Name of Sponsor/Company: Helsinn Healthcare SA	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Test Drug Netupitant	Volume:	
Name of Active Ingredient: Netupitant	Page:	

Title of Study: A Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Prospective Study to Assess the Efficacy, Safety and Tolerability of Three Oral Doses of Netupitant Given Once a Day (50, 100 and 200 mg) vs Placebo in Patients with Overactive Bladder.

Co-ordinating Investigator: Prof Haab, France

Study Centers:
This study was performed in 4 countries in Europe at 21 active centers (France 5, Germany 4, Romania 7, and Russia 5 centers).

Publication (Reference): none | **Phase of Development:** II

Studied Period:
Date of first patient first visit: 24 Nov 2008
Date of last patient last visit: 06 May 2010

Objectives:
Primary objective: To assess efficacy of three different, repeated oral doses of netupitant in patients with symptoms of overactive bladder (OAB).
Secondary objective: To assess safety and tolerability of three different, repeated oral doses of netupitant in patients with symptoms of OAB.

Methodology:
This was a phase II, international, multi-center, randomized, double-blind, parallel group, prospective study assessing the efficacy, safety and tolerability of 8 weeks of treatment with 3 different oral doses of netupitant versus placebo in the symptomatic treatment of OAB.
The patients participated in the study for 14 weeks. The treatment phase was preceded by a single-blind, run-in phase lasting 2 weeks, during which a placebo treatment was administered to the patients. Patients fulfilling the selection criteria at the end of the single-blind, run-in treatment period were randomized 1:1:1:1 into 1 of the 4 treatment groups (placebo, netupitant 50 mg, or 100 mg, or 200 mg) and treated for 8 weeks in a double-blind fashion. Four weeks after the end of the double-blind treatment period (or after early discontinuation) the patient returned to the clinic to undergo a final, follow-up visit.

Number of Patients (Planned and Analyzed):

Planned	It was anticipated that 400 patients had to be screened and 240 had to be randomized to achieve a total of 200 complete and evaluable patients.
Screened	325 patients (patients participating in the run-in period and receiving run-in placebo).
Randomized	246 patients
Safety Set	243 patients
Full Analysis Set (FAS)	233 patients
Per Protocol Set (PPS)	193 patients

Diagnosis and Main Criteria for Inclusion:
Female and male outpatients of at least 18 years of age, with symptoms of OAB lasting

for more than 6 months, were eligible for the single-blind, run-in treatment period. If, at the end of this period, the patients reported 10 - 20 micturitions/24 hours at each diary day, and ≥3 urgency episodes with or without ≥3 incontinence episodes during a Baseline 3-day diary period, and if they fulfilled further selection criteria, they were eligible for the double-blind treatment period.

Main Criteria for Exclusion:
Stress incontinence or mixed incontinence with prevailing stress incontinence, urinary incontinence due to causes other than OAB, residual urinary volume >200 ml, polyuria (diuresis >3L/24 hours), previous or concomitant treatment with or known contraindications to neurokinin 1 (NK_1) receptor antagonists, concomitant treatment with anti-muscarinic drugs, history of or predisposition to cardiac conduction abnormalities, history of interstitial cystitis or bladder related pain, neurological disease that could affect bladder function or muscle strength, certain types of diabetes and neoplastic disorders were the main criteria for not including a patient into the study or excluding a patient prior to randomization in the double-blind treatment phase.

Duration of Treatment:
The patients participated in the study for 14 weeks. The treatment phase was preceded by a single-blind, run-in phase lasting 2 weeks, during which a placebo treatment was administered to the patients. During the 8-week double-blind treatment phase patients received 1 of the 4 treatments (placebo, netupitant 50 mg, or 100 mg, or 200 mg). Four weeks after the end of the double-blind treatment period (or after early discontinuation) the patient returned to the clinic to undergo a final, follow-up visit.

Criteria for Evaluation:

Efficacy:
The variables used to evaluate the efficacy of the investigational drug were the following:

- Percentage change from Baseline in the average number of daily micturitions at Week 8 (primary variable).
- Percentage change from Baseline in the average number of daily micturitions at Week 4 and 12 (secondary variables)

Additional secondary variables evaluated at Week 8 were:

- Absolute change from Baseline in the average number of daily micturitions.
- Change from Baseline in the total number of Urge Urinary Incontinence (UUI) episodes, defined as accidental urine leakage because of an urge or pressure to urinate and the patient felt that he/she could not make it to the bathroom. Urgency was defined as a strong urge to urinate immediately. Episodes of stress incontinence were excluded.
- Change from Baseline in the total number of Urinary Incontinence (UI) episodes.
- Absolute change from Baseline in the total number of Urgency episodes.
- Change from Baseline in the total number of pads used.
- Absolute change from Baseline in the quality of life (QoL) measured by the King's Health Questionnaire (KHQ).
- Change from Baseline in the Patient Perception of Bladder Condition (PPBC).

Safety:
Safety assessments were performed at each visit including early discontinuation and consisted of:

- Adverse events
- Clinical laboratory parameters
- Vital signs
- 12-lead electrocardiogram (ECG)
- Physical examination

.

Drug concentration: At selected sites, blood samples were collected for measuring plasma concentrations of netupitant at each visit except Visit 1.

Statistical Methods:
The primary efficacy variable was the percentage change from Baseline in the average number of daily micturitions at Week 8. The primary analysis was based on the FAS. Missing diary data at Week 4 or at Week 8 were replaced using the last observation carried forward (LOCF) method after Baseline. Missing Baseline diary data were not imputed.

The study hypothesis was that at least one dose level of netupitant is superior to placebo, considering the percentage change from Baseline in the average number of daily micturitions at Week 8. In order to keep the overall Type I error of the study at 5%, a "step-down hypothesis testing procedure" was employed as follows:
The netupitant 200 mg/day group was tested against the placebo arm. The null hypothesis was that the active treatment is not different from placebo. The alternative hypothesis was that the active treatment is different from placebo. If the null hypothesis was rejected (i.e. $p<0.05$), the same approach was used for the comparison of the netupitant 100 mg/day group against the placebo group. Again, if the null hypothesis was rejected (i.e. $p<0.05$) also for that group, the same analysis was performed to compare the netupitant 50 mg/day group against the placebo group. In case the first test failed the same approach was applied to the 100 mg/day group with alpha = 2.5% (2-sided). Again, if the null hypothesis was rejected (i.e. $p<0.025$) also for that group, the same analysis was performed to compare the 50 mg/day group against the placebo group.
The hypotheses were tested using an analysis of covariance (ANCOVA) model including terms for treatment, gender, region, age group and Baseline average number of daily micturitions. Normal distribution assumptions for micturitions were checked graphically at the blind data review meeting (BDRM) in order to apply the ANCOVA model. A transformation of the data was not required. The categorical variables (gender, age group, region) were investigated at the 10% significance level. In case region had significant impact, an additional sensitivity analysis was to be performed by including "treatment by region" interaction in the above mentioned ANCOVA model. If the interaction had a significant effect (10% level) a Gail and Simon test at the 5% significance level was to be used to investigate if a qualitative interaction was present.
For the primary endpoint a sensitivity analysis was done for the FAS where diary data were presented as they were observed, i.e. without replacement of missing values using LOCF approach. An analysis based on the PPS was also performed for supportive and sensitivity purposes.
Furthermore descriptive statistics were provided for the primary endpoint based on the FAS in the following subgroups: gender, age group (<65 years and ≥65 years), region (France/Germany, Romania, and Russia), prior OAB medication (patients with and without prior OAB medication), and incontinence (patients with and without incontinence episodes).
For the secondary efficacy endpoints analyses were performed for the FAS only with the exception of the absolute change from Baseline in the average number of daily micturitions, which was also analyzed for the PPS. Data were presented as observed, i.e. without replacement of missing values. In addition, for percentage change from Baseline in the average number of daily micturitions at Week 4 there was an additional presentation with missing data replaced by the LOCF method. All results were interpreted in a descriptive manner. Therefore, no adjustments were made for multiple comparisons on secondary endpoints except the percentage change from Baseline in the average number of daily micturitions at Week 4 and 12 (tested with the same step-wise approach as used for the primary endpoint). Normal distribution assumptions for micturitions and urgency episodes were checked graphically at the BDRM in order to apply the ANCOVA model. A transformation of the data was not required. For the FAS, there was an additional presentation of the secondary efficacy endpoints by region, gender, age group, prior OAB medication, and incontinence.
For statistical testing of the change from Baseline in total number of UUI episodes, UI episodes and number of pads used at Week 8, a Chi-square test with 3 categories

(improvement, no change, deterioration) was performed. For interpretation of the test results, pairwise comparisons of each single active group vs. the placebo group were investigated at Week 8. If at least one result of these pairwise comparisons at Week 8 was statistically significant (α = 5%), the results at Week 12 were reviewed to explore the possible duration of the treatment effects. A subgroup analysis for the above mentioned subgroups was performed as well.
For the absolute change from Baseline in total number of urgency episodes at Week 8 the ANCOVA model as described for the primary endpoint was applied with the Baseline value in the model adapted to this endpoint.
For statistical testing of the absolute change from Baseline in QoL measured by KHQ at Week 8, the ANCOVA model as described for the primary endpoint was applied for the summary scores for each of the 9 domains (i.e. parts 1 and 2) with the Baseline value in the model adapted accordingly. For interpretation of the test results, pairwise comparisons of each single active group vs. the placebo group were investigated at Week 8. If at least one result of these pair-wise comparisons for at least one domain at Week 8 was statistically significant (α = 5%), the results of all domains at Week 12 were reviewed to explore the possible duration of the treatment effects.
For statistical testing of the change from Baseline in PPBC at Week 8, a Chi-square test was applied. Summary tables present p-values for all time points. For interpretation of the test results, if at least one result of these pair-wise comparisons at Week 8 was statistically significant (α = 5%), the results at Week 12 were reviewed to explore the possible duration of the treatment effects. The analysis for the above-mentioned subgroups was performed as well.
All safety analyses were performed for the safety set. All safety results were presented with the appropriate descriptive statistics and were listed. The incidence of treatment emergent adverse events (TEAEs) was calculated overall, by category, by system organ class (SOC) and by preferred term (PT). Subgroup analyses by region, gender, age group, prior OAB medication, and incontinence were performed for the overall summary of TEAEs. Laboratory data were summarized using mean tables, frequency tables, shift tables, and shift plots. Vital signs and physical examination data were listed and summarized by treatment group. ECG data recorded on scheduled visits were summarized by treatment group showing the interpretation of the Investigator and the cardiologist for each ECG at each visit. For all ECGs heart rate, RR, PR, QRS, QT, QTcB and QTcF were analyzed. Summary statistics including mean, median, standard deviation and range were presented for each visit as well as the change from Baseline. In addition to this central tendency analysis an outlier analysis for data reported at Visits 3 (Week 1) to 6 (Week 8) was performed. The morphological changes of interest included changes in rhythm, morphology, conduction, ectopy, myocardial infarction patterns, ST segment depression or elevation, change in T-waves and presence or absence of abnormal U-waves.

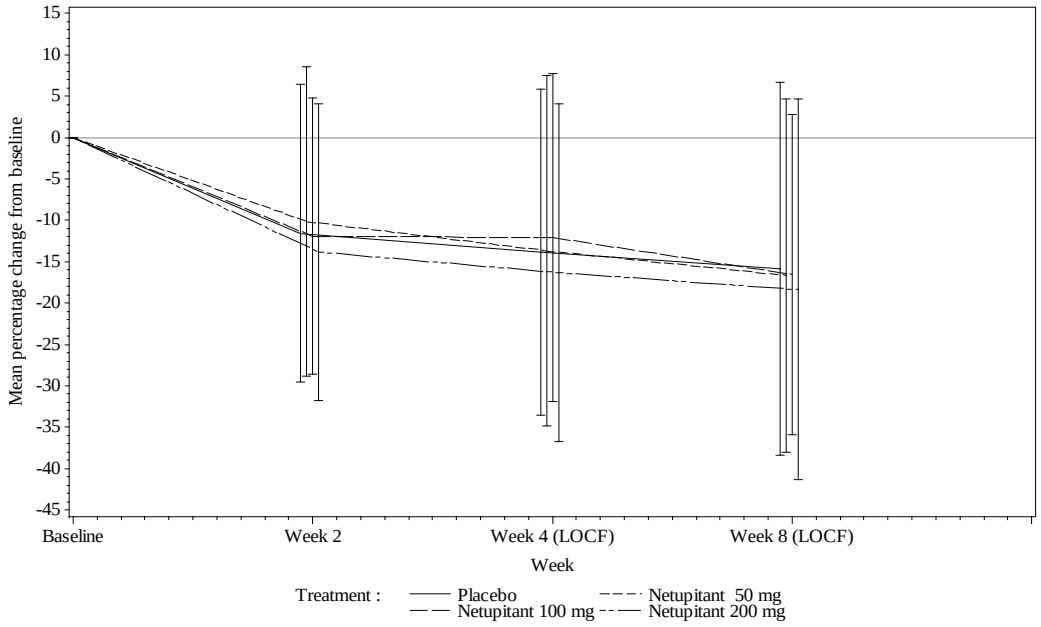
Summary – Conclusions:

Efficacy Results:

The primary efficacy variable was the percentage change from Baseline in the average number of daily micturitions at Week 8 based on the FAS and using the LOCF method to impute missing diary data. In each of the 4 treatment groups the data ranges (i.e. the differences between minimum and maximum values) were quite large, both at Baseline and after 8 weeks of treatment. The mean of the average number of micturitions per day decreased from approximately 13 micturitions at the randomization visit to approximately 11 micturitions at Week 8.

The percentage change from Baseline was similar in each of the 4 treatment groups (LSMeans about -14% in the placebo group to about -16% in the netupitant 200 mg group):

Percentage Change from Baseline in the Average Number of Daily Micturitions: Time Course (Mean ± SD) with LOCF – Full Analysis Set (N = 233)



SD = standard deviation
LOCF = last observation carried forward approach applied for Week 4 and Week 8

The difference between netupitant 200 mg/day and placebo was not statistically significant (significance level 5%, 2-sided) nor was the difference between netupitant 100 mg/day and placebo (significance level 2.5%, 2-sided):

Percentage Change from Baseline in the Average Number of Daily Micturitions at Week 8: ANCOVA Model with LOCF Approach – Full Analysis Set (N = 233)

	Placebo (N = 59)	Netupitant 50 mg (N = 60)	Netupitant 100 mg (N = 59)	Netupitant 200 mg (N = 55)
n	59	60	59	55
LSMeans (SE)	-13.85 (2.982)	-14.87 (2.833)	-15.09 (2.862)	-16.17 (3.064)
LSMeans diff (SE)		-1.02 (3.910)	-1.24 (3.914)	-2.33 (3.969)
95% CI LSMeans diff		[-8.72, 6.69]	[-8.96, 6.47]	[-10.15, 5.50]
ANCOVA p-value		0.7946	0.7507	0.5585

N = number of patients in specified treatment group
n = number of patients with data available
ANCOVA = analysis of covariance (level of significance: 5.0% 2-sided)
Baseline = last available value prior to first administration of double-blind study drug
CI = confidence interval
LOCF = last observation carried forward
LSMeans = means adjusted for covariates
LSMeans diff = difference of LSMeans compared to placebo
SE = standard error
Note: Weeks are counted from start of double-blind treatment (and not from Screening).
LSMeans, LSMeans diff, SE of LSMeans, SE of LSMeans diff, 95% CI and ANCOVA p-values are based on an ANCOVA model with factors Baseline value, treatment, gender, region and age group.

The study thus failed to demonstrate superiority of netupitant versus placebo with regard to the primary endpoint variable. The factor region had a significant impact on the results (p-value from ANCOVA: 0.0010). The inclusion of the treatment by region interaction in the model had no relevant impact on the overall outcome of the ANCOVA. A Gail and Simon test, performed to investigate if a qualitative interaction was present, was not statistically significant for any of the treatment comparisons. Results from sensitivity analyses based on the FAS (without LOCF) and the PPS were in agreement with the main analysis.

In addition to the analysis at Week 8 the percentage change from Baseline in the average number of daily micturitions was evaluated at weeks 2, 4 and 12. The absolute change from Baseline in the average number of daily micturitions at Weeks 2, 4, 8, and 12 was evaluated as well. Again, statistically significant differences for the netupitant groups relative to placebo were not detected (tests performed at Week 4 and 12 for percentage change and at Week 8 for absolute change).

The total number of UI, UUI, urgency episodes, and number of pads used for each visit considered was calculated as sum of occurrences on 3 valid diary days.

During the course of the study 35.6% to 76.4% of patients in the 4 treatment groups reported having no UUI episodes and 33.9% to 65.5% of patients reported having no UI episodes at all.

For UUI episodes a large discrepancy between treatment groups was already apparent at Baseline (35.6% to 63.6% of patients without UUI episodes and 8.5% to 18.6% of patients with >10 episodes). At Week 8 and Week 12 improvements relative to Baseline were considerably more frequent than deteriorations in all 4 treatment groups. In the group of patients receiving 100 mg netupitant/day the largest percentage with improvement (45.8% at Week 8 and 42.4% at Week 12) was observed. This resulted in a statistically significant difference in change from Baseline compared to placebo at

both visits, which most likely has to be attributed to the heterogeneity of Baseline values.
As for the occurrence of UUI episodes, a large discrepancy between treatment groups in the percentage of patients experiencing UI episodes was already apparent at Baseline (33.9% to 61.8% of patients without UI episodes and 16.9% to 32.2% of patients with >10 episodes). At Week 8 improvements relative to Baseline were considerably more frequent than deteriorations in all 4 treatment groups. None of the 3 active treatment groups was statistically significantly different from placebo with regard to the change from Baseline in total number of UI episodes. Results for the FAS at Week 12 were similar to those obtained at Week 8.
The mean number of urgency episodes at Baseline was comparable between treatment groups (25.80 in the netupitant 50 mg group to 26.96 in the netupitant 200 mg group). The number of episodes decreased in all 4 treatment groups during the course of the study. None of the 3 active treatment groups was statistically significantly different from placebo with regard to the absolute change from Baseline in total number of urgency episodes. There was, however, a trend for the highest decrease to occur in the netupitant 100 mg group. Results for the FAS at Week 12 were similar to those obtained at Week 8.
During the course of the study 33.9% to 69.1% of patients reported not using pads in the 4 treatment groups. As for the occurrence of UUI episodes and UI episodes, a large discrepancy between treatment groups was already apparent at Baseline (42.4% to 61.8% of patients not using pads and 9.1% to 18.6% of patients using >6 pads). At Week 8 improvements relative to Baseline were considerably more frequent than deteriorations in all 4 treatment groups. None of the 3 active treatment groups was statistically significantly different from placebo with regard to the change from Baseline in total number of pads used. Generally, a high number of patients had no data for use of pads. Results for the FAS at Week 12 were similar to those obtained at Week 8.
In addition QoL was evaluated with 2 questionnaires (KHQ and PPBC) at Week 8 and Week 12.
In the following KHQ part 1 and part 2 domains statistically significant differences between placebo and active treatment were observed for the change from Baseline to Week 8 or Week 12:

- Incontinence impact
    - Week 8: netupitant 100 mg and netupitant 200 mg
- Physical limitations
    - Week 8: netupitant 100 mg and 200 mg
- Social limitations
    - Week 8: netupitant 200 mg
- Severity measures
    - Week 8: netupitant 100 mg and 200 mg
    - Week 12: netupitant 50 mg, 100 mg and 200 mg

In all cases the treatment differences were in favor of the active treatment (netupitant).
The proportion of patients reporting to be affected “a lot” (as opposed to “a little” or “moderately”) by their various bladder problems (KHQ part 3) generally decreased from Baseline to Week 8 or Week 12 without notable differences between treatment groups.
About 20% to 40% of patients (depending on treatment group) did not perceive a change in their bladder condition at Week 8 (PPBC). However, more patients reported a major or minor improvement (about 40% to 60%) rather than a deterioration (5% to 12%). There were no statistically significant differences between placebo and any of

the active treatment groups. There was a trend for greatest improvement and least deterioration to occur in the netupitant 100 mg group.

Subgroup analyses revealed only a slight impact of geographical region, gender, age and use of prior OAB medication on the percentage and absolute change from Baseline in the average number of daily micturitions. In the group of patients with incontinence the percentage change and the absolute change from Baseline were larger in the active treatment groups compared to placebo at each study visit with the exception of percentage change from Baseline for netupitant 50 mg at Week 4 and Week 4 using LOCF, whereas in patients without incontinence the largest decreases were seen in the placebo group.

Improvements with regard to UUI episodes, UI episodes and number of pads used were reported considerably more frequently by female than by male patients. A statistically significant difference between treatment groups however was not detectable with one exception: for the change from Baseline in the total number of UUI episodes at Week 8 there was a statistically significant difference in female patients in favor of the netupitant 100 mg group compared to female patients in the placebo group (p=0.0258, Fisher's exact test).

Statistically significant differences in favor of netupitant 100 mg compared to placebo were found in the age group <65 years for the total number of UUI episodes at Week 8 and at Week 12 ($p = 0.0301$ and $p = 0.0119$, respectively), the total number of UI episodes at Week 8 ($p = 0.0336$) and the sensitivity analysis of total number of UI episodes at Week 8 and at Week 12 ($p = 0.0177$ and $p = 0.0156$, respectively).

In the placebo, netupitant 50 mg, and netupitant 100 mg treatment groups UUI and UI episodes at Baseline were reported more frequently by patients with prior OAB medication than by patients without prior OAB medication. In addition, patients in these 3 treatment groups with prior OAB medication used more pads at Baseline than patients without prior OAB medication. Statistically significant differences in favor of netupitant 100 mg compared to placebo were found in patients without prior OAB medication for the total number of UUI episodes at Week 8 and at Week 12 ($p = 0.0295$ and $p = 0.0068$, respectively).

The frequency of patients reporting no change in UUI or UI episodes or number of pads used was considerably higher in patients without incontinence than in patients with incontinence. A statistically significant difference in the occurrence of UUI episodes in favor of netupitant 100 mg compared to placebo was found in patients with incontinence ($p = 0.0240$).

In patients <65 years and in patients with incontinence the mean of the absolute change from Baseline in total number of urgency episodes was consistently higher in the active treatment groups compared to placebo at all visits. In patients with incontinence the 95% CIs for the mean change in the netupitant 100 mg group at Week 8 and in the 200 mg group at Week 12 did not overlap with the respective CIs for the placebo group at Week 8 and at Week 12.

For the KHQ a tendency to larger improvements in the active treatment groups compared to placebo was observed for female patients, patients aged <65 years, patients without prior OAB medication, and in patients with incontinence in many domains.

In patients without prior OAB medication the difference in PPBC between placebo and both netupitant 100 mg and netupitant 200 mg was statistically significant in favor of the active treatment at Week 8 ($p = 0.0055$ and $p = 0.0397$, respectively).

Safety Results:

A total of 243 patients were exposed to double-blind study medication and included in the safety set. In all 4 treatment groups the mean and median duration of exposure during the single-blind placebo run-in phase and the double-blind treatment phase were in agreement with the exposure as planned in the protocol (14 days of run-in and 56 days of double-blind treatment).

Plasma concentration data for netupitant and its metabolites (M1, M2 and M3) were obtained at selected sites from 47 patients in total. In the 3 active treatment groups netupitant plasma concentrations increased from randomization to Week 2 (netupitant 100 mg and 200 mg) or Week 4 (netupitant 50 mg) of the 8-week double-blind treatment phase. From Week 4 to Week 8 the plasma concentration decreased in all active treatment groups. At Week 12, i.e. 4 weeks after the last dose of study drug, netupitant was barely detectable. The plasma concentrations of the metabolites (M1, M2, and M3) showed similar patterns over time. Netupitant and its metabolites were not detected in plasma samples obtained from the placebo group.

Overall 143 TEAEs were reported by 71 out of 243 patients (29.2%). The percentage of patients with TEAEs was lowest in the placebo group (25.0% of patients) and increased with dose from 27.4% in the netupitant 50 mg treatment group to 33.3% in the netupitant 200 mg treatment group.

A dose dependency was also observed in patients aged 65 years and older: while only 14.3% of the patients in the placebo group experienced TEAEs, the frequencies in the active treatment groups ranged from 17.4% in the 50 mg netupitant treatment group to 50.0% in the 200 mg netupitant treatment group; however the relatively small number of patients in this subgroup (total 69) should be taken into account. In addition, the frequency in the placebo group was 14.3%; and thus considerably lower than that in the overall safety set (25.0%). No dose dependent pattern in percentages of patients with TEAEs could be detected for any other subgroup of patients.

Overall there was no evidence for dose dependency in the frequencies of patients with TEAEs in specific SOCs. Nervous system disorders were the most commonly reported SOC in the placebo group and the netupitant 200 mg group (10.0% and 15.0% of patients, respectively). In the netupitant 50 mg group infections and infestations SOC occurred with the highest incidence (11.3% of patients). In the netupitant 100 mg group nervous system disorders and gastrointestinal disorders SOCs occurred with equal frequency (13.1% of patients each). At the PT level somnolence, headache, and fatigue tended to be the most frequent events in all 4 treatment groups.

No dose dependent pattern in percentages of patients with TEAEs could be detected for related TEAEs, TEAEs by intensity, expected TEAEs or TEAEs leading to withdrawal.

Overall 43 out of 243 patients (17.7%) reported at least 1 TEAE assessed by the (blinded) study Investigator as related to the study drug. The frequency of patients with at least one related TEAE was highest in the netupitant 200 mg treatment group (13 patients, 21.7%) and lowest in the netupitant 50 mg treatment group (9 patients, 14.5%). More patients in the placebo group (11 patients, 18.3%) had at least 1 related TEAE than in the netupitant 100 mg group (10 patients, 16.4%).

Six patients experienced at least 1 severe TEAE; three of them experienced severe TEAEs assessed by the Investigator as related to the study drug: diarrhoea (placebo), fatigue, headache, and hypertension (all netupitant 100 mg).

No patient died during the study. Two patients experienced SAEs. Both patients had been treated with netupitant 200 mg. The events occurred after the last intake of study drug. One patient was hospitalized due to acute myocardial infarction of moderate

intensity, 19 days after last intake of study drug. The outcome was reported as recovering. Another patient was hospitalized due to severe anaemia aggravated, 3 days after last intake of study drug. The patient recovered after 50 days. Both events were assessed by the Investigator as unlikely related to study drug.
Thirteen patients (12 in the active treatment groups) were withdrawn from the study due to 20 TEAEs; 14 of these TEAEs were assessed as related to the study drug by the Investigator. The most frequently reported SOC for TEAEs leading to withdrawal was nervous system disorders (4.8% and 4.9% of patients in the netupitant 50 and 100 mg treatment groups, respectively) and gastrointestinal disorders (1.7% and 3.3% in the placebo and netupitant 200 mg treatment groups, respectively).
Expected TEAEs (defined as headache, fatigue, somnolence, and nausea) occurred in all 4 treatment groups with the exception of nausea, which was reported in the netupitant 100 mg and 200 mg treatment groups only. Except for a higher incidence of headache in the netupitant 100 mg group, there was no trend to higher percentages of patients with expected TEAEs in the active treatment groups compared to placebo. It should be noted that the number of events in each treatment group was too low for further comparisons between treatment groups.
The majority of clinical test results were within the reference range. Out-of-range results were isolated and the majority was considered not clinically relevant. No noteworthy differences between placebo and the active dose groups were detected for any laboratory parameter.
There were no relevant changes between Baseline and the respective visits in the mean and median values for systolic and diastolic blood pressure, pulse rate, body temperature and body weight in all 4 treatment groups.
There was a tendency for abnormal ECGs, new QT/QTc abnormalities and morphological ECG abnormalities to occur more often in the netupitant 50 mg treatment group than in the remaining groups. This tendency, however, was not reflected in the incidence of cardiac disorders reported as AEs since the highest percentage of patients with cardiac AEs was observed in the netupitant 200 mg group (13.3%).
Generally, it can be concluded that the analysis of vital signs, ECGs and physical examination data did not raise any safety concerns.

Conclusion: The study failed to demonstrate superiority of netupitant versus placebo with regard to the primary endpoint change from baseline in average number of daily micturitions at Week 8, since no statistically significant treatment differences between placebo and any of the active treatments were observed. The same was true for most secondary efficacy endpoints. There was, however, a trend for the greatest improvement and least deterioration to occur in the netupitant 100 mg group especially regarding UUI episodes, urgency episodes and PPBC. Heterogeneity between treatment groups regarding baseline values such as age and OAB characteristics needs to be taken into account when analyzing this study.
The overall incidence of AEs increased with netupitant dose whereas no evidence was found for the dose dependency to be manifested in specific SOCs or PTs. Furthermore, the dose dependency was not reflected in the percentages of patients with related TEAEs, TEAEs by intensity, expected TEAEs or TEAEs leading to withdrawal. Therefore, the analysis of AEs as well as of laboratory values, vital signs and 12-lead ECGs did not raise any safety concerns for the administration of netupitant in the treatment of OAB.

Date of Report: 31 Aug 2011