A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study of the Safety and Efficacy of a Single Treatment of BOTOX® (Botulinum Toxin Type A) Purified Neurotoxin Complex Followed by a Treatment with BOTOX® as Applicable in Patients with Idiopathic Overactive Bladder with Urinary Incontinence

Published: 11-09-2009
Last updated: 04-05-2024

To evaluate the efficacy and safety of BOTOX® 100 U compared with placebo in patientswith idiopathic OAB with urinary incontinence whose symptoms have not been adequatelymanaged with anticholinergic therapy.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Bladder and bladder neck disorders (excl calculi)
Study type	Interventional

Summary

ID

NL-OMON33418

Source
ToetsingOnline

Brief title
A study of Botox® in Patients with Idiopathic Overactive Bladder

Condition

- Bladder and bladder neck disorders (excl calculi)

Synonym
lack of bladder control and uncontrolled urination, Overactive bladder

Research involving
Human

Sponsors and support

Primary sponsor: Allergan Ltd.
Source(s) of monetary or material Support: Farmaceutisch bedrijf

Intervention

Keyword: BOTOX, Idiopathic Overactive Bladder, Urinary Incontinence

Outcome measures

Primary outcome

Primary Efficacy Measure:

There are two co-primary efficacy measures, (except for US FDA analyses-see

Section 10.7):

• Number of episodes of urinary incontinence

• The proportion of patients who have a positive treatment response on the

Treatment

Benefit Scale (score of either 1 or 2, representing *greatly improved* or

improved)

The primary time point is at Week 12 following the first treatment.

Secondary outcome

Secondary Efficacy Measures:

• Number of micturition episodes

• Urinary Incontinence-Specific Quality-of-Life Instrument (I-QOL)

• King*s Health Questionnaire (KHQ)

• Number of urgency episodes

Study description

Background summary

Botulinum Toxin Type A inhibits vesicle-bound neurotransmitters at the neuromuscular junction, including acetylcholine (ACh). Injection into the bladder wall can therefore inhibit the parasympathetic stimulated contraction of the detrusor muscle. Botulinum toxin has also been suggested to inhibit other neurotransmitters within the bladder associated with OAB (Apostolidis, 2006). Randomized controlled trials in idiopathic patients who have not been adequately managed with anticholinergic therapy have shown that the treatment is effective, safe and durable (Brubaker, 2008; Sahai, 2007). These data support the potential utility of BOTOX® for patients with idiopathic OAB. A phase 2 study in the idiopathic population has been completed.

Phase 2 Data

A total of 313 patients were enrolled into the study. A dose response was identified in efficacy and urodynamic parameters which was reflected in the patient perception of benefit. However, a dose response was also observed with certain safety parameters which were particularly related to the elevation in PVR urine. The risk/benefit balance was carefully evaluated, with the BOTOX® dose of 100U being considered the most appropriate for the pivotal phase 3 studies.

Following analysis of the phase 2 data it was determined that a dose of 100 U BOTOX® provides the appropriate balance between efficacy and safety in the treatment of patients with idiopathic OAB. This dose will therefore be evaluated further during this phase 3 study.

Based on this information, we can formulate the following hypothesis:

1. BOTOX® 100 U is more effective than placebo at improving the symptoms of idiopathic overactive bladder
as measured by the difference between treatment groups in the reduction of urinary incontinence episodes at Week 12.

2. BOTOX® 100 U is more effective than placebo as assessed by the difference

between treatment groups in the
proportion of patients with a positive treatment response on the Treatment Benefit Scale at Week 12.

3. BOTOX® 100 U has an acceptable safety profile when injected into the detrusor of patients with idiopathic
overactive bladder with urinary incontinence whose symptoms have not been adequately managed with
anticholinergic therapy.

Study objective

To evaluate the efficacy and safety of BOTOX® 100 U compared with placebo in patients
with idiopathic OAB with urinary incontinence whose symptoms have not been adequately
managed with anticholinergic therapy.

Study design

This is a phase 3 clinical research study, being conducted with consenting adults who are
affected by Idiopathic Overactive Bladders (OAB)and urinary incontinence who have not found
previous benefit from anticholinergic medications. The cause of the problems associated with
overactive bladders in this study are unknown.

This study asseses the safety and effectiveness of BOTOX® treatment injected into the bladder
for patients with idiopathic OAB. This study is placebo controlled meaning that some patients will
receive a dummy drug (placebo) whereas others will receive active drug (BOTOX 100U). Patients
are allocated at random to receive either the placebo or BOTOX® 100 U on a 1:1 basis. This study
is also doubleblind, meaning that neither the patients nor the investigator knows if they have been
allocated placebo or active drug.

The effect of BOTOX® in improving the condition of OAB is temporary, therefore re*treatment
will be necessary to regain the benefit. In clinical practice this treatment would be administered
to patients periodically when required. All patients participating in this study will receive active

treatment of BOTOX® 100 U if they request a second treatment before their exit visit.

The study will be conducted internationally with several different centres taking part in each country.
Each centre will have their own research team. Patients will have to meet certain requirements to join
this study * these are called the Inclusion and Exclusion Criteria. Patients will also be informed on entry
to 191622-520 that they may have the opportunity to participate in the long term followup study 191622-096
after completion of the current study and receive further active treatment.

To enable the investigator and patient to remain blinded to their treatment, the allocation of study
medication kits will be organised via a central, computerised system. This system has been used
effectively in many previous studies and is called Interactive Voice Response System (IVRS)/Interactive
Web Response System (IWRS) * the study site staff are given a choice of using the telephone to get
the medication information they require or using a computer with internet access. The patient will not
have to have any dealings with IVRS or IWRS.

Patient Visits and Procedures:
The patient could participate in the study for between 24 and 39 weeks depending on the number and
timing of study treatments that they qualify for.

The following visits occur:

PreScreening/Washout period

Patients who are currently receiving anticholinergic medications and who have consented to participate
in the study, will enter a washout period of at least 1 week prior to the start of the screening period.
Informed consent must be taken before commencing the washout period. Screening visit takes place
up to 3 weeks prior to randomisation/ day 1 to assess eligibility to enter the study. If not already taken
at the PreScreening/Washout period informed consent will be taken at the start of this visit. The patient
will be asked to complete a diary of their bladder function for three consecutive days in the week before
their Treatment 1 visit. They will also be required to record the volume of

urine voided during a 24 hour
period within these three days. The bladder diary will be competed before all of the following visits except
in the case of Treatment 2.

Treatment 1 (Randomization/ Day 1):

Eligible patients will be randomized and receive their initial treatment at the Randomization/Day 1 visit.

Treatment 1 Followup

Visits:
Following the initial treatment, all patients will be evaluated at scheduled clinic visits at Weeks 2, 6 and 12.
Further followup visits occur at Weeks 18, and 24 (Exit) if qualification for Treatment 2 is not initiated and/or
Treatment 2 not administered(see below).

Qualification for Treatment 2:
Request for Treatment 2 can be initiated by the patient at the Week 12, 18, or 24 scheduled clinic visits only
(which then turns into a Qualification for Treatment 2 visit). The patient must meet all qualification criteria before
Treatment 2 can occur (if all are not met, the patient returns to the Treatment 1 followup visit schedule).

Treatment 2:
A patient should be treated within 3 weeks of the Qualification for Treatment 2 visit, provided all
Treatment 2 criteria are met on day of treatment (if all are not met the patient returns to the
Treatment 1 followup visit schedule).

Treatment 2 Followup
Visits:
After Treatment 2, scheduled followup clinic visits will occur at Weeks 2, 6, and 12 (Exit) following
the Treatment 2 visit.

Exit Visit:

Patients will participate in the study until completion of 24 weeks post Randomization/Day 1,
and if a second treatment was received, 12 weeks post treatment followup after Treatment 2.
The minimum study participation is therefore 24 weeks and the maximum duration

is 39 weeks
(if patient qualified for Treatment 2 at week 24 and received it at Week 27).
Additional unscheduled
visits will occur if a patient has a post treatment PVR urine volume of >= 200mL
(for additional details
see Protocol section 8.3.2.8 Post Void Residual (PVR) Urine Volume).

Intervention

De studiemedicatie wordt in de blaaswand ingespoten door middel van cystoscopie onder vorm van 20 injecties van elk 0.5 ml. De injecties worden evenredig verspreid over de detrusor met uitzondering van de trigone en de basis.

The study medication is injected into the bladder wall through cystoscopy administered as 20 injections of 0.5ml each. The injections will be evenly distributed into the detrusor, avoiding the trigone and base.

Study burden and risks

A. The following side effects have been observed in patients treated with BOTOX® for the overactive bladder:

In conjunction with the study medication

•Weakness of the bladder muscle, resulting in difficult urination or inability to urinate (urinary retention) to empty
the bladder for a prolonged time (in most cases less than one month, but may be longer) after the treatment

•General weakness

In conjunction with the procedure (for example, with the injection, cystoscopy)

•Transient pain

•Transient bleeding at the injection site, resulting in formation of a blood clot in the bladder tissue

•Blood in the urine

•Difficulty with or pain during urination

•Urinary tract infection

B. The following side effects have not been seen to date with BOTOX® injections, but may possibly occur in you if you are

treated in this study for your overactive bladder:

In conjunction with the procedure (for example, with the injection, cystoscopy)

•Permanent tissue damage from the repeated injections

•Unintentional perforation of the bladder wall so that BOTOX® enters the abdominal cavity or adjacent structures

•Abnormal symptoms as a result of overactivity of the nerve supply of the bladder

•Reaction to the local anaesthetic used, for example, dizziness, nervousness, spasms, low blood pressure, slow
heart rate or cessation of heart and lung activity (cardio-circulatory arrest)

•Reactions to the anaesthetic (consciousness-lowering sedation), for example, sleepiness, shallow respiration,
nausea, vomiting, constipation, dry mouth and euphoria

•Injury by the cystoscope, resulting in temporary swelling of the urethra, injury to the urethra, blockage of the
urinary stream, urinary retention, overextension of the bladder, bleeding or a bladder infection

C. The side effects and discomforts that are associated with the study treatment and that you may experience include the
following side effects observed with BOTOX® as treatment for other disorders (i.e., not overactive bladder):

•Temporary muscle weakness at the injection site

•Slight weakness in other adjacent muscles

•Skin eruption

•Blurred vision

•Allergic reaction

•Itching

•Tingling or pricking sensation

•Reduced sensitivity to contact

•Flu-like symptoms such as muscle pain, chest discomfort, feeling of weakness

or illness, fever, sweating

•Gastrointestinal symptoms such as vomiting, nausea, diarrhea, abdominal pain and loss of appetite

D.As with any injection of a medication, there may be a possibility of local pain/ sensitivity, bleeding, blood effusion,
infection and/or swelling. Some people feel lightheaded or faint when they are injected with a medication.

E. The collection of blood for tests may be associated with pain from the needle prick, and a blood effusion may form at the
site where the blood was collected. The quantity of blood collected in one visit during this study is quite small
(approximately 6 teaspoonfuls (30 ml)) and therefore the taking of this blood is not hazardous to your health.

F. On the basis of the results of experimental study in animals there is a risk of a miscarriage or malformation of the foetus
(congenital abnormality) if you are pregnant or become pregnant during the study. The effects of this medication on
pregnancy have not been investigated in humans.

G. Side effects or discomforts that are not known at this time may occur as a result of the study medication.

H.Patients who perform clean intermittent catheterisation (CIC) can develop a urinary tract infection, become injured as a
result of the CIC resulting in blood in the urine or experience sensitivity in the urethra as a result of the repeated
catheterisation.

RARE RISKS OR DISCOMFORT FOR THE PATIENTS

A. Patients with certain muscle-weakening neurologic disorders (such as Lou Gehrig*s disease or amyotrophic lateral sclerosis (ALS)), myasthenia gravis, Lambert-Eaton syndrome or motor neuropathy) may be extra sensitive to the effects of this medication and may develop problems, such as severe difficulties with swallowing and/or breathing. In rare instances these problems last for several months, and a feeding tube may be necessary.

B. In rare instances, side effects have been reported as a result of spread from the injection site, hours to weeks after treatment with medications from the botulinum toxin class, including BOTOX®. This can cause symptoms in parts of the body far from the injection site, such as unexpected loss of muscle strength or muscle weakness, hoarseness or difficulty in speaking, difficulty in pronouncing words clearly, loss of bladder control, difficulties with

breathing, difficulties with swallowing, double vision, blurred vision and drooping eyelids. There have been rare reports of death, sometimes associated with difficulty in swallowing, pneumonia, breathing problems and/or other important disabilities.

Patients with disorders of the muscular or respiratory systems, such as COPD, who already had problems with swallowing or breathing, are at greater risk for these side effects. You are advised to call for medical assistance immediately if you have difficulties with swallowing, breathing or speaking.

C. There have also been infrequent reports of heart problems (including abnormal heart rhythm and heart attack, sometimes fatal) after treatment with this medication. However, it is not known whether this medication actually caused the problems; some of these patients already had an elevated risk of heart disorders. Patients (especially those who are very seriously ill) may develop such problems even without the use of this medication.

D. A number of cases have been reported of potentially life-threatening allergic reactions. In some of these cases, the study medication was administered in combination with another product, so that it was difficult to determine the cause of the allergic reaction, such as in a case where a patient died after being injected with the study medication that had been incorrectly diluted with a local anaesthetic (lidocaine) rather than with the physiologic salt solution.

E. This medication contains albumin from human blood. Although the blood was tested thoroughly, there is an extremely small chance that viruses and other similar infectious materials will be transmitted.

F. Although unusual, patients who receive this medication may develop antibodies to it (an antibody is part of the body*s natural defence system). As a result, later treatments with this medication may no longer be effective.

G. On the basis of the results of an experimental study in animals in which the study medication was injected into the prostate gland, an elevated risk of developing bladder stones may exist.

H. It is possible that in some patients who suffered from certain gastrointestinal disorders in which food and excreted materials are not normally passed from the stomach or the intestine, the use of this study medication may sometimes make the symptoms of the disorder reappear.

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 has been obtained.
2. Written Authorization for Use and Release of Health and Research Study Information (US sites only) has been obtained.
3. Written Data Protection Consent (EU sites only) has been obtained.
4. Written documentation has been obtained in accordance with the relevant country and local privacy requirements, where applicable.
5. Patient is male or female, aged >= 18 years old.
6. Patient weighs >= 40 kg (88 lbs).
7. Patient has symptoms of idiopathic OAB (frequency and urgency) with urinary incontinence for a period of at least 6 months immediately prior to screening, determined by documented patient history.
8. Patient experiences >= 3 episodes of urinary urgency incontinence, with no more

than one urgency incontinence-free day, in the 3-day patient bladder diary completed during the screening period (Screening Day -21 to Randomization/Day 1).
9. Patient experiences urinary frequency, defined as an average of >= 8 micturitions (toilet voids) per day i.e. a total >= 24 micturitions in the 3-day patient bladder diary completed during the screening period (Screening Day -21 to Randomization /Day 1).
10. Patient has not been adequately managed with one or more anticholinergic agents for treatment of their overactive bladder symptoms, in the opinion of the investigator.
Not adequately managed is defined as:
• an inadequate response after at least a 4-week period of anticholinergic therapy on an optimized dose(s), i.e., patient was still incontinent despite anticholinergic therapy, or
• limiting side effects after at least a 2-week period of anticholinergic therapy on an optimized dose(s). ;An optimized dose is defined as an approved dose for the indication of OAB.
11. Patient is willing to use clean intermittent catheterization (CIC) to empty the bladder at any time after study treatment if it is determined to be necessary by the investigator.
12. Patient has a negative pregnancy test result if female and of childbearing potential.
13. Patient has a negative urine dipstick reagent strip test at Randomization/Day 1 (for nitrites, blood and leukocyte esterase) and, in the investigator*s opinion, patient is asymptomatic for UTI on day of treatment.
14. Patient is able to complete study requirements including using the toilet without assistance, is able to collect volume voided per micturition measurements over a 24-hour period, complete bladder diaries and questionnaires, and attend all study visits in the opinion of the investigator.

Exclusion criteria

1. Patient has symptoms of overactive bladder due to any known neurological reason (eg, spinal cord injury, multiple sclerosis, cerebrovascular accident, Alzheimer*s disease, Parkinson*s disease, etc).
2. Patient has a predominance of stress incontinence in the opinion of the investigator, determined by patient history.
3. Patient has received anticholinergics or any other medications or therapies to treat symptoms of overactive bladder, including nocturia, within 28 days of Randomization/Day 1.
4. Patient uses CIC or indwelling catheter to manage their urinary incontinence.
5. Patient has been treated with any intravesical pharmacologic agent (eg, capsaicin, resiniferatoxin) within 12 months of Randomization/Day 1.
6. Patient has had previous or current botulinum toxin therapy of any serotype for any urological condition.

7. Patient has had previous or current botulinum toxin therapy of any serotype for any non-urological condition within 12 weeks of Randomization/Day 1.
8. Patient has been immunized for any botulinum toxin serotype.
9. Patient has history or evidence of any pelvic or urological abnormalities, bladder surgery or disease, other than *overactive bladder*, that may affect bladder function including but not limited to:
• Bladder stones and/or bladder stone surgery at the time of screening or within 6 months prior to screening
• Surgery (including minimally invasive surgery) within 1 year of screening for: stress incontinence, uterine prolapse, rectocele, or cystocele.
• Current or planned use of an implanted electrostimulation/neuromodulation device for treatment of urinary incontinence (if a device is still implanted, it must be inactive 4 weeks prior to Randomization/Day 1 and for the duration of the study); use of other non-implantable electrostimulatory devices is also exclusionary.
10. Patient has a history of interstitial cystitis/painful bladder syndrome, in the opinion of the investigator.
11. Patient has an active genital infection, other than genital warts, either concurrently or within 4 weeks prior to screening.
12. Patient has a history or current diagnosis of bladder cancer or other urothelial malignancy, and/or has uninvestigated suspicious urine cytology results. Suspicious urine cytology abnormalities require that urothelial malignancy is ruled out to the satisfaction of the investigator according to local site practice.
13. Patient is male with previous or current diagnosis of prostate cancer or a prostatespecific antigen (PSA) level of > 10 ng/L at screening. Patients with a PSA level of >= 4 ng/L but <= 10 ng/L must have prostate cancer ruled out to the satisfaction of the investigator according to local site practice.
14. Patient has evidence of urethral and/or bladder outlet obstruction, in the opinion of the investigator at screening or Randomization/Day 1.
15. Patient has a PVR urine volume of > 100 mL at screening. The PVR measurement can be repeated once; the patient is to be excluded if the repeated measure is above 100 mL.
16. Patient has had urinary retention or an elevated PVR urine volume that has been treated with an intervention (such as catheterization) within 6 months of screening.
Note: voiding difficulties as a result of surgical procedures that resolved within 24 hours are not exclusionary.
17. Patient has a 24-hour total volume of urine voided > 3000 mL, collected over 24 consecutive hours during the 3-day bladder diary collection period prior to Randomization/Day 1.
18. Patient has a history of 2 or more urinary tract infections within 6 months of screening.
19. Patient has a serum creatinine level > 2 times the upper limit of normal at screening.
20. Patient has current or previous uninvestigated hematuria. Patient with investigated hematuria may enter the study if urological/renal pathology has been ruled out to the satisfaction of the investigator.

21. Patient has hemophilia, or other clotting factor deficiencies, or disorders that cause bleeding diathesis.
22. Patient cannot withhold any antiplatelet, anticoagulant therapy or medications with anticoagulant effects for 3 days prior to Randomization/Day 1. Note: some medications may need to be withheld for > 3 days, per clinical judgment of the investigator. Please refer to Section 8.2.1 Permissible Medications/Treatments for additional details.
23. Patient has a known allergy or sensitivity to any components of the study medication, anesthetics or antibiotics to be used during the study.
24. Patient has any medical condition that may put them at increased risk with exposure to BOTOX® including diagnosed myasthenia gravis, Eaton-Lambert syndrome, or amyotrophic lateral sclerosis.
25. Females who are pregnant, nursing or planning a pregnancy during the study or females of childbearing potential who are unable or unwilling to use a reliable form of contraception during the study (see section 8.2.3).
26. Patient is currently participating in or has previously participated in another therapeutic study within 30 days of screening (or longer if local requirements specify).
27. Patient has any condition or situation which, in the investigator*s opinion, puts the patient at significant risk, could confound the study results, or may interfere significantly with the patient*s participation in the study.

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):	06-07-2010
Enrollment:	40

Type:	Actual

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:	11-09-2009
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-12-2009
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2009-013088-20-NL

Register	ID
CCMO	NL28921.078.09