2. Synopsis

Name of Sponsor: Allergan, Inc.

Name of Finished Product: AGN-214868

Name of Active Ingredient: [redacted]

Number and Title of Study: 214868-004
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

Coordinating Investigator: [redacted]

Study Centers: The study was conducted at a total of 22 sites; 15 in the US, 6 sites in France, and 1 site in the Netherlands

Study Period:
Study Initiation Date (First Patient Enrolled): 12 October 2010
Study Completion Date (Last Patient Completed): 03 May 2013

Phase of Development: 2a

Publications: None

Objectives:
To evaluate the safety and efficacy of AGN-214868 compared with placebo in the treatment of patients with idiopathic overactive bladder (IOAB) and urinary incontinence

Methodology:
This was a pilot, multicenter, double-blind, randomized, placebo-controlled, dose-escalation study to evaluate the efficacy and safety of AGN-214868 in patients with IOAB. On day 1 (randomization), patients were randomized to receive treatment with either AGN-214868 or placebo. Each patient received a single administration of study medication on day 1. Follow-up visits were at day 2, and weeks 1, 2, 6, 12, 18, and 24. The total duration of study participation for each patient was 24 weeks following randomization/day 1.

Randomization was specific to each cohort and based on the dose escalation scheme in the table below:

Cohort	Dose (ng) per Injection Site	Total Dose (ng)	Planned Number of Patients
1	25	500	12
	0 (placebo)	0 (placebo)	12
2	50	1000	12
	25	500	6
	0 (placebo)	0 (placebo)	6
3	100	2000	12
	50	1000	6
	25	500	3
	0 (placebo)	0 (placebo)	3
4	100	2000	12
	50	1000	6
	25	500	3
	0 (placebo)	0 (placebo)	3
5	300	6000	10
	100	2000	2
	0 (placebo)	0 (placebo)	2
6	900	18,000	16
	300	6000	4
	0 (placebo)	0 (placebo)	2
7	3000	60,000	18
	900	18,000	4
	0 (placebo)	0 (placebo)	2

Number of Patients (Planned and Enrolled):
Approximately 156 patients were planned to be enrolled at approximately 30 centers. A total of 160 patients were enrolled at 22 centers of which 157 patients were randomized and treated; 156 were included in the safety population; and 154 were included in the modified intent-to-treat (mITT) population. Of the 154 randomized patients included in the mITT population, 19 received 60,000 ng AGN-214868, 19 received 18,000 ng AGN-214868, 15 received 6000 ng AGN-214868, 27 received 2000 ng AGN-214868, 23 received 1000 ng AGN-214868, 22 received 500 ng AGN-214868, and 29 received placebo. Two patients were randomized to treatment, but had missing postbaseline micturition data and were therefore not included in the mITT population. Three patients were randomized, but did not receive study medication and one patient was randomized, but received a study medication dose that was not specified in the protocol (ie, 24,000 ng AGN-214868). Therefore, these patients were not included in the safety and mITT population.

Diagnosis and Main Criteria for Eligibility:

Key Inclusion Criteria

- male or female, 18 to 75 years of age
- IOAB with urinary incontinence
- patient not adequately managed with previous anticholinergic agents
- ≥ 24 micturitions during 3-day bladder diary
- ≥ 6 urgency episodes during 3-day bladder diary
- ≥ 1 urinary incontinence episode during 3-day bladder diary

- if female, of nonreproductive potential
- if male, willing to use a double-barrier method of contraception during sexual intercourse with partners of reproductive potential or abstain from intercourse

Key Exclusion Criteria

- neurogenic overactive bladder
- a predominance of stress incontinence
- previous botulinum toxin therapy of any serotype for any urologic condition
- post-void residual (PVR) urine volume of > 100 mL
- history or evidence of any condition, other than overactive bladder, that may affect bladder function or may put the patient at risk or interfere with the integrity of the data

Test Product, Dose and Mode of Administration, Batch Number: AGN-214868 administered via cystoscopy as 20 intradetrusor injections each of 0.5 mL (17 into the detrusor and 3 into the trigone, while avoiding the dome); 5-µg vial, or 20-µg vial,

Reference Therapy, Dose and Mode of Administration, Batch Number: AGN-214868 vehicle placebo, administered via cystoscopy as 20 intradetrusor injections each of 0.5 mL (17 into the detrusor and 3 into the trigone, while avoiding the dome);

Duration of Treatment: Single treatment administration on day 1 comprising 20 injections of AGN-214868 (or placebo), each of 0.5 mL; the total study duration per patient was 24 weeks posttreatment

Efficacy and Safety Measurements:

Primary Efficacy Measurement: the primary efficacy measure was the number of micturition episodes as captured by the 3-day bladder diary. No secondary efficacy measures were evaluated during the study.

Other Efficacy Measurements:

- number of urinary incontinence episodes
- number of urgency episodes
- intensity of urgency
- number of nocturia episodes
- volume voided per micturition
- Treatment Benefit Scale (TBS)
- the International Consultation on Incontinence Questionnaire – Overactive Bladder (ICIQ-OAB)
- urodynamic parameters

Safety Measurements: adverse events, physical examinations, vital signs, pregnancy testing, urine dipstick reagent test, central laboratory urine analysis, urine cytology, hematology and serum chemistry, kidney and bladder

ultrasound, PVR urine volume measurement, 12-lead electrocardiogram (ECG), and blood samples for pharmacokinetic assessment and immunogenicity analysis

Statistical Methods

Analysis Populations: Three populations were used in the analyses: mITT, per protocol (PP), and safety; the mITT population was considered the primary analysis population for the efficacy analyses. All efficacy and health outcome analyses were performed on the mITT population and included all randomized patients who received treatment and had both baseline and postbaseline measurements for the primary efficacy variable (ie, micturition episodes). All analyses were performed with patients analyzed by the actual treatment received. The PP population included randomized patients with no significant protocol deviation that affected the primary efficacy variable at the primary timepoint (week 12). Sensitivity analysis of the primary efficacy variable and other efficacy variables collected from the patient diary and pharmacokinetic analyses were also performed on the PP population. Safety and immunogenicity analyses were based on the safety population, which consisted of all patients who received study medication. All safety and immunogenicity analyses were performed with patients analyzed by their actual treatment received.

Efficacy Analyses: All hypotheses testing were 2-tailed with a significance level of 0.05. Pairwise comparisons were made for each AGN-214868 dose versus placebo and within each AGN-214868 dose. No multiplicity adjustments were made.

The primary efficacy variable was the change from baseline in the number of micturition episodes at week 12 with study baseline value defined as the number of micturition episodes recorded on the 3-day bladder diary prior to the treatment. The primary efficacy variable was analyzed by using a linear regression approach to assess the relationship of response across the AGN-214868 dose levels at week 12. A dose-response relationship was evaluated by testing the slope of the regression line. In the analysis, the cohort was included in the regression model and treated as a random effect. Comparisons of the AGN-214868 and placebo groups at week 12 were also made using analysis of covariance with baseline as a covariate and treatment as a factor.

Sensitivity analysis of the primary efficacy variable was performed using the PP population.

Other efficacy variables (eg, other measures assessed from the 3-day patient bladder diary, and urodynamic assessment) were analyzed using the methods described for the primary efficacy variable.

For the health outcome measure TBS, proportion of TBS responders between each AGN-214868 group and placebo group were compared using a Pearson's chi-square or Fisher's exact test. For ICIQ-OAB, the difference in the change from baseline scores between each AGN-214868 group and the placebo group were analyzed using the mixed-effects model with treatment group as a factor and fixed effect, baseline score as fixed effect and cohort as random effect. For all health outcome analyses, missing data were imputed up to week 24 using the last observation carried forward (LOCF); however, if patients did not have TBS or ICIQ-OAB data at all visits starting from week 12, LOCF was only applied up to and including week 12.

Safety Analyses: Safety data were summarized by descriptive statistical methods and/or frequency tables and analyzed by appropriate nonparametric statistical methods (ie, Pearson's chi-square test, Wilcoxon rank sum test, Fisher's exact test) and/or parametric tests (ie, analysis of variance [ANOVA]). The safety analyses were based on the safety population.

Immunogenicity Analyses: The number and percent of patients with AGN-214868 binding antibodies were summarized by treatment group at each visit. Similar analysis was done for AGN-214868 neutralizing antibody results (if applicable), nociception variant ligand binding antibodies, and binding antibody titers. No imputations were utilized for missing values or for patients who withdrew prior to completing the study.

Pharmacokinetic Analyses: The plasma AGN-214868 concentrations were summarized for each dose using descriptive statistics. Pharmacokinetic analysis AGN-214868 plasma concentrations were calculated using noncompartmental analysis.

Summary of Results

Patient Disposition and Demographics: A total of 156 patients were included in the safety population and 154 patients were included in the mITT populations (19, 19, 15, 27, 23, 22, and 29 in the 60,000 ng, 18,000 ng, 6000 ng, 2000 ng, 1000 ng, 500 ng, and placebo groups, respectively); 142/154 (92.2%) patients completed the study. "Other" was the most common reason for discontinuation overall. No patient discontinued the study due to an adverse event. The treatment groups were generally similar in demographic and baseline disease characteristics. The mean age was 59.6 years (range 31 to 76 years), and the majority of patients were Caucasian (77.3%) and female (92.2%).

Efficacy:

- The primary efficacy endpoint (change from baseline in the daily average number of micturition episodes at week 12) was not met for any AGN-214868 group (60,000 ng to 500 ng).
    - Although greater numerical improvements from baseline were observed in the 60,000-ng and 500-ng groups compared with the placebo group at week 12 (-2.7 and -2.6 episodes versus -1.9 episodes, respectively), these differences were not statistically significant. At week 24, this difference was no longer observed between the 60,000 ng and placebo groups only.
    - No statistically significant differences were observed between the AGN-214868 and placebo groups at any timepoint.
    - No dose-response trend was observed for efficacy between the AGN-214868 groups at any timepoint.
- Results were generally similar between the treatment groups for other efficacy analyses (ie, number of urinary incontinence episodes, urgency episodes, and nocturia episodes; voided volume per micturition; intensity of urgency; and urodynamic procedures) at all timepoints and no apparent dose-response was observed.
    - No statistically significant improvements from baseline were observed between the AGN-214868 and the placebo groups at week 12 or any other timepoint for other efficacy analyses, except for voided volume during the urodynamic procedure at week 6 favoring the 6000-ng group compared with the placebo group (70.9 mL versus 4.7 mL, respectively; $p = 0.038$). However, this difference was not considered clinically meaningful because of the large standard deviation in the data.
- Improvements in the health outcome measures, TBS and ICIQ-OAB, were similar between the treatment groups (including placebo) and no statistically significant differences were observed at any timepoint.

- Any improvements in efficacy were observed in all treatment groups, suggesting a marked placebo response in all overactive bladder (OAB) symptoms and on the health outcome measures.
- The results in the PP population (N = 130) were similar to that observed in the mITT population (N = 154).

Safety:

- A single administration of AGN-214868 ranging from 60,000 ng to 500 ng into the detrusor walls of the bladder were found to be safe and well tolerated compared to placebo in adult patients with IOAB.
- A total of 74.3% (116/156) of patient in the safety population had 1 or more adverse event reported during the study: 73.7% (14/19), 75.0% (15/20), 66.7% (10/15), 77.8% (21/27), 60.9% (14/23), and 82.6% (19/23) in the 60,000-ng, 18,000-ng, 6000-ng, 2000-ng, 1000-ng, and 500-ng AGN-214868 groups, respectively, and 79.3% (23/29) in the placebo group.
    - The incidence of adverse events was comparable between the AGN-214868 and placebo groups and did not increase with increasing dose.
- Dysuria was the most frequently reported adverse event among the treatment groups (15.4% [24/156]) of patients): 15.8% (3/19), 15.0% (3/20), 6.7% (1/15), 14.8% (4/27), 21.7% (5/23), and 26.1% (6/23) in the 60,000-ng, 18,000-ng, 6000-ng, 2000-ng, 1000-ng, and 500-ng AGN-214868 groups, respectively, and 6.9% (2/29) in the placebo group.
    - The incidence of dysuria did not increase with increasing dose.
    - Haematuria was the second most frequently reported adverse event (13.5% [21/156] of patients): 10.5% (2/19), 20.0% (4/20), 13.3% (2/15), 18.5% (5/27), 8.7% (2/23), and 4.3% (1/23) in the 60,000-ng, 18,000-ng, 6000-ng, 2000-ng, 1000-ng, and 500-ng AGN-214868 groups, respectively, and 17.3% (5/29) in the placebo group.
- The majority of adverse events were mild to moderate in severity.
    - One or more severe adverse event was reported in 11/156 (7.0%) patients overall: 3 in the 18,000-ng group, 3 in the 2000-ng group, 4 in the 500-ng group, and 1 in the placebo group.
- Overall, 39.1% (61/156) of patients experienced a treatment-related adverse events (ie, study medication or injection procedure): 42.1% (8/19), 35.0% (7/20), 40.0% (6/15), 33.3% (9/27), 26.1% (6/23), and 56.5% (13/23) of patients in the 60,000-ng, 18,000-ng, 6000-ng, 2000-ng, 1000-ng, and 500-ng AGN-214868 groups, respectively, and 41.4% (12/29) of patients in the placebo group. Treatment-related adverse events were higher in the 500-ng group compared with placebo and the other AGN-214868 groups.
    - Dysuria and haematuria were the most frequently reported treatment-related adverse events (overall: 12.8% [20/156] and 12.2% [19/156], respectively).
    - Higher proportions of patients in the 500-ng group compared with the other AGN-214868 and placebo groups experienced treatment-related dysuria.
        - 15.8% (3/19), 15.0% (3/20), 6.7% (1/15), 11.1% (3/27), 13.0% (3/23), and 21.7% (5/23) of patients in the 60,000-ng, 18,000-ng, 6000-ng, 2000-ng, 1000-ng, and 500-ng AGN-214868 groups, respectively, and 6.9% (2/29) of patients in the placebo group

  - Higher proportions of patients in the 60,000-ng, 18,000-ng, 6000-ng, 2000-ng, and placebo groups compared with the 1000-ng and 500-ng groups experienced treatment-related haematuria.
    - 10.5% (2/19), 15.0% (3/20), 13.3% (2/15), 18.5% (5/27), 8.7% (2/23), and 0.0% (0/23) of patients in the 60,000-ng, 18,000-ng, 6000-ng, 2000-ng, 1000-ng, and 500-ng AGN-214868 groups, respectively, and 17.2% (5/29) of patients in the placebo group
  - The incidence of adverse events considered by the investigator to be related to the study medication was higher in the 500-ng group (39.1%) compared with the placebo (13.8%) and other AGN-214868 groups (10.5% to 17.4%).
    - The most frequently reported study medication-related adverse event was dysuria (7/156 [4.5%] patients overall; 2 each in the 18,000-ng and 500-ng groups and 1 each in the 2000-ng, 10000-ng, and placebo groups).
  - The incidence of adverse events considered by the investigator to be related to the injection procedure was lower in the 1000-ng group (21.7%) compared with the placebo (41.4%) and other AGN-214868 groups (29.6% to 43.5%).
    - The most frequently reported injection procedure-related adverse events were dysuria and haematuria (overall: 20/156 [12.8%] and 19/156 [12.2%] patients, respectively).

- Urinary tract infection adverse events were low and reported in 16/156 (10.2%) patients overall: 2/19 (10.5%), 4/20 (20.0%), 0/15 (0.0%), 3/27 (11.1%), 2/23 (8.7%), and 2/23 (8.7%) in the 60,000-ng, 18,000-ng, 6000-ng, 2000-ng, 1000-ng, and 500-ng AGN-214868 groups, respectively, and 3/29 (10.3) in the placebo group.
  - No patient experienced urinary retention or residual urine during the study.
- One or more serious adverse event was reported in 7.0% (11/156) of patients during the study: pulmonary oedema (1 patient, 18,000 ng); atrioventricular block complete, device related infection, device malfunction, and cardiac failure congestive (1 patient, 18,000 ng); ureteric stenosis (1 patient, 18,000 ng); uterine cancer (1 patient, 6000 ng); arthralgia (1 patient, 2000 ng); basal cell carcinoma (2 patients, 2000 ng and 1000 ng); osteoarthritis (1 patient, 2000 ng); intevertebral disc degeneration (1 patient, 500 ng); breast mass (1 patient, 500 ng); and arthritis (1 patient, placebo).
  - No patient in the 60,000-ng group had a serious adverse event and none of the serious adverse events reported was consider to be related to the study medication or the injection procedure.
- There were no clinically meaningful changes from baseline between the treatment groups in clinical laboratory tests, vital signs, physical examination abnormalities, or PVR urine.
- Few patients (≤ 3 patients) had an abnormal bladder ultrasound finding at any timepoint during the study. More patients had an abnormal kidney ultrasound finding between screening and week 24 (ie, 32 to 40 patients overall at screening, week 12, and week 24).
  - No patient had abnormal bladder ultrasound findings that were reported as adverse events. Abnormal kidney ultrasound findings were reported as adverse events in 12 patients:
    - nephrolithiasis in 3 patients: 1 in the 500-ng and 2 in the placebo groups
    - hydronephrosis in 2 patients: 1 in the 18,000-ng and 1 in the 2000-ng groups

  - renal cyst in 7 patients: 2 in the 2000-ng, 4 in the 1000-ng, and 1 in the placebo groups

- Abnormal, clinically significant ECG findings were reported by the investigator in only 4 patients during the study (1 patient in the 18,000-ng, 2 patients in the 6000-ng, and 1 patient in the placebo groups).
- No deaths, discontinuations due to adverse event, or pregnancies were reported during the study.
- Overall, the antibody response following single intrabladder wall administration of AGN-214868 was low.
  - Binding antibodies to AGN 214868 were detected in 18.9% (24/127) of patients.
  - Binding antibodies towards the nociceptin variant domain of AGN-214868 were detected in only 1 patient (18,000 ng) and neutralizing antibodies against AGN-214868 were detected in 1 patient (60,000 ng).
- Systemic exposure, as measured by C_{max} and $AUC_{0\text{-}last}$, increased with AGN-214868 dose (ie, 2000 ng to 60,000 ng).
  - The highest C_{max} and $AUC_{0\text{-}last}$ values ± standard deviation were observed in the 60,000-ng group: 649 ± 582 pg/mL and 9488 ± 6917 pg•hr/mL, respectively.

Conclusions

The overall results of this study demonstrate that a single administration of AGN-214868 at doses ranging from 60,000 ng to 500 ng into the detrusor walls of the bladder is safe and well tolerated in adults with IOAB. Although greater numerical improvements from baseline were observed only for the primary efficacy variable (ie, number of micturition episodes) in the 60,000-ng and 500-ng groups compared with the placebo group at week 12 (primary timepoint), these differences were not statistically significant. At week 24, this difference was no longer observed between the 60,000-ng and placebo groups. In addition, no dose-response among the AGN-214868 groups for efficacy was observed at any timepoint.

Similar results were also observed between the AGN-214868 and placebo groups for other efficacy variables (ie, number of urinary incontinence episodes, urgency episodes, and nocturia episodes; voided volume per micturition; intensity of urgency; and urodynamic procedures) at all timepoints, and no apparent dose-response was observed. Furthermore, there was a marked placebo response in all OAB symptoms, the TBS, and the ICIQ-OAB. Based on results from this study, further development of AGN-214868 in IOAB is not planned.