</u>	<u>Wording Definition</u>
IRT	Interactive response technology
MCC	Maximum cystometric capacity
MDP	Maximum detrusor pressure
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intention to treat
mPGI-I	Modified patient global impression - improvement
MS	Multiple sclerosis
NDO	Neurogenic detrusor overactivity
PdetMax@1stIDC	Maximum detrusor pressure at first involuntary detrusor contraction
PP	Per protocol
QoL	Quality of life
SAE	Serious adverse event
SAP	Statistical analysis plan
SCI	Spinal cord injury
SOP	Standard operating procedure
U	Unit
UI	Urinary incontinence
USA	United States of America
UTI	Urinary tract infection
Vol@1stIDC	Volume at first involuntary detrusor contraction
WHODRUG	World Health Organisation Drug Dictionary

1 BACKGROUND INFORMATION

1.1 Introduction

Dysport® contains botulinum toxin type A (BTX-A) neurotoxin complex derived from the bacterium *Clostridium botulinum*. It prevents acetylcholine release at neuromuscular junctions, blocking neuronal transmission which in turn results in weakness or paresis of the injected muscle. Over a period of months, nerve function returns, thus treatment may need to be repeated periodically as required. Dysport® has been found to be of significant value in the treatment of a variety of ophthalmological and neurological disorders including blepharospasm, hemifacial spasm, spasticity and cervical dystonia. Further details can be found in the investigator's brochure (IB).

1.1.1 Disease Review

The central and peripheral nervous systems control storage of urine in the bladder and also control voiding to eliminate the urine. During the bladder cycle storage phase in healthy adults, inhibitory neuronal signals prevent detrusor muscle contraction, while excitatory inputs keep the urethral sphincters closed; so that urine in the bladder is stored until voluntary voiding is initiated. At the time of voluntary voiding there is a reverse of this process with a coordinated contraction of the detrusor muscle and relaxation of the urethral sphincters to enable controlled voluntary voiding. Thus, in the normal situation the detrusor muscle only contracts during the bladder cycle voiding phase and remains relaxed during the storage phase.

However, neurological disruption of the lower urinary tract may lead to disinhibition of the detrusor muscle and the occurrence of involuntary detrusor contractions (IDCs) during the storage phase, also known as detrusor overactivity. Urodynamic testing is required to identify IDCs during the bladder cycle storage phase, which typically appear as phasic rises in bladder pressure during filling cystometry [1].

Many diseases and events affecting the nervous system controlling the lower urinary tract can result in neurogenic detrusor overactivity (NDO); including multiple sclerosis (MS), spinal cord injury (SCI), Parkinson's disease, stroke and brain tumours. Unlike supraspinal lesions, MS and SCI both affect the spinal cord and share common characteristics. Since they are also relatively prevalent and often result in NDO, they have been frequently assessed together in clinical studies evaluating treatments for NDO. Neurogenic bladder dysfunction affects up to 80% of individuals with MS and SCI, with the majority of these individuals having NDO and urinary incontinence (UI) [2].

The principal NDO-related symptom is UI, which is an involuntary loss of urine due to IDCs during the bladder storage phase. Since patients with NDO can experience frequent UI episodes, along with other symptoms, such as increased urinary frequency, their quality of life (QoL) may be significantly impaired [2].

Patients with NDO, particularly those with suprasacral lesions, may also have voiding dysfunction due to the disruption of the innervation of the urethral sphincter mechanism. Such patients require regular clean intermittent catheterisation (CIC) to effectively empty the bladder. In addition, the regular emptying of the bladder using CIC may also help reduce UI frequency, however UI still often occurs between CIC usages. If there is a loss of coordinated detrusor and urethral sphincter activity then the patient may develop detrusor sphincter dyssynergia. This can result in markedly elevated bladder pressures due to detrusor contractions occurring against a closed bladder outlet. The raised bladder pressure due to NDO and detrusor sphincter dyssynergia may contribute to upper urinary tract damage and renal impairment [2]. The regular

use of CIC in these patients is key, not only for assisting with voiding and reducing UI, but also for managing the raised bladder pressure.

1.1.2 Medical Management and Unmet Need

The goals of treatment of NDO are:

- Treating UI and thus improving QoL
- Reducing bladder pressure to prevent upper urinary tract damage.

The current first line pharmacologic treatment for NDO consists of oral medications such as anticholinergics, which are often used in conjunction with CIC. However, long term treatment may be suboptimal, with patients stopping medication due to lack of efficacy and/or bothersome side-effects, particularly at the high doses required to control NDO symptoms [2].

For a long time, surgical bladder augmentation represented the only therapeutic option for patients who failed to respond to oral medications. However, this is major reconstructive surgery, which carries with it the associated risks of significant invasive open surgery and requires a long hospital stay. It is also frequently associated with serious postoperative complications such as metabolic disturbance and renal function deterioration [3].

Intradetrusor injection of BTX-A as a treatment for NDO was first reported in 1991 [4]. Subsequently there have been many publications of studies in this indication, using different BTX-A compounds [5, 6, 7]. This growing evidence supporting the efficacy and safety of BTX-A led to international recommendations supporting its use as a second-line therapy. Recently, two positive pivotal phase III studies led to the approval of onabotulinumtoxinA in NDO to treat UI in many countries including the United States of America (USA) and a number of European countries [8, 9].

1.2 Name and Description of Investigational Medicinal Product

BTX-A is a potent neurotoxin isolated from the bacterium *Clostridium botulinum*, a gram-positive, spore-forming anaerobe. BTX-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 botulinum toxin (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 provided in [Section 6.1.1](#) and [Section 6.1.2](#).

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 were treated by intramuscular administration of Dysport[®] in striated muscles (gluteus and gastrocnemius muscles). To support the NDO indication, the sponsor has added specific *in vivo* studies including pharmacology and toxicology studies in rats and monkeys. In these NDO bridging studies, animals were treated by administration of Dysport[®] into the detrusor muscle.

A chronic rat model of SCI (considered as a relevant experimental model mimicking the voiding pattern of patients with NDO) was used to test the efficacy of intradetrusor injections of

Dysport®. When considering the clinically relevant voiding contraction parameters, 22.5 units (U) of Dysport®/rat (67.5 U/kg), administered at either four or eight injection points, significantly decreased maximal pressure when compared with placebo, without affecting the voiding efficiency. In the toxicity studies, the no observed adverse effect level after single administration of Dysport® was assessed to be 67 U/kg in rats, and 40 U/kg in monkeys. At doses above the no observed adverse effect level, body weight loss, decreased activity, and signs of irregular breathing were reported in both species. Doses of 150 U/kg in rat and 80 U/kg in monkey were considered to be above the maximal tolerated dose as they were associated with mortality. No histopathological modification of the bladder or adjacent reproductive organs was detected.

The program conducted by intradetrusor administration of Dysport® complements the extensive program conducted in striated muscles and provides a robust safety and efficacy data set enabling proper evaluation adequate to support the use of Dysport® as a treatment in patients with NDO.

Further details may be found in the current Dysport® IB.

1.3.2 Summary of Clinical Studies

The efficacy of Dysport® as a treatment of UI related to NDO has been reported in several published studies [10, 11, 12, 13, 14, 15, 16]. Administered doses were 500 U, 750 U, or 1000 U in the detrusor muscle. Positive efficacy data were reported with all the doses for UI, urodynamic parameters, patient satisfaction and patient QoL. A possible dose effect was suggested in some studies, in particular, lower efficacy was observed with Dysport® 500 U compared with 750 U for clinical and urodynamic data in a randomised trial of 77 patients with NDO [15]. All doses were well tolerated with the only adverse event (AE) of note being transient muscular weakness occurring in 14 out of 427 patients (3.3%) after treatment with 1000 U (10 patients) and 750 U (4 patients) of Dysport®. All of these events resolved spontaneously within 4 to 8 weeks [12, 13, 14, 15].

An exploratory phase IIa placebo controlled study in 47 adult patients with NDO secondary to SCI or MS has been conducted (Ipsen Study Y-52-52120-155) [17]. The study compared a total dose of 750 U of Dysport® with placebo, divided as either 15 or 30 intradetrusor injection points (all at a volume of 0.5 mL per injection point). A dose of 750 U Dysport® showed a decrease in daily incontinence frequency by 76% (15 injection points) and 88% (30 injection points) at the 12-week timepoint. Improvements were observed in clinical and urodynamic variables, and patient QoL. No unexpected safety events occurred, although three muscular weakness episodes were reported as serious adverse events (SAEs) in 3 subjects with SCI treated at the higher concentration (750 U divided in 15 injection points), all of whom came from a single research site. The findings may therefore be attributed to either a site effect or a drug-concentration effect (double the drug concentration per injection site compared to the 30-injection points group). The study was not designed for a formal comparison between these two administration modes, but the benefit/risk profile appeared to be more favourable at the dose of 750 U in 30 injection points compared to 750 U in 15 injection points. The administration at 30 injection points remains the current gold standard for injecting BTX-A in the detrusor in NDO patients, and will be utilised in this phase III study.

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 80 countries for a

range of indications. The posology and safety of Dysport[®] has been established in numerous clinical studies and there is over 20 years of postmarketing experience.

Dysport[®] is generally well-tolerated, although temporary paralysis of nontargeted muscle groups may occur. AEs resulting from a possible remote spread of the toxin from its site of injection have been very rarely reported (including excessive muscle weakness, dysphagia, and aspiration pneumonia). Local spread of the toxin from the injection site has also been reported and therefore the safety profile is dependent on the site of injection. 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.

In adult patients treated with Dysport[®] for NDO in the Ipsen phase IIa study [17], the reported treatment-related AEs included muscular weakness, asthenia, suprapubic pain, pain in extremity, and procedural pain. The benefits included decreased UI with a maximal effect observed as early as Week 6. These findings were consistent with improvements reported with other BTX-A formulations in phase III placebo controlled studies [8, 9]. Importantly, the decrease in UI was consistent with improvements in objective urodynamic parameters and also translated into improvements in QoL.

Based on the available clinical data, the benefit/risk balance of doses of 600 U and 800 U of Dysport[®], is considered to be favourable for further evaluation in this patient population (see [Section 1.5](#)). Additional information regarding potential risks and benefits may be found in the current Dysport[®] IB.

1.5 Selection of Investigational Medicinal Products and Dosages

Published data provide information from over 400 patients with NDO treated with doses ranging from 500 to 1000 U Dysport[®]. Across a number of clinical studies, all doses were reported as efficacious. However, the 500 U dose has been reported to be less effective compared to higher doses [15, 11], while the 1000 U dose was associated with a higher incidence of treatment-related AEs [10, 11, 13].

Results from the Ipsen placebo controlled phase IIa study, which used the exploratory dose of 750 U, demonstrated a favourable benefit/risk balance [17] ([Section 1.3.2](#)). It is expected that a difference of 200 U will allow dose discrimination based on the balance between efficacy and safety; therefore, for phase III, doses of 600 U and 800 U have been selected for further evaluation. The dose of 600 U is anticipated to have greater efficacy than that reported with 500 U; while the 800 U dose is expected to demonstrate a higher degree of efficacy, without jeopardizing the safety profile and thus providing a second clinically relevant dose. Thus, it is anticipated that with a 200 U difference, the two doses are sufficiently differentiated to enable an evaluation of the benefit/risk of both doses without significantly increasing the safety risk.

1.6 Population to be Studied

This study will recruit adult subjects with UI caused by NDO due to either SCI or MS, who have not been adequately managed with oral medication.

In order to ensure a homogenous population of subjects with SCI and MS for efficacy and safety assessments, all subjects will be required to be routinely performing CIC to manage bladder function, prior to study entry. This is also expected to reduce the risk of urinary tract infection

(UTI) due to impaired voiding following BTX-A treatment, which is observed in subjects not performing CIC.

In addition to BTX-A bladder-naive subjects who have never previously received intradetrusor BTX-A for UI, the study will also enrol BTX-A bladder-non-naive subjects, who have previously received intradetrusor BTX-A for NDO. This will reflect real world usage and it has been demonstrated previously that treatment response does not vary significantly following retreatment in subjects treated with intradetrusor BTX-A for UI due to NDO [18]. In order to be eligible for entry into the study, more than 9 months must have elapsed since any previous intradetrusor BTX-A treatment administration.

1.7 Placebo Usage During Treatment 1

The use of placebo during the first IMP treatment administration ensures a rigorous, scientifically appropriate study design to assess the efficacy and safety of Dysport® in the treatment of UI due to NDO. The use of placebo is justified because:

- Although UI due to NDO is a symptomatic condition, which can lead to significantly impaired quality of life, it is not life-threatening. Therefore, a single administration of placebo with the opportunity to receive active IMP treatment from as early as 12 weeks later ensures that all subjects have the opportunity to receive the active IMP without prolonged delay. All further study treatment administrations will be active IMP, for up to 2 years post randomisation, ensuring all subjects also have the opportunity to be treated with active IMP multiple times during the study, if required.
- Treatment with BTX-A may be associated with an increased risk of UTIs in an NDO population that is already susceptible to UTIs. In order to accurately estimate the true incidence of UTIs associated with the active IMP, compared to the background incidence and the incidence due to the treatment administration procedure, a placebo group comparison is required.
- OnabotulinumtoxinA, is not authorised or marketed for the treatment of UI due to NDO in all the planned countries where this Dysport® phase 3 program is to be conducted; therefore, its use as an active comparator in these countries would not be appropriate. An objective of this program is to confirm the efficacy of Dysport® in this indication **CCI**

The study has been designed to ensure that subjects who receive placebo during the first study IMP administration are not exposed to the risks of being untreated for their condition.

- Subjects who require oral medication (such as anticholinergics) to reduce their UI and bladder pressure can continue these during the study. This ensures that subjects remain managed on their established medications without any withholding of usual oral treatment. Thus, there is no risk of being temporarily exposed to “no treatment” if they initially receive placebo.
- All subjects in the study will be required to continue to perform CIC to manage their bladder function, this ensures that the bladder is regularly and adequately emptied thus reducing the risks of upper urinary tract damage and UTIs. Thus, any safety risk of temporarily receiving inactive IMP are minimised due to the requirement for all subjects to use CIC in the study.

2 PURPOSE OF THE STUDY AND STUDY OBJECTIVES

2.1 Purpose of the Study

Dysport® is currently not registered in the indication of NDO. Following the positive outcome of the phase IIa proof-of-concept Study (Y-52-52120-155) [17], this phase III study is intended to provide confirmatory evidence of the safety and efficacy of Dysport® for the treatment of NDO **CCI**.

2.2 Study Objectives

Target Population:

Subjects with UI caused by NDO due to either SCI or MS, who have not been adequately managed with oral medication and who routinely require CIC to manage their bladder function.

Primary Study Objective:

- To assess the efficacy of two Dysport® doses (600 U and 800 U), compared to placebo in reducing UI from Baseline to Week 6 following the first IMP administration.

Secondary Study Objectives:

- To assess the efficacy of two Dysport® doses (600 U and 800 U), compared to placebo in improving bladder diary measures, urodynamic and patient-reported efficacy endpoints following the first IMP administration, including assessing duration of effect
- To assess the efficacy of two Dysport® doses (600 U and 800 U) in improving bladder diary measures and patient-reported efficacy endpoints following retreatment IMP administrations, including assessing duration of effect
- To assess the safety of two Dysport® doses (600 U and 800 U) for the treatment of UI due to NDO.

3 STUDY DESIGN

3.1 General Design and Study Schema

This is a phase III, multicentre, randomised, double blind, parallel group, placebo controlled study to assess the efficacy and safety of two doses of Dysport[®] (600 U and 800 U) in adult subjects with SCI or MS with UI due to NDO, who have not been adequately managed with oral medication and who routinely require CIC to manage their bladder function. The study will be conducted at approximately 90 study sites and 330 subjects are planned.

This study has two treatment periods:

- A double-blind placebo controlled period, where subjects receive a single IMP treatment administration of either 600 U or 800 U Dysport[®] or placebo
- A subsequent double blind active treatment period, where subjects can receive multiple active IMP retreatment administrations of either 600 U or 800 U Dysport[®]. This second period commences when subjects receive their first study retreatment.

Eligibility will be assessed during Screening (up to 30 days per subject, although can be extended in certain circumstances see Section 5.2.1). All subjects will complete study Baseline safety and efficacy evaluations (including bladder diary, urodynamics and patient-reported outcomes) during this period. Eligible subjects will be randomised to receive either 600 U Dysport[®], 800 U Dysport[®], or placebo during the initial IMP administration which will occur up to 14 days after screening period (but can be extended where UTI prevents administration of IMP see Section 5.2.3. The IMP will be administered into the detrusor via cystoscopy divided into 30 injection points of 0.5 mL each, which will be evenly distributed throughout the detrusor (avoiding the trigone). See Section 6 for full details of the treatment procedure.

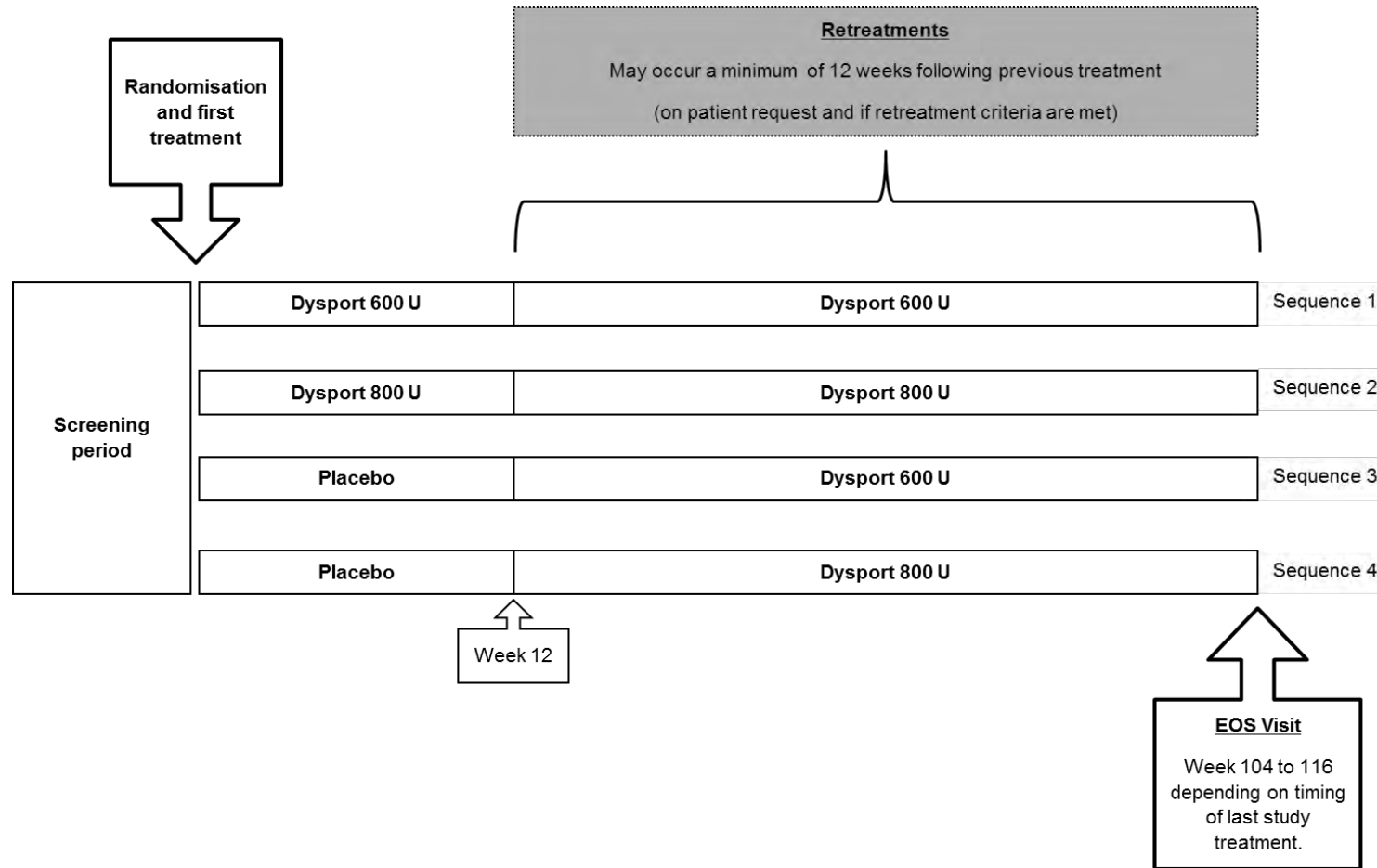
Subjects will be followed-up by telephone at Week 1 and Week 4; and will attend clinic visits at Week 2, Week 6 (primary study timepoint), and Week 12. Thereafter telephone visits will be scheduled every 12 weeks until end of study (EOS), or until retreatment is required. Details of the procedures performed at each study visit are described in Section 0.

The study design allows for subjects to request retreatment if clinically required after a minimum of 12 weeks following the previous IMP administration (see Section 5.2.5.3). The retreatment request may come at a scheduled visit or between visits. Subjects who request retreatment will be assessed and if they satisfy the retreatment criteria (Section 4.3) a Retreatment Visit will be scheduled for administration of the retreatment. All retreatments within the study are double blind treatments of either 600 U or 800 U of Dysport[®]. Follow-up after each retreatment will be per the same schedule as the first treatment (although urodynamic assessment and antibody testing at Week 6 is performed only after the first IMP administration).

Subjects should exit the study 104 weeks (2 years) after the first IMP administration. However, all subjects will be followed-up for at least 12 weeks after each retreatment; therefore, a subject who receives a study retreatment between Week 92 and Week 104 will have their study exit delayed until the Follow-up Visit scheduled for 12 weeks after their most recent retreatment.

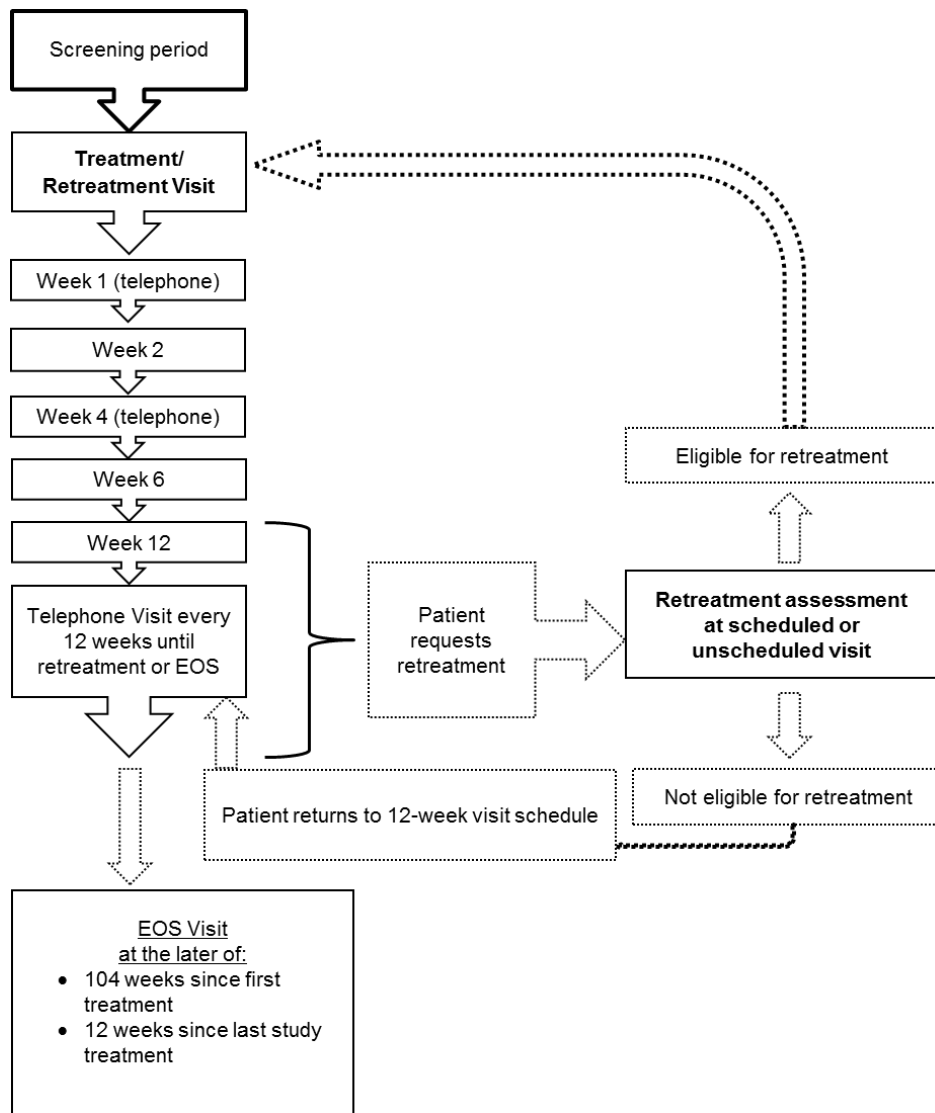
An overview of the study design is presented in Figure 1 and a visit flow chart is presented in Figure 2.

Figure 1 Study Design



U=unit; EOS=End of Study.

Figure 2 Visit Flow Chart



EOS=End of Study

3.2 Primary and Secondary Endpoints and Evaluations

3.2.1 Primary Efficacy Endpoint and Evaluations

Mean change from study Baseline (assessed at Screening) to Week 6 after the first IMP administration in the weekly number of UI episodes:

- measured on a 7-day bladder diary.

Seven-day bladder diaries that contain data recorded on at least 5 days will be included in the analysis. Where there are 1 or 2 days with no data, the arithmetic means will be used from the bladder diary parameters recorded on the 5 or 6 days that do have events recorded; for the days with no recorded bladder diary data.

3.2.2 Secondary Efficacy Endpoints and Evaluations

3.2.2.1 Overview of Secondary Measures

Mean change from study Baseline (assessed at Screening) or from treatment cycle baseline (assessed at Retreatment Assessment Visit) to post-treatment timepoints (timepoints listed in [Table 4](#) and [Table 5](#)):

- Bladder diary measures:
 - weekly number of UI episodes
 - daily urinary frequency (total, spontaneous void only, CIC only)
 - 24-hour voided volume (total, spontaneous void only, CIC only)
 - volume per void (total, spontaneous void only, CIC only).
- Urodynamic filling cystometry measures:
 - maximum cystometric capacity (MCC)
 - maximum detrusor pressure (MDP) during storage
 - volume at first involuntary detrusor contraction (Vol@1stIDC) (subjects without a post-treatment IDC will have their Vol@1stIDC imputed from their MCC)
 - maximum detrusor pressure at first involuntary detrusor contraction (PdetMax@1stIDC)
 - end fill pressure (EFP)
 - detrusor compliance (DC).
- Patient-reported outcome questionnaires:
 - incontinence quality of life (I-QoL) total summary score
 - EuroQol 5-dimension 5-level (EQ-5D-5L)
 - modified patient global impression - improvement (mPGI-I) score (to be assessed at each timepoint without comparison to baseline).

Proportion of subjects at post-treatment timepoints following the first and subsequent treatments with:

- no episodes of UI (i.e. continence is achieved)
- UI response at several levels (i.e. $\geq 30\%$ improvement, $\geq 50\%$ improvement, $\geq 75\%$ improvement etc.)
- no IDCs on urodynamic assessment (i.e. urodynamic cure is achieved).

Duration of effect following the first and subsequent treatments measured by:

- time to request retreatment

- time to eligibility for retreatment
- time between treatments.

3.2.2.2 Hierarchical Analysis of Secondary Endpoints

A hierarchical analysis will be performed in the order listed for the following secondary efficacy endpoints at Week 6 after the first IMP administration:

- 1) Mean change from study Baseline (assessed at Screening) in the **MCC**:
 - measured by urodynamic filling cystometry.
- 2) Mean change from study Baseline (assessed at Screening) in the **MDP during storage**:
 - measured by urodynamic filling cystometry.
- 3) Mean change from study Baseline (assessed at Screening) in the **Vol@1stIDC**:
 - measured by urodynamic filling cystometry.
- 4) **Proportion of subjects with no episodes of UI** (i.e. continence is achieved):
 - measured by 7-day bladder diary.
- 5) **Proportion of subjects with no IDCs during storage**:
 - measured by urodynamic filling cystometry.
- 6) Mean change from study Baseline (assessed at Screening) in the **I-QoL total summary score**:
 - measured by patient-reported questionnaire.

See [Section 9.3](#) for further details regarding control of type one error for these secondary efficacy endpoints. See [Table 19](#) in [Section 7.2](#) for the full list of secondary efficacy endpoints for both the initial treatment and for retreatments.

3.2.3 Safety Endpoints and Evaluations

Safety will be assessed throughout the study by evaluating:

- AEs
- vital signs
- laboratory blood parameters (haematology and serum chemistry)
- laboratory urine parameters (laboratory urinalysis/microscopy, culture and sensitivity)
- development of BTX-A antibodies
- usage of concomitant medications and therapies.

Timepoints for safety evaluations are detailed in [Table 4](#) and [Table 5](#).

3.3 Randomisation and Blinding

3.3.1 Randomisation

The randomisation will be done in a 2:2:1:1 ratio to one of four treatment sequences:

Sequence	Subjects	Treatment 1	Subsequent retreatment(s)
1	110 subjects	600 U Dysport®	600 U Dysport®
2	110 subjects	800 U Dysport®	800 U Dysport®
3	55 subjects	Placebo	600 U Dysport®
4	55 subjects	Placebo	800 U Dysport®

During analysis of study Treatment 1, the two placebo containing sequences will be pooled into a single arm.

Randomisation will be stratified by:

- 1) Aetiology of NDO (SCI or MS)
- 2) Previous intradetrusor BTX-A usage for UI (BTX-A naive vs. BTX-A non-naive in the bladder).

The sponsor's randomisation manager who is a statistician independent from the study, will prepare three lists which will be performed in blocks and will be based on computer-generated randomisation lists:

- List A: a list of randomisation numbers, which will be produced in an unbalanced ratio 2:2:1:1 for the four treatment sequences and which will be stratified by aetiology and prior intradetrusor BTX-A usage for UI
- List B: a list of double blind treatment numbers, which will be specified on the treatment packs to be dispatched to the sites in order to dispense the drug in Treatment 1 and possibly for subsequent retreatments. It will be produced in a balanced ratio 1:1:1 for 600 U Dysport[®], 800 U Dysport[®] and placebo
- List C: a list of double blind treatment numbers, which will be specified on the treatment packs to be dispatched to the sites in order to dispense the drug for retreatments (but not in Treatment 1). It will be produced in a balanced ratio 1:1 for 600 U Dysport[®] and 800 U Dysport[®].

The assignment of randomisation and treatment numbers at drug dispensing (at Treatment 1 and subsequent retreatments) will be managed by interactive response technology (IRT).

After eligibility is confirmed at the Treatment Visit (Day 1), subjects will be assigned by IRT to a randomisation number and to the associated treatment sequence, in a sequential order within each site (and within each level of strata). A treatment number will also be allocated by the IRT each time the drug is dispensed, according to the allocated treatment sequence. The IRT will also manage all the logistical aspects of treatments and associated incidents (e.g. drug supplies, replacement of lost, damaged, quarantined, expiring and expired kits).

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

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

Subjects who leave the study early will not be replaced.

The sponsor's randomisation manager will keep the master lists. A copy of the list of treatment numbers (Lists B and C) will be confidentially supplied to the Chemistry Manufacturing and

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the Contract Research Organisation (CRO) in charge of IRT. Similarly, a copy of the list of randomisation numbers (List A) will also be confidentially supplied to the CRO in charge of IRT will be kept confidential in a secure location. Access to the randomisation lists must be restricted until authorisation is given to release them for final analysis.

3.3.2 Blinding of Investigational Medicinal Product

All IMP administrations, including retreatments, will be double blind, although only the first treatment is placebo controlled. Subjects, investigators and all study staff will remain blinded to treatment assignment throughout the study.

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3.3.3 Maintenance of Randomisation and Blinding

The dose(s) administered as allocated by the randomisation sequence should remain blinded throughout the study. However, in the event of an SAE or unexpected AE, which requires the identification of the study treatment group, the investigator should first contact the pharmacovigilance representative as outlined in the protocol. The investigator should then review the case status and all pertinent information with the representative from Global Patient Safety who will consult with the therapeutic area drug safety physician prior to any code break.

In case of a medical emergency requiring an urgent unblinding, the investigator and/or Global Patient Safety may break the blind by asking the IRT to obtain the subject’s treatment identification. In addition, hard copy sealed code-break envelopes will be prepared by the sponsor’s randomisation manager, and held by Global Patient Safety at Ipsen in case of IRT failure. The final decision to unblind rests with the investigators as they are ultimately responsible for subject safety.

If a code break is 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).

3.4 Study Duration

For subjects, the study will consist of a Screening period for up to 30 days (but can be extended in certain circumstances, see Section 5.2.1), with randomisation at the Treatment Visit (Day 1) up to 14 days later (can be extended if UTI prevents IMP administration - see Section 5.2.3). Follow-up for each subject is planned to be 24 months (104 weeks) after the first IMP administration. However, as retreatments can occur up to Week 104, and 12 weeks of follow-up will occur following each study retreatment, the maximum planned subject participation following randomisation is 116 weeks. Each subject’s participation in the study will be considered to have ended at the time of their last study visit, including follow-up for AEs after the last IMP administration:

- CCI [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

[REDACTED]. The study will be considered to have started when the first subject has provided signed informed consent and to have ended after the last subject has completed their last study visit.

3.5 Stopping Rules and Discontinuation Criteria

During the conduct of the study, SAEs will be reviewed (see [Section 8.1.4](#)) as they are reported from the study sites to identify safety concerns.

The sponsor may terminate this study at any time. Reasons for termination include but are not limited to:

- The incidence or severity of AEs in this or other studies point to a potential health hazard for study subjects
- Insufficient subject enrolment
- Any information becoming available that substantially changes the expected benefit/risk profile of the study treatments.

A subject may discontinue participation in the study at any time for any reason (e.g. lack of efficacy, withdrawal of consent, AE) (see [Section 4.4](#)).

The investigator and/or sponsor can withdraw a subject from the study at any time for any reason (e.g. protocol deviation as defined in [Section 11.1.2](#), noncompliance with the protocol conditions or AE).

3.6 Source Data Recorded on the Case Report Form

Data will be collected by using an eCRF in compliance with Food and Drug Administration (FDA) 21 Code of Federal Regulations (CFR) Part 11. As required by Good Clinical Practice (GCP), the sponsor-assigned or sponsor designee-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, at 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 International Conference on Harmonisation (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, subject 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 or sponsor's representative'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

4.1 Inclusion Criteria

The following inclusion criteria will be assessed at the beginning of the Screening process:

- 1) Written informed consent prior to any study related procedure.
- 2) Male or female, aged 18 to 80 years inclusive.
- 3) UI for at least 3 months prior to Screening as a result of NDO due to SCI or MS.
- 4) Subjects with SCI must have a stable neurological injury at T1 level or below which occurred at least 6 months prior to Screening.

OR

Subjects with MS must be clinically stable in the investigator's opinion, with no exacerbation (relapse) of MS for at least 3 months prior to Screening.

- 5) Subjects must have an inadequate response after at least 4 weeks of oral medications used in the treatment of NDO (e.g. anticholinergics, beta-3 agonists) and/or have intolerable side-effects.

- 6) CCI [REDACTED]

[REDACTED]

- 8) Routinely performing CIC to ensure adequate bladder emptying CCI [REDACTED]

[REDACTED]

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

Reliable forms of contraception include but are not limited to:

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

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

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

- 11) Documented urinary tract ultrasound is available in the 6 months prior to Screening, confirming that no medical issues exist that would preclude entry to the study (e.g. bladder stones or unexplained renal mass).
 - If not performed in the 6 months prior to Screening or results are not available, then a urinary tract ultrasound must be conducted during Screening.
- 12) Ability to complete all study requirements in the opinion of the investigator, including regularly completing the 7-day bladder diary and attending all scheduled study visits. The caregiver may assist with the completion of study documentation and procedures (including the bladder diary and questionnaires), if required.

The following inclusion criteria will be assessed following completion of screening bladder diary:

- 13) An average of at least two episodes per day of UI recorded on the screening bladder diary.

CC [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

4.2 Exclusion Criteria

The following exclusion criteria will be assessed throughout the Screening process:

- 1) Any current condition (other than NDO) that may impact on bladder function, CCI [REDACTED]
 - [REDACTED]
 - [REDACTED]
 - [REDACTED]
 - [REDACTED]
 - [REDACTED]
 - [REDACTED]
 - [REDACTED]
 - [REDACTED]
- 2) Previous or current, tumour or malignancy affecting the spinal column or spinal cord, or any other nonstable cause of SCI.
- 3) Surgery less than 6 months prior to Screening for bladder stones.
- 4) Surgery less than 6 months prior to Screening for uterine prolapse, cystocele or rectocele.
- 5) Previous open surgery for NDO, e.g. augmentation cystoplasty.
- 6) Previous urethral stent placement or sphincterotomy.
- 7) Previous or current diagnosis of, or symptoms/signs/investigations suggestive of, significant urological or pelvic disease, CCI [REDACTED]
 - [REDACTED]
 - [REDACTED]
 - [REDACTED]

-
- CCI [REDACTED]
[REDACTED]
[REDACTED].
- 8) Previous or current uninvestigated haematuria. CCI [REDACTED]
[REDACTED]
[REDACTED].
 - 9) Any condition that will prevent cystoscopic treatment administration or CIC usage, e.g. urethral strictures.
 - 10) Current indwelling bladder catheter, or removal of indwelling bladder catheter less than 4 weeks prior to Screening.
 - 11) BTX-A treatment within 9 months prior to Screening for any urological condition (e.g. detrusor or urethral sphincter treatments).
 - 12) BTX-A treatment within 3 months prior to Screening for any non-urological condition.
 - 13) Bladder instillation with any pharmacologic agent less than 3 months prior to Screening.
 - 14) Use of capsaicin or resiniferatoxin less than 6 months prior to Screening.
 - 15) Any neuromodulation/electrostimulation usage for urinary symptoms/incontinence within 4 weeks prior to Screening. Any implanted neuromodulation device must be switched off at least 4 weeks prior to Screening and must remain off throughout study participation.
 - 16) Any concomitant therapy usage that, in the investigator's opinion, would interfere with the evaluation of safety or efficacy of the IMP, and/or confound the study results.
 - 17) History of chronic drug or alcohol abuse.
 - 18) Female subject who is pregnant or planning to become pregnant during the study, or is currently lactating (breastfeeding).
 - 19) Any medical condition or disease that might interfere with neuromuscular function, CCI [REDACTED].
 - 20) Use of medications that affect neuromuscular transmission, CCI [REDACTED]
[REDACTED]
[REDACTED] s.
 - 21) CCI [REDACTED]
[REDACTED].
 - 22) Known hypersensitivity to BTX-A or to any components in the IMP formulation (including cow's milk protein).
 - 23) History of allergy to, or intolerance to, the anaesthetic or antibiotic agents that the investigator intends to use during the study.
 - 24) Unable to stop medications with anticoagulant/antiplatelet effects for at least 3 days prior to each IMP administration and to recommence the day following each IMP administration (low molecular weight heparins may be used within 3 days of IMP administration).
 - 25) Any condition that may cause excessive bleeding (e.g. haemophilia or clotting factor deficiencies).

- 26) Any condition or situation which, in the investigator's opinion, puts the subject at significant risk, may confound the study results, or may interfere with the subject's participation in the study.
- 27) Treatment with any new investigational drug or device in the 4 weeks prior to Screening or scheduled to be used during the study period. CCI [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

4.3 Retreatment Criteria

For a study retreatment to occur all of the below retreatment criteria must be met.

Assessed prior to or during the Retreatment Assessment Visit:

- 1) Retreatment requested by subject;
- 2) More than 12 weeks (84 days) since the previous IMP administration;
- 3) CCI [REDACTED]
- [REDACTED]
- 5) In the investigator's opinion it is safe and appropriate to provide a retreatment.

CCI [REDACTED]

[REDACTED]

[REDACTED]

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 also has the right to withdraw a subject from the study in the event of concurrent illness, AEs, pregnancy (see [Section 8.1.5](#)), or other reasons concerning the health or wellbeing of the subject, or in the case of lack of cooperation. In addition, a subject may be withdrawn from the study as described in [Section 3.5](#) (stopping rules and discontinuation criteria), [Section 6.4.2](#) (concomitant medications not permitted) and [Section 8.1.7](#) (discontinuation due to AEs).

Should a subject decide to withdraw from the study after administration of IMP, or should the investigator decide to withdraw the subject, all efforts will be made to complete and report the observations up to the time of withdrawal as thoroughly as possible. A complete final evaluation at the time of the subject's withdrawal should be made (see [Section 5.2.7](#)) and an explanation given of why the subject is withdrawing or being withdrawn from the study.

As far as possible, all efforts should be made to ensure the subject attends the Withdrawal (EOS) Visit, with at least 12 weeks follow-up after their most recent IMP administration.

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 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 must be recorded on the eCRF.

5 STUDY PROCEDURES

5.1 Study Schedule

The schedule of procedures and assessments during the study is summarised in [Table 4](#) for Screening and Treatment 1 follow-up and in [Table 5](#) for retreatment assessment and follow-up.

Table 4 Study Procedures and Assessments for First Treatment and Follow-Up Until Retreatment or End Of Study

	Screening		Treatment	Post-Treatment 1 Follow-up						End of Study/ Withdrawal
	Screening Visit 1	Screening Visit 2 [h][p]	Treatment Visit (Day 1) [h]	Week 1 Visit (Day 8)	Week 2 Visit (Day 15)	Week 4 Visit (Day 29)	Week 6 Visit (Day 43)	Week 12 Visit (Day 85)	Routine Visit every 12 weeks (84 days) until retreatment occurs	End of Study Visit (Week 104 to Week 116) [o]
	Clinic	Clinic	Clinic	Telepho ne [m]	Clinic	Telepho ne [m]	Clinic	Clinic	Telephone [m]	Clinic
Visit window (days)	-30 to -1 [p]		Within 14 days of Screening Visit 2 [h]	±3 days	±3 days	±3 days	±3 days	±7 days	±14 days	±14 days
Informed consent	X									
Demographic data	X									
Medical/surgical/NDO history	X									
Prior medications and therapies	X									
Inclusion/exclusion criteria	X	X	X							
Concomitant medications and therapies	X	X	X	X	X	X	X	X	X	X
Prior and concomitant treatments for NDO [a]	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X
Physical examination (symptom-based)	X						X			X
Vital signs	X [f]		X [l]		X		X	X		X
Urinary tract ultrasound	X [g]									
Urine pregnancy test [b]	X		X							
Laboratory urinalysis/microscopy [c]	X						X	X		X
Urine culture [c]	X						X			
Dispense antibiotics		X [i]					X [n]			
Haematology and serum chemistry	X						X			X
Anti BTX-A antibodies	X						X			X
Dispense bladder diary & training [d]	X									
Bladder diary review		X [j]			X [j]		X [j]	X [j]	X [j]	X [j]
I-QoL and EQ-5D-5L			X				X	X		X
mPGI-I [e]					X		X	X	X	X
Urodynamics (filling cystometry)		X [k]					X			
Randomisation			X							
IMP administration			X							

BTX-A=botulinum toxin type A; EOS=End of Study; EQ-5D-5L=EuroQoL 5-dimension 5-level; IMP=investigational medicinal product; I-QoL=incontinence quality of life; mPGI-I=modified patient global impression - improvement; NDO=neurogenic detrusor overactivity.

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- a Concomitant treatments for NDO (e.g. anticholinergics, beta-3 agonists, clean intermittent catheterisation rate) should remain stable during the first 12 weeks after Treatment 1 (preferably for the entire duration of the study).
- b Pregnancy test to be performed only in females of childbearing potential. Must be performed prior to randomisation on the day of treatment.
- c Laboratory urinalysis/microscopy and urine culture to be performed at any follow-up visit if there is a suspicion of urinary tract infection based on subject symptoms. See [Section 6.4.1.3](#) for further details.
- d Bladder diary device to be returned when subject completes study (e.g. in the event of screen failure, EOS Visit, Early Withdrawal Visit, etc.)
- e mPGI-I will be completed on the electronic bladder diary device and should be completed at home prior to the visit.
- f Body weight and height will be measured at Screening Visit 1 only.
- g Urinary tract ultrasound is only required if no adequate documented urinary tract ultrasound is available in the 6 months prior to Screening (see inclusion criterion #11).
- h Treatment Visit should occur within 14 days of Screening Visit 2 (where a UTI occurs and impacts the ability to perform IMP administration the time to the Treatment Visit can be extended until the UTI is resolved). Both visits may be performed on the same day, as long as all Screening Visit 2 procedures are performed prior to the Treatment Visit procedures and antibiotics were commenced 3 or more days prior to treatment (see [Section 6.4.1.2](#)).
- i Adapted antibiotics based on screening urine culture sensitivities must be provided to cover both the urodynamic procedure (at least 2-day course starting on the day of the urodynamics) and to cover the treatment administration **CCCCI** See [Section 6.4.1.2](#) for further details.
- j Site should check if bladder diary has been commenced at least 8 days prior to visit. If not commenced then site should contact subject to remind subject (and/or caregiver) to commence collecting bladder diary data. Electronic bladder diary data may be reviewed by the site prior to the visit (recommended, to check if bladder diary is fully completed).
- k Screening urodynamics should only be performed if the subject is eligible based on a valid screening 7-day bladder diary.
- l At the Treatment Visit, vital signs will be recorded before and at least 30 minutes after treatment administration. In addition, blood pressure and heart rate will be monitored during the entire treatment procedure in subjects with spinal cord injury with vertebral lesions above the T6 level.
- m Telephone Visits may be conducted as clinic visits, if required in the investigator's opinion.
- n Empiric antibiotics should be provided to cover the Week 6 urodynamic procedure (at least 2-day course starting on the day of the urodynamic procedure). If there are any concerns regarding risk of infection then additional urine for culture and sensitivity should be sent to the central laboratory 1 to 2 weeks prior to the Week 6 urodynamic assessment, and adapted antibiotics based on the urine culture sensitivities should be used instead of empiric antibiotics.
- o The EOS Visit should be scheduled for Week 104 for subjects who had their most recent IMP administration at Week 92 or earlier; and at the same time as the Week 12 post-retreatment Visit for subjects who had their most recent study retreatment after Week 92.
- p The time to Screening Visit 2 can be extended to obtain an appropriately and fully completed bladder diary or to obtain a valid bladder diary. In addition, where a UTI occurs after completion of the bladder diary and impacts the ability to perform urodynamics the time to Screening Visit 2 can be extended until the UTI is resolved.

Table 5 Study Procedures and Assessments for Retreatment and Follow-Up Until Subsequent Retreatment or End Of Study

	Retreatment		Postretreatment Follow-up						End of Study/ Withdrawal
	Retreatment Assessment Visit [d]	Retreatment Visit (Day 1 of treatment cycle)	Week 1 Visit [i] (Day 8)	Week 2 Visit [i] (Day 15)	Week 4 Visit [i] (Day 29)	Week 6 Visit [i] (Day 43)	Week 12 Visit [i] (Day 85)	Routine Visit every 12 weeks (84 days) (until retreatment occurs) [i]	End of Study Visit (Week 104 to Week 116 relative to date of first treatment) [k]
	Clinic	Clinic	Telephone [j]	Clinic	Telephone [j]	Clinic	Clinic	Telephone [j]	Clinic
Visit window (days)	Within 14 days of request	Within 14 days of confirmed eligibility	±3 days [i]	±3 days [i]	±3 days [i]	±3 days [i]	±7 days [i]	±14 days [i]	±14 days
Concomitant medications and therapies	X	X	X	X	X	X	X	X	X
Concomitant treatments for NDO	X	X	X	X	X	X	X	X	X
Retreatment criteria	X [e]	X [e]							
Adverse events	X	X	X	X	X	X	X	X	X
Physical examination (symptom based)	X					X			X
Vital signs	X	X [h]		X		X	X		X
Urine pregnancy test [a]		X							
Laboratory urinalysis/microscopy [b]	X					X	X		X
Urine culture [b]	X								
Dispense antibiotics	X [f]								
Haematology and serum chemistry	X					X			X
Anti BTX-A antibodies	X								X
Bladder diary review	X [g]			X [g]		X [g]	X [g]	X [g]	X [g]
I-QoL and EQ-5D-5L	X					X	X		X
mPGI-I [c]	X			X		X	X	X	X
IMP administration		X							

BTX-A=botulinum toxin type A; EOS=End of Study; EQ-5D-5L=EuroQol 5-dimension 5-level; IMP=investigational medicinal product; I-QoL=incontinence quality of life; mPGI-I=modified patient global impression - improvement; NDO=neurogenic detrusor overactivity.

- a Pregnancy test to be performed only in females of childbearing potential. Must be performed prior to retreatment administration on the day of retreatment.
- b Laboratory urinalysis/microscopy and urine culture to be performed at any follow-up visit if there is a suspicion of urinary tract infection based on subject symptoms. See [Section 6.4.1.3](#) for further details.
- c mPGI-I will be completed on the electronic bladder diary device and should be completed at home prior to the visit.
- d The retreatment assessment can be performed at the same time as a scheduled visit (if a subject requests retreatment at the scheduled visit) or it can be performed as an unscheduled visit if the subject requests treatment between scheduled visits (subject should be requested to complete the 7-day bladder diary prior to attending for the unscheduled retreatment

assessment visit) see [Section 5.2.5](#) for further details. The Retreatment Assessment Visit may be repeated, for example, if a subject initially fails the retreatment criteria and makes a request for retreatment at a later time.

- e If the retreatment criteria are not met then the subject should continue on the follow-up schedule of the most recent treatment until the subject requests retreatment again.
- f Empiric antibiotics should be provided to cover the retreatment procedure (CCI [REDACTED]). However, if there are any concerns regarding risk of infection, then adapted antibiotics should be used. This will require waiting for the urine culture results to be available from the Retreatment Assessment Visit before dispensing adapted antibiotics. The adapted antibiotics must be commenced (CCI [REDACTED]) s.
- g Bladder diary device to be returned when subject completes study (e.g. in the event of screen failure, EOS Visit, Early Withdrawal Visit, etc.). Site should check if bladder diary has been commenced at least 8 days prior to visit. If not commenced then site should contact subject to remind subject (and/or caregiver) to commence collecting bladder diary data. Electronic bladder diary data may be reviewed by the site prior to the visit (recommended, to check if bladder diary is fully completed).
- h At the Retreatment Visit, vital signs will be recorded before and at least 30 minutes after treatment administration. In addition, blood pressure and heart rate will be monitored during the entire treatment procedure in subjects with spinal cord injury with lesions above the T6 level. See [Sections 8.4](#) and [6.2.4](#).
- i Visit window and timing relative to most recent Retreatment Visit
- j Telephone Visits may be conducted as clinic visits, if required in the investigator's opinion.
- k The EOS Visit will occur at Week 104 for subjects who had their most recent IMP administration at Week 92 or earlier. The EOS Visit will occur at the same time as the Week 12 post-retreatment Visit for subjects who had their most recent study retreatment after Week 92.

5.2 Study Visits

5.2.1 Screening Period

The Screening period (Days -30 to -1) consists of two study visits:

- Screening Visit 1
- Screening Visit 2.

The time to Screening Visit 2 can be extended to more than 30 days to obtain an appropriately and fully completed bladder diary or to obtain a valid bladder diary (see Section 17.6). In addition, where a UTI occurs after completion of the bladder diary and impacts the ability to perform urodynamics the time to Screening Visit 2 can be extended until the UTI is resolved.

5.2.1.1 Screening Visit 1

The suggested order of procedures for Screening Visit 1 is shown in [Table 6](#).

Table 6 Order of Procedures for Screening Visit 1

Suggested order of procedures	Comment	Details of procedure
1. Informed consent	Must be performed before all other study procedures	Section 5.2.2.1
2. Demographic data		Section 5.2.2.2
3. Medical/surgical/NDO history		Section 5.2.2.2
4. Prior medications and therapies		Section 5.2.2.2 Section 6.4
5. Concomitant medications and therapies		Section 5.2.2.2 Section 6.4
6. Prior and concomitant treatments for NDO		Section 5.2.2.2
7. Inclusion/exclusion criteria		Section 4.1 Section 4.2
8. Adverse events	To be monitored and collected from the time the subject signs the informed consent form	Section 8.1
9. Vital signs	Must be performed prior to any invasive procedure at the visit. Body weight and height to be measured as part of vital signs at Screening Visit 1.	Section 8.4
10. Physical examination (symptom based)	Clinically significant abnormalities should be reported as medical history.	Section 8.3
11. Urine pregnancy test	To assess inclusion criterion #10 and exclusion criterion #18	Section 8.2.5
12. Laboratory urinalysis/microscopy		Section 8.2.3
13. Urine culture	To select adapted antibiotics for screening urodynamics and Treatment 1	Section 8.2.4 Section 6.4.1.3
14. Haematology and serum chemistry	To assess exclusion criterion #29 when results are available	Section 8.2.1 Section 8.2.2
15. Anti BTX-A antibodies	Results will not be available until after study completion	Section 8.2.6
16. Urinary tract ultrasound	Only if necessary per inclusion criterion #11	Section 5.2.2.3
17. Dispense bladder diary	Including training subject (and caregiver) on proper usage of bladder diary	Section 7.3.1 and Appendix 1

BTX-A=botulinum toxin type A; NDO=neurogenic detrusor overactivity.

5.2.1.2 *Screening Visit 2*

Electronic bladder diary data may be reviewed by the site prior to Screening Visit 2. If there has been no issue with bladder diary completion (see Section 17.6) and the subject is ineligible (inclusion criterion #13, inclusion criterion #14, and exclusion criterion #28) then the subject may be considered as a “screen failure” at that point, and does not need to attend Screening Visit 2 (arrangements should be made to return the bladder diary device to the site). See Appendix 1 for details.

The suggested order of procedures for Screening Visit 2 is shown in Table 7.

Table 7 Order of Procedures for Screening Visit 2

Suggested order of procedures	Comment	Details of procedure
1. Bladder diary review	Must confirm bladder diary eligibility (inclusion criterion #13, inclusion criterion #14, and exclusion criterion #28) prior to commencing urodynamic (filling cystometry) procedure.	Section 7.3.1 and Appendix 1
2. Concomitant medications and therapies	In particular, antibiotic prophylaxis for the urodynamic procedure should be recorded.	Section 5.2.2.2 Section 6.4
3. Concomitant treatments for NDO		Section 5.2.2.2
4. Inclusion/exclusion criteria	Including check of laboratory results to verify exclusion criterion #29.	Section 4.1 Section 4.2
5. Adverse events		Section 8.1
6. Dispense antibiotics	<p> C [REDACTED] C [REDACTED] I [REDACTED] I [REDACTED] I [REDACTED] I [REDACTED] I [REDACTED] I [REDACTED] </p>	Section 6.4.1.2
7. Urodynamics (filling cystometry)	<p> C [REDACTED] C [REDACTED] I [REDACTED] I [REDACTED] I [REDACTED] I [REDACTED] I [REDACTED] </p>	Section 7.3.2 and Study Specific Urodynamic Manual Section 5.2.3 Section 6.4.1.2 Table 18

IDC=involuntary detrusor contraction; IMP=investigational medicinal product; NDO=neurogenic detrusor overactivity.

5.2.2 Procedures for Screening and Enrolment

5.2.2.1 *Informed Consent*

Signed and dated informed consent must be obtained prior to performing any Screening procedures.

After informed consent is obtained, subjects 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.

Patients who fail Screening cannot be re-screened for entry into this trial.

5.2.2.2 *Other Data to be Collected at Screening*

For full details of data collection refer to the eCRF completion guide. Data will be collected for the following variables:

- Demographic data
 - Date or year of birth, sex, race, and ethnicity according to local regulations
- Medical/surgical/NDO history
In particular relevant underlying neurological condition details including:
 - all subjects:
 - date of development of NDO symptoms.
 - subjects with SCI:
 - neurological level of stable SCI injury
 - date of stable SCI injury
 - cause of stable SCI (e.g. traumatic, vascular/infarction, focal mechanical compression)
 - American Spinal Injury Association (ASIA) Grade (A, B, C, D, E)
 - neurological syndrome (e.g. complete SCI, incomplete SCI, anterior cord, central cord, Brown-Sequard etc.).
 - subjects with MS:
 - date of onset of MS (initial diagnosis)
 - level of mobility (requirement for wheelchair)
 - classification (relapsing remitting, secondary progressive, primary progressive, relapsing progressive).
- Prior medications and therapies:
 - all non-NDO medications within the last 30 days
 - all previous medications taken for NDO (regardless of time period) in particular:
 - any previous BTX-A usage (including brand/trade name, dose, indication and location of injections)
 - previous usage of anticholinergic, beta-3 agonist, or any other medication for bladder/lower urinary tract symptoms
 - previous neuromodulation or electrostimulation usage (including date of insertion for implanted devices and date of switching device off)
 - previous catheterisation usage (including use of indwelling catheter and CIC).
- Concomitant medications and therapies (see [Section 6.4](#))
- Concomitant treatments for NDO (see [Section 6.4.2.1](#)).

5.2.2.3 *Urinary Tract Ultrasound at Screening*

This is only required if the subject does not have an adequate documented urinary tract ultrasound available from within 6 months prior to Screening which confirms that no medical issues exist that would preclude entry into the study (e.g. bladder stones or unexplained renal mass).

If required the ultrasound may be performed at any time during the Screening period. The results must be reviewed by the investigator prior to randomisation.

5.2.3 Treatment Visit (Day 1)

The Treatment Visit should be performed within 14 days of Screening Visit 2. However, where a UTI occurs and impacts the ability to perform IMP administration the time to the Treatment Visit can be extended until the UTI is resolved.

The suggested order of procedures for the Treatment Visit is shown in [Table 8](#).

Table 8 Order of Procedures for Treatment Visit (Day 1)

Suggested order of procedures	Comment	Details of procedure
1. I-QoL and EQ-5D-5L	This must be the first procedure performed at this visit.	Section 7.3.3 Section 7.3.3.1 Section 7.3.3.2
2. Concomitant medications and therapies	In particular, antibiotic prophylaxis for the treatment administration should be recorded.	Section 5.2.2.2 Section 6.4
3. Concomitant treatments for NDO		Section 6.4.2.1
4. Inclusion/exclusion criteria		Section 4.1 Section 4.2
5. Adverse events	Timing of adverse event (pre- or post-treatment) must be recorded.	Section 8.1
6. Vital signs	Must be performed prior to and approximately 30 minutes after treatment administration.	Section 8.4
7. Urine pregnancy test	Must be performed prior to randomisation (even if negative at Screening) in females of childbearing potential. If positive then subject must be considered a screen failure (inclusion criterion #10 and exclusion criterion #18).	Section 8.2.5
8. Randomisation	Must be performed only: <ul style="list-style-type: none"> when all inclusion and exclusion criteria are confirmed (final eligibility); if adapted prophylactic antibiotics were commenced 3 or more days prior; if the subject does not have any symptoms suggestive of a UTI; if medications with anticoagulant effects were stopped at least 3 days earlier. Under no circumstances will subjects be randomised more than once in the study.	Section 3.3.1 Section 6.3.1 Section 6.2.1 Section 6.2.2
9. IMP administration	Subjects to be observed for at least 30 minutes following administration.	Section 6

EQ-5D-5L=EuroQol 5-dimension 5-level; IMP=investigational medicinal product; I-QoL=incontinence quality of life; NDO=neurogenic detrusor overactivity; UTI=urinary tract infection.

It is permissible to perform the Treatment Visit on the same day as Screening Visit 2:

- If adapted prophylactic antibiotics (based on the screening urine culture and sensitivity) were started 3 days prior to the combined Screening Visit 2/Treatment Visit. See [Section 6.4.1.2](#) and [Table 18](#)
- If all Screening Visit 2 procedures are performed first and the subject is assessed as being eligible for treatment.

If Screening Visit 2 and the Treatment Visit are performed on the same day then procedures that are common to both visits do not need to be performed twice.

5.2.4 Follow-up Period (after First Treatment and Retreatments)

Routine Follow-up Visits after the first treatment and after retreatments are almost identical, therefore visit details in this section refers to follow-up for both the first treatment and retreatments (any differences in follow-up will be highlighted).

5.2.4.1 Week 1 and Week 4 Telephone Visits

The subject should be contacted by telephone and the following should be discussed. Telephone Visits may be conducted as clinic visits if required, in the investigator's opinion.

The suggested order of procedures for Week 1 and Week 4 Telephone Visits is shown in [Table 9](#).

Table 9 Order of Procedures for Week 1 and Week 4 Telephone Visits

Suggested order of procedures	Comment	Details of procedure
1. Concomitant medications and therapies		Section 5.2.2.2 Section 6.4
2. Concomitant treatments for NDO		Section 6.4.2.1
3. Adverse Events		Section 8.1
4. Reminder to commence 7-day bladder diary	Should ideally be completed in the 7 days immediately prior to the next visit. Should not be commenced: <ul style="list-style-type: none"> Any earlier than 10 days prior to the Week 2 Visit Any earlier than 14 days prior to the Week 6 Visit. 	Section 7.3.1 and Appendix 1 .

NDO=neurogenic detrusor overactivity.

5.2.4.2 Week 2 Clinic Visit

The suggested order of procedures for Week 2 Clinic Visit is shown in [Table 10](#).

Table 10 Order of procedures for Week 2 Clinic Visit

Suggested order of procedures	Comment	Details of procedure
1. mPGI-I	This should be performed electronically by the subject prior to attending the visit, otherwise subject should complete during the visit prior to undergoing any other procedures.	Section 7.3.3.3
2. Bladder diary review	May be reviewed prior to the visit. Review should occur during the visit if it has not been done beforehand.	Section 7.3.1 and Appendix 1 .
3. Concomitant medications and therapies		Section 5.2.2.2 Section 6.4
4. Concomitant treatments for NDO		Section 6.4.2.1
5. Adverse events		Section 8.1
6. Vital signs		Section 8.4

mPGI-I=modified patient global impression – improvement; NDO=neurogenic detrusor overactivity.

5.2.4.3 Week 6 Clinic Visit after First Treatment

The Week 6 Visit following the first study treatment is the primary study timepoint.

The suggested order of procedures shown in [Table 11](#) is to be performed at the Week 6 Visit following the first study treatment. For activities required at the Week 6 Visit after retreatments, refer to [Section 5.2.4.4](#).

Table 11 Order of Procedures for Week 6 Clinic Visit After First Treatment

Suggested order of procedures	Comment	Details of procedure
1. I-QoL and EQ-5D-5L	This must be performed prior to any other procedures at this visit.	Section 7.3.3 Section 7.3.3.1 Section 7.3.3.2
2. mPGI-I	This should be performed electronically by the subject prior to attending the visit, otherwise subject should complete during the visit prior to undergoing any other procedures.	Section 7.3.3.3
3. Bladder diary review	May be reviewed prior to the visit. Review should occur during the visit if it has not been done beforehand.	Section 7.3.1 and Appendix 1 .
4. Concomitant medications and therapies		Section 5.2.2.2 Section 6.4
5. Concomitant treatments for NDO		Section 6.4.2.1
6. Adverse events		Section 8.1
7. Vital signs	Must be performed prior to any physical procedure at the visit.	Section 8.4
8. Physical examination (symptom based)	New clinically significant abnormalities should be reported as AEs.	Section 8.3
9. Laboratory urinalysis/ microscopy		Section 8.2.3
10. Urine culture	Must be taken before commencing prophylactic empiric antibiotics for the urodynamics (can also be used for optional adapted prophylactic antibiotic selection).	Section 6.4.1.2 Section 8.2.4 Table 18
11. Haematology and serum chemistry		Section 8.2.1 Section 8.2.2
12. Anti BTX-A antibodies	To be sampled from subject at the same time as the haematology and serum chemistry samples.	Section 8.2.6
13. Dispense antibiotics	Empiric (or optional adapted) prophylactic antibiotics prior to the urodynamic procedure.	Section 6.4.1.2
14. Urodynamics (filling cystometry)		Section 7.3.2 and Study Specific Urodynamic Manual
15. Remind subject to complete the bladder diary	Should ideally be completed in the 7 days immediately prior to the next visit. Should not be commenced any earlier than 14 days prior to the Week 12 Visit	Section 7.3.1 and Appendix 1 .

AE=adverse event; BTX-A=botulinum toxin type A; EQ-5D-5L=EuroQol 5-dimension 5-level; I-QoL=incontinence quality of life; mPGI-I=modified patient global impression – improvement; NDO=neurogenic detrusor overactivity.

5.2.4.4 Week 6 Clinic Visit after Retreatments

The suggested order of procedures in [Table 12](#) is to be performed at the Week 6 Visit following any retreatment. For activities required at the Week 6 Visit after the first treatment, refer to [Section 5.2.4.3](#).

Table 12 Order of Procedures for Week 6 Clinic Visit After Retreatments

Suggested order of procedures	Comment	Details of procedure
1. I-QoL and EQ-5D-5L	This must be performed prior to any other procedures at this visit.	Section 7.3.3 Section 7.3.3.1 Section 7.3.3.2
2. mPGI-I	This should be performed electronically by the subject prior to attending the visit, otherwise subject should complete during the visit prior to undergoing any other procedures.	Section 7.3.3.3
3. Bladder diary review	May be reviewed prior to the visit. Review should occur during the visit if it has not been done beforehand.	Section 7.3.1 and Appendix 1
4. Concomitant medications and therapies		Section 5.2.2.2 Section 6.4
5. Concomitant treatments for NDO		Section 6.4.2.1
6. Adverse events		Section 8.1
7. Vital signs	Must be performed prior to any physical procedure at the visit.	Section 8.4
8. Physical examination (symptom based)	New clinically significant abnormalities should be reported as AEs.	Section 8.3
9. Laboratory urinalysis/ microscopy		Section 8.2.3
10. Haematology and serum chemistry		Section 8.2.1 Section 8.2.2
11. Remind subject to complete the bladder diary	Should ideally be completed in the 7 days immediately prior to the next visit. Should not be commenced any earlier than 14 days prior to the Week 12 Visit	Section 7.3.1 and Appendix 1

AE=adverse event; EQ-5D-5L=EuroQol 5-dimension 5-level; I-QoL=incontinence quality of life; mPGI-I=modified patient global impression – improvement; NDO=neurogenic detrusor overactivity.

5.2.4.5 Week 12 Clinic Visit

The suggested order of procedures for Week 12 Clinic Visit is shown in [Table 13](#).

Table 13 Order of Procedures for Week 12 Clinic Visit

Suggested order of procedures	Comment	Details of procedure
1. I-QoL and EQ-5D-5L	This must be performed prior to any other procedures at this visit.	Section 7.3.3 Section 7.3.3.1 Section 7.3.3.2
2. mPGI-I	This should be performed electronically by the subject prior to attending the visit, otherwise subject should complete during the visit prior to undergoing any other procedures.	Section 7.3.3.3
3. Bladder diary review	May be reviewed prior to the visit. Review should occur during the visit if it has not been done beforehand.	Section 7.3.1 and Appendix 1.
4. Concomitant medications and therapies		Section 5.2.2.2 Section 6.4
5. Concomitant treatments for NDO		Section 6.4.2.1
6. Adverse events		Section 8.1
7. Vital signs	Must be performed prior to any physical procedure at the visit.	Section 8.4
8. Laboratory urinalysis/microscopy		Section 8.2.3
9. Remind subject to complete the bladder diary	Should ideally be completed in the 7 days immediately prior to the next scheduled visit. Should not be commenced any earlier than 14 days prior to the next scheduled visit (unless retreatment request occurs prior to the next scheduled visit)	Section 7.3.1 Appendix 1.

EQ-5D-5L=EuroQol 5-dimension 5-level; I-QoL=incontinence quality of life; mPGI-I=modified patient global impression – improvement; NDO=neurogenic detrusor overactivity.

5.2.4.6 Routine Telephone Visits Every 12 weeks

The subject should be contacted by telephone and the following should be discussed. Telephone Visits may be conducted as clinic visits if required, in the investigator's opinion.

The suggested order of procedures for Routine Telephone Visits every 12 weeks is shown in [Table 14](#).

Table 14 Order of Procedures for Routine 12 Weekly Telephone Visits

Suggested order of procedures	Comment	Details of procedure
1. mPGI-I	This should be performed electronically by the subject prior to attending the telephone or clinic visit, otherwise subject should complete during the visit prior to undergoing any other procedures.	Section 7.3.3.3
2. Bladder diary review	May be reviewed prior to the visit. Review should occur during the visit if it has not been done beforehand.	Section 7.3.1 and Appendix 1 .
3. Concomitant medications and therapies		Section 5.2.2.2 Section 6.4
4. Concomitant treatments for NDO		Section 6.4.2.1
5. Adverse events		Section 8.1
6. Remind subject to complete the bladder diary	Should ideally be completed in the 7 days immediately prior to the next scheduled visit. Should not be commenced any earlier than 14 days prior to the next scheduled visit (unless retreatment request occurs prior to the next scheduled visit)	Section 7.3.1 and Appendix 1 .

mPGI-I=modified patient global impression – improvement; NDO=neurogenic detrusor overactivity.

5.2.5 *Retreatment Period*

Subjects may request retreatment after a minimum of 12 weeks following the previous treatment. Retreatment request may occur at:

- A scheduled Telephone Follow-up Visit:
 - eligibility for retreatment to be assessed as far as possible
 - Retreatment Assessment Visit to be scheduled if the subject is potentially eligible.
- During an unscheduled contact, between visits:
 - subject to be instructed to commence 7-day bladder diary to assess eligibility
 - eligibility for retreatment to be assessed as far as possible
 - Retreatment Assessment Visit to be scheduled if the subject is potentially eligible.
- A scheduled Clinic Follow-up Visit:
 - Retreatment Assessment Visit procedures to be performed at this visit if bladder diary indicates potential eligibility for retreatment.

5.2.5.1 *Retreatment Request at a Scheduled Telephone Follow-up Visit*

If the subject requests retreatment at a scheduled Telephone Visit, a preliminary assessment of eligibility should be performed to the extent possible by telephone, based on current (commenced within 14 days prior to the scheduled Telephone Visit) electronic 7-day bladder diary data and discussion with the subject. If the subject is clearly not eligible for retreatment (see [Section 4.3](#) for retreatment criteria) then the Retreatment Assessment Visit should not be scheduled. The retreatment request and reason(s) for ineligibility should be documented.

If the subject is potentially eligible for retreatment, then the Retreatment Assessment Visit should be scheduled. Ideally this visit should occur within 14 days of retreatment request. Alternatively, a combined Retreatment Assessment Visit/Treatment Visit may be scheduled, if urine sample and dispensing of antibiotics can be performed in accordance with [Section 6.4.1.2](#).

5.2.5.2 Retreatment Request during an unscheduled contact

If it has been more than 12 weeks since the last IMP administration, and the subject requests retreatment between scheduled visits then the subject should be asked to commence the 7-day bladder diary collection. As soon as possible after completing the diary, the bladder diary data should be reviewed by the site.

If the subject is clearly not eligible for retreatment (e.g. safety issues, or on the basis of current UI frequency) then the Retreatment Assessment Visit should not be scheduled. The retreatment request and reason(s) for ineligibility should be documented.

If the subject is potentially eligible for retreatment, then the Retreatment Assessment Visit should be scheduled. Ideally this visit should occur within 14 days of retreatment request. Alternatively, a combined Retreatment Assessment Visit/Treatment Visit may be scheduled, if urine sample and dispensing of antibiotics can be performed in accordance with [Section 6.4.1.2](#).

5.2.5.3 Retreatment Request at a scheduled Clinic Follow-up Visit

If the subject requests retreatment at a scheduled visit, a preliminary assessment of eligibility should be performed as far as possible based on current (commenced within 14 days prior to the scheduled clinic visit) electronic 7-day bladder diary data and discussion with the subject. If the subject is clearly not eligible for retreatment (see [Section 4.3](#) for retreatment criteria) then the Retreatment Assessment Visit procedures should not be performed. The retreatment request and reason(s) for ineligibility should be documented.

If the subject is potentially eligible for retreatment, then the Retreatment Assessment Visit procedures should be performed at the clinic visit in accordance with [Section 5.2.5.4](#).

5.2.5.4 Retreatment Assessment Visit

The suggested order of procedures for Retreatment Assessment Visit is shown in [Table 15](#).

Table 15 Order of Procedures for Retreatment Assessment Visit

Suggested order of procedures	Comment	Details of procedure
1. I-QoL and EQ-5D-5L	This must be performed prior to any other procedures at this visit.	Section 7.3.3 Section 7.3.3.1 Section 7.3.3.2
2. mPGI-I	This should be performed electronically by the subject prior to attending the visit, otherwise subject should complete during the visit prior to undergoing any other procedures.	Section 7.3.3.3
3. Bladder diary review	May be reviewed prior to the visit. Review should occur during the visit if it has not been done beforehand.	Section 7.3.1 and Appendix 1
4. Concomitant medications and therapies		Section 5.2.2.2 Section 6.4
5. Concomitant treatments for NDO		Section 6.4.2.1
6. Adverse events		Section 8.1
7. Retreatment criteria	Assess all retreatment criteria. If subject does not meet retreatment criteria then the following procedures do not need to be performed and subject should continue follow-up per current schedule.	Section 4.3
8. Vital signs	Must be performed prior to any physical procedure at the visit.	Section 8.4
9. Physical examination (symptom based)	New clinically significant abnormalities should be reported as AEs.	Section 8.3
10. Laboratory urinalysis/microscopy		Section 8.2.3
11. Urine culture	Must be taken before commencing prophylactic empiric antibiotics for the treatment procedure (can also be used for optional adapted prophylactic antibiotic selection).	Section 6.4.1.3
12. Haematology and serum chemistry		Section 8.2.1 Section 8.2.2
13. Anti BTX-A antibodies	To be sampled from subject at the same time as the haematology and serum chemistry samples.	Section 8.2.6
14. Dispense antibiotics	Empiric (or optional adapted) prophylactic antibiotics to be commenced at least 3 days prior to the Retreatment Visit.	Section 6.4.1.2

AE=adverse event; BTX-A=botulinum toxin type A; EQ-5D-5L=EuroQol 5-dimension 5-level; I-QoL=incontinence quality of life; mPGI-I=modified patient global impression – improvement; NDO=neurogenic detrusor overactivity.

The Retreatment Assessment Visit may be repeated, for example, if a subject initially fails the retreatment criteria and makes a request for retreatment at a later time.

5.2.6 Retreatment Visit

The Retreatment Visit should ideally be performed within 14 days of confirmed eligibility for retreatment.

It may be performed on the same day as the Retreatment Assessment Visit only if urine culture was taken and prophylactic antibiotics (empiric or adapted) were commenced at least 3 days prior to the combined visit.

The suggested order of procedures for Retreatment Visit is shown in [Table 16](#).

Table 16 Order of Procedures for Retreatment Visit

Suggested order of procedures	Comment	Details of procedure
1. Concomitant medications and therapies		Section 5.2.2.2 Section 6.4
2. Concomitant treatments for NDO		Section 6.4.2.1
3. Retreatment criteria	Confirm subject still meets all retreatment criteria.	Section 4.3
4. Adverse events	Timing of adverse event (pre- or postretreatment) must be recorded.	Section 8.1
5. Vital signs	Must be performed prior to and approximately 30 minutes after treatment administration.	Section 8.4
6. Urine pregnancy test	Must be performed prior to commencing IMP reconstitution in females of childbearing potential. If positive then subject must not receive retreatment.	Section 8.2.5
7. IMP administration	Must be performed only: <ul style="list-style-type: none"> • If all retreatment criteria are met • If prophylactic antibiotics were commenced 3 or more days prior • If the subject does not have any symptoms suggestive of a UTI • If medications with anticoagulant effects were stopped at least 3 days earlier. Subjects to be observed for at least 30 minutes following administration.	Section 6 Section 6.2.1 Section 6.2.2 Section 6.3 Section 6.3.1

IMP=investigational medicinal product; NDO=neurogenic detrusor overactivity; UTI=urinary tract infection.

5.2.7 End of Study Visit or Early Withdrawal Visit

The procedures at an EOS Visit and an Early Withdrawal Visit are identical.

For those subjects completing the study, the EOS Visit will occur:

- 104 weeks after the first IMP administration; if it has been more than 12 weeks since the previous IMP administration
- At the Week 12 Retreatment Follow-up Visit, if the subject received their most recent IMP administration between Week 92 and Week 104 following their first IMP administration.

For those subjects who withdraw prematurely from the study (see [Section 4.4](#)), final evaluations will be performed at an Early Withdrawal Visit.

The suggested order of procedures for EOS Visit or Early Withdrawal Visit is shown in [Table 17](#).

Table 17 Order of Procedures for End of Study Visit or Early Withdrawal Visit

Suggested order of procedures	Comment	Details of procedure
1. I-QoL and EQ-5D-5L	This must be performed prior to any other procedures at this visit.	Section 7.3.3 Section 7.3.3.1 Section 7.3.3.2
2. mPGI-I	This should be performed electronically by the subject prior to attending the visit, otherwise subject should complete during the visit prior to undergoing any other procedures.	Section 7.3.3.3
3. Bladder diary review	May be reviewed prior to the visit. Review should occur during the visit if it has not been done beforehand.	Section 7.3.1 and Appendix 1.
4. Concomitant medications and therapies		Section 5.2.2.2 Section 6.4
5. Concomitant treatments for NDO		Section 6.4.2.1
6. Adverse events		Section 8.1
7. Vital signs	Must be performed prior to any physical procedure at the visit.	Section 8.4
8. Physical examination (symptom based)	New clinically significant abnormalities should be reported as AEs.	Section 8.3
9. Laboratory urinalysis/ microscopy		Section 8.2.3
10. Haematology and serum chemistry		Section 8.2.1 Section 8.2.2
11. Anti BTX-A antibodies	To be sampled from subject at the same time as the haematology and serum chemistry samples.	Section 8.2.6
12. Collect bladder diary	The bladder diary device should be collected from the subject.	Section 7.3.1 and Appendix 1.

AE=adverse event; BTX-A=botulinum toxin type A; EQ-5D-5L=EuroQol 5-dimension 5-level; I-QoL=incontinence quality of life; mPGI-I=modified patient global impression – improvement; NDO=neurogenic detrusor overactivity.

Subjects who participate in the study in compliance with the protocol and 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 8.1.3](#) and [Section 8.1.2.4](#), respectively.

6 TREATMENT OF SUBJECTS

The IMP will be administered at the Treatment Visit (Day 1) for the first IMP administration and at Retreatment Visits for subsequent IMP retreatment administrations.

6.1 Investigational Medicinal Product Administered

At Screening, subjects will be allocated a subject number. Following confirmation of eligibility for the study, subjects will be randomised to one of four treatment sequences (see Section 3.3.1). Treatments that may be received are 600 U Dysport®, 800 U Dysport®, or placebo for the initial IMP administration and 600 U Dysport® or 800 U Dysport® for subsequent IMP retreatment administrations. All IMP treatments will be administered to the detrusor muscle via cystoscopy in a total volume of 15 mL divided into 30 injection points of 0.5 mL each.

The term IMP refers to both active drug and the matching placebo (comparator).

6.1.1 Dysport®

Dysport® is provided in glass vials containing 300 U or 500 U of BTX-A-HAC as a white lyophilised powder for reconstitution.

Active Constituent:	Per Vial	Per Vial
Clostridium BTX-A-HAC	500 U*	300 U*
Other Constituents:		
Human serum albumin	125 µg	125 µg
Lactose monohydrate	2.5 mg	2.5 mg

*One U is defined as the median lethal intraperitoneal dose in mice.

6.1.2 Placebo

Placebo is provided in glass vials as a white lyophilised powder for reconstitution and is undistinguishable from the active Dysport® product. CCI [REDACTED]

[REDACTED]

[REDACTED]

6.1.3 Investigational Medicinal Product Storage, Preparation and Accountability

6.1.3.1 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.

Prior to reconstitution, the IMP should be stored between +2°C and +8°C, should not be frozen, and should be protected from light.

6.1.3.2 *Investigational Medicinal Product Preparation*

The IMP **CCI** will be reconstituted at the investigational site with sterile, preservative-free, sodium chloride for injection (0.9%); to a total volume of 15 mL. The method of reconstitution and preparation is identical regardless of the treatment assignment (800 U Dysport[®], 600 U Dysport[®], or placebo).

Following reconstitution, the IMP may be stored for up to 4 hours at +2°C to +8°C in the vials in controlled and aseptic conditions. The product does not contain any antimicrobial agent; it is therefore recommended that the product be used immediately after reconstitution. The IMP should not be frozen and should be protected from light.

Detailed instructions for storage, reconstitution, and preparation before treatment administration will be provided in the IMP instruction leaflet and IMP manual.

The investigator, or an approved representative (e.g. pharmacist), will ensure that all IMP is reconstituted and dispensed/administered by qualified staff members according to the procedures detailed in the IMP instruction leaflet, IMP manual and this protocol.

6.1.3.3 *Investigational Medicinal Product Accountability*

All IMP and any other study-related material is to be accounted for on the IMP accountability log provided by the sponsor.

Any reconstituted unused IMP has to be inactivated using bleach and used/partly used vials should be destroyed after use at the site for safety reason. In addition, all disposable ancillary materials (e.g. needles and syringes) must be discarded in suitable containers intended for incineration after use at the site.

However, labels and empty boxes as well as unused supplies must be retained for verification and accountability (by the sponsor or sponsor's representative) prior to destruction. They will be destroyed preferably at the site; if not, at the interim storage facility or returned to CMC SC for destruction (Beaufour Ipsen Industrie, 20 Rue d'Ethé Virton, 28100 Dreux, France).

The investigator should ensure adequate records are maintained in the IMP accountability log.

6.1.4 *Investigational Medicinal Product Packaging, Release, and Labelling*

The IMP will be packaged and released by Beaufour Ipsen Industrie (CMC SC) and delivered to the investigational sites or interim storage facilities. 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 the IMP batches of the study, and the certificate of compliance which reflects the product release statement, and will provide them to sites according to local requirements.

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

A description of the core text of the IMP labels is displayed below:

- sponsor name, study number
- pharmaceutical dosage form
- route of administration
- quantity of dose units
- batch number

-
- investigator's name (to be completed by the site)
 - treatment number
 - "For clinical study use only" (outside of the USA)
 - "Caution: new drug limited by Federal Law to Investigational use" (within the USA)
 - storage conditions
 - expiry date.

The investigator, or designee, will only administer the IMP to subjects included in this study. Each subject will only be administered the IMP carrying his/her number. The dispensing for each subject will be documented in the eCRF.

6.1.5 Compliance

The IMP will be administered periodically in the study by the investigator, thus, monitoring of subject compliance with IMP administration is not applicable.

Drug accountability records, documenting that the subject received allocated IMP administration, will be maintained by the investigator.

6.2 Procedures Associated with Investigational Medicinal Product Administration

6.2.1 Antibiotic Prophylaxis

All subjects must receive appropriate prophylactic antibiotics CCI

- Treatment 1:
 - antibiotics must be adapted based on screening culture and sensitivity.
- Retreatments:
 - antibiotics may be empiric or adapted.

See [Section 6.4.1.2](#) for full details on antibiotic prophylaxis within the study.

The choice of antibiotic, dose, and start and stop dates must be recorded in the eCRF.

6.2.2 Anticoagulant/Antiplatelet Usage

Medications with anticoagulant effects must be stopped at least 3 days prior to IMP administration and only restarted on the day following IMP administration. They may be stopped for a longer period if deemed necessary in the opinion of the investigator. These medications include but are not limited to:

- Warfarin and other coumadin derivatives
- Acetylsalicylic acid (including low-dose aspirin)
- Clopidogrel/ticlopidine.

If medically indicated, low molecular weight heparins are permitted with the last dose of administration 24 hours prior to IMP administration and may be restarted on the day following IMP administration.

6.2.3 Anaesthesia

Local or general anaesthesia may be used if required. The choice of anaesthesia for the treatment procedure should be determined by the investigator and/or anaesthetist (anaesthesiologist) to ensure appropriate safety and comfort for the subject (taking into account factors such as risk of autonomic dysreflexia, spasticity and tolerance to cystoscopic

procedures). It is acceptable to perform the procedure with no anaesthesia if medically appropriate.

The following anaesthetic options (either alone or in combination) are permitted:

- (a) Local anaesthesia to the urethra:
 - e.g. intra-urethral lidocaine gel (or similar local anaesthetic gel), to facilitate comfortable cystoscope insertion.
- (b) Local anaesthesia to the bladder wall via instillation:
 - e.g. 1 2% lidocaine solution (or similar local anaesthetic solution), to reduce sensation of the intradetrusor injections
 - instilled immediately prior to the procedure and must remain in the bladder for approximately 30 minutes to ensure sufficient anaesthesia
 - prior to commencing the intradetrusor injections the local anaesthetic solution must be drained, then the bladder must be instilled (rinsed) with saline and drained again.
- (c) Sedation:
 - oral, inhalational, or intravenous sedative(s)
 - used per local site practice and if medically required.
- (d) General anaesthesia:
 - light and short duration general anaesthesia
 - used per local site practice and if medically required
 - must be administered by an appropriately qualified anaesthetist (anaesthesiologist)
 - neuromuscular blocking agents are however prohibited.

Details of anaesthetic(s) used must be recorded in the eCRF.

6.2.4 Safety Monitoring During Treatment Administration

Appropriate resuscitation equipment and trained personnel must be available at the site to treat any life-threatening emergencies (e.g. anaphylaxis, autonomic dysreflexia or cardiorespiratory arrest) during the IMP administration and during the immediate post-treatment observation period.

All subjects must be monitored throughout the procedure if sedatives or general anaesthesia are being used, per local site practice.

In addition, subjects with SCI with a vertebral lesion above T6 are at a greater risk of developing autonomic dysreflexia during invasive procedures [19]. Therefore, these subjects must:

- Have their blood pressure (BP) and heart rate (HR) continually monitored throughout the treatment administration procedure. There is no need to record BP or HR monitoring data, other than abnormalities that are clinically significant in the investigator's opinion; which should be reported as AEs.

If there are any symptoms or signs of autonomic dysreflexia developing, then:

- Immediate treatment for the autonomic dysreflexia should be instituted per local site practice and appropriate guidelines
- The treatment procedure should be immediately stopped until the autonomic dysreflexia has resolved. The treatment procedure should only be recommenced if deemed clinically safe

- 7) CCI [REDACTED]
[REDACTED]
[REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
[REDACTED]
[REDACTED]
- [REDACTED]
[REDACTED]
 - | [REDACTED]
 - | [REDACTED]
 - | [REDACTED]
 - | [REDACTED]
 - | [REDACTED]
 - | [REDACTED]
 - | [REDACTED]
 - | [REDACTED]
 - | [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
[REDACTED]

CCI

CCI

CCI

6.3.3 Post-treatment Observation

Vital signs should be recorded approximately 30 minutes following the procedure.

If sedation or general anaesthesia was used then post-treatment observation must also be performed according to local site practice (e.g. monitoring of BP and HR until recovered).

For any AEs that occur on the day of treatment/retreatment it should be clearly documented if the AE occurred before or after the treatment procedure.

All subjects must be observed for a minimum of 30 minutes following the IMP administration. Subjects should only leave the clinic when it is safe and appropriate, according to the investigator's judgement and local site practice.

Subjects should be instructed to contact the site if there are any AEs post-treatment.

6.4 Concomitant Medications and Therapies

The following should be recorded in the eCRF:

- Any prior or concomitant NDO therapy or medication given to a subject before Screening or during the study
- Any prior or concomitant non-NDO therapy or medication given to a subject in the 30 days before Screening or during the study.

6.4.1 Permissible Medications and Therapies

The following concomitant medications are permitted but they must be monitored closely and the dose and dose regimen should preferably remain constant throughout the study:

- Oral medication for NDO (e.g. anticholinergics and beta-3 agonists):
 - must be stable for 4 weeks prior to Screening (inclusion criterion #6)
 - must remain stable for at least 12 weeks following the first IMP administration (inclusion criterion #7)
 - preferably should remain stable throughout the study
 - subjects should be counselled to only change these medications following discussion with the investigator. Change in usage will not be considered as a protocol deviation if it occurs after 12 weeks following the first IMP administration.
- Medications/therapies required for other conditions (including for SCI and MS), as long as the treatment has no known interaction with the IMP is not listed in the prohibited medications (Section 6.4.2), or is not expected to have any significant lower urinary tract effects according to clinical judgement of the investigator, that may confound the study results.

6.4.1.1 Clean Intermittent Catheterisation

All subjects in this study have significant bladder dysfunction and voiding difficulty, requiring routine CIC usage to adequately and regularly drain urine from the bladder.

At Screening, subjects must be routinely performing CIC to manage their bladder function, and ensure regular and adequate bladder emptying. CCI [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

The CIC regimen should be maintained throughout the study; CCI [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

6.4.1.2 *Antibiotic Prophylaxis*

Antibiotic prophylaxis is required in the study to cover:

(a) All urodynamic procedures:

- CCI [REDACTED]

(b) All IMP cystoscopic treatment administration procedures:

- CCI [REDACTED]

The minimum duration of the antibiotics can be lengthened per clinical judgment of the investigator.

Antibiotics may be:

- Adapted:
 - based on a recent urine culture and sensitivity test from the subject to determine the most appropriate antibiotic.
- Empiric:
 - based on the best judgement of the investigator, using knowledge of the likely bacteria, the individual subject and local antibiotic resistance and sensitivity patterns.
 - the investigator should ensure that there is no potential risk of colonisation with resistant bacteria to the chosen antibiotic (e.g. multiple recent courses of the same class of antibiotic).

Permitted Antibiotics

All oral antibiotics (except aminoglycoside antibiotics) available locally for the treatment of UTIs may be used at the discretion of the investigator.

The investigator must ensure that the subject has no known history of contraindications (e.g. allergy) to any antibiotics that are dispensed during the study.

Appropriate Usage of Prophylactic Antibiotics

CCI [REDACTED]

[REDACTED]

[REDACTED]

Antibiotic Prophylaxis During Screening

CCI [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

Antibiotic Prophylaxis During Follow-up

CCI [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

[REDACTED]
[REDACTED]

CCI



CCI [REDACTED]

[REDACTED]

CCI



6.4.1.3 *Antibiotics for Symptomatic UTI*

Subjects with NDO may demonstrate atypical symptoms for UTI. If there is any suspicion of a UTI then the subject should be immediately commenced on appropriate antibiotics:

- CCI [REDACTED]
[REDACTED]
 - | [REDACTED]
[REDACTED]
[REDACTED]
 - | [REDACTED]
[REDACTED]
- | [REDACTED]
 - | [REDACTED]
[REDACTED]
[REDACTED]
 - | [REDACTED]
[REDACTED]

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

6.4.1.4 *Definition of Urinary Tract Infection*

- CCI [REDACTED]
 - | [REDACTED] [REDACTED]
 - | [REDACTED]
 - | [REDACTED]
 - | [REDACTED]
 - | [REDACTED]
 - | [REDACTED]
- [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

6.4.2 *Prohibited Medications/Therapies*

Prohibited throughout the study:

- Treatment at any anatomical location with any BTX (with the exception of IMP treatments and retreatments as part of this study)
- Medications that affect neuromuscular transmission, such as curare-like depolarising agents, lincosamides, polymyxins, anticholinesterases and aminoglycoside antibiotics (exclusion criterion #20).

Prohibited in the 9 months prior to Screening:

- BTX for any urological condition, e.g. detrusor or urethral sphincter treatments (exclusion criterion #11).

Prohibited in the 6 months prior to Screening and throughout the study:

- Capsaicin or resiniferatoxin (exclusion criterion #14).

Prohibited in the 3 months prior to Screening and throughout the study:

- BTX for any non-urological condition (exclusion criterion #12)
- Bladder installation with any pharmacologic agent (exclusion criterion #13).

Prohibited in the 4 weeks prior to Screening and throughout the study:

- Indwelling bladder catheter (exclusion criterion #10)
- Any neuromodulation/electrostimulation usage for urinary symptoms/incontinence (exclusion criterion #15)
- **CCI** [REDACTED]
- Any new investigational drug or device (exclusion criterion #27).

6.4.2.1 Concomitant treatment for Neurogenic Detrusor Overactivity

These data are to be collected at Screening and at other timepoints. In particular, the following should be collected:

- Daily CIC frequency (at Screening, and if there is a clinically significant change in frequency postbaseline)
- Current anticholinergic or beta-3 agonist usage (at Screening, and if there is a change in medication/frequency/dosage postbaseline).

7 ASSESSMENT OF EFFICACY

For the timing of assessments in this study, refer to the schedules in [Table 4](#), [Table 5](#), and [Table 19](#).

7.1 Primary Efficacy Endpoint and Evaluations

See [Section 3.2.1](#).

7.2 Secondary Efficacy Endpoints and Evaluations

See [Section 3.2.2](#) and [Table 19](#).

Table 19 Efficacy Endpoints During Initial Treatment and Retreatment

Measure	Planned timepoints (dependent on timing of retreatments)	Variable	Endpoint
Weekly number of urinary incontinence episodes on 7-day bladder diary	Study Baseline (Screening) or treatment cycle baseline Week 2 Week 6 Week 12 Every 12 weeks thereafter until retreatment EOS Visit.	Weekly number of urinary incontinence episodes	<ul style="list-style-type: none"> • Mean change from study baseline to each subsequent timepoint within the treatment cycle in weekly number of urinary incontinence episodes • Proportion of subjects with no episodes of urinary incontinence (i.e. continence is achieved) at each timepoint • Proportion of subjects with a urinary incontinence response at several levels (i.e. $\geq 30\%$ improvement, $\geq 50\%$ improvement, $\geq 75\%$ improvement etc.) at each timepoint
Total daily urinary frequency (CIC and spontaneous voiding) on 7-day bladder diary	Study Baseline (Screening) or treatment cycle baseline Week 2 Week 6 Week 12 Every 12 weeks thereafter until retreatment EOS Visit	Total daily urinary frequency	Mean change from study baseline to each subsequent timepoint within the treatment cycle in total daily urinary frequency
Daily spontaneous voiding frequency on 7-day bladder diary	Study Baseline (Screening) or treatment cycle baseline Week 2 Week 6 Week 12 Every 12 weeks thereafter until retreatment EOS Visit.	Daily spontaneous voiding frequency	Mean change from study baseline to each subsequent timepoint within the treatment cycle in daily spontaneous voiding frequency

Measure	Planned timepoints (dependent on timing of retreatments)	Variable	Endpoint
Daily CIC frequency on 7-day bladder diary	Study Baseline (Screening) or treatment cycle baseline Week 2 Week 6 Week 12 Every 12 weeks thereafter until retreatment EOS Visit.	Daily CIC frequency	Mean change from study baseline to each subsequent timepoint within the treatment cycle in daily CIC frequency
Total 24-hour voided volume on 1 day of 7-day bladder diary (CIC and spontaneous voiding)	Study Baseline (Screening) or treatment cycle baseline Week 2 Week 6 Week 12 Every 12 weeks thereafter until retreatment EOS Visit.	Total 24-hour voided volume	Mean change from study baseline to each subsequent timepoint within the treatment cycle in total 24-hour voided volume
24-hour voided volume on 1 day of 7-day bladder diary (spontaneous voiding only)	Study Baseline (Screening) or treatment cycle baseline Week 2 Week 6 Week 12 Every 12 weeks thereafter until retreatment EOS Visit.	24-hour voided volume (spontaneous voiding only)	Mean change from study baseline to each subsequent timepoint within the treatment cycle in 24- hour voided volume (spontaneous voiding only)
24-hour voided volume on 1 day of 7-day bladder diary (CIC only)	Study Baseline (Screening) or treatment cycle baseline Week 2 Week 6 Week 12 Every 12 weeks thereafter until retreatment EOS Visit.	24-hour voided volume (CIC only)	Mean change from study baseline to each subsequent timepoint within the treatment cycle in 24- hour voided volume (CIC only)

Measure	Planned timepoints (dependent on timing of retreatments)	Variable	Endpoint
Total volume per void (spontaneous and CIC) on 1 day of 7-day bladder diary	Study Baseline (Screening) or treatment cycle baseline Week 2 Week 6 Week 12 Every 12 weeks thereafter until retreatment EOS Visit.	Total volume per void	Mean change from study baseline to each subsequent timepoint within the treatment cycle in total volume per void
Volume per void (spontaneous voiding only) on 1 day of 7-day bladder diary	Study Baseline (Screening) or treatment cycle baseline Week 2 Week 6 Week 12 Every 12 weeks thereafter until retreatment EOS Visit.	Volume per void (spontaneous voiding only)	Mean change from study baseline to each subsequent timepoint within the treatment cycle in volume per void (spontaneous voiding only)
Volume per void (CIC only) on 1 day of 7-day bladder diary	Study Baseline (Screening) or treatment cycle baseline Week 2 Week 6 Week 12 Every 12 weeks thereafter until retreatment EOS Visit.	Volume per void (CIC only)	Mean change from study baseline to each subsequent timepoint within the treatment cycle in volume per void (CIC only)
MCC measured by urodynamic filling cystometry	Study Baseline (Screening), Week 6	MCC	Mean change from study Baseline to Week 6 in MCC
MDP during storage measured by urodynamic filling cystometry	Study Baseline (Screening), Week 6	MDP	Mean change from study Baseline to Week 6 in MDP
Vol@1 st IDC measured by urodynamic filling cystometry	Study Baseline (Screening), Week 6	Vol@1 st IDC	Mean change from study Baseline to Week 6 in Vol@1 st IDC
PdetMax@1 st IDC measured by urodynamic filling cystometry	Study Baseline (Screening), Week 6	PdetMax@1 st IDC	Mean change from study Baseline to Week 6 in PdetMax@1 st IDC
Presence of IDCs measured by urodynamic filling cystometry	Study Baseline (Screening), Week 6	Presence of IDCs	Proportion of subjects with no IDCs on urodynamic assessment (i.e. urodynamic cure is achieved)

Measure	Planned timepoints (dependent on timing of retreatments)	Variable	Endpoint
EFP measured by urodynamic filling cystometry	Study Baseline (Screening), Week 6	EFP	Mean change from study Baseline to Week 6 in EFP
DC measured by urodynamic filling cystometry	Study Baseline (Screening), Week 6	DC	Mean change from study Baseline to Week 6 in DC
Treatment response according to I-QoL total and domain summary score	Study Baseline (Treatment Visit) or baseline Week 6 Week 12 EOS Visit.	I-QoL total and domain summary score	Mean change from study baseline to each subsequent timepoint within the treatment cycle in I-QoL total and domain summary scores.
Treatment response according to EQ-5D-5L	Study Baseline (Treatment Visit) or baseline Week 6 Week 12 EOS Visit.	EQ-5D-5L score	Mean change from study baseline to each subsequent timepoint within the treatment cycle in EQ-5D-5L score
Treatment response according to mPGI-I score	Week 2 Week 6 Week 12 Every 12 weeks thereafter until retreatment EOS Visit.	mPGI-I score	Mean mPGI-I score at each timepoint following each IMP administration
Duration of effect measured by time from previous treatment until next treatment requested (if subsequently found to be eligible for retreatment)	<ul style="list-style-type: none"> • Treatment Visit (Day 1) until date of request of first retreatment (for first treatment cycle) • Retreatment Visit until date of request of next retreatment (for second and subsequent treatment cycles) 	Time to request retreatment	<ul style="list-style-type: none"> • Mean number of days before retreatment is requested • Median number of days before retreatment is requested

Measure	Planned timepoints (dependent on timing of retreatments)	Variable	Endpoint
Duration of effect measured by time from previous treatment until subject is confirmed eligible for next treatment	<ul style="list-style-type: none"> • Treatment Visit (Day 1) until date subject is confirmed as eligible for retreatment (for first treatment cycle) • Retreatment Visit until date subject is confirmed as eligible for next retreatment (for second and subsequent treatment cycles) 	Time to eligibility for retreatment	<ul style="list-style-type: none"> • Mean number of days before eligible for retreatment • Median number of days before eligible for retreatment
Duration of effect measured by time between two treatment administrations	<ul style="list-style-type: none"> • Treatment Visit (Day 1) until first Retreatment Visit (for first treatment cycle) • Retreatment Visit until next retreatment visit (for second and above treatment cycles) 	Time between treatments	<ul style="list-style-type: none"> • Mean number of days between two treatment administrations • Median number of days between two treatment administrations

CIC=clean intermittent catheterisation; DC=detrusor compliance; EFP=end fill pressure; EOS=end of study; EQ-5D-5L=EuroQoL 5-dimension 5-level; IDC=involuntary detrusor contraction; IMP=investigational medicinal product; I-QoL=incontinence quality of life; MCC=maximum cystometric capacity; MDP=maximum detrusor pressure; mPGI-I=modified patient global impression – improvement; PdetMax@1stIDC=maximum detrusor pressure at first involuntary detrusor contraction; Vol@1stIDC=volume at first involuntary detrusor contraction.

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

Methods for assessing efficacy data are described below. Timing of efficacy assessments are discussed in [Section 0](#). Procedures for recording efficacy data are discussed in [Section 13.1](#), and methods of analysis are discussed in [Section 9.4.5](#).

7.3.1 Bladder Diary

A 7-day bladder diary will be completed by subjects (with the caregiver's assistance if necessary) at Screening and regularly throughout the study to record the following parameters:

- Weekly number of UI episodes
- Daily urinary frequency (total, spontaneous void only, CIC only)
- 24-hour voided volume (total, spontaneous void only, CIC only)
- Volume per void (total, spontaneous void only, CIC only).

Refer to [Appendix 1](#) for full details regarding bladder diary usage.

7.3.2 Urodynamic Examination

All subjects will have a standardised urodynamic (filling cystometry) assessment at Screening and again at Week 6 following the first IMP administration.

Urodynamics will be conducted according to International Continence Society recommendations [20]. Full details of the urodynamic procedures including standardisation, training, equipment setup, subject preparation, trace annotations, calculations and central review process are contained in a separate Study Specific Urodynamic Manual.

All urodynamic procedures will be covered with a minimum of 2 days of appropriate prophylactic antibiotics. See Section 6.4.1.2 for further details on antibiotic prophylaxis in the study.

All urodynamic data will be reviewed by independent central reviewers to determine the final values for the urodynamic parameters. The central reader's determination will be used for analysis purposes.

During Screening the site will determine if the subject has NDO via the presence of IDCs (inclusion criterion #15); without confirmation from the central reader.

The following urodynamic parameters will be obtained (Table 20):

Table 20 Urodynamic Parameters

Parameter	Unit	Calculation
MCC	mL	Total instilled volume or instilled volume just prior to the terminal IDC minus incontinent volume
MDP	cm H ₂ O	Peak detrusor pressure during storage (filling) phase minus trace baseline pressure
Presence of IDC(s)	N/A	N/A
Vol@1 st IDC	mL	Instilled volume when first IDC commences
PdetMax@1 st IDC	cm H ₂ O	Peak detrusor pressure during first IDC minus trace baseline pressure
EFP	cm H ₂ O	Detrusor pressure at end of filling or just prior to the terminal IDC minus trace baseline pressure
DC	mL/cm H ₂ O	Change in bladder volume divided by change in detrusor pressure (usually measured as MCC divided by EFP)

DC=detrusor compliance; EFP=end fill pressure; IDC=involuntary detrusor contraction; MCC=maximum cystometric capacity; MDP=maximum detrusor pressure; PdetMax@1stIDC=maximum detrusor pressure at first involuntary detrusor contraction; Vol@1stIDC=volume at first involuntary detrusor contraction.

7.3.3 Patient Reported Questionnaires

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

- The mPQI-I should be completed by the subject (with the caregiver's assistance, if necessary) prior to the visit (expected to be performed at the beginning of the bladder diary collection period). If it has not been completed prior to the visit it should be completed as the first activity at the visit
- The I-QoL and EQ-5D-5L should be completed by the subject (with the caregiver's assistance, if necessary), at the beginning of the site visit
- Questionnaires should be checked for completeness, in the subject's presence (every question should be answered)
- Study site personnel should not change responses on the questionnaires.

7.3.3.1 *Incontinence Quality of Life*

The I-QoL is a highly used, widely recommended, validated, disease-specific questionnaire designed to measure the effect of UI on subjects' QoL [21, 22, 23, 24]. It contains 22 items covering three domains of QoL:

- Avoidance and limiting behaviour
- Psychosocial impact
- Social embarrassment.

Subjects use a 5-point response scale with values ranging from 1 (extremely) to 5 (not at all). Each domain can be scored separately, and a total score can be calculated. Higher scores represent a better QoL.

7.3.3.2 *EuroQol 5-dimension 5-level*

The EQ-5D-5L is a widely used non-disease-specific, validated instrument developed by the EuroQol Group (Rotterdam, The Netherlands, www.euroqol.org) to assess health status. It consists of five dimensions covering:

- Mobility
- Self-care
- Usual activities
- Pain/discomfort
- Anxiety/depression.

Each dimension has five responses and therefore records five levels of severity.

The EQ-5D-5L also contains a visual analogue scale to record the subject's self-rated health.

7.3.3.3 *Modified Patient Global Impression of Improvement*

The subject's global impression of treatment response will be assessed using the mPGI-I scale. The mPGI-I will be completed on the electronic device used for the bladder diary. It should be completed before the visit, but may be completed at the beginning of the visit if not completed beforehand.

Subjects will assess any change in their UI compared to the situation immediately prior to their most recent treatment using a 7-point rating scale ("Very much better", "Much better", "A little better", "No change", "A little worse", "Much worse", "Very much worse").

8 ASSESSMENT OF SAFETY

8.1 Adverse Events

AEs will be monitored from the time that the subject gives informed consent and throughout the study (see [Section 3.4](#) for a definition of the study duration) and will be elicited by direct, nonleading questioning, or as volunteered by a subject. Further details for AE reporting can be found in [Section 8.1.2](#).

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 3.4](#)).

8.1.2 *Categorisation of Adverse Events*

8.1.2.1 *Intensity Classification*

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

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

8.1.2.2 *Causality Classification*

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

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

8.1.2.3 *Assessment of Expectedness*

The reference document for assessing expectedness of AEs/events in this study will be the current Dysport® 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 dose, delay in administration, IMP discontinuation)
- They require intervention or a diagnostic 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*

New clinically significant findings (in the judgement of the investigator) should be reported as AEs.

8.1.2.6 *Other Investigation Abnormal Findings*

Abnormal test findings from any other investigation of the subject should be recorded as AEs if they:

- Are judged by the investigator to be clinically significant
- Result in a change in IMP dose or administration schedule
- Result in discontinuation of the IMP
- Require intervention or diagnostic evaluation to assess the risk to the subject.

8.1.2.7 *Definition of Urinary Tract Infection Adverse Events*

Refer to [Section 6.4.1.4](#).

8.1.2.8 *Adverse Events related to Progression of Neurogenic Detrusor Overactivity*

Natural progression or deterioration of the NDO symptoms under study will be recorded as part of the efficacy evaluation and should not normally be reported as an AE.

Natural progression or deterioration of the NDO symptoms under study should only be reported as an AE if:

- The investigator considers the progression/deterioration to be unusually severe or suggestive of accelerated disease; or
- The investigator considers the progression/deterioration to be caused directly by the IMP.

If there is any uncertainty about an AE being due to natural disease progression or deterioration of the NDO symptoms under study, then it should be reported as an AE.

8.1.2.9 *Neurological Adverse Events in Subjects with Multiple Sclerosis*

CCI
[Redacted text block]

8.1.2.10 *Suspicion of Exacerbation (Relapse) of Multiple Sclerosis*

CCI
[Redacted text block]

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CI

8.1.2.11 *Adverse Events of Special Interest*

The effects of Dysport® and all BTX products may spread from the area of injection to produce symptoms consistent with BTX effects. These symptoms have been reported hours to weeks after injection. Remote spread of toxin that affects swallowing and breathing can be life threatening, and there have been reports of death. The risk of symptoms is increased in subjects who have underlying conditions (e.g. disorders of the neuromuscular junction) that would predispose them to these symptoms.

Dysport® is contraindicated in individuals with known hypersensitivity to any BTX preparation or to any of the components in the formulation.

Adverse events of special interest (AESIs) for Dysport® are AEs that suggest a possible remote spread of effect of the toxin or hypersensitivity. A list of preferred terms of AESIs is provided in the Statistical Analysis Plan (SAP).

All AEs will be monitored by the sponsor to determine if they meet the criteria of AESIs. These AESIs will be further analysed to determine if there is a plausible possibility that they represent distant spread of toxin or hypersensitivity. In order to perform the analysis, variables including alternate aetiology (medical history, concomitant medication, or diagnosis which could account for the symptoms), location of Dysport® administration, and temporal relationship to Dysport® administration will be considered by the sponsor.

8.1.3 *Recording and Follow-up of Adverse Events*

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

All observed or volunteered AEs, regardless of treatment group or suspected causal relationship to IMP, will be recorded on the AE page(s) of the eCRF. Events involving drug reactions, accidents, illnesses with onset during the treatment phase of the study, or exacerbation of pre-existing illnesses should be recorded (see also [Section 8.1.2.7](#) and [Section 8.1.2.10](#)).

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

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

8.1.4 *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) to the pharmacovigilance contact 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.

An SAE is any AE that:

- 1) Results in death
- 2) Is life threatening, that is any event that places the subject at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death
- 3) Results in in-patient hospitalisation or prolongation of existing hospitalisation, excluding admission for social or administrative reasons (see further)
- 4) Results in a persistent or significant disability/incapacity, where disability is a substantial disruption of a person's ability to conduct normal life functions
- 5) Results in congenital anomaly/birth defect in the offspring of a subject who received the IMP
- 6) Is an important medical event that may not result in death, be life threatening, or require hospitalisation when, based upon appropriate medical judgement, may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalisation, or the development of drug dependency or drug abuse.

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

- Hospitalisation is defined as any in-patient admission (even if less than 24 hours). For chronic or long-term in-patients, in-patient admission also includes transfer within the hospital to an acute/intensive care in-patient unit
- **Prolongation of hospitalisation** is defined as any extension of an in-patient hospitalisation beyond the stay anticipated/required in relation to the original reason for the initial admission, as determined by **the investigator or treating physician**. For protocol-specified hospitalisation in clinical studies, prolongation is defined as any extension beyond the length of stay described in the protocol. Prolongation in the absence of a precipitating, treatment emergent, clinical AE (i.e. not associated with the development of a new AE or worsening of a pre-existing condition) may meet criteria for "seriousness" but is not an adverse experience and thus is not subject to immediate reporting to the sponsor
- Preplanned or elective treatments/surgical procedures should be noted in the subject's screening documentation. Hospitalisation for a preplanned or elective treatment/surgical procedure should not be reported as an SAE unless there are complications or sequelae which meet the criteria for seriousness described above.

Any SAE must be reported immediately (within 24 hours), 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 pharmacovigilance contact within 24 hours for each SAE:

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

The additional information included in the SAE form must be provided to the sponsor or representative as soon as it is available. The investigator should always provide an assessment of causality for each event reported to the sponsor. Upon receipt of the initial report, the sponsor will ask for the investigator's causality assessment if it was not provided with the initial report. The investigator should report a diagnosis or a syndrome rather than individual signs or symptoms. The investigator should also try to separate a primary AE considered as the foremost untoward medical occurrence from secondary AEs which occurred as complications.

8.1.5 Pregnancy

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IMP may have interfered with the effectiveness of a contraceptive method. The outcome of any pregnancy will then need to be collected even if this occurs after the end of the study.

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 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 the outcome of the pregnancy becomes known, which may involve follow-up after the subject's involvement in the study has ended.

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

8.1.6 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:

- AE 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".

8.1.7 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](#)). Every effort should be made to try to attribute withdrawal to a single episode of a particular AE and not AEs in general.

If the IMP is discontinued due to a SAE, it must be reported immediately to the sponsor's designated representative (see [Section 8.1.4](#)).

In all cases, the investigator must ensure the subject receives appropriate medical follow-up (see [Section 8.1.3](#)).

8.1.8 Reporting to Competent Authorities/Independent Ethics Committees/Institutional Review Boards/Other Investigators

The sponsor or sponsor's representative will ensure that processes are in place for submission of reports of Suspected Unexpected Serious Adverse Reactions occurring during the study to the CAs, Independent Ethics Committees (IECs) and other investigators concerned by the IMP. Reporting will be done in accordance with the applicable regulatory requirements.

For study sites in the USA, Investigational New Drug application Safety Reports will be submitted directly to the investigators. It is the investigators' responsibility to notify their Institutional Review Board (IRB) in a timely manner.

8.2 Clinical Laboratory Tests

Blood and urine samples will be collected as indicated in the schedule of assessments in [Table 4](#) and [Table 5](#), for the evaluation of haematology, serum chemistry, laboratory urinalysis/microscopy, urine culture and sensitivity, and anti BTX-A antibodies. Analysis will be performed by central laboratories. Full details regarding clinical laboratory tests are contained in the study central laboratory manual and trial master file.

The investigator will review the laboratory urinalysis/microscopy, urine culture and sensitivity, haematology, and serum chemistry laboratory 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, and [Section 8.2.3](#) regarding specific information related to laboratory urinalysis/microscopy).

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 (see [Section 8.2.3](#) for specific details regarding laboratory urinalysis/microscopy abnormalities).

8.2.1 Haematology

Blood samples (approximately 3.0 mL) will be collected in a potassium ethylenediaminetetraacetic 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)
 - Platelet count.

At Screening, the investigator should only randomise the subject if in the investigator's opinion there are no clinically significant abnormalities that require further investigation or management.

For handling of abnormalities identified after Screening, refer to [Section 8.1.2.4](#).

8.2.2 Serum Chemistry

Blood samples (approximately 4.0 mL) 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, fasting glucose.

At Screening:

- The investigator should review the serum creatinine to determine eligibility (exclusion criterion #29)
- In addition, the investigator should only randomise the subject if in the investigator's opinion there are no clinically significant abnormalities that require further investigation or management.

For handling of abnormalities identified after Screening, refer to [Section 8.1.2.4](#).

8.2.3 Laboratory urinalysis/microscopy

Fresh urine samples (at least 10 mL) will be collected to assess the following parameters: pH, protein, ketones, bilirubin, blood, urobilinogen, nitrites, leukocytes, glucose and specific gravity. Microscopy will be performed, if indicated, but results will not be collected in the eCRF.

Due to the frequent urethral instrumentation (e.g. CIC) and the voiding dysfunction in this population, it is anticipated that there will be frequent abnormalities on laboratory urinalysis/microscopy testing (e.g. microscopic haematuria).

Screening

The investigator should determine the clinical significance of any abnormalities for the individual subject and should only continue with Screening and randomisation/treatment if in the investigator's opinion it is safe and appropriate. If there are any unexpected clinically significant findings then the subject should be considered as a screen failure and appropriately investigated/managed.

During follow-up

If in the opinion of the investigator there are any clinically significant abnormalities (or changes) specific for the individual subject in urinalyses/microscopy, then the subject should be appropriately investigated and managed and this should be recorded as an AE in the eCRF (see [Section 6.4.1.3](#) for further details regarding UTIs).

If there is any suspicion of a symptomatic UTI, laboratory urinalysis/microscopy and urine culture and sensitivity should be sent to the central laboratory (prior to commencing antibiotics, if possible). See [Section 6.4.1.3](#) for further details.

Discretionary dipstick urinalysis

Urine dipstick may also be used at the discretion of the investigator when required for a rapid assessment (e.g. if there is a suspicion of a UTI), although laboratory urinalysis/microscopy, and urine culture and sensitivity samples should be sent to the central laboratory for formal confirmation of findings. See [Section 6.4.1.3](#) for managing a symptomatic UTI and [Section 6.4.1.4](#) for the definition of a UTI.

8.2.4 Urine Culture and Sensitivity

Fresh urine samples (at least 10 mL) for culture and sensitivity will be collected prior to invasive study procedures to:

- Assist in adapted antibiotic prophylaxis selection (see [Section 6.4.1.2](#)) for the procedure; or
- If empiric antibiotics are used to cover the procedure, to ensure that a baseline urine culture (prior to the procedure) is available to allow for rapid switching of antibiotics to an appropriate (adapted) antibiotic if the subject develops a symptomatic UTI following the procedure (see [Section 6.4.1.3](#)).

During follow-up, if there is any suspicion of a symptomatic UTI, laboratory urinalysis/microscopy and urine culture and sensitivity should be sent to the central laboratory (prior to commencing antibiotics, if possible). See [Section 6.4.1.3](#) for further details.

8.2.5 Pregnancy Test

A urine sample will be collected for a human chorionic gonadotropin pregnancy test as per the schedule in [Table 4](#) and [Table 5](#), for all female subjects of childbearing potential. If this is found to be positive, it will be followed-up with a serum pregnancy test (β -human chorionic gonadotropin).

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 8.1.5](#).

8.2.6 Antibody Testing

Blood samples (2 × 6 mL samples) will be collected and serum samples will be sent to the central laboratory for subsequent antibody testing per the schedule in [Table 4](#) and [Table 5](#) for the assay of putative antitoxin-A antibodies.

Batch shipping to specific laboratories in charge of the analyses 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 positive for the presence of binding antibodies will be analysed for the presence of neutralising antibodies using another validated assay. Full details regarding the processing, labelling and shipment processes for these samples are provided in the study manual.

These data will only be provided to the site after the end of the study (database lock).

8.2.7 Other Laboratory Safety Tests

Other laboratory safety tests may be performed at the discretion of the investigator to ensure the safety of the subjects.

8.2.8 Blood Volume to be Collected During the Study

The blood volume collected during the 24-month course of the study depends on the number of treatment cycles received. Assuming 3 mL of blood sampled for each haematology test, 4 mL of blood sampled for each biochemistry test (for serum chemistry), and 12 mL of blood sampled for each antibody test:

- A subject who receives a single study treatment will provide 57 mL of blood
- For each additional treatment cycle, the subject will provide a further 26 mL of blood.

A subject who receives 3 study treatments will therefore provide 109 mL of blood during their study participation.

The maximum amount of blood collected at a single visit is 19 mL (for visits at which samples are collected for all blood tests).

8.3 Physical Examination

Symptom-driven physical examinations will be conducted per the schedule in [Table 4](#) and [Table 5](#), and may also be performed at any other time during the study if clinically indicated.

The first physical examination is conducted at Screening Visit 1. Accordingly, any physical examination abnormalities observed at this visit are to be recorded as medical history, and not as AEs. Any new clinically significant physical examination findings (abnormalities) observed during the study will be reported as AEs. Please see [Section 8.1.2.9](#) and [Section 8.1.2.10](#) regarding neurological AEs, or findings that may represent an MS exacerbation.

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 Vital Signs

Vital signs consist of HR, respiratory rate, BP and body temperature:

- HR, respiratory rate and BP should be measured in the sitting or supine position, but must be performed consistently throughout the study
- Body temperature should be measured using a consistent method throughout the study (oral or tympanic is preferred).

Screening Visit 1

Body weight and height will also be measured as part of the vital sign assessment at Screening Visit 1 only.

Treatment and Retreatment Visits

During the Treatment and Retreatment Visits vital signs must be measured:

- Prior to treatment administration;
and
- Approximately 30 minutes after completion of treatment administration.

9 STATISTICS

9.1 Analysis Populations

The following populations will be used during statistical analyses:

- **Screened population:** All subjects screened (i.e. who signed the informed consent)
- **Safety population:** All subjects who received at least one IMP administration (including only partial administration) of the IMP. Subjects will be analysed as treated (actual treatment)
- **Modified intention to treat (mITT) population:** All randomised subjects who received at least one IMP administration. Subjects will be analysed as randomised (planned treatment)
- **Per protocol (PP) population:** All subjects in the mITT population who have no impacting major protocol deviations (i.e. that could potentially affect the primary efficacy endpoint outcome for the subject) as described in the protocol deviations document. Subjects will be analysed as randomised.

The following protocol deviations will impact the PP population (for further details of protocol deviations see Sections 9.1.2 and 11.1.2):

- 1) Subject does not receive the full first administration of the IMP
- 2) Subject does not have a valid (non-missing) UI data point at the Week 6 Visit following the first administration of the IMP.

9.1.1 Populations Analysed

The primary analysis based on the primary efficacy endpoint will be performed on the mITT population. In addition, a supportive analysis will be conducted on the PP population.

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

9.1.2 Subject Allocation and Reasons for Exclusion from the Analyses

Any major protocol deviation (see Section 11.1.2 for definition) will be described in the Protocol Deviation Document and its impact on inclusion in each analysis population (mITT, PP and safety populations) for any subject will be specified. The final list of protocol deviations impacting the safety, mITT and PP populations will be reviewed prior to database lock, before any unblinding of treatment groups. The list may be updated up to the database lock to include any additional major protocol deviations impacting inclusion in the PP population.

9.2 Sample Size Determination

The sample size is based on the ability to detect a statistically significant treatment difference in the weekly number of UI episodes at Week 6 following treatment in the two Dysport[®] arms compared to the placebo arm.

Assuming a decrease of 21 UI episodes per week in each Dysport[®] arm and a decrease of 12 UI episodes per week in the placebo arm, with a common standard deviation of 20 UI episodes, 80% power, and an alpha of 0.025 (as testing of both the 600 U and 800 U doses vs. the placebo dose will be performed simultaneously), a sample size of N=96 subjects per dose group for the primary analysis (a total of 288 subjects) is needed.

Assuming a treatment group random allocation ratio 1:1:1, a sample size of 106 subjects in each treatment group will have 80% power to detect a difference in UI of 9 episodes (the difference between UI in Dysport[®] 600 U and Dysport[®] 800 U groups and in placebo group assuming a common standard deviation equal to 20 episodes and a dropout rate equal to 10% with a 0.025

two-sided type one error rate. A total of 318 subjects would therefore need to be enrolled. However, in order to ensure that the development program will deliver adequate Dysport exposure data to meet ICH E1 guideline recommendations, a total of 330 subjects are planned to be randomised.

9.3 Significance Testing and Estimations

All statistical tests will be performed two-sided with a type one error rate set at 5%.

Experiment-wise control of type one error for the primary endpoint will be performed using a conservative approach. The primary efficacy hypotheses are as follows:

- 1) Ho: There is **no** difference between treatment with 600 U or 800 U Dysport[®] and treatment with placebo with respect to the change from pretreatment to Week 6 after the first study treatment in the number of UI episodes per week
- 2) Ha: There **is** a difference between treatment with 600 U or 800 U Dysport[®] and treatment with placebo with respect to the change from pretreatment to Week 6 after the first study treatment in the number of UI episodes per week.

For the primary endpoint, due to multiple comparisons of more than two treatments, a Hochberg correction will be applied to control the global type one error at 5% significance level. If both p-values for the two primary tests (the test of 800 U vs. placebo and the test of 600 U vs. placebo) are lower than 0.05, both will be declared statistically significant. If one of the primary tests has a p-value greater or equal to 0.05, then the other test will be declared statistically significant if its p-value is lower than 0.025 (and thus half of the overall experiment wise alpha of 0.05).

The six ordered secondary endpoints will be tested for both doses at the 0.05 level (using a hierarchical methodology) if, for both doses, the two primary tests achieve a p-value lower than 0.05. If one of the primary tests has a p-value greater or equal to 0.05, and the other has a p-value lower than 0.025, secondary endpoints will be assessed (using hierarchical methodology) for the dose group with p-value lower than 0.025, at the 0.025 significance level.

In order to control the family-wise type one error, the following hierarchical testing procedure will be applied for the testing of the superiority of both Dysport[®] doses to placebo for the primary and selected secondary endpoints (ordered as described in [Section 3.2.2.2](#)):

- Step 1: The 800 U Dysport[®] and 600 U Dysport[®] doses will be compared to placebo on the primary endpoint. If the p-values associated with both doses are <0.05 then both doses will be declared statistically significant and the testing will proceed at the 0.05 level from step 2 onwards. If one dose has $p \geq 0.05$ but the other has $p < 0.025$ (significant dose) then testing will proceed at the 0.025 level from step 2 onwards on the significant dose only. If both dose groups have $p \geq 0.05$ or one dose group has $p \geq 0.05$ and the other dose group has $p \geq 0.025$, the testing procedure will be stopped
- Step 2: The 800 U Dysport[®] and 600 U Dysport[®] doses will be compared to placebo for the first secondary endpoint. Testing will be at the significance level defined in step 1 (0.05 or 0.025). If the p-value associated with this test is lower than the significance level defined in step 1 then it will be considered significant and testing will proceed to step 3. Otherwise the testing procedure will be stopped
- Up to a further five steps will be performed, in each case testing the second through sixth hierarchical secondary endpoints in sequence. Testing will be conducted in the same manner as for the first hierarchical secondary endpoint. Significance testing will only

proceed to the next hierarchical endpoint if the test is considered significant for each respective endpoint.

The above testing rules ensure that the hierarchical procedure controls the experiment-wise type one error (i.e. over the seven tests) at the 0.05 level for relevant secondary endpoints.

In the event the hierarchical testing procedure is stopped at the end of any particular step, the testing of the following steps will be considered descriptive only and no formal statistical conclusion will be drawn.

Each other secondary endpoint not included within the hierarchical testing procedure will be analysed for exploratory purposes only to compare each Dysport[®] dose to placebo at a 0.05 type one error rate.

9.4 Statistical/Analytical Methods

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

A SAP describing the planned statistical analysis in detail will be developed as a separate document.

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

9.4.1 Demographic and Other Baseline Characteristics

In order to ensure balance of treatment groups, descriptive summary statistics (number of patients, mean, standard deviation, standard error mean, 95% confidence interval, median, minimum, maximum) or frequency counts of demographic and baseline data (medical history, pre-existing conditions and ongoing medical history, prior medications/therapies etc.) will be presented by treatment group and overall for the mITT population.

Unless prohibited by local regulation, race and ethnicity are collected to ensure data robustness for safety and efficacy evaluation, and to prevent adverse reactions or improve benefits in the target population.

9.4.2 Homogeneity of Treatment Groups

In order to assess the homogeneity of treatment groups at Baseline, 95% confidence intervals will be provided to detect any clinical nonhomogeneity.

9.4.3 Data Imputation

No imputation is planned for the primary analysis of the primary endpoint. For sensitivity analyses, imputation will be performed using a multiple imputation approach for handling missing data on the mITT population.

9.4.4 Subject Disposition and Withdrawals

The numbers and percentages of subjects enrolled and included in the analysis populations mentioned in [Section 9.1.1](#) will be tabulated by country and site. The reasons for subject exclusions from each of the populations will also be tabulated. In addition, the numbers of subjects who were randomised, treated, prematurely discontinued and completed at each of the study periods (e.g. double-blind treatment period, active follow-up period) will be tabulated by treatment group (600 U, 800 U, placebo for Treatment 1; 600 U, 800 U for subsequent treatments). Primary reasons for discontinuation of study treatment will be tabulated.

9.4.5 *Efficacy Evaluation*

As indicated in [Section 7.1](#), the primary efficacy variable is the change in the weekly number of UI episodes from Baseline (Day 1) to Week 6 after the first treatment.

Secondary efficacy variables are:

- weekly number of UI episodes
- MCC
- MDP during storage
- Vol@1stIDC
- proportion of subjects with no episodes of UI
- proportion of subjects with no IDCs on urodynamic assessment
- I-QoL total summary score (as well as individual domain scores i.e. avoidance and limiting behaviour, psychosocial impact, and social embarrassment)
- urinary frequency (total, spontaneous only, CIC only)
- 24-hour voided volume (total, spontaneous only, CIC only)
- volume per void (total, spontaneous only, CIC only)
- PdetMax@1stIDC
- EFP
- DC
- EQ-5D-5L score
- mPGI-I score
- proportion of subjects with UI response at several levels (i.e. $\geq 30\%$ improvement, $\geq 50\%$ improvement, $\geq 75\%$ improvement, etc.)
- time to retreatment request
- time to eligibility for retreatment
- time between treatments.

Full details of these assessments and timings are given in [Section 7.2](#).

The study Baseline value will be defined as the last value available prior to the first study IMP treatment administration.

The aetiology of NDO (SCI or MS) and prior intradetrusor BTX-A usage for UI (BTX-naive and BTX-non-naive) will be used as covariates in the primary model. The results of the treatment effect will be presented for each subgroup formed by the covariates (see [Section 9.5](#) for further details). In order to assess the impact of missing data on the conclusion of the primary analysis, a sensitivity analysis of the primary efficacy endpoint will be performed using a multiple imputation approach.

If the parametric assumptions of the analysis are not satisfied, then a suitable transformation or a nonparametric procedure will be sought.

Secondary efficacy endpoints will be assessed according to their scale (categorical or continuous), using a logistic regression model, mixed model, or survival analysis-type methods (e.g. Kaplan-Meier plots, log-rank statistics).

Time to event data will be analysed by using survival methods. The results will be presented both in summary tables and graphically in Kaplan-Meier plots.

Responders defined as subjects having an improvement in UI will be presented at several levels (i.e. $\geq 30\%$ of improvement, $\geq 50\%$ of improvement, $\geq 75\%$ of improvement, etc.) for exploratory purposes.

9.4.6 Adjustment for Country/Site Effect

No stratification for country/site is to be performed, and no adjustment for country or site effect is planned.

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

Incidence of all reported AEs/treatment emergent AEs, AESIs, and SAEs will be tabulated by treatment group (600 U, 800 U, placebo for Treatment 1 and 600 U, 800 U for subsequent treatment(s)) and overall. In addition, summary tables will be presented by maximum intensity, drug relationship and AEs associated with premature withdrawal of IMP.

A treatment emergent AE 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 at any point in the study following the first dose of IMP.

Concomitant medication will be coded by using World Health Organisation Drug Dictionary (WHODRUG; current version at the time of database lock) and will be summarised by treatment group (600 U, 800 U, placebo for Treatment 1 and 600 U, 800 U for subsequent treatment(s)) and overall, with the number and percentage of subjects receiving concomitant medication by drug class and preferred drug name.

Summary statistics (mean, median, standard deviation, standard error mean, and range as appropriate) by treatment group and overall will be presented for vital signs, laboratory safety tests, laboratory urinalysis/microscopy etc. at each assessment with change from Baseline. For laboratory safety data, abnormal values will be flagged in the data listings and a list of clinically significant abnormal values will be presented. Shift tables from Baseline of the number and percentage of subjects with low, normal or high values and normal or abnormal examinations will be presented by treatment group (600 U, 800 U, placebo for Treatment 1 and 600 U, 800 U for subsequent treatment(s)).

9.4.8 Antibody Testing

The number and percentage of subjects with the presence of neutralising BTX-A antibodies at Baseline will be described. The number of seroconverters (subjects having a negative result at Baseline and at least one positive result at one post-treatment timepoint) for neutralising antibodies will be reported for each treatment group.

9.5 Subgroup Analyses

Descriptive statistics for the primary and selected secondary endpoints (to be defined in the SAP) will be provided for the mITT population within each category of the randomisation stratification variables: aetiology of NDO (SCI or MS) and also BTX-A bladder naive and

BTX-A bladder non-naive). Additional subgroup analyses will be planned according to clinical interest and detailed in the SAP.

Subjects will also be categorised as follows:

- 1) No previous BTX-A treatment at any anatomical location
- 2) No previous intradetrusor BTX-A usage for UI but with previous BTX-A treatment at any other anatomical location
- 3) Previous intradetrusor BTX-A usage for UI, with or without previous BTX-A treatment of any other anatomical location (stratified according to this category).

9.6 Primary Analyses

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10 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 11.4](#), 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.

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Protocol Amendments and Protocol Deviations

11.1.1 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 coordinating investigator as well as the principal investigator and the sponsor will sign the protocol amendment.

11.1.2 Protocol Deviations and Exceptions

All protocol deviations will be identified and recorded by the sponsor or sponsor's representative (see Sections 11.3, 11.4, and 11.5).

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

Generally, a protocol deviation qualifies as major if:

- 1) The deviation has harmed or posed a significant or substantive risk of harm to the research subject
- 2) The deviation compromises the scientific integrity of the data collected for the study
- 3) The deviation is a wilful or knowing breach of human subject protection regulations, policies, or procedures on the part of the investigator(s)
- 4) The deviation involves a serious or continuing noncompliance with any applicable human subject protection regulations, policies, or procedures
- 5) The deviation is inconsistent with Ipsen's research, medical, and ethical principles.

See also [Section 9.1.2](#) for details on the impact of major protocol deviations on the inclusion of subjects in each analysis population.

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

11.2 Information to Study Personnel

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.

11.3 Study Monitoring

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

The sponsor or sponsor's representative 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 according to the monitoring manual, of the subject's visit and on an ongoing basis to allow regular review by the study monitor, both remotely by the internet and during site visits. The study monitor will use functions of the electronic data capture (EDC) system to address any queries raised while reviewing the data entered by the study site personnel in a timely manner.

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

Enrolment will be monitored across study sites to attempt to balance the study population between subjects with MS and subjects with SCI, if possible.

11.4 Audit and Inspection

Authorised personnel from external CAs and the sponsor's authorised Quality Assurance personnel may carry out inspections and audits (see [Section 10](#)).

11.5 Data Quality Assurance

Monitored eCRFs transferred electronically from the investigational site to the assigned Data Management group at the CRO will be reviewed (secondary monitoring) for completeness, accuracy, consistency, 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.

12 ETHICS

12.1 Compliance with Good Clinical Practice and Ethical Considerations

This study will be conducted in compliance with IECs/IRBs, informed consent regulations, all applicable local regulations, the Declaration of Helsinki and ICH GCP Guidelines (Section 1 or 1.6).

In addition, this study will adhere to FDA, 21 CFR Part 11, Electronic Records, Electronic Signatures, and FDA, Guidance for Industry: Computerized Systems Used in Clinical Trials, and 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, if any), 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.

12.2 Informed Consent

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 or subject's legally acceptable representative. 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 or sponsor's representative will provide a sample informed consent form. The final version controlled form must be agreed to by the sponsor or sponsor's representative 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 impartial witness, if applicable, 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.

12.3 Health Authorities and Independent Ethics Committees/Institutional Review Boards

As required by local regulations, the sponsor's or sponsor's representative'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.

12.4 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 by a unique subject identification code.

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.

13 DATA HANDLING AND RECORD KEEPING

13.1 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. In the event of premature termination, all records up to the time of premature termination should be completed. If the subject did not receive IMP the primary reason for not administering IMP should be recorded.

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.

13.2 Data Management

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

Data management will be conducted by a CRO, directed by the sponsor's data management department. All data management procedures will be completed in accordance with CRO standard operating procedures (SOPs) or with sponsor SOPs if CRO SOPs do not exist. The data will be monitored at the investigator site (for further details please see [Section 11.3 Study Monitoring](#)). Any 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.

Any queries generated during the data management process will be raised within the EDC system. It is the central study monitor's responsibility to ensure that all queries are resolved by the relevant parties.

The investigator will receive their data, from the clinical study, in an electronic format (PDF files) which will be an exact copy of the eCRF, and will include the full audit trail, for archiving purposes and future reference.

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 and concomitant medication terms will be performed by the sponsor's Central Coding Group, and reviewed and approved by the sponsor. Concomitant medications will be coded using WHODRUG (current version at the time of database lock),

and AEs/medical history terms will be coded using MedDRA (current version at the time of database lock).

13.3 Record Archiving and Retention

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

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

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

14 FINANCING AND INSURANCE

14.1 Contractual and Financial Details

The investigator (and/or, as appropriate, the hospital administrative representative) and the sponsor's representative 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.

14.2 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.

15 REPORTING AND PUBLICATIONS OF RESULTS

15.1 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. 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.

15.2 Clinical Study Report

In order to support regulatory submission an ICH E3-compliant clinical study report (CSR) may be prepared prior to completion of the study. See [Section 9.6](#) for details regarding this primary analysis.

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

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