A placebo-controlled, randomized, safety and efficacy study of BOTOX® (Bolulinum Toxin Type A) Purified Neurotoxin Complex in patients with neurogenic detrusor overactivity and neurological respiratory impairment.

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To evaluate the safety and efficacy of 2 dose levels of BOTOX® (200 U or 300 U) compared to placebo injected into the detrusor for the treatment of urinary incontinence caused by neurogenic detrusor overactivity in patients who have not been...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Spinal cord and nerve root disorders
Study type	Interventional

Summary

ID

NL-OMON31185

Source
ToetsingOnline

Brief title
Safety of Botox® in patients with NDO and respiratory impairment.

Condition

- Spinal cord and nerve root disorders
- Respiratory disorders NEC

Synonym
Neurogenic Overactive Bladder: urine incontinence due to illness or damage of the spinal cord

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Botox®, Neurogenic Detrusor Overactivity, Neurological Respiratory Impairment

Outcome measures

Primary outcome

Safety measures are the primary study parameters:

Primary safety measures:

* Forced Vital Capacity (FVC) (percent predicted and absolute value)

* Forced Expiratory Volume (FEV1) (percent predicted and absolute value)

* Oxyhemoglobin Saturation

* Maximum Inspiratory Pressure (MIP)

* Maximum Expiratory Pressure (MEP)

Secondary outcome

Secondary safety measures:

* Serious Medical Events

* Adverse Events

* Physical Examination

* Vital signs

* Hematology and non-fasting chemistry

* Urinalysis

* Bladder and kidney ultrasound

* Post void residual

Secondary efficacy measures:

* Number of episodes of urinary incontinence as recorded in the patient bladder

diary

* Number of episodes voided as recorded in the patient bladder diary

* Urodynamic parameters

Study description

Background summary

Recently, studies have been carried out using BOTOX® in the treatment of patients who suffer from bladder overactivity.

There is evidence for the successful use of BOTOX® in the management of neurogenic incontinence. It has been shown that botulinum toxin injections of 200 U to 300 U into the detrusor across 20 to 30 injection sites (10 units per mL per injection site) have been effective in restoring continence and enabling reduction or cessation of anticholinergic medication in such patients. In one study enrolling 21 patients, 17 of the 19 patients with follow-up data had restored continence within 6 weeks. To date, treatment of over 900 neurogenic overactive bladder patients with BOTOX® at doses ranging from 200 U to 300 U in 20 to 30 injection sites has been reported. Treatment benefit has been described to last between 6 and 12 months with an acceptable site effect profile.

Allergan conducted a placebo-controlled phase 2 study to assess the safety and efficacy of BOTOX® (study AGN 191622-511). Fifty-nine patients were enrolled in this study and received a single treatment of 200 U BOTOX®, 300 U BOTOX® or placebo and followed for 24 weeks post-treatment. Treatment effect in both active groups was observed for the duration of the 24-week study. Urodynamic parameters, also indicative of efficacy, supported the effectiveness of BOTOX®. Increased bladder capacity, as determined by maximum cystometric capacity, was consistently and significantly greater in the BOTOX®-treated patients through 24 weeks post-treatment. Although statistically significant

superiority to placebo was consistently observed for the 200 U and 300 U doses throughout the follow-up period, the study was not designed to compare the two active doses. There were no significant safety observations noted and no treatment related adverse events were reported in any patients. Therefore, it was not possible to differentiate between the two doses with respect to duration of effect. Although the study was not designed to evaluate treatment duration of effect, study data are consistent with those seen in the literature of a mean duration of effect for both the 200 U and 300 U doses of at least 6 months.
Based on data from the 191622-511 study and literature reports of BOTOX® treatment for overactive bladder, Allergan is pursing further clinical development in both neurogenic and idiopathic clinical patients. A phase 2 dose-response study has been initiated in idiopathic overactive bladder patients. Two pivotal safety and efficacy studies are planned to support a neurogenic overactive bladder indication. One phase 3 safety and efficacy study (191622-515) has been initiated recently and the second, pivotal phase 3 study will be conducted to confirm safety and efficacy in this same patient population (191622-516).
This phase 3 safety study will evaluate patients with neurogenic detrusor overactivity who have respiratory impairment due to their underlying neurologic disease, namely spinal cord injury or multiple sclerosis. Although, there are no reports of respiratory failure in patients who have received BOTOX® for overactive bladder or for treatment of detrusor sphincter dyssynergia and urethral sphincter injections, no acute complications of respiratory depression were observed, there is a theoretical possibility of systemic spread of BOTOX®. Thus, a potential safety concern arises with BOTOX® if it were to cause respiratory failure due to paralysis of the diaphragm and other respiratory muscles. MS and spinal cord injury patients who already have respiratory compromise would be especially vulnerable to the development of respiratory failure were this to occur.

Study objective

To evaluate the safety and efficacy of 2 dose levels of BOTOX® (200 U or 300 U) compared to placebo injected into the detrusor for the treatment of urinary incontinence caused by neurogenic detrusor overactivity in patients who have not been adequately managed with anticholinergic therapy and have neurological respiratory impairment.

Study design

Structure:
Multicenter, double-blind, randomized, placebo-controlled, parallel group study.

Duration:
Patients will complete a 52 week post-treatment follow up period following

Randomization/Day 1. Patients are eligible for up to 2 treatments during the study with a minimum of 12 weeks between treatments.

Controls:
BOTOX® placebo (saline)

Randomization:
Patients will be centrally randomized and assigned a randomization number prior to the first treatment, which will be associated with one of the following treatment sequences:
1) BOTOX® 200 U (treatment 1)/BOTOX® 200 U (treatment 2)
2) BOTOX® 300 U (treatment 1)/BOTOX® 300 U (treatment 2)
3) Placebo (treatment 1)/BOTOX® 200 U (treatment 2)
4) Placebo (treatment 1)/BOTOX® 300 U (treatment 2)

Patients will be randomized to the above treatment sequences in a ratio of 1:1:0.5:0.5, respectively. In order to ensure balance across treatment arms, patients will be stratified to treatment according to overactive bladder etiology (multiple sclerosis or spinal cord injury).

Study Design
Dosage/Dose regimen:
Each study treatment will be administered via cystoscopy as 30 injections, each of 1 mL, evaly distributed into the detrusor (including dome), avoiding the bladder base and trigone.

Treatment 1:
All eligible patients will receive their first treatment with BOTOX® 200 U or BOTOX® 300 U or placebo. The first treatment will be administered after randomization on Randomization/Day 1.

Treatment 2:
All eligbible patients will receiv BOTOX® for their second treatment which may be administered no sooner than Week 12 if the patient meets re-treatment criteria. Patients receiving BOTOX® for their first treatment will continue to be treated with the same dose received in the first treatment. Patients receiving placebo for the first treatment will receive either BOTOX® 200 U or 300 U for the second treatment, according to the pre-assigned randomization schedule. In order to allow for appropriate study follow-up, treatment 2 must occur by Week 40 following Randomization/Day 1.

Intervention

Yes, BOTOX® 200 U, BOTOX® 300 U or placebo will be administered via cystoscopy as 30 injections, each of 1 mL, evenly distributed into the detrusor (including dome), avoiding the bladder base and trigone.

Study burden and risks

From the risk benefit assessment it seemed that treatment effect will be greater than the risks for the patients when participating in the study.

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

7. Patient has urinary incontinence as a result of neurogenic detrusor overactivity for a period of at least 3 months prior to Screening Day -21 due to spinal cord injury or multiple sclerosis, determined by documented patient history. In addition:
* Spinal cord injured patients must have a stable neurological injury between cervical level 5 (C5) and cervical level 8 (C8), inclusively as determined by the neurological definition of SCI;

complete or incomplete. The spinal cord injury must have occurred >< = 12 months prior to Screening Day -21
* Multiple sclerosis patients must be clinically stable, in the investigator's opinion, for >< = 3 months prior to Screening and through Randomization/Day 1. Patients must have an Expanded Disability Status Scale score between 7.0 and 8.0, inclusively.
9. Patient has a Forced Vital Capacity (FVC) between 50% and 80% of predicted value on two separate testing days during Screening (Day -21 to Day -1). Note: The difference between the largest FVC observed on each testing day must not exceed 20%. There should be at least 7 days between the two screening PFTs and the second PFT must occur withing 0-5 days prior to Randomization/Day 1 Visit.
10. Patient has detrusor overactivity (defined as a phasic rise in bladder pressure during the filling phase as determined by urodynamics) demonstrated during the Screening period (Day -21 to Day -1) or Randomization/Day -1.
12. Patient has not been adequately managed with one or more anticholinergics for their urinary incontinence, in the opinion of the investigator. "Not adequately managed' is defined as an inadequate response to, or intolerable side effects while taking an optimized dose for at least one month.
15. Both multiple sclerosis (MS) and spinal cord injury (SCI) patients must be willing to use intermittent catherization (IC) to empty the bladder and maintain an established catheterization frequency throughout the study. Caregiver may perform IC for patient, if patient is unable to do this. (Indwelling catheters are not permitted).
16. Patient experiences >< = 4 episodes of urinary incontinence (leakage) over 3 days determined by completion of a bladder diary during the Screening period.

Exclusion criteria

1. Patient has had previous or current botulinum toxin therapy of any serotype for any urological condition or treatment within 3 months of Randomization/Day 1 for any other condition.
3. Patient has history or evidence of any significant pelvic or urological abnormality, including, but not limited to, the following:
* elevated serum creatinin > 2 times the upper limit of normal (reference range)
* history of or current hematuria, 1) if the hematuria is determined to be due to a pathologic condition or 2) is uninvestigated
* interstitial cystitis in the opinion of the investigator
* bladder stones within 6 months of Screening Day -21
* surgery or bladder disease other than detrusor overactivity that may impact bladder function with the exception of surgeries for bladder stones (>6 months) and stress incontinence, uterine prolapse, rectocele, or cystocele (> 1 year from Screening Day -21)
6. Patient has discontinued anticholinergic medication for the treatment of overactive bladder <21 days prior to Randomization/Day1.
7. Patient has an untreated or symptomatic (e.g. fever, recent change in neurological status) urinary tract infection (UTI) on Randomization/Day 1.
10. Patient has an acute respiratory tract infection. Patient may qualify for re-screening upon clinical resolution and stabilization (one month, or longer based on the investigator's opinion,

has elapsed after clinical resolution without recurrent symptoms).
11. Patient has a clinically significant abnormal chest X-ray (CXR) finding. Patient may qualify for re-screening upon resolution, or the CXR finding is no longer considered clinically significant.
12. Patient has clinically significant intrinsic lung disease (e.g. sarcoidosis, pulmonary fibrosis, bronchiectasis).
13. Asthmatics whose disease is not stable (i.e., have had exacerbation(s) of asthma within 3 months prior to Screening Day -21) Note: Stable, preventative respiratory medications/therapy are permitted
14. Patient has a history of, or acute exacerbation of COPD within 3 months prior to Screening Day -21.
15. Patient has a pulmonary embolus (PE) within 6 months of screening Day -21, or a history of recurrent pulmonary emboli (i.e., a diagnosis of PE on more than one occasion per lifetime)
16. Patient has aspiration pneumonia, aspiration pneumonitis or acute respiratory failure wihin 12 months prior to Screening Day -21.
17. Patient requires supplemental oxygen and/or ventilatory support.
18. Patient has evidence of carbon dioxide (CO2) retention as indicated by a serum bicarbonate level greater than the upper limit of the normal (reference range) at Screening Day -21.
19. Patient has used any antiplatelet or anticoagulant therapy or is using medications with anticoagulative effects within 3 days prior to treatment. Some medications may need to be withheld for > 3 days per clinical judgement of the investigator (refer to Section 8.2.2 Prohibited Medications/Treatments for details).
21. Patient is currently using, or plans to use, an implanted or non-implantable electrostimulation/neuromodulation device for treatment of overactive bladder.
22. Patient is currently being treated with an intrathecal baclofen pump.

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:	Will not start
Start date (anticipated):	01-08-2007
Enrollment:	5
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	BOTOX®
Generic name:	Botulinum Toxin Type A
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	08-08-2007
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-04-2008
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-04-2008
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-05-2008
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	EUCTR2006-006299-39-NL
CCMO	NL17079.029.07