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

Published: 26-04-2016
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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 beenadequately managed with oral medication and who routinely...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON47110

Source
ToetsingOnline

Brief title
Ipsen 222

Condition

- Other condition
- Neuromuscular disorders
- Urinary tract signs and symptoms

Synonym
Urinary disorder

Health condition

urine-incontinentie

Research involving
Human

Sponsors and support

Primary sponsor: Ipsen Innovation
Source(s) of monetary or material Support: Ipsen Innovation

Intervention

Keyword: Dysport, Neurogenic detrusor, Spinal cord injury, urinary incontinence

Outcome measures

Primary outcome

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 outcome

Secondary efficacy endpoints

Timepoints following the first and subsequent treatments for efficacy endpoint assessments

are listed in Table 1 and Table 2:

* 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. *30% improvement, *50% improvement,

*75% improvement, etc.)

* no IDCs on urodynamic assessment (i.e. urodynamic cure is

Study description

Background summary

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).

Study objective

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.
Primary Study Objective:
* 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.
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.

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:
* 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®.

Intervention

Study medication, Bladder diary measures, Urodynamic filling cystometry measures, Questionnaires

Study burden and risks

Side effects of Dysport®
Side effects that have been reported after the injection of Dysport® into the bladder in clinical studies are usually mild or moderate, and include temporary muscle weakness, general weakness, pain just above your bladder, pain in hands and feet, urinary tract infections, blood in the urine, and pain due to the procedure. Some patients have also reported muscle weakness in arms after Dysport injection in the bladder.
Due to injection into the bladder muscle, sometimes patients may experience excessive relaxation of the bladder muscle that may result in a temporary increase in urine volume in the bladder after passing urine, or temporary retention of urine (inability to urinate). This is a concern in patients that

are not routinely performing catheterization, however all patients invited for this study are performing catheterization routinely, and will be able to manage the excessive relaxation by continuing the catheterization.
Side effects, in general, commonly seen with the use of Dysport® in any location, are general weakness, tiredness, flu-like illness and injection site reactions, such as pain or bruising. Much more uncommon reactions include itching and rash. Hypersensitivity (allergic reaction) may occasionally be experienced.
Side effects resulting from spread of the effects of Dysport® to parts of the body away from the site of injection have been very rarely reported. These include excessive muscle weakness, difficulty breathing or swallowing which may lead to pneumonia (lung infection), which can result in death in extremely rare cases in patients who are ill due to spasticity. Please contact your doctor immediately if you experience any such symptoms. Excessive muscle weakness after Dysport® injection may impair your ability to drive.
As with any drug, side effects that were not previously known may occur. Side effects may go away after the treatment is stopped, but it is also possible that side effects may last a long time or may never go away. They may range from mild to life threatening and/or fatal.

It is important that you report to your study doctor all symptoms and side effects that you experience (however mild or severe), as soon as they appear, whether or not you think they are related to the study drug. More information in Appendix D of the Informed Consent form

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

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 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) Subjects who are to continue on concomitant oral medications for NDO during the study must be on a stable dose for at least 4 weeks prior to Screening.
7) Subjects who are to continue on concomitant oral medications for NDO during the study must be willing to continue on the same medications and doses during Screening and for at least 12 weeks following the first IMP administration.
8) Routinely performing CIC to ensure adequate bladder emptying (regularly performing CIC at a regimen of every 4*6 hours during waking hours, or more frequently). CIC regimen must be stable for at least 4 weeks prior to Screening (CIC may be performed by the subject or caregiver).
9) Subjects must be willing to continue on the same CIC regimen during Screening and for at least 12 weeks following the first IMP administration.
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 ofchildbearing 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.
14) No more than two incontinent-free days documented on the screening bladder diary.
The following inclusion criterion will be assessed following completion of screening urodynamic assessment:
15) NDO (defined as the presence of involuntary detrusor contractions (IDCs) during the storage phase of urodynamic filling cystometry).

Exclusion criteria

1) Any current condition (other than NDO) that may impact on bladder function, including but not limited to:
* predominant stress UI (rather than NDO-related incontinence)
* bladder stones
* current symptomatic urinary tract infection
* current active genitourinary infection, e.g. genital warts
* uterine prolapse
* cystocele
* rectocele.
Mild uterine prolapse, cystocele or rectocele that does not impact on bladder function is not exclusionary.
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, including but not limited to:
* urinary tract malignancy (e.g. bladder, prostate, urethral or kidney cancer)
* hydronephrosis
* interstitial cystitis/bladder pain syndrome
* müllerian duct cysts
* radiation cystitis
* genitourinary tuberculosis.
8) Previous or current uninvestigated haematuria. Subjects with investigated haematuria may enter the study if significant urological/renal pathology has been ruled out to the satisfaction of the investigator.
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, e.g. diagnosed myasthenia gravis, Lambert-Eaton syndrome or amyotrophic lateral sclerosis.
20) Use of medications that affect neuromuscular transmission, such as curare-like depolarising agents, lincosamides, polymyxins, anticholinesterases and aminoglycoside antibiotics.
21) Previous primary or secondary non response to any botulinum toxins for the targeted condition.
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. In addition, at least 5 elimination half-lives must have occurred since discontinuing any new investigational drug prior to Screening.
The following exclusion criteria will be assessed following completion of screening bladder diary and when screening laboratory blood results become available:
28) Voided urine volume *3 L during a single 24-hour period on the screening bladder diary.
29) Serum creatinine *2 times the upper limit of normal on screening serum chemistry testing.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	20-04-2017
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine

Brand name:	Dysport
Generic name:	Clostridium botulinum toxin type A-haemagglutinin complex
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	26-04-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-11-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-03-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-04-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-04-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-07-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-11-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-05-2018

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-06-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-11-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2015-003471-30-NL
Other	IND 122205
CCMO	NL56929.029.16