BOTOX® in the Treatment of Urinary Incontinence Due to Overactive Bladder in Patients 12 to 17 Years of Age

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To evaluate the safety and efficacy of BOTOX for the treatment of urinary incontinencedue to overactive bladder (OAB) in patients 12 to 17 years of age who have not been adequately managed with anticholinergic therapy. To evaluate the safety and...

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

Summary

ID

NL-OMON42096

Source
ToetsingOnline

Brief title
BOTOX® for Paediatric Urinary Incontinence

Condition

- Bladder and bladder neck disorders (excl calculi)

Synonym
Overactive Bladder, urinary incontinence

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Bladder, BOTOX, Paediatric, Urinary Incontinence

Outcome measures

Primary outcome

* number of daytime urinary incontinence episodes

Secondary outcome

Efficacy:

* number of daytime micturition episodes

* number of daytime urgency episodes

* presence or absence of night time urinary incontinence

* volume voided per micturition

Health Outcomes:

* Pediatric Incontinence Questionnaire (PinQ)

* modified Treatment Benefit Scale (TBS)

Safety:

* adverse events

* serious adverse events

* physical examination

* vital signs (heart rate, blood pressure, respiration rate, and body

temperature)

* urine dipstick reagent strip test

* urinalysis (with urine culture/sensitivity, as applicable)

* hematology and clinical chemistry

* PVR urine

* immunogenicity testing

* kidney and bladder ultrasound

* urine pregnancy test for females who are postmenarche

* concomitant medications

* concurrent procedures

Study description

Background summary

The purpose of this study is to investigate the safety and effectiveness of BOTOX® injections into the bladder of children that have accidental loss of urine due to Overactive Bladder. Approximately 108 patients will participate in this study at approximately 35 to 45 sites across Europe and the Middle East, Asia Pacific and North America.
BOTOX® is marketed in various countries for treatment of crossed eyes (strabismus) in patients 12 years and older, eyelid twitching (blepharospasm) in patients 12 years and older, movement disorders of the head and neck (cervical dystonia), for prophylaxis of chronic migraine (*15 days per month with headache lasting 4 hours a day or longer), upper limb spasticity in adults, upper and lower limb spasticity associated with cerebral palsy in children 2 years of age and older, excessive sweating (severe primary axillary hyperhidrosis), to treat leakage of urine (incontinence) in adults with overactive bladder due to neurological disease (e.g. spinal cord injury or multiple sclerosis), frown lines (glabellar lines) and crows feet lines (lateral canthal rhytids).
BOTOX® is also marketed in various countries including several European countries, U.S. and Canada for treatment of overactive bladder in adults with symptoms of urge urinary incontinence, urgency and frequency of unknown cause, but is not approved for use in children and is considered investigational.

Study objective

To evaluate the safety and efficacy of BOTOX for the treatment of urinary incontinence
due to overactive bladder (OAB) in patients 12 to 17 years of age who have not

been adequately managed with anticholinergic therapy. To evaluate the safety and efficacy of repeated BOTOX treatments in this patient population.

Study design

Structure: Multicenter, randomized, double-blind, parallel-group, multiple-dose study

Duration: Patients will participate in the study for at least 96 weeks following entry into the study and should have at least 12 weeks follow-up since the last treatment prior to exiting the study. The minimum duration is therefore 96 weeks, and the maximum duration is approximately 108 weeks (for patients who received their last treatment at week 96 with 12 weeks posttreatment follow-up).

Study Treatment Groups: Eligible patients will be initially allocated to 1 of 3 treatment groups:
* 25 units (U) BOTOX (not to exceed 6 U/kg)
* 50 U BOTOX (not to exceed 6 U/kg)
* 100 U BOTOX (not to exceed 6 U/kg)
In order that an upper dosing limit of 6 U/kg is not exceeded, the actual dose administered will be adjusted based on patient weight if necessary.

At each retreatment, the investigator can elect to keep the dose the same or increase the dose one level; if it is deemed that a dose reduction would be warranted then the patient should be exited from the study (see Section 5.5 for further details). The dose decision will be based on the response to the previous treatment. Both the preceding and subsequent dose will remain blinded until the primary analysis has been reported (see Section 7). The dosing options will depend on the investigator*s decision as summarized below:
* investigator may elect to keep the same dose as received at the previous treatment (dose not to exceed 6 U/kg)
* investigator may elect to increase the dose compared with the previous treatment (dose not to exceed 6 U/kg) as follows:
o if the patient received 25 U at the previous treatment, they would receive 50 U
o if the patient received 50 U at the previous treatment, they would receive 100 U
o if the patient received 100 U at the previous treatment, they would remain at 100 U

However, for any patient who is already on the highest dose (100 U), if a dose escalation is requested by the investigator on 2 occasions, the patient will be exited from the study upon the second escalation request without receiving any further treatments. In addition, if the investigator assesses that the patient should not be retreated with the current dose and that a dose reduction would be warranted, the patient should be exited from the study as a reduction of

dose in this study is not an option. In such cases, the patient will be followed up for a minimum of 12 weeks since their last treatment.

Controls: None

Dosage/Dose Regimen: Multiple treatments may be administered in this study (between 1 and 7 treatments at 25 U, 50 U, or 100 U BOTOX). The first treatment will be administered on day 1 once all *day of treatment criteria* are fulfilled (see Section 5.9.1).

Request for retreatment can occur at scheduled clinic visits, scheduled telephone visits, or between scheduled visits. If the request is made at a scheduled clinic visit, then that visit will also become the qualification for retreatment visit, otherwise a qualification for retreatment clinic visit should be conducted within approximately 1 to 2 weeks of the patient/parent/legally authorized representative request.

The qualification for retreatment criteria are:
* patient/parent/legally authorized representative requests retreatment
* patient has a total of at least 1 daytime urinary incontinence episodes over the 2-day diary collection period
* at least 12 weeks have elapsed since the patient*s previous study treatment
* patient has not experienced a serious treatment-related adverse event at any time

Treatment will be administered within 4 weeks (28 days) after a patient qualifies for retreatment.
Retreatment(s) can be administered up to 96 weeks from randomization on day 1 and will only occur once all *day of treatment criteria* are fulfilled (see Section 5.9.1).

Treatment will be administered via cystoscopy (rigid or flexible cystoscope) as 20 intradetrusor injections of 0.5 mL each evenly distributed, sparing the trigone. Administration can be under local anesthesia (with or without sedation), or general anesthesia.

Visit Schedule: Patients will be evaluated during a screening period for eligibility. Eligible patients will be randomized and receive treatment on day 1. All patients will be evaluated at scheduled clinic visits at weeks 2, 6, and 12 posttreatment, and thereafter at alternating telephone and clinic visits every 6 weeks until the patient qualifies for further retreatment or exits the study. Patients can request retreatment from week 12 since the previous study treatment at scheduled clinic visits, telephone visits, or between scheduled visits. If the request is made at a scheduled clinic visit then this also becomes the qualification for retreatment visit, otherwise a qualification for retreatment clinic visit should be conducted within approximately 1 to 2 weeks of the patient/parent/legally authorized representative request. Once qualified

for retreatment, the same visit schedule will be followed as described above for the first retreatment. Patients exit once 96 weeks from entry into the study at day 1 has occurred, and at least 12 weeks follow-up since their last treatment has occurred (eg, if a patient receives retreatment at week 96, he/she would exit 108 weeks after day 1).

Intervention

Patients will initially be randomized on day 1 to one of 3 treatment groups in a 1:1:1 ratio:
* 25 U BOTOX (not to exceed 6 U/kg)
* 50 U BOTOX (not to exceed 6 U/kg)
* 100 U BOTOX (not to exceed 6 U/kg)

Patients will be centrally randomized and assigned a randomization number prior to treatment. In order to ensure balance across treatment groups, patients will be stratified by baseline daytime urinary urgency incontinence episodes (a total of * 6 episodes or > 6 episodes over the 2-day diary collection period).

Doses received at subsequent retreatments will be determined by the investigator and will be based upon the patient*s response to their previous treatment.

Study burden and risks

Patients may not receive any direct medical benefit from participating in this study. However their participation may help others with the same condition as a result of the knowledge gained from this research for future treatments. BOTOX® is currently licensed in the Netherlands for use in Overactive Bladder with adult patients, at a dose of 100 units (U). In this study patients will receive 25 U, 50 U or 100 U, with each individuals maximum dose capped at 6 U /kg.

The following risks and side effects have been associated with the study treatment, and are detailed in the Patient Information Sheet. There may also be side effects from the injection procedure, blood sampling and anaesthesia/pain relief:

Side Effects Due to BOTOX®
Side effects and discomforts associated with the study treatment that the patient could experience include the following events which have been observed with BOTOX® when used to treat conditions other than overactive bladder:
* temporary muscle weakness at the area of injection
* slight weakness in other nearby muscles
* flu-like symptoms such as muscle pain, chest discomfort, feeling of weakness or sickness, fever, sweating

* gastrointestinal symptoms such as abdominal pain, diarrhea, nausea and vomiting
* facial paresis (partial inability to move)
* skin rash
* blurred vision
* itching
* tingling or pricking sensation
* decreased sensitivity to touch
* difficulty breathing

Side Effects Due to BOTOX® for Overactive Bladder (OAB)
Side effects and discomforts that have been observed in patients who have received treatment with BOTOX® for their overactive bladder include:
* weakness of the bladder muscle resulting in difficulty in urination or an inability to urinate or empty his/her bladder (urinary retention) for some extended period of time (less than a month in most cases but could be longer)
* generalized weakness
* blood in the urine
* difficulty or painful urination
* urinary tract infection with sometimes the infection spreading to the blood (urosepsis)
* constipation

Unknown Side Effects
There may be side effects or discomforts from the study treatment which are not yet known.
Based on the results of experimental testing in animals, if a patient is pregnant or becomes pregnant during the study, there may be a risk of miscarriage or foetal malformations (birth defects). The effects of this medication on human pregnancies have not been studied which is why pregnancy tests are required throughout the study for menstruating girls.

Rare Risks or Discomfort
* In rare instances, side effects due to spread from the injection site have been reported hours to weeks after treatment with the botulinum toxin class of medications including BOTOX®. This may cause symptoms in areas of the body away from the site of injection including unexpected loss of strength or muscle weakness, hoarseness or trouble talking, trouble saying words clearly, loss of bladder control, difficulties with bowel movement, trouble breathing, trouble swallowing, double vision, blurred vision, and drooping eyelids. There have been rare reports of death, sometimes associated with difficulty swallowing, pneumonia, breathing, and/or other significant debility.
* Patients are advised to seek immediate medical care if they experience difficulty swallowing, breathing, or speaking.
* Patients with certain muscle-weakening neurological disorders (such as Lou Gehrig*s Disease / ALS, myasthenia gravis, Lambert-Eaton syndrome, or motor

neuropathy) can be extra-sensitive to the effects of this medication, and could develop problems such as severe difficulty with swallowing and/or breathing. In rare cases, these problems may last for several months and feeding tubes may be required.
* There have also been rare reports of heart problems (including abnormal heart rhythm and heart-attack, some with fatal outcomes) after treatment with this medication. However, it is not known if this medication actually caused these problems; some of these patients were already at risk for heart disease. Patients (especially those who are very ill) can develop such problems even without taking this medication.
* New onset or recurrent seizures have been reported, typically in patients who are predisposed to experiencing these events. The exact relationship of these events to the BOTOX® injection has not been established. The reports in children were predominantly from cerebral palsy patients treated for spasticity.
* A few cases of potentially life-threatening allergic reactions have been reported. However, it is unknown if this medication was the cause of those reactions; generally in these cases, the patient had been given another product that could have caused the allergic response.
* This medication contains albumin, which comes from human blood. Although the blood is rigorously tested, there is an extremely remote risk for the transmission of viruses and similar infectious agents.
* Although uncommon, patients receiving this medication may develop antibodies to it (an antibody is part of our body*s natural defense system). This could make later treatments with this medication ineffective.
* Based on the results of experimental testing in animals that were injected with the study medication into the prostate gland, there may be an increased risk of developing bladder stones.
* It is possible that in some patients who have a past history of certain gastrointestinal diseases that don*t allow food and secretions to empty normally from the stomach or intestine, that use of the study medication may sometimes cause the symptoms of the condition to occur again.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)

Inclusion criteria

* male or female, aged * 12 years to * 17 years of age at the time of informed consent;* patient has symptoms of OAB (frequency and urgency) with urinary incontinence for a period of at least 6 months immediately prior to screening, determined by patient history;* patient experiences a total of * 2 episodes of daytime urinary urgency incontinence in the 2-day patient bladder diary completed during the screening period (daytime is defined as time between waking up to start the day and going to bed to sleep for the night);* patient experiences urinary frequency, defined as an average of * 8 micturitions (toilet voids) per day, ie, a total of * 16 micturitions in the 2-day patient bladder diary completed during the screening period;* patient has not been adequately managed with 1 or more anticholinergic agents for the treatment of OAB in the opinion of the investigator, ie, all patients are incontinent despite anticholinergic therapy, experiencing intolerable side effects, or are unwilling to continue to take the medication for any reason;* patient is willing and able 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;* patient agrees to a minimum fluid intake of 1500 mL/m2 body surface area (BSA) per day, not to exceed 3000 mL/m2 BSA per day, during the patient bladder diary completion days at screening and prior to clinic visits during the study;* negative urine pregnancy test for females who are postmenarche

Exclusion criteria

1. patient has an uncontrolled systemic disease, previous or current diagnosis of malignancy;2. patient has symptoms of OAB due to any known neurological reason (eg, spina bifida, spinal cord injury, or cerebral palsy);3. patient has a history of 2 or more urinary tract

infections (UTIs) treated with antibiotics within 6 months of randomization/day 1 or is taking prophylactic antibiotics to prevent chronic UTI;4. patient has a history or evidence of any pelvic or urological abnormalities, except OAB, including:
o bladder neck surgery resulting in an open bladder neck, or reconstructive surgery of the lower urinary tract (eg, urostomy, urinary diversion, or bladder augmentation)
o anatomical evidence of bladder outlet obstruction (including functional outlet obstruction), urethral or urethral valve obstruction/stricture at screening
o surgery of the urinary tract (including minimally invasive surgery) within 6 months of screening (except those listed above which are exclusionary for any time period)
o circumcision within 1 month of screening
o clinically relevant kidney abnormality, or clinically relevant vesicoureteric reflux, or disease of the bladder (other than OAB) that may affect bladder function;5. patient has predominance of stress incontinence, or *giggle* incontinence, or any condition other than OAB that in the investigator*s opinion may account for the patient being incontinent;6. patient has unmanaged, unresolved bowel problems (eg, constipation, encopresis);7. patient currently uses or plans to use medications or therapies to treat symptons of OAB, including nocturnal enuresis or nocturia. Patients previously receiving these medications must have discontinued their use prior to the start of the first screening procedure as follows:
-for desmopressin, at least one day prior
-for anticholinergic therapy, at least 7 days prior
-for intravesical anticholinergic therapy, at least 4 weeks prior
-for mirabegron, at least 14 days prior;8. patient currently uses or plans to use an implantable or nonimplantable electrostimulation/ neuromodulation device for treatment of OAB. (If a nonimplantable device is used, it must be discontinued at least 7 days prior to the first screening procedure; if a device is implanted, it must be inactive for at least 4 weeks prior to the first screening procedure; neither should be used during the study.);9. patient plans to start using psychiatric medications or medications for attention deficit hyperactivity disorder during the study. If the patient is already using such medications they should be on a stable dose prior to randomization/day 1 and agree to remain on the same dose during the study if possible when medically indicated.;10. patient uses CIC or an indwelling catheter to manage their OAB;11. patient has had previous or current botulinum toxin therapy of any serotype for any urological condition, or treatment with botulinum toxin of any serotype within 3 months of randomization/ day 1 for any other condition or use;12. patient has been treated with intravesical capsaicin or resiniferatoxin within 12 months of screening ;13. patient has a post-void residual (PVR) urine volume of > 40 mL at screening. The PVR measurement can be repeated once on the same day; the patient is to be excluded if the repeated measure is above 40 mL.;14. patient has a daytime (waking hours) total volume of urine voided > 3000 mL, collected over one daytime period during the 2-day bladder diary collection period prior to randomization/
day 1;15. postmenarche female patients of childbearing potential who are pregnant, nursing, or planning to become pregnant during the study (postmenarche female patients must also either be sexually abstinent or use another acceptable form of contraception * see protocol section 4.5.1.1);16. patient has known allergy or sensitivity to components of any botulinum toxin preparation (including the study medication preparation), anesthetics or antibiotics to be used during the study;17. Patient has hemophilia, or other clotting factor deficiencies, or disorders that cause bleeding diathesis;18. Patient cannot withhold any antiplatelet, anticoagulant therapy, or other 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 judgement of the investigator;19. Patient has any medical condition that may put them at increased risk with exposure to BOTOX including diagnosed myasthenia gravis, Eaton-Lambert syndrome, or amyothrophic lateral slcerosis.;20. current enrollment in an investigational drug or device study, or participation in such a study within 30 days of entry into this study (or longer if local requirements specify).;21. patient has a condition or is in a situation that in the investigator*s opinion may put the patient at significant risk, may 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
Masking:	Double blinded (masking used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-05-2014
Enrollment:	15
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:	14-10-2014
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	01-06-2015
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	21-07-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	24-07-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2014-000464-17-NL
ClinicalTrials.gov	NCT02097121
CCMO	NL50232.091.14