2. Synopsis

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Title of study: A randomized, multi-center, double-blind, placebo- and active-controlled, 5-way, parallel group study to investigate the efficacy, safety and tolerability of ONO-8539 in subjects with overactive bladder

Study centers: This was a multicenter study conducted at 64 centers (who enrolled subjects) in 9 countries

Publication(s) (reference: None

Studied period : **Phase of development:** 2
The clinical phase of the study was performed from 14 May 2009 until 25 May 2010

Objectives:
The primary objective was to compare the effect of 3 different doses of ONO-8539 (30-mg twice daily [BID], 100-mg BID, and 300-mg BID) with placebo on the mean change in the number of micturitions per 24 hours from Baseline to 12 weeks (last observation carried forward [(LOCF]).

The secondary objectives of this study were as follows:

- To compare the effect of 3 different doses of ONO-8539 and tolterodine versus placebo on the number of micturitions per 24 hours, number of urinary urgency incontinence (UUI) episodes per 24 hours, number of urgency episodes per 24 hours, severity of urgency, mean volume voided per micturition, number of micturitions during daytime, number of micturitions during sleeping time, and number of continent days (among incontinent subjects) during the course of treatment
- To compare the effect of 3 different doses of ONO-8539 and tolterodine versus placebo on subjective scales of treatment effect and quality-of-life during the course of treatment
- To compare the safety and tolerability of 3 different doses of ONO-8539 and tolterodine versus placebo

The exploratory objectives of this study were as follows:

- To investigate the plasma concentrations of ONO-8539
- To investigate the association between the changes in efficacy parameters of ONO-8539 and the plasma concentrations of ONO-8539
- To investigate the concentration of prostaglandin E_2 (PGE_2) in urine
- To undertake subgroup analyses using appropriate clinical and biological factors

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Methodology:

This was a randomized, double-blind, placebo- and active-controlled, 5-way parallel group Phase 2 study to investigate the efficacy of ONO-8539 in at least 400 adult male and female subjects with overactive bladder (OAB). Subjects were scheduled to make 7 visits to the study center over 16 weeks; a screening visit, a randomization visit, 4 treatment visits, and a follow-up visit.

Subjects attended a screening visit up to 3 weeks before Visit 1 (Week 0) for the informed consent process, a check of inclusion and exclusion criteria, and training on study procedures.

Subjects completed a bladder diary for 3 consecutive days immediately before each study visit except Visit 6 (Week 14)/Follow-up.

Eligible subjects entered a 2-week single-blind, placebo run-in study phase after which they attended a randomization visit (Visit 1; Week 0) when they had their bladder diary reviewed and assessed for urinary symptoms. They gave samples for clinical laboratory tests, including a pregnancy test (if applicable) and drugs of abuse screen, had a 12-lead electrocardiogram (ECG), and had systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate, an ultrasound to measure postvoid residual (PVR) volume, and uroflow (as the maximum flow rate [Q_{max}]) measured, as applicable.

Subjects still eligible for the study entered the double-blind treatment phase and were randomly assigned to receive 12 weeks of study drug (1 of 3 ONO-8539 doses [30-mg BID, 100-mg BID, or 300-mg BID] or tolterodine 4-mg once daily [OD], or matching placebo). After receiving their treatment assignment, subjects underwent laboratory safety tests, gave a urine sample to measure PGE_2 concentration, and received a 12-lead ECG. They completed the subjective scales (treatment benefit scale [TBS], patient perception of bladder condition [PPBC], and the International Consultation on Incontinence Questionnaire - relating to OAB symptoms [ICIQ-OAB]) and the quality-of-life King's Health Questionnaire. They also received a new bladder diary and compliance diary.

At Visit 2 (Week 2) before study drug administration, blood samples were taken to measure plasma ONO-8539 concentration and SBP, DBP, and pulse rate were measured. Following study drug administration, subjects had their bladder and compliance diaries reviewed and also had concomitant medication and adverse events (AEs) assessed following study drug administration.

At Visit 3 (Week 4) before study drug administration, blood samples were taken to measure plasma ONO-8539

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concentration and laboratory safety tests, and subjects gave a urine sample for urinalysis, had a 12-lead ECG, and had SBP, DBP, pulse rate, and ultrasound PVR volume measured. Following study drug administration, subjects had their bladder and compliance diaries reviewed and returned their study drug. Concomitant medication and AEs were assessed.

At Visit 4 (Week 8) before study drug administration, blood samples were taken to measure plasma ONO-8539 concentration and laboratory safety tests, and subjects gave a urine sample for urinalysis, and had SBP, DBP, pulse rate and ultrasound PVR volume measured. Following study drug administration, subjects had their bladder and compliance diaries reviewed and also returned study drug. Concomitant medication and AEs were assessed.

At Visit 5 (Week 12), blood samples were taken to measure plasma ONO-8539 concentration and for laboratory safety tests. Subjects gave urine samples for urinalysis, PGE_2 concentration, and, if applicable, for a pregnancy test, had SBP, DBP, pulse rate, ultrasound PVR volume, and uroflow (Q_{max}) measured, had their bladder and compliance diaries reviewed, had concomitant medication and AEs assessed, returned study drug, completed a quality-of-life King's Health Questionnaire and subjective scales, and had a physical examination.

At Visit 6 (Week 14), the follow-up visit, blood samples were taken for clinical laboratory tests, and subjects gave a urine sample for urinalysis, had concomitant medication and AEs assessed and had a physical examination. Investigators then discharged subjects from the study but followed up any ongoing AEs until they were resolved or until there was a reasonable explanation for their persistence.

Number of subjects (planned and analyzed): It was planned to randomly assign at least 400 subjects to treatment. There were 434, 435, 415, and 348, subjects included in the safety population, (SP), randomized set, full analysis set (FAS), and per protocol set (PPS), respectively. The SP was presented by received treatment but the other analysis sets were presented by randomized treatment.

Analysis Set	Total	Placebo	ONO-8539 BID			Tolterodine
			30 mg	100 mg	300 mg	4 mg OD
Randomized set	435	85	88	87	88	87
SP	434	85	88	86	87	88
FAS	415	80	87	83	82	83
PPS	348	64	73	71	69	71

Abbreviations: BID, twice daily; OD, once daily; FAS, full-analysis set; PPS, per-protocol set; SP, safety population

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Diagnosis and main criteria for inclusion: Males and nonpregnant and nonbreastfeeding females aged 18 to 80 years were eligible for this study if they had OAB defined by the standardization subcommittee of the International Continence Society as urgency, with or without UUI, usually with frequency and nocturia, in the absence of local pathological or metabolic factors for at least 6 months.

Test product, dose and mode of administration, batch number(s):

Test Product	Dose and Mode of Administration	Batch Number
ONO-8539	30 mg BID oral tablets (administered as 10-mg tablets)	J7Y1 and J951
ONO-8539	100 mg BID oral tablets (administered as 50-mg tablets)	J7Y2, J7Y3, J7Z2, and J7Z1
ONO-8539	300 mg BID oral tablets (administered as 50-mg tablets)	J7Y2, J7Y3, J7Z2, and J7Z1

Duration of treatment: Subjects received randomized study drug for 12 weeks, preceded by placebo for 2 weeks during the 2-week run-in phase.

Reference therapy, dose and mode of administration, batch number(s):

Reference Product	Dose and Mode of Administration	Batch Number
Tolterodine (Detrusitol® XL)	4 mg OD (4-mg oral capsules)	0800899A and 0805512B
Placebo	Matching tablets and capsules	Not Applicable

Criteria for evaluation:

Efficacy

The bladder diary was used to collect number of micturitions, urgency episodes, UUI episodes, incontinence episodes, urinary events during the day and during sleeping time, and urine volume for 3 days for each visit, to calculate the following parameters:

- Number of micturitions per 24 hours
- Number of UUI episodes per 24 hours
- Number of urgency episodes (Patient Perception of Intensity of Urgency Scale [PPIUS] Grade 3 and 4) per 24 hours
- Most frequent severity of urinary urgency
- Number of continent days per week
- Number of incontinence episodes per 24 hours
- Mean volume voided per micturition
- Number of micturitions during daytime
- Number of micturitions during sleeping time (nocturia)

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- Sensation of bladder discomfort
- Other efficacy study parameters comprised:
- Subjective Scales (TBS, PPBC, and ICIQ-OAB)
- Quality-of-life King's Health Questionnaire
- Exploratory efficacy study parameters comprised:
- Assessment of the effect of plasma ONO-8539 concentration on secondary efficacy parameters
- Assessment of the effect of urine biomarkers (urine PGE_2 concentration) and the effect of creatinine

Safety:

Safety assessments included AE monitoring, concomitant medication, physical examination, vital sign measurements, 12-lead ECG readings, hematology, biochemistry, and urinalysis tests, ultrasound PVR, and uroflow (Q_{max}).

Statistical methods

The statistical analyses were performed using a 2-sided hypothesis test at the overall 5% significance level. Subjects were classified into 5 analysis sets; the entered single-blind set, the randomized set, SP, the FAS, and the PPS. The efficacy analysis was based on data collected in subject bladder diaries and on subject completed questionnaires. There was no adjustment for multiple treatment comparisons.

Primary efficacy analysis

The primary efficacy endpoint was the mean change in number of micturitions per 24 hours from Baseline to Week 12 (LOCF). The primary analysis population was the FAS. The primary hypothesis was that 1 or more of the ONO-8539 doses will lead to a mean relative decrease in the number of micturitions per 24 hours of at least 1.5 compared with placebo at Visit 5 (Week 12) (LOCF) controlling for Baseline. An analysis of covariance (ANCOVA) was used to compare each ONO-8539 dose with placebo with treatment, country, age (<65 years, ≥65 years), gender, and with or without UUI at Baseline as factors and the baseline value as a covariate. Subjects randomly assigned to receive tolterodine (Detrusitol® XL) were included in the analysis but not considered part of the primary analysis.

An estimate of the least squares means for each treatment group, estimates of the treatment difference compared with placebo and 95% confidence intervals (CIs) and the *P* value of the difference was calculated. To account for subjects who withdrew before 12 weeks, the final on-therapy data were used, defined as the last postbaseline

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recorded number of micturitions per 24 hours, and using the last LOCF method.

Subgroup analysis was conducted for the primary endpoint at Visit 5 (Week 12) (LOCF) for the FAS. Each of the following variables was removed from the ANCOVA model (where appropriate) and added individually as a by value in the analysis:

- Age group (<65 years, ≥65 years)
- Gender
- With or without UUI at Baseline
- Prior OAB medication naïve/not naïve

Secondary efficacy analysis

The analysis population for secondary efficacy endpoints was the FAS. The key secondary efficacy endpoints were

- Number of urgency episodes (PPIUS) Grade 3 or 4 per 24 hours
- Number of UUI episodes per 24 hours for subjects with UUI as Baseline
- Mean volume voided per micturition

Other secondary efficacy endpoints were:

- Number of micturitions per 24 hours (at Weeks 2, 4, and 8)
- Most frequent severity of urinary urgency
- Number of continent days per week for subjects with UUI at Baseline
- Number of incontinence episodes per 24 hours
- Number of micturitions during daytime
- Number of micturitions during sleeping time (nocturia)

The analysis of the primary and key secondary endpoints was repeated for the per-protocol set (PPS). The analysis of the other secondary efficacy endpoints was repeated for the PPS since the difference between the number of subjects in the FAS and PPS was at least 10%. The analysis of the primary and key secondary endpoints was repeated for the per-protocol set (PPS). The analysis of the other secondary efficacy endpoints was repeated for the PPS since the difference between the number of subjects in the FAS and PPS was at least 10%.

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For each urinary symptom data endpoint, except the most frequent severity of urinary urgency, the mean and percentage change from Baseline was calculated for each postbaseline visit. An ANCOVA was used to analyze the secondary efficacy bladder diary endpoints as for the primary efficacy endpoint, comparing ONO-8539 doses and tolterodine with placebo. Exceptions to this were the endpoints number of UUI episodes and number of continent days per week that did not have with or without UUI at Baseline as a factor in the model. Due to the data type, the most frequent severity of urinary urgency was analyzed using logistic regression.

As for the primary analysis, an estimate of the least squares means for each treatment group, estimates of the treatment difference compared with placebo and 95% CIs and *P* value of the difference was calculated. Endpoints were analyzed for Visit 2 (Week 2), Visit 3, (Week 4), Visit 4, (Week 8), Visit 5 (Week 12), and Visit 5 (Week 12) LOCF.

Sensation of bladder discomfort was summarized. Subjective scales and quality-of-life questionnaire data were analyzed as other secondary endpoints. Treatment response, PPBC, and ICIQ-OAB were analyzed with logistic regression modeled using the same factors as the primary analysis. The odds ratio (with 95% CI and *P* value) compared each active treatment to placebo. Each ONO-8539 dose was compared with tolterodine for number of micturitions per 24 hours, number of urgency episodes (PPIUS Grade 3 and 4) per 24 hours, number of UUI episodes per 24 hours, and mean volume voided per micturition. The ANCOVA model used for this analysis was as for the primary efficacy analysis. An ANCOVA was used to analyze the change from Baseline in PGE_2 as for the primary efficacy endpoint, and compare ONO-8539 doses and tolterodine versus placebo.

Safety

All AEs were monitored throughout the study. Hematology and biochemistry parameters were summarized for actual and change from Baseline and key parameters were plotted from Baseline to the lowest or highest (worst) postbaseline value as applicable. Vital sign parameters were presented for Baseline and by visit for the actual result and change from Baseline for subjects with Baseline and relevant postbaseline visit data. The physical examination assessments were summarized with number and percentage of subjects at each visit, by system organ class, and assessment result. The 12-lead ECG parameters were presented by treatment as summary statistics. The results obtained from the uroflow test and ultrasound PVR test were listed and also summarized by visit.

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Summary

Efficacy results:

Primary endpoint

There was no statistically significant improvement or tendency for improvement in the primary endpoint. The subgroup analyses also did not show any improvement for any ONO-8539 group compared with placebo.

For the tolterodine group, there was a statistically significant improvement in the change from Baseline in the number of micturitions per 24 hours at Week 12 (LOCF), compared with the placebo group. The subgroup analyses showed a significant improvement (decrease) in the number of micturitions per 24 hours at Week 12 (LOCF) for subjects who were at least 65 years-of-age.

Key secondary endpoints

There was no statistically significant improvement or tendency for improvement in any ONO-8539 group, compared with placebo for the number of UUI episodes per 24 hours, the number of urgency episodes per 24 hour or the mean volume voided per micturition. There were no significant improvements for the ONO-8539 100-mg and 300-mg groups for the number of incontinence episodes per 24 hours. There were significantly more incontinence episodes in the ONO-8539 30-mg group compared with placebo. Improvements were significantly greater in the ONO-8539 300-mg group, than in the placebo group, for the most frequent severity of urinary urgency.

For the tolterodine group, there was no statistically significant improvement or tendency for improvement, compared with placebo, for the number of UUI episodes per 24 hours. There was a statistically significant improvement for tolterodine, compared with placebo, for the number of urgency episodes per 24 hours and mean volume voided per micturition. Improvements were significantly greater in the tolterodine group, compared with placebo, for the most frequent severity of urinary urgency.

Safety Results:

ONO-8539 was generally well tolerated and no significant safety concerns were observed or identified.

Treatment exposure and compliance

During the run-in phase, mean exposure was 15.4 days. During the treatment phase, the majority of subjects completed study treatment with mean exposure ranging from 76.6 to 79.9 days across treatment groups. Mean compliance was high whether based on the number of tablets or capsules taken or subject-filled diaries with the vast majority of subjects (> 90%) having compliance of 80% or higher throughout the study.

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Adverse events

Overall during the treatment phase, there was no difference in the number of subjects who had AEs between treatment groups and no evidence of any relationship in the number of subjects who had AEs with increasing ONO-8539 doses.

However, the total number of AEs reported was higher in the ONO-8539 300-mg and tolterodine groups than in the placebo and lower ONO-8539 dose groups.

Gastrointestinal events were the most common class of AEs with some evidence of more subjects reporting events of this class with ONO-8539 300-mg than with placebo and lower ONO-8539 doses but comparable with the number on tolterodine. During treatment with ONO-8539, subjects most commonly reported diarrhea but with no evidence of a dose relationship while dry mouth was reported most commonly by subjects receiving tolterodine. Gastrointestinal events were also the most commonly reported AEs considered treatment related.

Six subjects, 5 in the ONO-8539 300-mg group and 1 in the ONO-8539 100-mg group, reported AEs relating to the elevation of 1 or more hepatic enzymes.

The majority (64.2%) of treatment phase AEs were mild in nature with the proportion of subjects with mild, moderate, and severe AEs similar for all treatment groups for TEAEs within each severity category. Most (83.8%) treatment phase AEs had resolved by the end of the study.

Review of the AEs reported at study center 0708 showed that the nature of the AEs reported at this center was comparable to the total population and thus their inclusion will not have affected the overall interpretation of the findings.

Deaths, serious adverse events, and adverse events leading to withdrawal

There were no deaths during this study. There were 9 subjects with at least 1 SAE, 2 in the run-in phase and 7 in the treatment phase, all isolated reports. There was 1 suspected unexpected serious adverse reaction, toxic hepatitis, in the ONO-8539 300-mg group considered possibly study drug related. There were 25 subjects with AEs leading to withdrawal, 16 during the treatment phase.

Clinical laboratory evaluation

Mean hematology, biochemistry, and urinalysis values were within the normal ranges at Baseline and remained so throughout the study. Low neutrophil counts predominantly seen in subjects from Russia and Ukraine and occurring at all time points from screening and across all treatment groups were considered due to extraneous causes and not of clinical concern. One subject in the ONO-8539 300-mg group and diagnosed with toxic

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hepatitis had significant elevation in all hepatic parameters. There were no other changes seen in hematology, biochemistry, or urinalysis of clinical concern.

Vital signs, electrocardiograms, physical findings, and other safety observations

There were no clinically significant changes observed in mean values over time for vital signs or ECG parameters for any of the ONO-8539 doses, tolterodine, or placebo. The number of subjects with abnormal findings at the screening visit did not substantially alter at any of the subsequent assessments for any of the system organ classes examined. There was no clinically significant change in PVR or uroflow (Q_{max}) for any treatment group.

Conclusions:

There was no significant improvement or tendency for improvement observed in any ONO−8539 group compared with placebo for the primary endpoint of number of micturitions per 24 hours or any key secondary endpoints. There were also no specific endpoints where ONO-8539 showed a good improvement in the overall study population. ONO-8539 was generally well-tolerated and no significant safety concerns were observed in OAB subjects.

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