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SYNOPSIS

Title of Study:

A study to evaluate the overall effect of solifenacin 5 mg and 10 mg on bladder wall thickness and urinary nerve growth factor in female subjects with overactive bladder and a diagnosis of detrusor overactivity – a double-blind, randomized, placebo-controlled, parallel-group, multi-center study (SHRINK)

Investigators/Coordinating Investigators:

[redacted], Italy.

[redacted] United Kingdom.

Study Centers:

This was a multi-center study. A total of 79 sites in Austria, Belgium, Bulgaria, Canada, Czech Republic, France, Germany, Hungary, Israel, Italy, Norway, Poland, Romania, Russian Federation, Slovakia, Spain, Sweden, Turkey, United Kingdom and United States participated in the study.

Publication (reference): Not applicable.

Study Period:

Date of first enrollment (Study initiation date): 19 January 2010

Date of last evaluation (Study completion date): 23 June 2011

Phase of Development: Phase 4

Objectives:

The primary objectives were:

- To evaluate the effect of solifenacin vs placebo on bladder wall thickness (BWT) after 12 weeks of treatment
- To evaluate the effect of solifenacin vs placebo on urinary Nerve Growth Factor (uNGF) normalized by urine creatinine level (uNGF/Cr) after 12 weeks of treatment in patients with uNGF above laboratory quantification limit at baseline

The secondary objectives of the study were:

- To evaluate the effect on BWT of
  - Solifenacin vs placebo after 6 weeks of treatment
  - 5 mg and 10 mg of solifenacin (dose response).
- To evaluate the relationship of BWT and
  - Overactive Bladder (OAB) symptoms at baseline and changes observed during the study
  - Changes observed in patient perceived satisfaction scales.

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- To evaluate the effect on uNGF/Cr of
  - Solifenacin vs. placebo after 6 weeks of treatment
  - 5 mg and 10 mg of solifenacin (dose response).
- To evaluate the relationship of uNGF/Cr and
  - OAB symptoms at baseline and changes observed during the study
  - Changes observed in patient perceived satisfaction scales.
- To evaluate the relationship between BWT and uNGF/Cr.
- To evaluate the safety and tolerability of 5 mg and 10 mg solifenacin.

In addition the association between each co-primary efficacy variable (BWT and uNGF/Cr) and the following non-efficacy baseline characteristics were explored at baseline and for change from baseline during treatment:

- Duration of OAB.
- Patient quality of life.
- Patients categorized according to those with (wet) or without (dry) leakage.
- Patient age.
- Patient height and body mass index (BMI).
- Patients categorized according to previous OAB treatment experience, i.e. naïve or 6-months treatment free.
- Patients categorized by menopausal status and further categorized to hormone replacement therapy (HRT) use.
- Patients categorized according to childbirth status i.e. nulliparous or multiparous and according to different types of deliveries.

During the conduct of the study it was decided to measure urinary brain derived neurotrophic factor normalized by urine creatinine level (uBDNF/Cr) as a key secondary biomarker.

Methodology:

This was a multi-center, randomized, double-blind, placebo-controlled, 3-arm parallel-group study to evaluate the overall effect of 2 fixed dosages of solifenacin (5 mg and 10 mg) on BWT and uNGF in female patients with OAB and a diagnosis of detrusor overactivity.

Patients satisfying all selection criteria at the end of the 2-week, single blind, placebo run-in period (visit 2) were randomized to receive 12-week double-blind treatment with once daily either solifenacin 5 mg, solifenacin 10 mg, or placebo.

Patients visited the study site at screening (within 2 weeks of the start of the single-blind placebo run-in period; visit 1), at the end of the run-in period/Randomization (visit 2), and at week 6 (visit 3) and week 12 (end of the double-blind treatment period; visit 4).

Number of Patients (planned, enrolled and analyzed):

A total of 537 randomized patients were planned in order to obtain 471 patients for analysis of the primary variables.

A total of 673 patients were screened of whom 547 patients were randomized and took at least 1 dose of the study drug(s). Thirty-five patients (6.4%) prematurely discontinued from the study after the start of the double-blind treatment period.

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Diagnosis and Main Criteria for Inclusion:

The study population consisted of women, ≥ 18 years of age, who had symptoms of OAB, including urinary frequency, urgency or urge incontinence, for ≥ 3 months, and an urodynamic diagnosis of detrusor overactivity. Furthermore, patients had to be either naïve to antimuscarinic treatment or 6-months antimuscarinic treatment free prior to the screening visit, and had a bladder post-void residual (PVR) urine volume of < 30 mL.

Test Product, Dose and Mode of Administration, Batch Numbers:

Solifenacin (Vesicare®) tablets; 5 mg or 10 mg once daily, orally. Batch number: [redacted].

Duration of Treatment (or Duration of Study, if applicable):

Two week, single blind, placebo run-in period followed by 12-week double-blind treatment with once daily solifenacin 5 mg or 10 mg or placebo.

Reference Products, Dose and Mode of Administration, Batch Numbers:

Placebo solifenacin tablets, once daily, orally. Batch number: [redacted].

Criteria for Evaluation:

Efficacy was assessed from:

Two co-primary efficacy endpoints:

- Change from baseline to week 12 Last Observation Carried Forward (LOCF) in BWT measured with transvaginal ultrasound (TVUS).
- Absolute value at week 12 LOCF in free (neutralized) uNGF/Cr.

BWT measurements were completed by both local investigators at site and by two central readers (and a third central reader as adjudicator, when there were large differences in the mean BWT assessment based on three bladder wall locations (anterior wall, dome, trigone). uNGF values were measured at a standardized PH value and then normalized for the amount of fluid intake by dividing with the corresponding urinary creatinine value.

Key secondary efficacy endpoints were:

- Absolute value of total (acidified) uNGF/Cr at week 12 LOCF
- Absolute value of uBDNF/Cr (normalized value) at week 12 LOCF.

The following variables were considered secondary variables:

- Change from baseline in BWT, as measured with TVUS, at week 6.
- Absolute values and change from baseline in free (neutralized) uNGF/Cr and total (acidified) uNGF/Cr at week 6 or week 12.
- Change from baseline to week 12 LOCF in the following variables derived from the micturition diary and Patient Perception of Intensity of Urgency Scale (PPIUS):
  - Mean number of events (micturitions plus incontinence episodes) per 24 hours
  - Mean number of urgency events (micturitions plus incontinence episodes) with PPIUS grade 3 or 4 per 24 hours
  - Mean number of micturitions per 24 hours,

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  - Mean number of urgency micturitions with PPIUS grade 3 or 4 per 24 hours
  - Mean number of incontinence episodes per 24 hours
  - Mean number of urgency incontinence episodes with PPIUS grade 3 or 4 per 24 hours
  - Mean number of urgency incontinence episodes with PPIUS grade 4 per 24 hours
  - Mean level of urgency
  - Total urgency score of PPIUS
- Change from baseline to week 12 LOCF in Patient Perception of Bladder Condition (PPBC).
- Change from baseline to week 12 LOCF in Urgency Bother - Visual Analogue Scale (UB-VAS).
- Change from baseline to week 12 LOCF in Treatment Satisfaction - Visual Analogue Scale (TS-VAS).
- Change from baseline to week 12 LOCF in total EuroQoL 5-Dimension Questionnaire (EQ-5D) score (dimensions and EQ-5D VAS score).
- Change from baseline to week 12 LOCF in total score (and subscale scores) of the Overactive Bladder Symptom and Health-Related Quality of Life Questionnaire (OABq).
- Change from baseline to week 12 LOCF in uBDNF/Cr (normalized value)

Safety was assessed from incidence and severity of adverse events (AEs), Clinical laboratory variables (urinalysis), vital signs, physical examination and post-void residual volume measurements.

Statistical Methods:

Analyses of the 2 co-primary and 2 key-secondary efficacy variables were performed for the Full Analysis Set (FAS) and Per Protocol Set (PPS) populations which were defined separately for BWT, uNGF and uNGF0 (uNGF values above the laboratory quantification limit at baseline) and uBDNF . Secondary efficacy variables were only analyzed for the FAS populations.

Co-primary efficacy endpoint BWT

The primary efficacy analysis was the change from baseline to week 12 LOCF in BWT (based on overall image mean values per subject from central reading) analyzed in the FAS_BWT (those patients who had a mean BWT measurement at baseline) with an Analysis of Covariance (ANCOVA) model which contained treatment (3 levels: placebo, 5 mg solifenacin and 10 mg solifenacin) and region as fixed factors and the baseline BWT as a covariate. The treatment difference of the pooled solifenacin treatment arm (5 mg + 10 mg solifenacin) vs placebo was estimated as a 2-sided contrast with 95% CIs. BWT measurements were included in this primary model as an overall image mean value per patient. (These mean values have been estimated by the central imaging service provider [BMS] as least-square-means with an ANOVA model including image, reader, bladder wall location as fixed factors and reader-by-location as interaction term). The pooled solifenacin vs placebo was the primary comparison. Other treatment comparisons were considered explorative and a hierarchical testing rule was applied as follows to adjust for the multiplicity of the secondary treatment comparisons: after the primary comparison, the 10 mg solifenacin *vs*. placebo was tested, and if significant at the α=0.05 level, then the 5 mg solifenacin *vs*. placebo was tested. In addition, the 10 mg *vs*. 5 mg solifenacin was tested. Primary efficacy analyses were repeated for the PPS_BWT.

Co-primary endpoint uNGF

The uNGF/Cr at week 12 LOCF was analyzed as observed values in the FAS_uNGF0 with a similar ANCOVA model as used for the primary analysis of change in BWT; however, uNGF/Cr was used as the baseline covariate. The significance level for the primary treatment comparisons of BWT and free (neutralized) uNGF/Cr was adjusted for the 2 co-primary endpoints using the Hochberg method for controlling the overall risk of type I error of 5%. In addition, non-parametric Wilcoxon rank-sum tests were used for the same comparisons as in the ANCOVA model for free (neutralized) uNGF/Cr. The Wilcoxon rank-sum test was to be

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considered secondary except if there were serious concerns about normality. The ANCOVA analyses were repeated as post-hoc analyses for the FAS_uNGF after applying a log10 transformation, since results showed that uNGF/Cr followed a log-normal distribution.

Treatment by baseline interaction and treatment by region interaction were explored for both co-primary endpoints by adding these interaction terms in separate analyses to the primary ANCOVA model. A second ANCOVA model was applied to the central reader raw assessments by adding reader, bladder wall location as fixed factors and treatment by location interaction term to explore the treatment effect on each individual bladder wall location and for supporting the results from the primary ANCOVA model which included estimated overall mean BWT values per subject.

Analysis of the reader variability for BWT

Intrareader variability was analyzed for the central readers by calculation of mean difference for a subset of 40 repeated images, with corresponding SD and 95%CI of mean between the readers' first and second read and the corresponding paired t-test P-value. Statistics were calculated separately for all 3 readers, for all 3 locations anterior, trigone and dome, and for the mean across all locations.

Interreader variability was analyzed by calculating the mean difference of Reader 1 vs Reader 2, Reader 1 vs Reader 3 (adjudicator) and Reader 2 vs Reader 3 together with the corresponding Bland-Altman ~~tables and~~ plots. The mean differences were calculated both per location of the image and for the mean image value. The estimates for interreader variability were based on pooled baseline, week 6 and week 12 data and separately on the single visits (BMS excluded the 2nd session intrareader reads from the calculation).

Observed values for BWT and uNGF/Cr as well as their change from baseline were summarized by visit and treatment arm (including pooled solifenacin group) with descriptive statistics for continuous variables.

Analyses of secondary efficacy variables

The analysis of the 2 key-secondary efficacy endpoints and most other secondary efficacy variables at week 12 and week 6 were done with ANCOVA models analogously to the primary model. The association between some baseline characteristics, the co-primary variables at baseline and their change from baseline were explored. Also the association between the co-primary efficacy variables and the secondary efficacy variables were explored at baseline. Equally these were explored for change from baseline, including the association between the two co-primary variables. This was done using scatter plots, correlation coefficients and regression models. Post-hoc analyses (shown in the CSR) include BWT analyses based on anterior wall and dome only, as well as BWT analyses stratified by BWT value at baseline ($\leq$ 5 mm, > 5 mm). The cut-off value was chosen for comparisons with publications which used > 5 mm BWT as inclusion criterion for enrolment.

Safety variables were analyzed with descriptive statistics only.

Summary of Results/Conclusions:

Population:

- The SAF consisted of 543 patients who were randomized and treated and for whom any data was reported after the first dose of study drug. It was decided at the BDRM to exclude 3 patients from the SAF and also from the FAS because they received by mistake medications from 2 different treatment arms during the study. This is documented in the BDRM addendum dated 05 Oct 2011. The exclusion of these 3 patients was expected to reduce some noise from the analysis of efficacy parameters, and had no impact on the safety conclusions, as only 1 of the 3 patients had a treatment-emergent adverse event (TEAE) and the number of patients in each treatment group was quite large. After unblinding it turned out that these 3 patients were randomized to

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solifenacin, but received a different treatment dose during the first 6 weeks compared to the treatment dose thereafter.

- The FAS_BWT consisted of 501 patients who were randomized and treated and who had a mean BWT measurement at baseline, and 478 subjects had BWT assessments on at least 1 visit thereafter.
- The FAS_uNGF consisted of 523 patients who were randomized and treated and who had an uNGF/Cr measurement at baseline and on at least 1 visit thereafter. Three patients had uNGF values ≤ LLOQ. The FAS_uNGF0 therefore consisted of 520 patients.
- 506 patients gave consent for additional analysis of uBDNF; none of them had values ≤ LLOQ, therefore FAS_uBDNF and FAS_uBDNF0 were identical (i.e., included 506 patients.
- The PPS_BWT consisted of 434 randomized patients who were included in the FAS_BWT, had a BWT measurement at week 12 and completed the study without major protocol deviations.
- The PPS_uNGF consisted of 443 randomized patients who were included in the FAS_uNGF, had an uNGF/Cr measurement at week 12 and completed the study without major protocol deviations. The PPS_uNGF0 consisted of 440 patients.
- The PPS_uBDNF consisted of 425 randomized patients who were included in the FAS_uBDNF, had an uBDNF/Cr measurement at week 12 and completed the study without major protocol deviations. The PPS_uBDNF0 was identical to the PPS_uBDNF.

The baseline demographics and child delivery history at baseline for the SAF showed no relevant differences between the treatment groups [Table 1, Table 2].
The primary diagnosis of OAB at baseline was for almost all patients (99.4%) detrusor overactivity, with (54.5%) or without (45.5%) leakage and 9.0% of the patients had received prior treatment for OAB. The mean duration of OAB at baseline was 45.4 months [Table 3].

Efficacy Results:

Co-primary Efficacy Variable – BWT

The mean (SD) BWT image value at baseline was 5.07 (1.19) mm in the Solifenacin 5 mg group, 5.16 (1.14) mm in the solifenacin 10 mg group and 5.00 (1.08) mm in the placebo group. The values pooled over all subjects followed a normal distribution. The normality assumption was also accepted for the residuals of the ANCOVA models used to analyze BWT.

The mean and mean change from baseline at week 12 LOCF for BWT are presented in Table 4 and Figure 1.

The p-values from the primary ANCOVA model are shown in Table 5, together with the LSmeans and the corresponding 95% CIs. The change from baseline at week 6 and week 12 were considered secondary variables, but are presented for completeness with the week 12 LOCF results.

There was a small decrease observed in BWT with solifenacin 5 mg and 10 mg compared to baseline, but the estimated difference for the pooled solifenacin treatment contrast *vs*. placebo at week 12 LOCF was not statistically significantly different from the mean change from baseline estimated for the placebo group (P = 0.095;Table 5). This means that the primary treatment comparison is not statistically significant.

The treatment comparison of solifenacin 10 mg *vs*. placebo (first test in a hierarchical testing rule for secondary treatment comparisons) was not statistically significant (p=0.477). For solifenacin 5 mg vs placebo a mean treatment difference of -0.25 mm was estimated (95% CI: -0.48 to -0.03 mm). The corresponding test was statistically significant (p=0.030), however this test should be considered as exploratory, since a hierarchical testing rule was applied.

The difference between solifenacin 5 mg and 10 mg was also not statistically significant.

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The results of PPS_BWT were similar, except that the treatment comparison of solifenacin 5 mg vs placebo was no longer statistically significant.

Secondary Analyses of BWT, 3 locations

The results for estimated mean change in BWT per treatment arm for the 4 exploratory ANCOVA models based on the central reader assessments are summarized in Table 6, and show in addition also the result from the local reader assessments. ANCOVA Model 2 and also separate analyses of the data from Central Reader 1 and 2 show a significant reduction of BWT in the pooled solifenacin arm compared to placebo at week 12 LOCF (P = 0.011, 0.043 and 0.024, respectively). Model 2 and Model 1a, which both include data from all 3 central readers show very similar estimates for the mean treatment difference (-0.169 mm in the primary Model 1a, -0.129 mm in Model 2), however the width of the corresponding 95% CIs is larger in the primary ANCOVA model 1a compared to ANCOVA Model 2.

The results of all 4 ANCOVA models show reductions on solifenacin 5 mg treatment arm compared to placebo which would be statistically significant if the hierarchical testing rule for multiplicity adjustment is ignored. . Based on the 95% CI for the treatment difference is the real treatment effect size for the reduction of the average BWT not larger than -0.484 mm and for solifenacin 10 mg not larger than -0.318 mm in a target population similar to the study population.

The change from baseline to week 12 LOCF in BWT based on 3 locations (central reading) analyzed by means of ANCOVA Model 1a for the FAS_BWT showed a statistically significant effect of geographic region (P = 0.0413). However, the treatment by region effect was not statistically significant (ANCOVA Model 1b, P = 0.6126).

Intra- and Inter-reader Variability

The intra-reader variability in mean BWT (estimated in a subset of 40 images) was statistically significant for each bladder wall location and for the average BWT for Reader 2 only. The results indicated that Reader 2 tended to give on Session 2 systematically about 0.4 mm smaller assessments compared to Session 1, with variability similar to those of the other 2 readers.

The inter-reader BWT variability between the readers has been explored on the level of the 3 bladder wall locations and also on the level of their image mean values, calculated as the arithmetic mean value across at least 2 locations with a numerical assessment. Results of the comparison of the mean values across all images from all patients included in the study show that Reader 2 assessed the average BWT per image on average 0.391 mm larger than Reader 1.

Assessments from the adjudicator are consistent larger for each bladder wall location compared to assessments from central Reader 1. The difference in the assessments compared to central Reader 1 are statistically significant for all 3 locations at each visit and also for the image mean values at each visit. This can be derived from the 95% CI, since they do not include the value zero.

There is a systematic difference between Reader 2 and the adjudicator with respect to the size of the trigone. This difference is statistically significant per visit and pooled across visits. The trigone is assessed by Reader 3 on average 1.009 mm smaller than assessed by Reader 2. Differences at the 2 other bladder wall locations are not statistically significant.

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Co-primary Efficacy Variable – Free (neutralized) uNGF/Cr

From the descriptive statistics and also from the residuals of the pre-specified ANCOVA analyses it was derived that the uNGF/Cr data do not follow a normal distribution. Therefore, the Wilcoxon Rank Sum Test became the primary statistical test. The results of the non-parametric Wilcoxon Rank Sum Test show no statistical significant difference between the distribution of the uNGF/Cr values in the pooled solifenacin treatment group compared to the placebo group [Table 7; Figure 2]. It was decided post-hoc to apply a log-transformation to the primary ANCOVA model which also showed no significant differences [Table 8].

Key Secondary Efficacy Variables – acidified uNGF/Cr

A descriptive summary of acidified uNGF/Cr at each visit, including changes from baseline is provided in Table 9. The results from the ANCOVA Model 1a, based on log-transformed data, as described above, showed no significant differences between the pooled solifenacin and placebo group [Table 10].

Key Secondary Efficacy Variables – uBDNF/Cr

As uBDNF data did not follow a normal distribution, the Wilcoxon Rank Sum test was considered the primary analysis. All treatment comparisons performed with the Wilcoxon Rank Sum test at week 12 and week 12 LOCF showed no statistical difference between treatment groups (P-values in range 0.112 to 0.292 for treatment comparisons vs placebo)[Table 11]. Results from the primary ANCOVA Model 1a, with a log-transformation performed post-hoc, also showed no significant differences at these time points [Table 12].

Secondary Efficacy Variables – Micturition Diary and Other Patient Reported Outcomes

A summary overview of the baseline values and ANCOVA analysis of change from baseline at week 12 LOCF for the secondary efficacy variables derived from the micturition diary and PPIUS is provided in Table 13 and Table 14. A comparable summary overview of the other patient reported outcomes is provided in Table 15.

Statistically significant decreases from baseline were found for the solifenacin 5 mg group vs the placebo group, for mean number of events (total of micturitions plus incontinence episodes) per 24 hours, mean number of urgency events with PPIUS Grade 3 or 4 per 24 hours, mean number of incontinence events per 24 hours and the total urgency frequency score of PPIUS. Additionally, numerically larger decreases were found in the solifenacin groups vs the placebo group for mean number of micturitions per 24 hours and mean number of urgency incontinence events with PPIUS Grade 3 and/or Grade 4 per 24 hours.

Solifenacin also showed a statistically significant effect on PPBC, UB-VAS, TS-VAS and OAB-q. The majority of patients were not responders for EQ-5D. The mean EQ-5D VAS score was increased at week 12, with a numerically larger improvement for the solifenacin groups vs the placebo group, but the differences were not statistically significant.

It should be noted that the present study didn't select patients based on severity of bladder diary variables and therefore patients could have lower values at baseline and thus less room for improvement.

Analysis of Associations - BWT

The analysis based on three locations showed statistically significant though weak correlations between mean BWT at baseline and age, weight, BMI, parity, PPBC and OAB-q symptom severity score. No other association between BWT and baseline variables was revealed. The correlations between change in BWT and change in secondary efficacy variables were mostly very small, and not statistically significant. A negative correlation was found between baseline value of BWT and reduction in BWT, i.e., patients with a higher baseline value had a statistically significantly greater reduction from baseline in BWT.

The analysis based on two locations (anterior and dome) showed similar results, except that also TS-VAS showed a statistically significant, though weak, correlation to mean BWT at baseline.

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Analysis of Associations – uNGF/Cr

The association between the change in neutralized uNGF/Cr and type of OAB at baseline and during the study at week 12 LOCF, was close to significant for pooled solifenacin vs placebo (P =0.056) in the subgroup of patients assessed by the investigator as OAB wet. A significant treatment effect compared to placebo is only seen in the subgroup of patients who were wet at baseline and became dry during the study. The estimated geometric mean value in solifenacin 10 mg (30.6) is by about 31% increased compared to placebo (23.3)(P = 0.022; 95% CI for the GM ratio ranges from 1.04 to 1.65)

Analysis of Associations – uBDNF/Cr

The correlation between change in neutralized uBDNF/Cr and change in other secondary efficacy variables was only significant for neutralized and acidified uNGF/Cr at week 12 LOCF (P < 0.0001).

Safety Results:

A summary table of AEs during the double-blind treatment period is presented in Table 16 and Table 17.

AEs were reported for 41 patients (22.5%) during the solifenacin 5 mg treatment period, for 57 patients (32.6%) during the solifenacin 10 mg treatment period and for 53 patients (28.5%) during the placebo treatment period.

The most common AEs reported during solifenacin treatment were gastrointestinal disorders, in particular dry mouth (i.e., 8.8% of patients with solifenacin 5 mg and 17.1% of patients with solifenacin 10 mg) and constipation (i.e., 4.4% of patients with solifenacin 5 mg and 5.1% of patients with solifenacin 10 mg). The incidence of dry mouth and constipation in the placebo group was low (1.1% and 3.8%). All events except 1 case of constipation in the placebo group were considered related to treatment by the investigator.

Infections and infestations were commonly reported with all treatments, but most of the AEs within this system-organ class were considered not related to treatment by the investigator. Urinary tract infections were reported for 6 patients treated with solifenacin 10 mg and 6 placebo-treated patients. In the solifenacin 10 mg group, the event was of moderate and mild intensity in 3 patients each; all events were considered unrelated to treatment. In the placebo group, the event was of moderate intensity in 1 patient and of mild intensity in 5 patients; 2 events were considered possibly related to treatment and 4 events were considered unrelated to treatment. One additional patient in the solifenacin 10 mg group had cystitis of mild intensity. The event was considered not related to treatment.

Most AEs were of mild or moderate severity. Severe adverse events were infrequent. The most commonly reported AE of severe intensity was dry mouth, reported by 5 patients (2.9%) in the solifenacin 10 mg group and by 1 patient (0.5%) treated with solifenacin 5 mg.

One patient in the solifenacin 5 mg treatment group died during the study. Patient [redacted] was a [redacted] patient who started treatment with solifenacin 5 mg. The next day, [redacted] was hospitalized with upper abdominal pain, nausea and vomiting. During the hospitalization, the status of the patient deteriorated and [redacted] developed acute necrotizing cholecystopancreatitis and endotoxic shock which resulted in cardiovascular and respiratory insufficiency. [redacted] died 2 weeks later. All AEs leading to death were considered unrelated to treatment by the investigator.

Four patients in the solifenacin 10 mg treatment group had a serious adverse event (SAE). These SAEs were pyelonephritis (of severe intensity and considered by the investigator to be probably related to treatment); mouth haemorrhage (mild, probably related), gastric neoplasm (severe, unrelated) and sciatica (moderate, unrelated). One patient in the placebo group had an SAE of chronic obstructive pulmonary disease of moderate severity and considered unrelated to treatment.

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Two additional patients had an SAE during the placebo run-in period: bladder disorder [redacted] of severe intensity and considered medically significant, and hospitalization for headache of moderate intensity. Both SAEs were considered unrelated to treatment.

Eleven patients discontinued from the study due to the occurrence of AEs. Six patients were in the solifenacin 5 mg group, 2 patients were in the solifenacin 10 mg group and 3 patients were treated with placebo. The most common AE leading to study discontinuation were dry mouth (3 patients) and fatigue, headache and nausea (2 patients each).

Overall, there were no clinically relevant differences between treatment groups in changes from baseline in urinalysis, vital signs, physical examination findings and PVR urine volume. Two patients in the solifenacin 5 mg group and 1 patient in the placebo group) had an AE of residual urine/residual urine volume increased. The event was of severe intensity and led to permanent treatment discontinuation in 1 patient. The other 2 cases were of mild severity. One of these patients also had an AE of residual urine during the placebo run-in period. All events resolved before the end of the study.

CONCLUSIONS:

- There was no clear effect of solifenacin 5 mg and 10 mg on the 2 co-primary efficacy variables ultrasonographically (TVUS) measured BWT and uNGF.
- There was a statistically significant and clinically relevant effect of solifenacin 5 mg and 10 mg on micturition diary-derived variables and on TS-VAS and OAB-q. Changes on the EQ-5D were also in line with previous studies.
- Correlations between BWT and baseline disease characteristics were low, and only few associations reached statistical significance. There were no statistically significant correlations between changes in BWT and treatment response.
- There was a poor correlation between uNGF and disease characteristics, and also between uNGF and treatment response.
- There were no statistically significant correlations between changes in uNGF and changes in BWT.
- The most common AEs reported during treatment with solifenacin were those consistent with the SPC (dry mouth and constipation).
- One patient in the solifenacin 5 mg treatment group died. The cause of death was considered unrelated to treatment.
- There were 2 SAEs considered related to treatment by the investigator. Both were in the solifenacin 10 mg treatment group. The events were severe pyelonephritis and mild mouth haemorrhage.
- Six patients in the solifenacin 5 mg group, 2 patients in the solifenacin 10 mg group and 3 patients in the placebo group discontinued due to AEs. The most common AEs leading to study discontinuation were dry mouth, fatigue, headache and nausea.
- In summary, the results of this study suggest, that neither BWT (as measured by TVUS) nor uNGF are useful biomarkers for diagnosis, disease severity and for predicting treatment response and clinical outcomes in patients with OAB disease.

Date of Report: 11 February 2014; Final

Table 1 Demographic Characteristics at Baseline (SAF)

		Solifenacin 5 mg (N = 182)	Solifenacin 10 mg (N = 175)	Placebo (N = 186)	Total (N = 543)
Race (n [%])	White	177 (97.3%)	165 (94.3%)	177 (95.2%)	519 (95.6%)
	Black or African American	1 (0.5%)	2 (1.1%)	1 (0.5%)	4 (0.7%)
	Asian	1 (0.5%)	2 (1.1%)	4 (2.2%)	7 (1.3%)
	Other	3 (1.6%)	6 (3.4%)	4 (2.2%)	13 (2.4%)
Ethnic (n [%])	Not Hispanic or Latino	174 (98.9%)	164 (98.2%)	170 (97.7%)	508 (98.3%)
	Hispanic or Latino	2 (1.1%)	3 (1.8%)	4 (2.3%)	9 (1.7%)
Age (years)	Mean (SD)	55.5 (13.0)	55.5 (13.3)	53.7 (13.0)	54.9 (13.1)
Weight (kg)	Mean (SD)	76.0 (15.6)	74.3 (15.4)	73.0 (14.2)	74.4 (15.1)
Height (cm)	Mean (SD)	163.6 (6.2)	163.1 (6.5)	163.1 (6.7)	163.3 (6.5)
BMI (kg/m^2)	Mean (SD)	28.4 (5.7)	27.9 (5.4)	27.5 (5.5)	27.9 (5.5)

BMI: body mass index; SAF: Safety Analysis Set.

Source: Table 12.1.2.1.3

Table 2 Overview of Child Delivery History (SAF)

		Solifenacin 5 mg (N = 182)	Solifenacin 10 mg (N = 175)	Placebo (N = 186)	Total (N = 543)
Previous delivery of birth (n [%])	Yes	148 (81.3%)	153 (87.4%)	161 (86.6%)	462 (85.1%)
	No	34 (18.7%)	22 (12.6%)	25 (13.4%)	81 (14.9%)
Number of children	Mean (SD)	1.6 (1.1)	1.7 (1.2)	1.8 (1.1)	1.7 (1.2)
	Median (min; max)	2 (0; 6)	2 (0; 10)	2 (0; 8)	2 (0; 10)
Number of children (category) (n [%])	0	34 (18.7%)	22 (12.6%)	25 (13.4%)	81 (14.9%)
	1	45 (24.7%)	58 (33.1%)	41 (22.0%)	144 (26.5%)
	2 or more	103 (56.6%)	95 (54.3%)	120 (64.5%)	318 (58.6%)
Kind of delivery (n [%])	Natural birth	136 (74.7%)	141 (80.6%)	147 (79.0%)	424 (78.1%)
	Cesarean section	16 (8.8%)	17 (9.7%)	18 (9.7%)	51 (9.4%)
	Assisted delivery	4 (2.2%)	3 (1.7%)	6 (3.2%)	13 (2.4%)

Source: Table 12.1.2.4.1

Table 3 Primary Diagnosis of Overactive Bladder (SAF)

		Solifenacin 5 mg (N = 182)	Solifenacin 10 mg (N = 175)	Placebo (N = 186)	Total (N = 543)
Diagnosis of detrusor overactivity (n [%])	Yes	180 (98.9%)	174 (99.4%)	186 (100.0%)	540 (99.4%)
	No	2 (1.1%)	1 (0.6%)	0	3 (0.6%)
Any previous OAB treatment (n [%])	Yes	17 (9.3%)	13 (7.4%)	19 (10.2%)	49 (9.0%)
	No	165 (90.7%)	162 (92.6%)	167 (89.8%)	494 (91.0%)
Duration of OAB (months)	Mean (SD)	43.3 (60.6)	43.3 (66.4)	49.6 (83.6)	45.4 (71.0)
	Median (min; max)	23.8 (0; 355.0)	24.8 (0; 500.9)	18.5 (0; 712.1)	21.4 (0; 712.1)
Type of OAB (n [%])	Leakage	95 (52.2%)	100 (57.1%)	101 (54.3%)	296 (54.5%)
	Without leakage	87 (47.8%)	75 (42.9%)	85 (45.7%)	247 (45.5%)

OAB: overactive bladder

Source: Table 12.1.2.2.3

Table 4 Summary of Mean Bladder Wall Thickness (in mm) (TVUS, 3 Locations) (FAS_BWT)

	Solifenacin 5 mg (N = 171)	Solifenacin 10 mg (N = 155)	Pooled Solifenacin (N = 326)	Placebo (N = 175)
n† at baseline	171	155	326	175
Baseline	5.07 (1.19)	5.16 (1.15)	5.11 (1.17)	5.00 (1.08)
n† at week 6	145	141	286	157
Week 6	5.02 (1.30)	5.05 (1.20)	5.03 (1.25)	5.00 (1.12)
CFB at week 6	-0.04 (1.27)	-0.14 (1.15)	-0.09 (1.21)	-0.01 (1.16)
n† at week 12	143	135	278	160
Week 12	4.83 (1.20)	4.97 (1.13)	4.90 (1.17)	5.04 (1.13)
CFB at week 12	-0.26 (1.37)	-0.22 (1.18)	-0.24 (1.28)	0.02 (1.28)
n† at week 12 LOCF	160	150	310	168
Week 12 LOCF	4.80 (1.18)	4.99 (1.13)	4.89 (1.16)	5.00 (1.12)
CFB at week 12 LOCF	-0.29 (1.37)	-0.18 (1.18)	-0.24 (1.28)	0.00 (1.26)

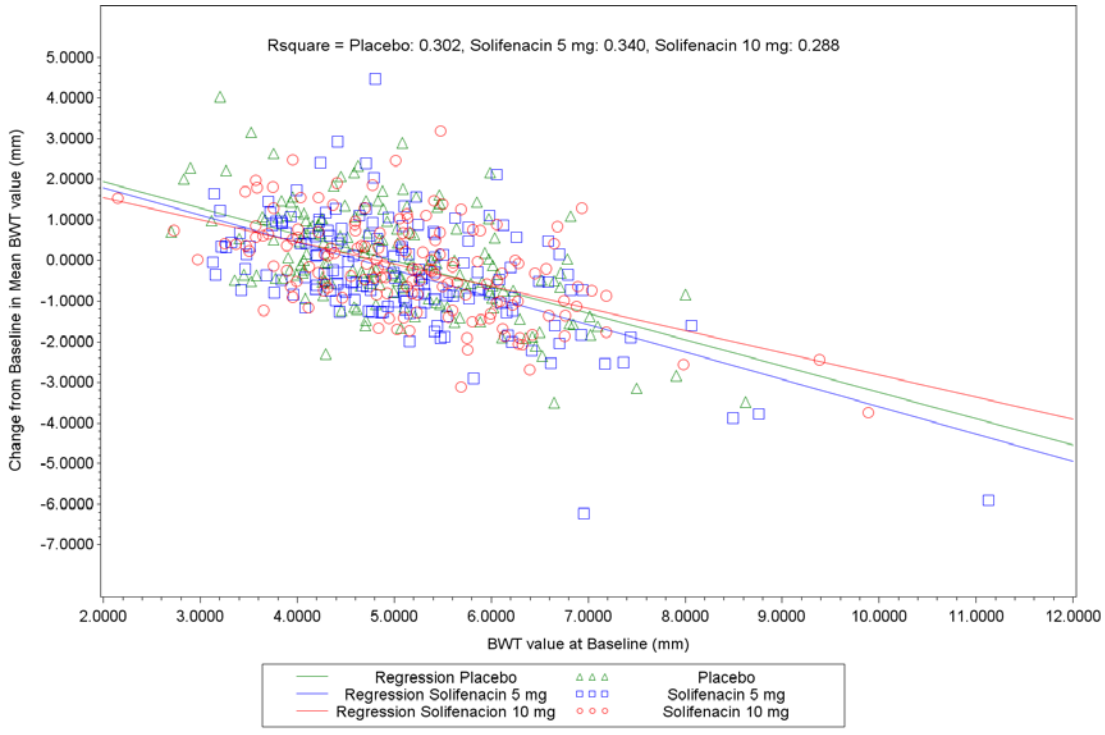
All values are presented as mean (SD). FAS_BWT includes 23 patients with baseline BWT who have no post-baseline BWT. Week 12 LOCF includes also post-baseline data outside of the visit window for week 6 or week 12

BWT: bladder wall thickness; CFB: change from baseline; FAS_BWT: Full Analysis Set Bladder Wall Thickness; LOCF: last observation carried forward; TVUS: transvaginal ultrasound.

† Number of patients with data

Source: Table 12.3.1.1.1

Figure 1 Scatter Plot of Change from Baseline to Week 12 vs Baseline Bladder Wall Thickness (in mm) (3 Locations) (FAS_BWT)



Source: Figure 12.3.8.1.1

Table 5 Analysis of Covariance for Change From Baseline in Mean Bladder Wall Thickness (in mm) (TVUS, 3 Locations, ANCOVA Model 1a) (FAS_BWT)

	Solifenacin 5 mg (N = 171)	**Solifenacin 10 mg (N = 155)**	**Pooled Solifenacin (N = 326)**	**Placebo (N = 175)**
n† at week 6	145	141	286	157
LSmean CFB at week 6	-0.044	-0.084	--	-0.041
Estimated difference to placebo	-0.003	-0.043	-0.023	--
95% CI	(-0.248; 0.241)	(-0.290; 0.204)	(-0.234; 0.188)	--
P-value	0.980	0.734	0.831	--
n† at week 12	143	135	278	160
LSmean CFB at week 12	-0.394	-0.304	--	-0.149
Estimated difference to placebo	-0.246	-0.155	-0.200	--
95% CI	(-0.487; -0.005)	(-0.400; 0.090)	(-0.409; 0.008)	--
P-value	0.045	0.215	0.059	--
n† at week 12 LOCF	160	150	310	168
LSmean CFB at week 12 LOCF	-0.416	-0.246	--	-0.162
Estimated difference to placebo	-0.254	-0.084	-0.169	--
95% CI	(-0.484; -0.025)	(-0.318; 0.149)	(-0.368; 0.030)	--
P-value	0.030	0.477	0.095	--

Week 12 LOCF includes also post-baseline data outside of the visit window for week 6 or week 12. All P-values based on an ANCOVA model with fixed effects for treatment and region and baseline of LSmean BWT as covariate.

ANCOVA: Analysis of covariance; CFB: change from baseline; FAS_BWT: Full Analysis Set Bladder Wall Thickness; LOCF: last observation carried forward; TVUS: transvaginal ultrasound.

† Number of patients with data

Source: Table 12.3.1.1.1 and Table 12.3.1.3.1.1

Table 6 Overview of Mean Bladder Wall Thickness Results (mm) from Different Models at Week 12 LOCF (FAS_BWT)

ANCOVA Model	Statistics	Solifenacin 5 mg (N_{CFB} =160)	Solifenacin 10 mg (N_{CFB} = 150)	Pooled Solifenacin (N_{CFB} = 310)	Placebo (N_{CFB} = 168)
	n†	144	131	275	151
Image LSmean	Baseline: mean (SD)	5.07 (1.19)	5.16 (1.15)	5.11 (1.17)	5.00 (1.08)
	CFB: mean (SD)	-0.29 (1.37)	-0.18 (1.18)	-0.24 (1.28)	0.00 (1.26)
Model 1a	LSmean CFB	-0.416	-0.246	--	-0.162
	Difference to placebo	-0.254	-0.084	-0.169	--
	95% CI	(-0.484; -0.025)	(-0.318; 0.149)	(-0.368; 0.030)	--
	P-value	0.030	0.477	0.095	--
Model 2	LSmean CFB	-0.373	-0.198	--	-0.156
	Difference to placebo	-0.217	-0.042	-0.129	--
	95% CI	(-0.332; -0.101)	(-0.160;0.076)	(-0.230;-0.029)	--
	P-value	< 0.001	0.483	0.011	--
Reader 1 only (Model 5)	LSmean CFB	-0.492	-0.221	--	-0.217
	Difference to placebo	-0.274	-0.004	-0.139	--
	95% CI	(-0.430; -0.119)	(-0.162;0.155)	(-0.274;-0.004)	--
	P-value	< 0.001	0.962	0.043	--
Reader 2 only (Model 5)	LSmean CFB	-0.487	-0.427		-0.282
	Difference to placebo	-0.2060	-0.1457	-0.1756	--
	95% CI	(-0.381; -0.030)	(-0.325; 0.034)	(-0.328; -0.023)	--
	P-value	0.022	0.112	0.024	--
	n	(N_{CFB} =171)	(N_{CFB} =155)	(N_{CFB} =326)	(N_{CFB} =175)
Local Readers (Model 4)	LSmean CFB	-0.093	-0.135	--	-0.126
	Difference to placebo	0.033	-0.009	0.012	--
	95% CI	(-0.128; 0.194)	(-0.173; 0.155)	(-0.128; 0.152)	--
	P-value	0.688	0.914	0.866	--

Overall Image Mean estimated with ANOVA model (image = reader + location + reader*location) as an adjusted mean (LSmean) prior to inclusion into Model 1a.

Effects estimated per model:
Model 1a: CFB_LSmean = treatment + region + baseline LSMean BWT
Model 2: CFB_raw data = treatment + region + reader + location + treatment*location + reader*location + baseline
Model 4 and Model 5: CFB_raw data = treatment+ region + location, treatment*location + baseline

ANOVA: analysis of variance; ANCOVA: Analysis of covariance; CFB: change from baseline; FAS_BWT: Full Analysis Set Bladder Wall Thickness; LOCF: last observation carried forward; TVUS: transvaginal ultrasound.

† Number of patients with data

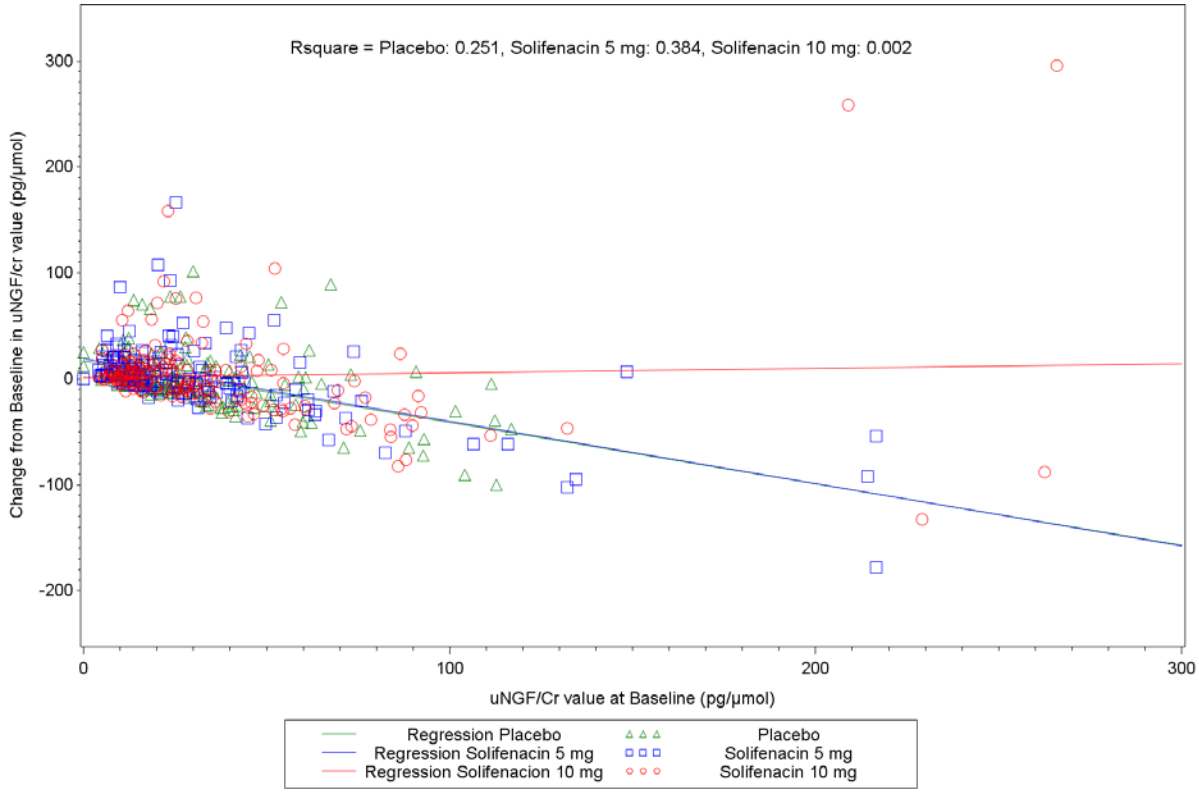
Sources: Tables 12.3.1.1.1, 12.3.1.3.1.1, 12.3.2.3.1, 12.3.2.8.1, 12.3.2.10.1 and 12.3.2.6.1

Table 7 **Summary of Neutralized uNGF/Cr (in pg/µmol) Over Time With Wilcoxon Rank Sum Test for Primary Treatment Comparison (FAS_uNGF0)**

	Pooled Solifenacin (N = 344)					Placebo (N = 176)					
	Mean	(SD)	Min	Med	Max	Mean	(SD)	Min	Med	Max	P-value
n† at baseline	344					176					
Baseline	33.5	(37.4)	4.0	22.7	265.9	32.6	(27.5)	4.2	24.5	214.4	
n† at week 6	323					168					
Week 6	38.6	(69.0)	0.0	24.0	1016.6	28.1	(22.4)	0.0	20.6	114.8	0.134
CFB at week 6	4.5	(68.3)	-214.6	-0.3	1004.5	-4.6	(30.7)	-197.5	-1.5	84.8	
n† at week 12	337					173					
Week 12	35.4	(47.7)	0.0	24.7	561.5	30.4	(26.3)	3.6	20.9	156.7	0.295
CFB at week 12	1.7	(38.9)	-178.1	-0.6	295.6	-1.3	(28.0)	-100.2	-1.6	101.2	
n† at week 12 LOCF	344					176					
Week 12 LOCF	35.3	(47.3)	0.0	24.7	561.5	30.4	(26.2)	3.6	20.8	156.7	0.250
CFB at week 12 LOCF	1.8	(38.6)	-178.1	-0.4	295.6	-2.3	(31.5)	-197.5	-1.5	101.2	

values < LLoQ were set to zero. CFB: change from baseline; FAS_uNGF0: Full Analysis Set urinary Nerve Growth Factor subset; LOCF: last observation carried forward; uNGF/Cr: Normalized urinary nerve growth factor (calculated as uNGF/urine creatinine).
† Number of patients with data
Source: Table 12.3.3.1.2

Figure 2 **Scatter Plot of Neutralized uNGF/Cr at Baseline vs Change From Baseline to Week 12 uNGF/Cr (FAS_uNGF)**



Note: The regression line for placebo and solifenacin 5 mg overlay each other. The graph shows 2 extreme outlying data points in the solifenacin treatment arm (patients with baseline value > 200 and change from baseline increase by almost 300 pg/µmol).
Source: Figure 12.3.8.2

Table 8 Post-hoc Analysis of Covariance for $Log_{(Neutralized\ uNGF/Cr)}$ (in pg/µmol) (ANCOVA Model 1a) (FAS_uNGF)

	Solifenacin 5 mg (N = 176)	Solifenacin 10 mg (N = 169)	Pooled Solifenacin (N = 345)	Placebo (N = 178)
Week 6, n†	164	160	324	170
Adj. Geometric Mean	28.6	27.9	28.3‡	23.4
Ratio GM Active drug/placebo	1.22	1.19	1.21	--
95% CI	(1.05; 1.43)	(1.02; 1.39)	(1.05; 1.38)	--
P-value	0.012	0.029	0.006	--
Week 12, n†	172	166	338	175
Adj. Geometric Mean	26.5	26.0	26.3‡	24.0
Ratio GM Active drug/placebo	1.11	1.08	1.10	--
95% CI	(0.95; 1.28)	(0.93; 1.26)	(0.96; 1.25)	--
P-value	0.180	0.286	0.163	--
Week 12 LOCF, n†	176	169	345	178
Adj. Geometric Mean	26.6	26.2	26.4‡	23.9
Ratio GM Active drug/placebo	1.11	1.10	1.11	--
95% CI	(0.96; 1.29)	(0.95: 1.27)	(0.97; 1.26)	--
P-value	0.154	0.214	0.122	--

All P-values based on an ANCOVA model with fixed effects for treatment and region and log(baseline of uNGF/Cr) as covariate. uNGF < LLoQ are set equal to LLoQ before the calculation of log(uNGF/Cr). Results were back transformed to original scale. GM = Geometric Mean (corresponds to LSmean of ANCOVA, back transformed to pg/µmol)

ANCOVA: analysis of covariance; CFB: change from baseline; LOCF: last observation carried forward; FAS_uNGF: Full Analysis Set urinary Nerve Growth Factor.

† Number of patients with data at baseline and post-baseline visit

‡ Adj. Geometric mean for pooled = (Adj. GM 5 mg + Adj. GM 10 mg) / 2

Source: Table 12.3.3.7.1 and Table 12.3.3.1.1

Table 9 Summary of Acidified uNGF/Cr (in pg/µmol) Over Time (FAS_uNGF)

	Solifenacin 5 mg (N = 176)			Solifenacin 10 mg (N = 169)			Pooled Solifenacin (N = 345)			Placebo (N = 178)		
	Median	Mean	(SD)	Median	Mean	(SD)	Median	Mean	(SD)	Median	Mean	(SD)
n† at baseline	175			169			344			178		
Baseline	17.5	27.3	(31.5)	20.8	30.3	(33.9)	18.9	28.8	(32.7)	21.2	27.2	(22.4)
n† at week 6	164			160			324			168		
Week 6	19.9	33.9	(54.5)	21.7	37.7	(87.5)	20.9	35.8	(72.6)	18.9	26.8	(28.2)
CFB at week 6	0.2	6.1	(44.8)	-0.2	7.0	(91.1)	0.1	6.6	(71.5)	0.9	-0.7	(29.0)
n† at week 12	171			164			335			173		
Week 12	19.2	29.9	(47.7)	20.9	34.3	(57.0)	19.8	32.1	(52.4)	18.2	26.4	(23.2)
CFB at week 12	0.9	2.5	(49.4)	0.6	4.0	(44.6)	0.9	3.2	(47.0)	-0.8	-1.1	(24.3)
n† at week 12 LOCF	174			169			343			178		
Week 12 LOCF	19.4	30.0	(47.3)	20.9	34.2	(56.2)	20.1	32.0	(51.9)	18.2	26.4	(23.0)
CFB at week 12 LOCF	0.9	2.7	(48.9)	0.7	3.9	(44.0)	0.9	3.3	(46.5)	-0.5	-0.8	(24.1)

CFB: change from baseline; FAS_uNGF: Full Analysis Set urinary Nerve Growth Factor; LOCF: last observation carried forward; uNGF/Cr: Normalized urinary nerve growth factor (calculated as uNGF/urine creatinine). † Number of patients with data

Source: Table 12.3.3.1.1

Table 10 Analysis of Covariance for $Log_{(Acidified\ uNGF/Cr)}$ (in pg/µmol) (ANCOVA Model 1a) (FAS_uNGF)

	Solifenacin 5 mg (N = 176)	Solifenacin 10 mg (N = 169)	Pooled Solifenacin (N = 345)	Placebo (N = 178)
Week 6, n†	164	160	324	168
Adj. Geometric Mean	26.2	25.0	25.6‡	22.66
Ratio GM Active drug/placebo	1.16	1.10	1.13	--
95% CI	(0.99; 1.35)	(0.95; 1.29)	(0.99; 1.29)	--
P-value	0.061	0.2131	0.071	--
Week 12, n†	171	164	335	173
Adj. Geometric Mean	23.1	22.7	22.9‡	21.04
Ratio GM Active drug/placebo	1.10	1.08	1.09	--
95% CI	(0.95; 1.28)	(0.93; 1.25)	(0.96; 1.24)	--
P-value	0.206	0.3123	0.188	--
Week 12 LOCF, n†	174	169	343	178
Adj. Geometric Mean	23.3	23.2	23.3‡	21.31
Ratio GM Active drug/placebo	1.09	1.09	1.1	--
95% CI	(0.95; 1.26)	(0.94; 1.26)	(0.96; 1.24)	--
P-value	0.231	0.264	0.180	--

All P-values based on an ANCOVA model with fixed effects for treatment and region and log(baseline of uNGF/Cr) as covariate. uNGF < LLoQ are set equal to LLoQ before the calculation of log(uNGF/Cr). Results were back transformed to original scale. GM = Geometric Mean (corresponds to LSmean of ANCOVA, back transformed to pg/µmol)

ANCOVA: analysis of covariance; Full Analysis Set urinary Nerve Growth Factor; LOCF: last observation carried forward; uNGF/Cr: Normalized urinary nerve growth factor (calculated as uNGF/urine creatinine).

† Number of patients with data at baseline and post-baseline visit

‡ Adj. Geometric mean for pooled = (Adj. GM 5 mg + Adj. GM 10 mg) / 2

Source: Table 12.3.3.7.1 and Table 12.3.3.1.1

Table 11 Summary of Neutralized uBDNF/Cr (in pg/µmol) Over Time (FAS_uBDNF)

	Solifenacin 5 mg (N = 170)			Solifenacin 10 mg (N = 166)			Pooled Solifenacin (N = 336)			Placebo (N = 170)		
	Median	Mean	(SD)	Median	Mean	(SD)	Median	Mean	(SD)	Median	Mean	(SD)
n† at baseline	170			166			336			170		
Baseline	37.4	126.9	(374.4)	42.8	248.5	(948.1)	39.5	187.0	(719.1)	40.9	144.2	(292.6)
n† at week 6	157			155			312			162		
Week 6	37.2	170.2	(527.9)	53.3	162.8	(406.7)	42.4	166.5	(470.9)	29.7	172.3	(556.5)
CFB at week 6	2.5	35.5	(405.3)	4.0	-90.5	(974.1)	2.7	-27.1	(745.8)	-2.7	23.1	(522.5)
n† at week 12	162			160			322			167		
Week 12	39.5	156.6	(492.2)	43.7	162.3	(379.5)	40.8	159.4	(439.1)	33.3	118.4	(262.6)
CFB at week 12	0.9	28.1	(433.4)	1.4	8.1	(444.1)	0.9	18.2	(438.2)	-1.2	-27.6	(320.4)
n† at week 12 LOCF	170			166			336			170		
Week 12 LOCF	39.5	158.1	(483.0)	43.7	160.4	(373.0)	41.5	159.2	(431.6)	32.8	116.9	(260.5)
CFB at week 12 LOCF	0.2	31.1	(426.9)	0.6	-88.1	(980.6)	0.6	-27.8	(754.4)	-1.0	-27.4	(317.6)

Wilcoxon rank sum test for treatment comparisons of active treatment versus placebo: P-values in range 0.004 to 0.292. CFB: change from baseline; FAS_uBDNF: Full Analysis Set urinary Brain Derived Neurotrophic Factor; LOCF: last observation carried forward.

† Number of patients with data

Source: Table 12.3.4.1.1

Table 12 Analysis of Covariance for Change From Baseline in $Log_{(uBDNF/Cr)}$ (in pg/µmol) (ANCOVA Model 1a) (FAS_uBDNF)

	Solifenacin 5 mg (N = 176)	Solifenacin 10 mg (N = 169)	Pooled Solifenacin (N = 345)	Placebo (N = 178)
Week 6, n†	157	155	312	162
Adj. Geometric Mean	54.2	58.4	56.3‡	42.5
Ratio GM Active drug/placebo	1.27	1.37	1.32	--
95% CI	(0.98; 1.65)	(1.06; 1.78)	(1.06; 1.66)	--
P-value	0.069	0.018	0.015	--
Week 12, n†	162	160	322	167
Adj. Geometric Mean	54.4	53.3	53.9‡	44.8
Ratio GM Active drug/placebo	1.22	1.19	1.20	--
95% CI	(0.94; 1.57)	(0.92; 1.54)	(0.96; 1.50)	--
P-value	0.137	0.184	0.103	--
Week 12 LOCF, n†	170	166	336	170
Adj. Geometric Mean	57.6	54.4	56.0‡	46.2
Ratio GM Active drug/placebo	1.25	1.18	1.21	--
95% CI	(0.97; 1.61)	(0.91; 1.52)	(0.97; 1.51)	--
P-value	0.087	0.208	0.086	--

All P-values based on an ANCOVA model with fixed effects for treatment and region and log(baseline of uBDNF/Cr) as covariate. uBDNF < LLoQ are set equal to LLoQ before the calculation of log(uBDNF /Cr). Results were back transformed to original scale. GM = Geometric Mean (corresponds to LSmean of ANCOVA, back transformed to pg/µmol)

ANCOVA: analysis of covariance; FAS_uBDNF: Full Analysis Set urinary Brain Derived Neurotrophic Factor; LOCF: last observation carried forward; uBDNF/Cr: Normalized urinary nerve growth factor (calculated as uNGF/urine creatinine).

† Number of patients with data at baseline and post-baseline visit

‡ Adj. Geometric mean for pooled = (Adj. GM 5 mg + Adj. GM 10 mg) / 2

Source: Table 12.3.4.7.1 and Table 12.3.4.1.1

Table 13 Summary Overview of Descriptive Statistics at Baseline and Analysis of Covariance for Change from Baseline at Week 12 LOCF in Secondary Efficacy Variables Derived From Micturition Diary. Part 1: Results for FAS_BWT

Statistics	Solifenacin 5 mg (N = 171)	Solifenacin 10 mg (N = 155)	Pooled Solifenacin (N = 326)	Placebo (N = 175)
Mean Number of Events (Micturitions Plus Incontinence Episodes) per 24 Hours				
n† at baseline	142	132	274	151
Baseline, mean (SD)	10.48 (4.00)	9.60 (3.56)	10.06 (3.81)	9.96 (3.16)
n† at week 12 LOCF	137	122	259	144
LSmean CFB at week 12 LOCF	-2.066	-1.923	--	-1.387
Estimated difference to placebo	-0.680	-0.536	-0.608	--
95% CI	(-1.212; -0.148)	(-1.084; 0.011)	(-1.071; -0.145)	--
P-value	0.012	0.055	0.010	--
Mean Number of Micturitions per 24 Hours				
n† at baseline	142	132	274	151
Baseline, mean (SD)	9.57 (4.39)	8.55 (3.53)	9.08 (4.02)	9.21 (3.39)
n† at week 12 LOCF	137	122	259	144
LSmean CFB at week 12 LOCF	-1.651	-1.689	--	-1.235
Estimated difference to placebo	-0.416	-0.454	-0.435	--
95% CI	(-0.957; 0.126)	(-1.013; 0.105)	(-0.906; 0.037)	--
P-value	0.132	0.111	0.071	--
Total Urgency Frequency Score of PPIUS				
n† at baseline	142	132	274	151
Baseline, mean (SD)	69.90 (33.82)	63.85 (29.08)	66.99 (31.71)	67.25 (27.97)
n† at week 12 LOCF	137	122	259	144
LSmean CFB at week 12 LOCF	-20.606	-18.832	--	-14.047
Estimated difference to placebo	-6.559	-4.785	-5.672	--
95% CI	(-11.070; -2.048)	(-9.433; -0.137)	(-9.600; -1.744)	--
P-value	0.004	0.044	0.005	--

All P-values based on an ANCOVA model with fixed effects for treatment and region and baseline of micturitions as covariate.

ANCOVA: analysis of covariance; CFB: change from baseline; FAS_BWT: Full Analysis Set Bladder Wall Thickness; LOCF: Last observation carried forward; LSmean: least square mean; PPIUS: Patient Perception of Intensity of Urgency Scale

† Number of patients with data

Source: Table 12.3.5.1 and Table 12.3.5.1.2

Table 14 Summary Overview of Descriptive Statistics at Baseline and Analysis of Covariance for Change from Baseline at Week 12 LOCF in Secondary Efficacy Variables Derived From Micturition Diary. Part 2: Results for FAS, Patients with Events at Baseline Only

Statistics	Solifenacin 5 mg (N = 181)	Solifenacin 10 mg (N = 173)	Pooled Solifenacin (N = 354)	Placebo (N = 186)
Mean Number of Urgency Events With PPIUS Grade 3 or 4 per 24 Hours				
n† at baseline	140	133	273	147
Baseline, mean (SD)	4.17 (3.34)	4.30 (2.87)	4.23 (3.12)	4.25 (2.84)
n† at week 12 LOCF	133	124	257	139
LSmean CFB at week 12 LOCF	-2.161	-1.816	--	-1.591
Estimated difference to placebo	-0.570	-0.225	-0.397	--
95% CI	(-1.074; -0.066)	(-0.738; 0.288)	(-0.835; 0.040)	--
P-value	0.027	0.389	0.075	--
Mean Number of Urgency Micturitions With PPIUS Grade 3 or 4 per 24 Hours				
n† at baseline	136	124	260	145
Baseline, mean (SD)	3.52 (3.15)	3.53 (2.63)	3.53 (2.90)	3.65 (2.61)
n† at week 12 LOCF	130	117	247	137
LSmean CFB at week 12 LOCF	-1.858	-1.690	--	-1.410
Estimated difference to placebo	-0.448	-0.280	-0.364	--
95% CI	(-0.892; -0.004)	(-0.736; 0.175)	(-0.750; 0.022)	--
P-value	0.048	0.227	0.064	--
Mean Number of Incontinence Events per 24 Hours				
n† at baseline	63	82	145	71
Baseline, mean (SD)	2.15 (2.36)	2.09 (2.37)	2.11 (2.36)	1.66 (1.78)
n† at week 12 LOCF	62	74	136	67
LSmean CFB at week 12 LOCF	-1.344	-0.962	--	-0.736
Estimated difference to placebo	-0.609	-0.227	-0.418	--
95% CI	(-1.092; -0.125)	(-0.688; 0.235)	(-0.828; -0.007)	--
P-value	0.014	0.334	0.046	--
Mean Number of Urgency Incontinence Events With PPIUS Grade 3 or 4 per 24 Hours				
n† at baseline	57	76	133	62
Baseline, mean (SD)	1.85 (2.24)	1.74 (1.98)	1.79 (2.09)	1.54 (1.66)
n† at week 12 LOCF	56	69	125	59
LSmean CFB at week 12 LOCF	-1.203	-0.873	--	-0.798
Estimated difference to placebo	-0.406	-0.075	-0.241	--
95% CI	(-0.845; 0.033)	(-0.492; 0.341)	(-0.613; 0.132)	--
P-value	0.070	0.721	0.205	--
Mean Number of Urgency Incontinence Events With PPIUS Grade 4 per 24 Hours				
n† at baseline	49	67	116	51
Baseline, mean (SD)	1.45 (1.62)	1.46 (1.75)	1.45 (1.69)	1.47 (1.44)
n† at week 12 LOCF	49	61	110	50
LSmean CFB at week 12 LOCF	-0.845	-0.609	--	-0.649
Estimated difference to placebo	-0.196	0.040	-0.078	--
95% CI	(-0.627; 0.236)	-0.369; 0.449)	(-0.446; 0.290)	--
P-value	0.372	0.847	0.677	--

Footnotes are provided on next page

All P-values based on an ANCOVA model with fixed effects for treatment and region and baseline of micturitions as covariate.

ANCOVA: analysis of covariance; CFB: change from baseline; FAS_BWT: Full Analysis Set Bladder Wall Thickness; LOCF: Last observation carried forward; LSmean: least square mean; PPIUS: Patient Perception of Intensity of Urgency Scale

† Number of patients with data

Source: Table 12.3.5.1a and Table 12.3.5.1.2a

Table 15 Summary Overview of Descriptive Statistics at Baseline, Logistic Regression Analysis or Analysis of Covariance for Change from Baseline at Week 12 LOCF in Other Patient Reported Outcomes (FAS_BWT)

	Solifenacin 5 mg (N = 171)	**Solifenacin 10 mg (N = 155)**	**Pooled Solifenacin (N = 326)**	**Placebo (N = 175)**
PPBC				
n ‡	171	155	326	175
Baseline, mean (SD)	4.20 (0.98)	4.10 (1.05)	4.10 (1.01)	3.90 (1.08)
≥ 1 point improvement at Week 12 LOCF, n (%)	123 (71.9%)	114 (74.5%)	237 (73.1%)	87 (49.7%)
≥ 2 point improvement at Week 12 LOCF, n (%)	68 (39.8%)	68 (44.4%)	136 (42.0%)	48 (27.4%)
Odds ratio ≥ 1 point improvement from baseline, relative to placebo	2.49	3.15	2.80	
95% CI	(1.54; 4.04)	(1.89; 5.25)	(1.84; 4.26)	
P-value	< 0.001	< 0.001	< 0.001	
Odds ratio ≥ 2 points improvement from baseline, relative to placebo	1.60	2.06	1.82	
95% CI	(1.00; 2.57)	(1.27; 3.34)	(1.20; 2.76)	
P-value	0.050	0.003	0.005	
UB-VAS				
n† at baseline	171	155	326	175
Baseline, mean (SD)	58.80 (24.14)	57.40 (23.72)	58.20 (23.92)	56.50 (24.86)
n† at week 12 LOCF	171	153	324	175
LSmean CFB at week 12 LOCF	-25.387	-27.399	--	-11.906
Estimated difference to placebo	-13.480	-15.493	-14.487	--
95% CI	(-18.714; -8.247)	(-20.886; -10.099)	(-19.058; -9.915)	--
P-value	< 0.001	< 0.001	< 0.001	--
TS-VAS				
n† at baseline	171	155	326	175
Baseline, mean (SD)	44.30 (35.38)	39.20 (36.67)	41.90 (36.04)	42.10 (33.99)
n† at week 12 LOCF	171	153	324	175
LSmean CFB at week 12 LOCF	24.928	28.092	--	17.299
Estimated difference to placebo	7.629	10.793	9.211	--
95% CI	(1.174; 14.083)	(4.138; 17.447)	(3.575; 14.846)	--
P-value	0.021	0.002	0.001	--

Table continued on next page

	Solifenacin 5 mg (N = 171)	Solifenacin 10 mg (N = 155)	Pooled Solifenacin (N = 326)	Placebo (N = 175)
EQ-5D VAS				
n† at baseline	171	155	326	175
Baseline, mean (SD)	67.00 (20.77)	67.20 (19.05)	67.10 (19.94)	67.60 (19.74)
n† at week 12 LOCF	171	153	324	175
LSmean CFB at week 12 LOCF	6.577	6.920	--	5.665
Estimated difference to placebo	0.912	1.255	1.084	--
95% CI	(-2.207; 4.030)	(-1.960; 4.470)	(-1.641; 3.808)	--
P-value	0.566	0.443	0.435	--

All P-values, except for PPBC, based on an ANCOVA model with fixed effects for treatment and region and baseline of VAS as covariate. PPBC analyzed with logistic regression model, adjusting for baseline.

CFB: change from baseline; EQ-5D VAS: EuroQoL 5-Dimension Questionnaire Visual Analogue Scale; FAS_BWT: Full Analysis Set Bladder Wall Thickness; LOCF: last observation carried forward; LSmean: least square mean; TS-VAS: Treatment Satisfaction – Visual Analogue Scale; UB-VAS: Urgency Bother – Visual Analogue Scale

† Number of patients with data.

‡ Number of patients with value at baseline; n might slightly differ at each visit.

Source: Table 12.3.5.4.1, Table 12.3.5.4..4, Table 12.3.5.4.5, Table 12.3.5.5.1, Table 12.3.5.5.2, Table 12.3.5.6.3 and Table 12.3.5.6.4

Table 16 Summary Table of Treatment-emergent Adverse Events (SAF)

		Solifenacin 5 mg (N = 182)	Solifenacin 10 mg (N = 175)	Placebo (N = 186)	Total (N = 543)
N (%) with any TEAE		41 (22.5%)	57 (32.6%)	53 (28.5%)	151 (27.8%)
Total TEAEs		81	85	69	235
N (%) with serious TEAEs (incl. death)		1 (0.5%)	4 (2.3%)	1 (0.5%)	6 (1.1%)
Total serious TEAEs		6	4	1	11
N (%) deaths		1 (0.5%)	0	0	1 (0.2%)
N (%) discontinued due to TEAE†		6 (3.3%)	2 (1.1%)	3 (1.6%)	11 (2.0%)
N (%) with TEAE by severity	Mild	28 (15.4%)	37 (21.1%)	32 (17.2%)	97 (17.9%)
	Moderate	14 (7.7%)	19 (10.9%)	20 (10.8%)	53 (9.8%)
	Severe	5 (2.7%)	6 (3.4%)	5 (2.7%)	16 (2.9%)
N (%) with treatment-related ‡ TEAEs		25 (13.7%)	37 (21.1%)	20 (10.8%)	82 (15.1%)
Total treatment-related TEAEs		41	54	22	117

TEAE: treatment-emergent adverse event

† Only AEs that were the primary reason for discontinuation are taken into account.

‡ AEs that are possibly or probably treatment-related, or for which the relationship is missing.

Source: Table 12.6.1.1.2 and Table 12.6.1.4.

Table 17 Treatment-emergent Adverse Events in Two or More Patients Overall (SAF)

MedDRA System-Organ Class Preferred Term	Solifenacin 5 mg (N = 182) n	 (%)	Solifenacin 10 mg (N = 175) n	 (%)	Placebo (N = 186) n	 (%)	Total (N = 543) n	 (%)
Overall	**41**	**(22.5%)**	**57**	**(32.6%)**	**53**	**(28.5%)**	**151**	**(27.8%)**
Gastrointestinal disorders	**24**	**(13.2%)**	**40**	**(22.9%)**	**15**	**(8.1%)**	**79**	**(14.5%)**
Dry mouth	16	(8.8%)	30	(17.1%)	2	(1.1%)	48	(8.8%)
Constipation	8	(4.4%)	9	(5.1%)	7	(3.8%)	24	(4.4%)
Nausea	2	(1.1%)	1	(0.6%)	2	(1.1%)	5	(0.9%)
Abdominal pain upper	0		2	(1.1%)	1	(0.5%)	3	(0.6%)
Diarrhoea	0		0		2	(1.1%)	2	(0.4%)
Dyspepsia	1	(0.5%)	1	(0.6%)	0		2	(0.4%)
Infections and infestations	**10**	**(5.5%)**	**14**	**(8.0%)**	**18**	**(9.7%)**	**42**	**(7.7%)**
Urinary tract infection	0		6	(3.4%)	6	(3.2%)	12	(2.2%)
Nasopharyngitis	3	(1.6%)	1	(0.6%)	5	(2.7%)	9	(1.7%)
Bronchitis	2	(1.1%)	1	(0.6%)	2	(1.1%)	5	(0.9%)
Gastroenteritis	1	(0.5%)	1	(0.6%)	0		2	(0.4%)
Upper respiratory tract infection	1	(0.5%)	1	(0.6%)	0		2	(0.4%)
General disorders and administration site conditions	**3**	**(1.6%)**	**3**	**(1.7%)**	**7**	**(3.8%)**	**13**	**(2.4%)**
Fatigue	1	(0.5%)	1	(0.6%)	1	(0.5%)	3	(0.6%)
Influenza like illness	0		1	(0.6%)	1	(0.5%)	2	(0.4%)
Oedema peripheral	0		1	(0.6%)	1	(0.5%)	2	(0.4%)
Musculoskeletal and connective tissue disorders	**3**	**(1.6%)**	**3**	**(1.7%)**	**6**	**(3.2%)**	**12**	**(2.2%)**
Pain in extremity	0		0		3	(1.6%)	3	(0.6%)
Back pain	1	(0.5%)	0		1	(0.5%)	2	(0.4%)
Myalgia	0		1	(0.6%)	1	(0.5%)	2	(0.4%)
Nervous system disorders	**5**	**(2.7%)**	**3**	**(1.7%)**	**4**	**(2.2%)**	**12**	**(2.2%)**
Headache	3	(1.6%)	1	(0.6%)	1	(0.5%)	5	(0.9%)
Dizziness	1	(0.5%)	0		1	(0.5%)	2	(0.4%)
Sciatica	0		1	(0.6%)	1	(0.5%)	2	(0.4%)
Eye disorders	**3**	**(1.6%)**	**4**	**(2.3%)**	**1**	**(0.5%)**	**8**	**(1.5%)**
Vision blurred	1	(0.5%)	3	(1.7%)	0		4	(0.7%)
Respiratory, thoracic and mediastinal disorders	**3**	**(1.6%)**	**1**	**(0.6%)**	**3**	**(1.6%)**	**7**	**(1.3%)**
Cough	0		0		2	(1.1%)	2	(0.4%)
Dyspnoea	1	(0.5%)	0		1	(0.5%)	2	(0.4%)
Investigations	**2**	**(1.1%)**	**2**	**(1.1%)**	**1**	**(0.5%)**	**5**	**(0.9%)**
Weight increased	2	(1.1%)	1	(0.6%)	0		3	(0.6%)
Renal and urinary disorders	**2**	**(1.1%)**	**1**	**(0.6%)**	**2**	**(1.1%)**	**5**	**(0.9%)**
Residual urine	2	(1.1%)	0		0		2	(0.4%)
Skin and subcutaneous tissue disorders	**3**	**(1.6%)**	**0**		**2**	**(1.1%)**	**5**	**(0.9%)**
Rash	1	(0.5%)	0		1	(0.5%)	2	(0.4%)
Vascular disorders	**1**	**(0.5%)**	**1**	**(0.6%)**	**2**	**(1.1%)**	**4**	**(0.7%)**
Hypertension	1	(0.5%)	1	(0.6%)	2	(1.1%)	4	(0.7%)
Psychiatric disorders	**1**	**(0.5%)**	**1**	**(0.6%)**	**0**		**2**	**(0.4%)**
Insomnia	1	(0.5%)	1	(0.6%)	0		2	(0.4%)

Source: Table 12.6.1.2.2.