Clinical Study Report Synopsis for Public Disclosure

This Clinical Study Report Synopsis is provided to the public for informational purposes only in accordance with legal requirements. Being part of the clinical study report it had been prepared according to legal/regulatory requirements and best practice at the time of study completion.

The study listed may include information about approved and non-approved uses, doses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Patients should always seek medical advice before making any decisions on their treatment. Healthcare professionals should always refer to the specific prescribing information approved for the patient's country or region.

Page numbering in the Clinical Study Report Synopsis may be inconsistent due to the fact that it is part of a comprehensive clinical study report. Information not relevant for the Clinical Study Report Synopsis is crossed-out. Information in the Clinical Study Report Synopsis may have been redacted (blacked out) to fulfill legal requirements (e.g. statutory obligations on protection of personal data) or to protect commercially confidential information of Merz Pharmaceuticals GmbH.

2. SYNOPSIS

Study identifier MRZ 92579/TI/3001

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 Austria (5 sites), Germany (25 sites), Portugal (3 sites), Spain (11 sites) and the UK (11 sites).
Co-ordinating investigator: [redacted]
Germany

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

Study period	First subject enrolled:	09-SEP-2008	**Phase 3**
	Last subject completed:	24-FEB-2010	

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

Study design and methodology
Randomized, double-blind, placebo-controlled, multi-national, two-arm, parallel-group, multicenter study with an initial up-titration period.

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

Diagnosis and main criteria for inclusion
Out-patients with a diagnosis of first-onset, persistent, uni- or bilateral subjective tinnitus were included. The main inclusion criteria were:

- Tinnitus-Beeinträchtigungs-Fragebogen-12 (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

The main exclusion criteria were:

- Clinical diagnosis of intermittent or pulsatile tinnitus
- Patients who have tinnitus as a concomitant symptom of an otological/neurological disease (such as otitis media, Menière's disease, otosclerosis, etc.)
- Hearing impairment related to disturbance of sound conduction

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 subjects with body weight <90 kg and 75 mg for subjects with 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 (in subjects with the target daily dose of 50 mg/d) or 5-week up-titration period (in subjects with the target daily dose of 75 mg/d).

Criteria for evaluation

Efficacy

Primary:

- TBF-12 total score change from Baseline to end of treatment (Week 17 or at early termination (ET))

Co-primary (only for US FDA approval):

- Tinnitus annoyance (Likert-like item from the Tinnitus Rating Scale, TRS) absolute change from Baseline to end of treatment (Week 17 / ET)

Key –secondary:
Responder rate (responder defined as a subject with a decrease of at least 4 score points on the TBF-12 total score)

Secondary:

- TBF-12 total score at all time points
- TBF-12 subscores
- TRS (Likert-scores of tinnitus with items: loudness/strength, 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 (AEs) – voluntary reporting by subjects and enquiry by the investigator
- Clinical chemistry, hematology, coagulation and urinalysis
- 12-lead electrocardiography (ECG)
- Vital signs (pulse rate, blood pressure)
- Physical examination

Ancillary parameters
- Plasma levels of study drug for determination of population pharmacokinetics
- Optional: blood sampling for pharmacogenetic testing
- Audiological testing and psychoacoustical tinnitus characterization at screening:
  - Pure tone audiometry thresholds
  - Psychoacoustic assessment of tinnitus frequency, loudness matching and minimal masking level for the most troublesome tinnitus
- Concomitant medications
- Concomitant treatments

Statistical methods

Primary efficacy analysis: The primary efficacy variable was the absolute change in the TBF-12 total score from Baseline to end of treatment (Week 17 / ET). The comparison with placebo was performed by using an ANCOVA (analysis of covariance) model with baseline TBF-12 as covariate and country, gender and treatment as factors ($\alpha = 0.05$, two-sided).

The confirmatory analysis was performed on the Full Analysis Set (FAS) based on the last observation carried forward (LOCF) principle. The FAS population was defined as subjects in which the value for the primary efficacy variable (TBF-12) was available at Baseline and at least one post-baseline visit. The analyses on FAS observed cases (i.e., with only values observed at the respective visit being included), FAS treatment completers (i.e., subjects in the FAS who completed the treatment period) and the Per Protocol Set (PPS: subset of subjects in the FAS with no major protocol deviations) were used as a measure of sensitivity.

For US FDA approval, the change between Baseline and end of treatment in tinnitus annoyance was regarded as a co-primary variable. As both primary variables have to show significant treatment differences, no α-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) were compared by exploratory Cochran–Mantel–Haenszel tests with country and gender 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 and preferred term (Medical dictionary for regulatory activities (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 555 tinnitus patients were screened, and of these 411 were randomized and 406 treated: 204 with neramexane and 202 with placebo. Treated subjects were included in the SES. In the neramexane group 146 subjects, and in the placebo group 169 subjects, completed the study. The FAS comprised respectively 203 and 198 subjects, and the per-protocol set 174 and 178 subjects. The rate of discontinuation was higher in the neramexane group (28.4%) than in the placebo group (16.3%). Most subjects in the neramexane group discontinued during the up-titration period (16.2%) compared to subjects treated with placebo who discontinued most commonly during the fixed-dose period (9.9%). There were more discontinuations from the study due to adverse events in the neramexane group; other reasons for discontinuation were balanced between the treatment groups. Major deviations from the protocol were likewise balanced except for "insufficient treatment" (defined as a total intake of less than 56 tablets) which was found for substantially more subjects in the neramexane group (12.1%) than in the placebo group (4.4%).

The two treatment groups were similar in respect of all demographic variables recorded, and only minor differences between the two groups in respect of tinnitus history, other medical history and concomitant diseases were found. There were small differences in the use of concomitant medication, but without likely relevance for the study.

Compliance with the study medication regimen (number of tablets taken divided by the number of tablets expected to be taken during the subjects' individual participation in the double-blind period multiplied by 100) was good: for the SES, 96.1% of subjects in the neramexane group and 95.0% of those in the placebo group were within the "compliance window" of 80–120%.

Efficacy results

Note: For FAS LOCF analyses, the end of treatment value (Week 17 / ET) will be further indicated as Week 17, for purposes of easier reading.

In the primary analysis, conducted with the FAS on the basis of LOCF, the mean (± standard deviation) TBF-12 total scores at Baseline were 12.6 ± 3.0 for the neramexane group and 13.1 ± 3.2 for the placebo group; in Week 17, they were respectively 10.1 ± 4.5 and 10.9 ± 4.3. The least-squares (LS) mean difference in the change, for verum group minus placebo group, was -0.5 score points (negative values indicate differences in favor of neramexane), with $p = 0.1997$.

The sensitivity analyses on change from Baseline to Week 17 in TBF-12 score using the population of FAS treatment completers gave an LS mean difference of -0.9 score points with $p = 0.0369$. The PPS analysis resembled the FAS LOCF analysis in that the result at the last visit (i.e, last available visit, LOCF applied for early termination / lost to follow-up) did not show statistical significance at the descriptive level, but analysis of the PPS for patients who completed Week 17 did so ($p = 0.0423$).

With regard to the stratification of the TBF-12 total score by country it is not possible to place any strong interpretation upon results from single countries due to relatively small numbers of subjects recruited in countries other than Germany.

However, stratification of the TBF-12 total score by the subject's gender, weight and actual daily dose (50 or 75 mg neramexane or corresponding placebo) showed, unexpectedly, a better response to the active treatment among female subjects ($p < 0.05$, clinically relevant treatment differences of - 1.7 score units). This result is the more remarkable as the female subjects only made up about 1/3 of the FAS. Furthermore, an LS mean difference of -0.9 score points (in favor of neramexane, $p = 0.0565$) was observed among subjects whose daily dose was 50 mg neramexane rather than 75 mg dose group foreseen for subjects weighing ≥90 kg ($p = 0.4781$).

In the co-primary analysis (also FAS LOCF), the TRS subscores for annoyance at Baseline were 6.0 ± 1.9 for the neramexane group and 5.9 ± 2.0 for the placebo group; in Week 17 these were respectively 4.9 ± 2.2 and 5.3 ± 2.1. The LS mean difference in the change from Baseline was – 0.5 score points (i.e., the difference was in favor of the active treatment) with $p = 0.0160$; thus the criterion for statistical significance ($p < 0.05$) was met for this variable. As for TBF-12, female subjects showed a relatively strong treatment-group-related reduction in tinnitus annoyance, with $p < 0.05$ at the assessment after 13 and 17 weeks and at the end of treatment. This trend was found in all three analysis populations (FAS LOCF, FAS observed cases and PPS).

In analyses of the TBF-12 subscores (functional-communicational and emotional-cognitive) the neramexane-treated subjects showed at all time points a slightly greater improvement in their tinnitus than did the placebo-treated subjects. However, the statistical significance threshold was not reached.

Analyses on the key secondary efficacy variable responder rates (response defined as improvement of at least 4 points in the TBF-12 total score from Baseline to Week 17, FAS LOCF) revealed a slight, advantage of neramexane (40.9% responder) over placebo (35.4%); $p = 0.2120$.

The analysis of the TRS results included total score and component subscores (loudness/strength, annoyance, and impact on life). The TRS score showed a greater sensitivity to the treatment. Thus, in the FAS LOCF analysis the TRS total score showed a difference of - 1.3 points (on a scale of 0–30) with $p = 0.0089$ in Week 17. All three subscores showed a similar advantage of the active treatment, with $p < 0.05$ in each case. As TRS annoyance was the co-primary variable, it was also examined by strata as was done for TBF-12.

The Hospital Anxiety and Depression Scale, the SF-B sleep questionnaire and the SF-36 quality-of-life questionnaire were analyzed as planned, but none of these yielded any clinically relevant results; specifically, there was no improvement in the HADS score.

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 in the treatment with 50 and 75 mg) was consistent with the known pharmacokinetics of neramexane. Population pharmacokinetic analyses will be reported in a separate document.

Safety results

Of the 204 actively treated subjects, 150 were assigned to receive 50 mg neramexane daily as their body weight was <90 kg. The remaining 54 subjects were assigned to receive 75 mg neramexane daily. Of these, 47 maintained this dose level throughout and 7 had dose reduction to 50 mg (six because of poor tolerance and one because this subject had initially been incorrectly assigned). The mean duration of exposure to study medication was 109.8 days (placebo) and 97.7 days (neramexane).

The number of subjects with TEAEs was greater in the neramexane group (72.1%) than in the placebo group (59.4%), and the number of subjects with TEAEs related to the study treatment was substantially greater among the subjects treated with neramexane (44.1%, compared with 18.3% in the placebo group). The numbers of subjects with treatment emergent serious adverse events were similar in both treatment groups (for neramexane 8 subjects, 3.9%; for placebo 6 subjects, 3.0%). The number of these events was greater in the neramexane group (19) than in the placebo group (7), partly because one subject incurred multiple injuries, recorded as 7 separate events, in a road accident. Serious adverse events were considered by investigator to be related to treatment in four subjects in the neramexane group and in one subject in the placebo group. No direct relationship could be traced to the study treatment. Specifically, hypertension, panic attack and depression in the verum group were not considered related to the study treatment.

Treatment emergent adverse events leading to discontinuation from the study (21.6% in the neramexane treatment group – 8.9% in the placebo treatment group) and especially adverse events that were both considered related to treatment and led to discontinuation (18.6% – 4.0%, respectively) revealed higher incidence rates in the verum group in comparison to placebo. Treatment emergent adverse events leading to discontinuation were mainly: dizziness (7.4% neramexane-treated subjects and 0.5% placebo-treated subjects), worsening of tinnitus (4.9% and 3.5%), vertigo (2.9% and 0.5%) and erectile dysfunction (2.0% and 0%). Other relatively frequent (preferred terms reported in ≥ 1.5% of subjects in the

neramexane group) causes of discontinuation included headache, disturbance in attention, somnolence, sleep disorders and hypertension.

Dizziness was reported more frequently – and for more subjects – in the neramexane group (19.1%) than in the placebo group (2.5%). A similar trend was seen for vertigo and less strongly, for somnolence, disturbance in attention, nasopharyngitis, influenza, hypertension, and erectile dysfunction. Of those subjects who experienced dizziness, most reported its first onset within the first 30 days of treatment.

The incidence of subjects with at least one severe adverse event was greater in the neramexane group (14.2%) than in the placebo group (6.4%), and the number with adverse events rated as moderate in intensity was also higher in the neramexane group (44.6% – 36.1%). The distribution of severe events among the system organ classes (SOCs) and event types followed the general distribution of events already described. Treatment-related adverse events in the SOCs "nervous system disorders" and "ear and labyrinth disorders" were reported more often for neramexane-treated (26.0% and 15.2%) than placebo-treated (5.0% and 3.0%) subjects. The same tendency was seen for erectile dysfunction and, less clearly, for fatigue, feeling abnormal, hypertension, sleep disorder and agitation.

None of the laboratory values monitored in this study gave rise to concern about the safety of the study treatment; no specific trend related to the treatment with neramexane is suggested by these data. Although incidence rates for the most commonly observed laboratory-related TEAE (increase of blood creatine phosphokinase) was higher in female subjects treated with neramexane (3 subjects) compared to the placebo group (none), the cluster of occurrence of this adverse event appears to have been a coincidence. Nevertheless, it should be kept under observation in future studies.

The assessments of vital signs, body weight and electrocardiograms, including a detailed analysis of QTc, did not reveal any trends, patterns or other concrete reasons for concern about the safety of the treatment with neramexane.

Addendum report

Following the completion of the prospectively defined analyses, the sponsor decided that a complete *post hoc* analysis of the female subjects data should be performed. The results of that analysis are presented in a separate document (Clinical Study Report Addendum).

Conclusions

In patients suffering from subacute subjective tinnitus, a 3-month oral treatment with a stable and weight-adapted dose of neramexane mesylate, resulted in greater reduction of the TBF-12 total score as compared to placebo treatment. However, the differences between placebo and verum group in the FAS LOCF population did not reach the level of statistical significance and the pre-defined level of clinical relevance with regard to the primary efficacy variable, TBF 12 total score. In the population of treatment completers, there was a statistically significant difference between the treatment groups for TBF 12 total score. This difference between the treatment groups was close to the pre-defined level of clinical relevance.

All tinnitus ratings related to TRS (total score and individual subscores) in the FAS LOCF population showed consistent improvement for subjects receiving treatment with neramexane as compared with placebo, with $p < 0.05$ at Week 17 (FAS, LOCF). Especially the co primary variable on tinnitus annoyance showed statistically significant treatment effects.

In female subjects the treatment effects in the primary and co-primary efficacy variables were statistically significant and clinically meaningful. This is a remarkable finding, since significance levels were already reached with the rather small number of female patients in this study. Additional analyses will be required to provide a full understanding of this finding. There were no relevant treatment emergent adverse events that gave rise to concern about the safety of neramexane. Overall, the safety and tolerability of neramexane as revealed by this study were in accordance with the known safety profile of the drug.