A Pilot, Multicenter, Double-blind, Placebo-controlled, Dose-escalation Study of the Safety and Efficacy of AGN-214868 in Patients with Idiopathic Overactive Bladder and Urinary Incontinence

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

Summary

ID

NL-OMON38323

Source
ToetsingOnline

Brief title
TVEM-004 iOAB

Condition

- Bladder and bladder neck disorders (excl calculi)

Synonym
idiopathic overactive bladder and urinary incontinence

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Dose-escalation, iopathic Overactive Bladder, Micturition, Urinary incontinence

Outcome measures

Primary outcome

Safety measure: AGN-214868 has an acceptable safety profile in patients with

IOAB

Secondary outcome

Efficacy measure: AGN-214868 is more efficacious than placebo in reducing the

symptoms of IOAB

Study description

Background summary

Idiopathic overactive bladder (IOAB) is a common disease that increases in prevalence with age and is defined as *urgency, with or without urgency incontinence, usually with increased daytime frequency and nocturia*. The condition may have a significant impact on a patient*s quality of life and activities of daily living. In Europe, approximately 12.8% of women and 10.8% of men have reported symptoms of IOAB . First line medical treatment for IOAB (oral anticholinergic medications) are not effective in a significant proportion of patients; in addition side effects such as dry mouth are common, and many patients are not able to tolerate these medications. Other limitations include potential interactions with other medications, the requirement for continuous treatment (adherence issues), low therapeutic index, lack of disease modification, and small margin of efficacy over placebo.

In 2008, Allergan sponsored a retrospective claims review analysis to better

understand the natural history for IOAB-treated patients living in the US. Roughly 80% of patients discontinued oral therapy within 6 months, and of the patients that discontinued, 81% did so within 91 days of starting therapy and only 4% tried more than one OAB oral therapy. These data confirm that there is a significant unmet medical need for therapies with better patient compliance, lack of associated side effects, and improved safety profiles.

AGN 214868 is a novel recombinant fusion protein being developed as an injectable, locally acting treatment for IOAB, as well as for neuropathic pain. The mechanism of action of AGN 214868 is modulation of vesicular exocytosis, with at least a 1000-fold greater selectivity to sensory nerves versus motor axons . AGN-214868 exerts its effect by reducing or down-regulating the sensitization of the peripheral nerve ending directly, and therefore has an indirect reduction of central sensitization. IOAB is believed to be mediated, in part, by a sensitized response of the sensory afferent within the bladder. If IOAB is indeed generated and maintained through a sensory-driven etiology, then therapy with AGN-214868 should lead to a reduction of IOAB symptoms. In addition, due to this afferent selectivity, clinical impairment of bladder detrusor muscle function (with subsequent development of raised post void residual [PVR] urine volumes) should not occur. The purpose of this study is to evaluate the safety and efficacy of AGN-214868 in patients with IOAB.

Study objective

The objectives of this study are to evaluate the safety and efficacy of AGN-214868 compared with placebo in the treatment of patients with IOAB and urinary incontinence.
The clinical hypotheses for this study are:
• AGN-214868 has an acceptable safety profile in patients with IOAB
• AGN-214868 is more efficacious than placebo in reducing the symptoms of IOAB

Study design

This study is a multicenter, double-blind, randomized, 24-week, dose-escalation study to evaluate the efficacy and tolerability of AGN-214868 in patients with IOAB. The total duration of study participation for each patient is 24 weeks following randomization/day 1. Patients will attend the following 9 clinic visits: screening, randomization/day 1, day 2, week 1, week 2, week 6, week 12, week 18, and week 24.

Intervention

Treatment will be administered via cystoscopy as 20 injections each of 0.5 mL (total volume 10 mL); 17 injections will be into the detrusor, and 3 injections

will be placed into the trigone.

Study burden and risks

The risks involved in this study have been carefully assessed based on bladder injections in animal studies and skin injections in human studies with much higher doses than used in this study. Overall, the risks are considered to be acceptable although some risks are unforeseeable as this drug is still in an early stage in testing in humans. This means that there is a chance of minor side effects and a small chance of serious side effects happening.

In animal studies of AGN 214868, there have been no major safety concerns with single or multiple doses. This includes animal studies where the drug was injected directly into the bloodstream (intravenous dosing).

AGN 214868 is not yet available by prescription for use in humans. The clinical safety of AGN-214868 has been evaluated in 2 phase 1 clinical studies: 214868 001 and 214868-501. A total of 321 subjects were enrolled, with 263 receiving AGN 214868 across a wide dose range of 10 to 88,000 ng, and 58 subjects receiving placebo. In the current study (Study 214868-004), 69 patients have been treated, with 49 patients receiving AGN-214868 at either 500, 1000 or 2000ng total dose, and 20 patients receiving placebo. Study 214868-002 (PHN) has enrolled 294 patients to either AGN-214868 at 3250 or 16250ng total dose, or placebo in a 2:2:3 ratio. Study 214868-003 (an ongoing biocomparability study between 2 different formulations of AGN-214868) has dosed 77 healthy subjects at either 2200, 4400, 11000, or 22000ng total dose of AGN-214868.

Side effects and discomforts experienced by volunteers injected with AGN 214868 into the skin are mild redness and swelling around the sites of injection, symptoms of upper respiratory tract infections, headache, and mild/temporary increases in liver function blood tests. In these studies of healthy volunteers, elevation of liver function blood tests was noted in 8 of 263 (3%) of subjects indicating there might have been damage to the liver. It is not clear whether this finding is related to injection of AGN 214868. However, due to the timing of the elevations and the medical histories of the volunteers, none of the elevations were considered by the investigators to be related to the AGN 214868. The increases in LFTs were mild (except for the ones that were considered exercise related), and had no consistent time pattern in relationship to dosing, were not dose dependent, and were not associated with any other adverse events. In addition, independent, reviews of this ongoing trial in OAB (214868-004) and also the ongoing phase 2 trial in patients with post herpetic neuralgia (214868-002), have not demonstrated any issues with LFT elevations. Nonetheless, liver function tests will be monitored through the patients participation in the study.

There may be side effects or discomforts from the study treatment which are not yet known. As with all drugs there is a small chance of serious, potentially

life-threatening, immediate allergic or inflammatory reactions. The study drug is not expected to directly affect systems in the body that might produce such a response. Life-threatening allergic reactions have not been observed with AGN 214868 in any of the past or ongoing studies.

The patient may experience the side effects and discomforts listed for skin injections. However as the patient will be receiving the injection in the bladder, they may not have the same experience as those injected in the skin. There are no side effects and discomforts specifically expected with injection of AGN214868. There are some side effects and discomforts expected from the procedure of injecting into the bladder regardless of the medication. These may include:
- mild discomfort from insertion of the cystoscope into the bladder. Numbing gel may be used to lessen the discomfort;
- slight feeling of pressure in the bladder during the injections;
- temporary bleeding (for example: bleeding at the injection sites showing up as blood in the urine);
- temporary pain after the procedure (for example: pain in the urethra, abdomen or pelvis or pain when urinating), or feeling faint during or immediately after the procedure;
- urinary tract infections (UTIs);
- urinary tract trauma caused by the cytoscopy;
- inadvertent bladder wall puncture causing the study drug to be inserted into the abdominal space or nearby area
- reactions from the local anesthetic such as dizziness, nervousness, convulsions, low blood pressure, slow heart rate, or cardio-respiratory arrest.

Because the patient will stop taking any current medication for your IOAB at least 7 days before entering the study and continue without the medication for the duration of the study, there is a possibility that some symptoms that were controlled with the medications may return or even worsen.

The patients should be aware of the possible development of antibodies to AGN 214868. Antibodies are proteins that the body makes in response to unknown molecules, such as AGN 214868, entering your body. These antibodies are produced by the immune system to defend the body should the unknown molecule enter the body again. This may make AGN 214868 or similar products such as BOTOX® less effective if the patient receives them in the future.

To explore the safety and efficacy of an additional dose of intravesicle treatment with AGN 214868, this protocol has been amended to add 1 additional cohort (Cohort 7). This cohort will introduce a total bladder dose of 60000ng. Phase 1 studies with intradermal injections have assessed total doses up to 88000ng with no dose limiting toxicity seen.

In addition, there has been an acceptable safety profile in the current study, as determined by ongoing independent Data Review Committee (DRC) review of the

unblinded safety, efficacy, pharmacokinetic and antibody data. The DRC has reviewed cumulative data from all patients treated in Cohorts 1 to 5 and some of the patients treated in Cohort 6; with patients receiving up to the maximum planned study dose of 18000ng. The DRC has recommended that it is acceptable to amend the protocol for doses greater than 18000ng to be assessed in this proof of concept study, for the purpose of determining a safe and efficacious dose range for further clinical development. Further DRC review (with cumulative data from all patients from Cohort 6 and earlier) will occur prior to escalating to the 60000ng dose.

There may be pain associated from the needle prick during the collection of blood samples and a slight risk of bruising or inflammation of the vein. This normally clears up with no further trouble. Some patients may also feel faint when the blood is collected.

The patients may experience slight skin irritation when the ECG adhesive pads are removed.

In addition, if female patients are pregnant or become pregnant, there may be a risk to the fetus. Therefore, it is important that only women who are unable to bear a child participate in the study.

The patient might have side effects or discomforts that are not listed in this form. Some side effects may not be known yet. New ones could happen, therefore patients are encouraged to tell the study doctor or study staff right away if they have any problems.

Contacts

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Scientific
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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
2. Written Authorization for Use and Release of Health and Research Study Information (US sites only)
3. Written documentation in accordance with the relevant country and local privacy requirements, where applicable
4. Male or female 18 to 75 years of age
5. If female, must be of nonreproductive potential
6. If male, must agree to use acceptable contraception
7. Symptoms of IOAB (urgency, with or without urgency incontinence, usually with increased daytime frequency and nocturia) for at least 6 months prior to screening
8. Not adequately managed with 1 or more anticholinergic agents for the treatment of their OAB symptoms, in the opinion of the investigator, defined as:
* an inadequate response after at least a 4-week period of anticholinergic therapy on an optimized dose(s)
or
* rate-limiting side effects after at least a 2-week period of anticholinergic therapy on an optimized dose(s)
(an optimized dose is an approved dose for the indication of OAB)
9. A mean of >= 8 micturitions per day during the screening 3-day bladder diary assessment (ie, >= 24 micturitions during this screening 3-day bladder diary assessment)
10. A mean of >= 2 urgency episodes per day during the screening 3-day bladder diary assessment (ie, >= 6 urgency episodes during the screening 3-day bladder diary assessment)
11. One or more urinary urgency incontinence episodes during the screening 3-day bladder diary assessment
12. Not taken anticholinergic medication or any other medications or therapies to treat lower urinary tract symptoms (including nocturia) in the 7 days prior to the start of any screening procedures (medication washout instructions in Section 8.2)

13. A negative urine dipstick reagent strip test (for leukocyte esterase and/or nitrites) and, in the investigator*s opinion, asymptomatic for urinary tract infection (UTI) on the day of study treatment
14. Commenced prophylactic antibiotics within 24 hours of study treatment
15. Willing to use clean intermittent catheterization (CIC) to empty the bladder after study treatment if determined to be necessary by the investigator
16. The ability to follow study instructions, complete all required visits, and be willing and able to complete study assessment tools (e.g. questionnaires, bladder diary) without any assistance or alteration to the assessment tools.

Exclusion criteria

1. Symptoms of OAB due to any known neurological reason (eg, spinal cord injury, multiple sclerosis, cerebrovascular accident, Alzheimer*s disease, Parkinson*s disease, etc)
2. A predominance of stress incontinence, in the opinion of the investigator
3. A history or evidence of any pelvic or urological abnormalities, bladder surgery, or disease (other than *idiopathic overactive bladder*) that may affect bladder function, including but not limited to:
* Surgery (including minimally invasive surgery, such as tape procedures) within 1 year of screening for stress incontinence, uterine prolapse, rectocele, or cystocele
* Male with prostate disorders (eg, benign prostatic hyperplasia [BPH], bladder outlet obstruction (BOO), or any previous surgery for BPH or BOO)
* Male with previous or current diagnosis of prostate cancer or a prostate-specific antigen (PSA) level of > 10 ng/mL; patients with a PSA of >= 4 ng/mL but <= 10 ng/mL must have prostate cancer ruled out to the satisfaction of the investigator according to local site practice prior to enrolment in the study
* History or suspicion of interstitial cystitis/painful bladder syndrome, in the opinion of the investigator
* A previous 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; the result of the investigation is to be recorded in the source documents)
* History of >= 2 UTIs within 6 months of randomization/day 1
* History or evidence of urethral obstruction/stricture, in the opinion of the investigator, that would prevent cystoscopic administration of study medication
4. Current or previous uninvestigated hematuria. A patient with investigated hematuria may enter the study if urological/renal pathology has been ruled out to the satisfaction of the investigator.
5. Evidence of bladder stones on abdominal kidney/bladder ultrasound
6. Evidence of symptomatic kidney stones or kidney stones requiring an intervention

7. Use of CIC or an indwelling catheter
8. Has had urinary retention or an elevated PVR urine volume that was not procedurally-related (e.g. following urethral instrumentation), and has been treated with an intervention (such as catheterization) within 6 months of screening.
9. A PVR urine volume of > 100 mL at screening (the PVR measurement can be immediately repeated; if the repeat PVR remains > 100 mL, then the patient is to be excluded)
10. A 24-hour total volume of urine voided > 3000 mL, collected over 24 consecutive hours during the screening 3-day patient bladder diary
11. Treatment with any intravesical pharmacologic agent (eg, capsaicin, resiniferatoxin) within 12 months of screening
12. Current or planned use of an electrostimulation/neuromodulation device (implanted or external) for the treatment of lower urinary tract symptoms and urinary incontinence (if a device is implanted, it must be inactive 4 weeks prior to randomization/day 1 and for the duration of the study).
13. Previous or current botulinum toxin therapy of any serotype for any urological condition or previous immunization for botulinum toxin of any serotype.
14. Treatment with botulinum toxin therapy for any nonurological condition (eg, cosmetic) within 12 weeks of the day of treatment
15. A screening creatinine level >= 2.0 times the ULN
16. History or evidence of active liver disease
17. Screening liver function tests (ALT, AST, GGT, and bilirubin) > 1.5 times the ULN
18. A current or past history, in the opinion of the investigator, of excessive alcohol use
19. History of human immunodeficiency virus (HIV) infection
20. A confirmed positive serology result at screening for the presence of hepatitis B surface antigen or hepatitis C antibodies
21. Any uncontrolled systemic disease
22. Unable to discontinue any medications with anti-platelet or anti-coagulant effects, including aspirin (acetylsalicylic acid) for a minimum of 3 days (or longer according to clinical judgment of the investigator) prior to randomization/day 1
23. Hemophilia or other clotting factor deficiencies or disorders that may cause excessive bleeding
24. Known allergy or sensitivity to any of the components of the study medication, anesthetics, sedatives, or prophylactic antibiotics to be used during the study
25. Current enrollment in an investigational drug or device study or participation in such a study within 30 days of entry into this study
26. A condition or 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:	2
Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	30-05-2011
Enrollment:	4
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Endopedase AGN214868
Generic name:	NVT

Ethics review

Approved WMO Date:	05-11-2010
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-03-2011
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-07-2011
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-10-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-11-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-12-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-07-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-08-2012
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
Other	CCMO - NL33838.029.10.
EudraCT	EUCTR2010-021718-41-NL
CCMO	NL33838.029.10