## Clinical Study Report Synopsis for Public Disclosure

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## 2. SYNOPSIS

**Study identifier** MRZ 92579/TI/3002

**Title of study**
A Randomized, Double-Blind, Placebo-Controlled, Clinical Evaluation of the Efficacy, Safety and Tolerability of Neramexane in Patients with Subjective Tinnitus

**Investigator(s), study site(s)**
Multinational study conducted at 55 investigation sites in Belgium (7 sites), the Czech Republic (10 sites), France (10 sites), the Netherlands (7 sites), Poland (14 sites) and South Africa (7 sites).
Co-ordinating investigator: [redacted]

**Publication (reference)**
The findings of this study had not been published at the time of preparation of this report.

| | | | |
|---|---|---|---|
| **Study period** | First subject enrolled: | 06-NOV-2008 | **Phase 3** |
| | Last subject completed: | 22-JUN-2010 | |

**Objectives**
The objective of this study was to evaluate the efficacy, safety and tolerability of neramexane in comparison to placebo in patients with subjective tinnitus.

**Study design and methodology**
Randomized, double-blind, placebo-controlled, two-arm, multicenter study; the main dosing period was preceded by an initial up-titration period and followed by a blinded, treatment-free follow-up period for efficacy and safety assessment.

**Number of subjects planned**
Approximately 400 subjects (200 per treatment arm), estimated by a sample-size calculation based upon the results of a preceding Phase 2 study.

**Diagnosis and main criteria for inclusion**
Out-patients aged ≥18 and ≤75 years with a diagnosis of first-onset, persistent, uni- or bilateral subjective tinnitus were included. The main inclusion criteria were:

- *Tinnitus-Beeinträchtigungs-Fragebogen* (TBF-12, Tinnitus Handicap Inventory-12) total score ≥ 9 at screening and at baseline

- Tinnitus duration ≥ 3 and ≤ 12 months at screening
- Hospital Anxiety and Depression Scale (HADS) depression and anxiety subscores each ≤ 10 at screening

**Test product**
Neramexane mesylate, 12.5 mg (batch: 3924101), 25 mg (batch: 3924201), and 37.5 mg (batch: 3924401) immediate-release film-coated tablets for oral administration.
The target daily dose of study drug was 50 mg for body weight <90 kg and 75 mg for body weight ≥ 90 kg.

**Reference product**
Matching placebo, 12.5 mg (batch: 3924001), 25 mg (batch: 3924301), and 37.5 mg (batch: 3924501).

**Duration of study treatment**
For each subject, the duration of double-blind treatment with neramexane or placebo was planned to be 17 weeks. This included a 4-week (50 mg/d) or 5-week up-titration period (75 mg/d). Including the initial screening period (maximum 4 weeks) and the 12-week treatment-free follow-up after the end of treatment, the maximum total study duration for each subject was 33 weeks.

**Criteria for evaluation**

*Efficacy*

Primary:
- TBF-12 total score change from baseline to end of treatment

Co-primary (only for US FDA approval):
- Tinnitus annoyance (Likert-like item from the Tinnitus Rating Scale) absolute change from baseline to end of treatment

Secondary:
- TBF-12 total score at further time points
- TBF-12 factorial scores
- Individual responder rate (a subject showing a decrease between baseline and end of treatment in TBF-12 score of ≥ 4 points, key secondary)
- Tinnitus Rating Scale (Likert-scores of tinnitus loudness, annoyance and impact on life – single scores and sum score)
- Abridged Sleep Questionnaire B (SF-B)
- Short Form-36 Health Survey (SF-36)
- Hospital Anxiety and Depression Scale (HADS)

*Safety*
- Adverse events
- Clinical chemistry, hematology, coagulation and urine analysis

- 12-lead electrocardiography (ECG)
- Vital signs (pulse rate, blood pressure)
- Physical examination

*Ancillary parameters*
- Plasma levels of study drug for determination of Population Pharmacokinetics (PopPK)
- Optional: blood sampling for pharmacogenetic testing
- Audiological testing and psychoacoustical tinnitus characterization at screening:
  - Pure tone audiometry thresholds
  - Psychoacoustic assessment of tinnitus frequency, loudness and masking level for the most troublesome tinnitus
- Concomitant medications
- Concomitant non drug treatments

**Statistical methods**

Originally, the analysis was planned to be performed on the total population. Results of the first Phase 3 study indicated that efficacy might be expected mainly for the female subpopulation. Therefore, the study protocol was amended and the analysis was changed to a hierarchical test procedure starting in the female subpopulation as outlined below. All analyses were performed for female and male subjects separately as well as for the total population.

**Primary efficacy analysis:** The primary efficacy variable was the absolute change in the TBF-12 total score from baseline to Week 17. The comparison with placebo was performed by using an ANCOVA (analysis of covariance) model with baseline TBF-12 as covariate and country and treatment as factors ($\alpha = 0.05$) for the analyses of female and male subjects, while in the analysis of the total population the factor gender was added.

The confirmatory analysis was performed on the Full Analysis Set (FAS) based on the 'last observation carried forward' (LOCF) principle. A hierarchical test procedure was applied as follows: First, the female population was to be tested at a confirmatory level. In the event of significant treatment differences being found, the confirmatory analysis was to proceed with the total population, and if a statistical significance was found with the total population then the analysis was to proceed with the male population. Observed cases (OC), treatment completers, the Per Protocol Set (PPS) and a Mixed Model Repeated Measures (MMRM) analysis were to be used as measures of sensitivity.

For US FDA approval, the change between baseline and end of treatment in the Likert-like item 'tinnitus annoyance' from the Tinnitus Rating Scale was regarded as a co-primary variable. As both primary variables have to show significant treatment differences, no $\alpha$-adjustment for multiplicity was necessary. The analysis strategy for this variable was identical to that described for the primary variable.

**Secondary efficacy analyses:** The complete time course of values and changes from baseline for the TBF-12 as well as of remaining secondary variables were analyzed descriptively. Additionally, least-squares means, and *p* values from ANCOVA where appropriate, were given for continuous variables. *N*, % were given for qualitative variables. Responder rates

(key secondary variable, a 'responder' being defined as a subject showing a decrease in TBF-12 score of ≥ 4 points) were compared by exploratory Cochran–Mantel–Haenszel tests with country (and gender for the total population only) as strata. Continuous responder curves were provided, to display the responder rates for different absolute and percentage-based cut-off points for responder criteria.

**Safety variables**: The analysis was performed on the Safety Evaluation Set (SES). Incidence rates were calculated for treatment-emergent adverse events (TEAEs) at the levels of system organ class (SOC) and preferred term (MedDRA coding). Listings and, if applicable, incidences of TEAEs leading to discontinuation, serious TEAEs and deaths were also given. Laboratory, vital-signs and ECG variables were analyzed descriptively and screened for individual clinically relevant values and changes.

**Meta-analysis**: This study will be integrated into a meta-analysis of all pivotal studies with neramexane in the indication tinnitus. Details have been specified in a separate statistical analysis plan that was prepared before the first of these studies was unblinded.

**Interim analysis**
No interim analysis was performed.

**Summary of results**

Study subjects
A total of 532 tinnitus patients were screened, and of these 406 were randomized and 405 treated: 205 (81 women and 124 men) with neramexane and 200 (81 women and 119 men) with placebo. All subjects treated were included in the SES. In the neramexane group 155 subjects, and in the placebo group 172 subjects, completed the study. The FAS comprised respectively 197 and 191 subjects, and the per-protocol set 176 and 173 subjects. More subjects in the neramexane group discontinued their participation in the study during the fixed-dose period compared with subjects treated with placebo (15.1% and 7.0%, respectively), while roughly equal numbers discontinued during the up-titration period (9.3% and 7.0%). There were more discontinuations from the study due to adverse events and to withdrawal of consent in the neramexane group; other reasons for discontinuation were balanced between the treatment groups. The overall percentages of subjects for whom deviations from protocol were considered "major" were comparable between the two treatment groups, as were the individual reasons; "insufficient treatment" (defined as a total intake of less than 56 tablets) was found for rather more subjects in the neramexane group (6.8%, compared with 4.5% for placebo), and this was more pronounced among the female subjects (7.4% and 2.8% respectively).
The treatment groups were well comparable in terms of demographic variables, medical history and the use of concomitant medication at study entry; baseline condition as assessed by the TBF-12 and TRS was slightly worse in the placebo group. The percentages of women in the two treatment groups were almost identical, and there were no unexpected differences in demographic or baseline variables between the male and female subpopulations although more men than women in both treatment groups had tinnitus because of acute or chronic noise trauma. Compliance with the protocol in respect of the intake of study medication (defined as

an intake of 80–120% of that stipulated) was good (≥94% of subjects) in both treatment groups.

Efficacy results

Note: The end-of-treatment value (Week 17 / ET) is denoted in the rest of this section as Week 17, for easier reading.

In the hierarchical primary analysis, conducted with the FAS on the basis of LOCF in the female population (first step), the mean (± standard deviation) TBF-12 total scores at baseline were 13.5 ± 3.3 for the neramexane group and 14.5 ± 3.5 for the placebo group; in Week 17, they were respectively 10.3 ± 4.5 and 10.9 ± 3.8. The least-squares (LS) mean difference in the change, for verum group minus placebo group, was zero score points (a negative value would have indicated a differences in favor of neramexane), with $p = 0.9817$; thus the criteria for clinical significance (a difference between the treatment groups of at least 1 score point on the scale of 0–24) and statistical significance ($p < 0.05$) were not met. The subsequent analyses of the total and male populations were therefore conducted at a descriptive level only. These too revealed neither clinical nor statistical significance.

Higher responder rates (decrease in TBF-12 score of ≥4 points) were found among the neramexane-treated subjects, without statistical significance. Cumulative responder rates for absolute improvement at the assessment in Week 17 (FAS LOCF) showed a slightly greater improvement in the neramexane group than in the placebo group when the definition of response was set at any level from 3 to 7 score points changes in TBF-12. Outside this range no advantage of the active treatment was seen.

The sensitivity analysis of change from baseline to Week 17 in TBF-12 score using the analysis set of female FAS treatment completers gave an LS mean difference of –0.9 score points with $p = 0.1715$. The corresponding PPS analysis gave an LS mean difference of –0.8 score points with $p = 0.2028$. None of these analyses showed clinically relevant differences or $p$ values suggesting statistical significance at other time points, either for the female, the male or the total population.

In the co-primary analysis (also FAS LOCF, female population), the TRS subscores for annoyance at baseline were 5.9 ± 2.4 for the neramexane group and 6.2 ± 1.9 for the placebo group; in Week 17 these were respectively 4.8 ± 2.2 and 4.8 ± 2.4. The LS mean difference in the change from baseline was 0.1 score points (the positive value indicates a differences in favor of placebo) with $p = 0.6846$. The results for the male and total populations and from analyses of the TBF-12 subscores (functional-communicational and emotional-cognitive) were similar.

A potentially significant difference was seen in the TBF-12 total score (FAS observed cases) for the female subjects who received 50 mg (rather than 75 mg) neramexane daily, with an LS mean difference of –1.2 (i.e., in favor of neramexane) in Week 17, –1.3 and respective $p$ value of 0.0702,.

Further efficacy results in the female population are summarized in the following table:

| Variable [range] | Change from baseline to Week 17 | | Least-squares mean difference |
|---|---|---|---|
| | Neramexane | Placebo | |
| TBF-12 total score [0–24] *(primary variable)* | –3.2 ± 4.3 | –3.6 ± 3.9 | 0.0 |
| TBF-12 emotional–cognitive subscore [0–14] | –2.1 + 2.8 | –2.5 ± 2.6 | 0.2 |
| TBF-12 functional–communicative subscore [0–10] | –1.1 ± 1.9 | –1.2 ± 1.8 | –0.1 |
| TRS total score [0–30] | –2.6 ± 5.5 | –3.4 ± 5.4 | 0.4 |
| TRS loudness [0–10] | –0.7 ± 1.9 | –0.9 ± 1.8 | –0.0 |
| TRS annoyance [0–10] *(co-primary variable)* | –0.8 ± 2.0 | –1.0 ± 2.0 | 0.1 |
| TRS impact on life [0–10] | –0.8 ± 2.3 | –1.2 ± 2.2 | 0.1 |

The HADS, the abridged SF-B sleep questionnaire and the SF-36 quality-of-life questionnaire were analyzed as planned, but none of these yielded any clinically or statistically relevant results; specifically, there was no improvement in the HADS score in either group.

Pharmacokinetic results

Neramexane plasma levels measured after 5, 9 and 17 weeks of treatment were closely similar within each dosing level. The dose-dependence (plasma levels following treatment with 50 or 75 mg) was consistent with the known pharmacokinetics of neramexane. Population pharmacokinetic analyses will be reported in a separate document.

Safety results

Of the 205 actively treated female and male subjects, 159 were assigned to receive 50 mg neramexane daily as their body weight was <90 kg. The remaining 46 subjects were assigned to receive 75 mg neramexane daily. Of these, 35 maintained this dose level throughout and 11 had dose reduction to 50 mg because of poor tolerance. A total of 200 subjects received placebo. The mean duration of overall exposure was 103.5 days (neramexane) and 110.2 days (placebo).

The number of subjects with treatment-emergent adverse events was about the same in the neramexane and placebo groups (64.9% and 64.0%), while the number of subjects with adverse events considered to be related to the study treatment was greater among the subjects treated with neramexane (35.1% compared with 18.0% of placebo subjects). Treatment-emergent adverse events leading to discontinuation of study participation (14.1% and 5.5%), and events related to treatment that led to discontinuation (10.7% and 4.0%) were more frequent in the verum group. The most frequent treatment-emergent adverse events leading to discontinuation were: dizziness (11 neramexane-treated subjects and no placebo-treated subjects), headache (6 and 2), worsening of tinnitus (7 and 2), vertigo (5 and 1), nausea (3 and none), hypertension (3 and none) and depression (3 and 1).

The numbers of subjects with treatment-emergent serious adverse events were similar in the two treatment groups (for neramexane 3 subjects, for placebo 5 subjects). None of these events were considered causally related to the study treatment.

Dizziness was reported more frequently – and for more subjects – in the neramexane group than in the placebo group. A similar trend was seen for vertigo and, less strongly, for irritability, disturbance in attention, fatigue and hypertension. Of those subjects who experienced dizziness (a known side effect of neramexane), most reported its first onset within the first 30 days of treatment.
The distribution of severe events among the SOCs and event types followed the general distribution of events already described. In the neramexane group 9.8% of subjects and in the placebo group 6.5% were recorded as having had at least one severe adverse event.
No death cases were reported.
None of the laboratory values monitored in this study gave rise to concern about the safety of the study treatment; no treatment-specific trend is suggested by these data or by the pattern of laboratory-related adverse events. Four notable above-range values for blood creatine phosphokinase were recorded in the neramexane group only; it is not clear whether this has any possible relationship to the treatment.
The assessments of vital signs, body weight and electrocardiograms, including a detailed analysis of QTc, did not reveal any trends, patterns or other possible reasons for concern about the safety of the treatment with neramexane.

**Conclusions**
In none of the study populations investigated (females, males, and total population) statistically significant or clinically relevant treatment differences between the neramexane group and the placebo group in either the primary or the secondary efficacy variables were observed.
The absolute improvement as measured by the primary outcome variable, TBF-12, in the female target population after three months stable-dose treatment with 50 or 75 mg neramexane mesylate per day is in accordance with the results of previous neramexane studies in the tinnitus indication. The same holds true for the observed standard deviations. However, an unexpectedly strong response in the placebo group prevented a separation of the two treatment groups. Only after cessation of the study medication, from Week 17 onwards, did the differences in the female target population start to increase in favor of the neramexane group. However, this observation should be regarded with caution, as it is biased by the fact that it applies only to subjects who completed the 17-week treatment period
There were no medically relevant treatment-emergent adverse events of major concern. Overall, safety and tolerability of neramexane were in accordance with the known drug profile.