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2. SYNOPSIS

Study identifier MRZ 92579/TI/3003

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)

This multinational study was conducted at 75 investigation sites in: Austria (4 sites), Brazil (7 sites), Germany (12 sites), Mexico (14 sites) and the U.S.A. (38 sites).

The international co-ordinating investigator of this study was:

[redacted] U.S.A.

The co-ordinating investigator for European sites was:

[redacted] Germany

Publication (reference)

The findings of this study had not been published at the time when the study report was prepared.

Study period	First subject enrolled:	17-SEP-2009	**Phase: 3**
	Last subject enrolled:	21-SEP-2010	

Objective

To evaluate the efficacy, safety and tolerability of neramexane, in comparison with placebo, in patients with subjective tinnitus.

Study design and methodology

The study was conducted according to a multi-center, multi-national, placebo-controlled, two-arm, randomized (1:1), double-blind, parallel-group design. Subjects were out-patients aged 18–75 years with a diagnosis of first-onset, persistent, uni- or bilateral,

subjective tinnitus. The study comprised a screening period (1–4 weeks) and a double-blind treatment period (29 weeks). Subjects who completed treatment were eligible to enter an open-label extension study with active treatment only; for those who did not enter the extension study, or who did so with >35 days delay, a safety follow-up examination was scheduled.

Number of subjects planned

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

Diagnosis and main criteria for inclusion

The diagnosis for inclusion in the study was first onset, persistent (i.e. never absent for > 24 hours in a row), subjective, uni- or bilateral tinnitus present for at least 3 months but not more than 12 months. In cases of bilateral tinnitus this criterion applied to both ears. Principal inclusion criteria were:

- *Tinnitus-Beeinträchtigungs-Fragebogen* (TBF-12, Tinnitus Handicap Inventory-12) total score ≥ 9 at screening and at baseline
- Tinnitus Severity Score, 1-week version (TSSw) ≥ 4 at screening and at baseline
- Hospital Anxiety and Depression Scale (HADS) depression and anxiety subscores each ≤ 10 at screening

Test product

Neramexane mesylate, 12.5 mg, 25 mg and 37.5 mg immediate-release film-coated tablets for oral administration. (For batch numbers see the report text and appendices.)

The target daily dose of study drug was 50 mg (given as 25 mg twice daily) for body weight <90 kg and 75 mg (given as 37.5 mg twice daily) for body weight ≥90 kg. Subjects receiving 75 mg per day who experienced intolerance were allowed to reduce their dose to 50 mg per day; other dosage changes were not allowed.

Reference product

Matching placebo, for 12.5 mg, 25 mg and 37.5 mg. (For batch numbers see the report text and appendices.)

Duration of study treatment

For each subject, the duration of double-blind treatment with neramexane or placebo was 29 weeks. This included a 4-week (50 mg/d) or 5-week (75 mg/d) up-titration period. Including the initial screening period (maximum 4 weeks) and the ≤35-day interval up to the safety follow-up examination, the maximum total study duration for each subject was 38 weeks.

Criteria for evaluation

Efficacy

Primary:

- TBF 12: absolute change in total score from baseline to Weeks 17 and 29, or to premature discontinuation if the subject ended treatment before Week 17 or Week 29 (hierarchical statistical testing).

Co-primary (for U.S. FDA approval only):

- TSSw: absolute change from baseline to Weeks 17 and 29, or to premature discontinuation.

Secondary:

- TBF-12 total score at further time points
- TBF-12 factorial scores
- Individual responder rate (subjects showing a decrease in TBF-12 score of ≥ 4 points, key secondary variable)
- Tinnitus Rating Scale (Likert-scores of tinnitus loudness, annoyance and impact on life – single scores and sum score; 1-week version, TRSw)
- TSSw
- Attention and Performance Self-Assessment questionnaire (APSA)
- Quality-of-life questionnaire (SF-36 Health Survey)
- HADS.

Safety

- Adverse events
- Clinical chemistry, hematology, coagulation, and urinalysis
- Vital signs (pulse rate, blood pressure)
- 12-lead electrocardiography (ECG)
- Ophthalmological examination (visual acuity, refraction, accommodation and tonometry)
- Physical examination
- Inquiry about sexual dysfunction
- Pure-tone audiometry thresholds.

Ancillary variables

- Pharmacokinetics (plasma drug levels for population-pharmacokinetic analysis)
- Pharmacogenetics (expression of a defined list of cytochromes; blood sampling for pharmacogenetic testing was optional and required separate informed consent)
- Concomitant medications
- Concomitant treatments
- Psychoacoustic assessment of tinnitus.

Statistical methods

All analyses were performed for the total population and also for the subpopulation of study subjects reporting acute hearing loss (AHL) as the reason for their tinnitus.

Primary efficacy analysis: The primary efficacy variables were the absolute change in the TBF-12 total score from baseline to Weeks 17 and 29 or to premature discontinuation if the subject ended treatment before Week 17/29. The comparison with placebo was performed by using an ANCOVA model with 'baseline TBF-12' as covariate and 'country', 'gender' and 'treatment' as factors ($\alpha = 0.05$). Tests were performed in a pre-defined sequence with regard to analysis population and time point, as outlined below.

The confirmatory analysis was performed on the Full Analysis Set (FAS), based on the 'last observation carried forward' (LOCF) principle. Observed cases, complete cases, as well as the Per Protocol Set (PPS) and a Mixed Model Repeated Measures (MMRM) analysis were used as measures of sensitivity.

For U.S. FDA approval the change between baseline and end of treatment (Weeks 17 and 29) in the TSSw was regarded as a co-primary variable.

The hierarchical test procedure was as follows:

Step 1: Test of the primary variable(s) as measured in Week 29 in subjects reporting acute hearing loss as reason for tinnitus,

Step 2: Test of the primary variable(s) as measured in Week 17 in subjects reporting acute hearing loss as reason for tinnitus,

Step 3: Test of the primary variable(s) as measured in Week 29 in the total population,

Step 4: Test of the primary variable(s) as measured in Week 17 in the total population.

If significant results were obtained in the first step, the next step was also to be considered as confirmatory, and so on. As soon as a non-significant result was obtained in one step, the confirmatory procedure was to stop and remaining *p* values were to be interpreted as exploratory.

Since in each step for the U.S. analysis both primary variables had to show significant treatment differences to allow continuation of the hierarchical testing procedure, no α-adjustment for multiplicity was necessary. The analysis strategy for tinnitus severity was identical to that described for the TBF-12.

Secondary efficacy analysis: The complete time course of values and changes from baseline for the TBF-12 as well as of remaining secondary variables was analyzed descriptively. Additionally, least-squares means (ANCOVA), differences of least-squares means, respective confidence limits and descriptive *p* values, where appropriate, were given for continuous variables. Frequencies (*n*, %) were given for qualitative variables. Responder rates (a 'responder' being defined as a subject showing a decrease in TBF-12 score of $\geq$4 points) were compared by exploratory Cochrane–Mantel–Haenszel tests with 'country' and 'gender' as strata. Continuous responder curves were used to show the responder rates for different absolute and percent-based cut-off points for responder criteria.

Safety variables: The analysis was performed on the Safety Evaluation Set (SES), both (i) for the total SES population and (ii) for the subpopulation of SES subjects reporting acute hearing loss as reason for their tinnitus. 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, TEAEs of special interest and deaths were also provided. Laboratory, vital-signs and ECG variables were analyzed descriptively and screened for individual clinically relevant values and changes. Pure-tone audiometric results were analyzed descriptively and screened for notable individual changes. Ophthalmological results were analyzed descriptively.

Meta-analysis: This study was planned to 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 and which was amended before unblinding of the present study.

Interim analysis

No interim analysis was performed.

Summary of results

Study subjects

A total of 788 tinnitus patients were screened, and of these 455 were randomized and 454 treated: 225 with neramexane and 229 with placebo. These subjects were included in the safety evaluation set (SES). In the neramexane group 149 subjects, and in the placebo group 166 subjects, completed the study. The full analysis set (FAS: primary efficacy endpoint available) comprised respectively 216 and 221 patients, and the per-protocol set (PPS: no major protocol violations) 188 and 195 patients. 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 duration, which, corresponding to the discontinuations, was more frequent in the neramexane group.

The two treatment groups were similar in respect of all demographic variables recorded, and of medical history and concomitant disorders. There were small differences in the use of concomitant medication, but without likely relevance for the study results.

Compliance with the study medication regimen in the SES was within the “compliance window” of 80–120% for 92.9% of subjects in the neramexane group and for 93.9% of those in the placebo group.

The sub-population of AHL subjects comprised 32 subjects treated with neramexane and 43 treated with placebo. This subset of subjects did not differ in any other important way from the total population.

Efficacy results

In the primary efficacy analysis (ANCOVA on change in the TBF-12 total score from baseline to end of treatment) no statistically significant or clinically relevant difference between treatment groups was observed in the first step of the test procedure ($p = 0.7693$ for the AHL subjects in Week 29). The hierarchical confirmatory analysis was therefore stopped at this stage, and the procedure was continued at the descriptive level (AHL subjects in Week 17, total population in Weeks 17 and 29). These tests also yielded *p* values greater than 0.7. Therefore, the study did not show any statistical superiority of the active treatment with neramexane over a matching treatment with placebo. The co-primary analysis with the target variable TSSw gave a qualitatively similar result. None of the secondary analyses, of the total population or the AHL subpopulation, was indicative of a meaningful superiority of the active treatment over placebo.

Pharmacokinetic results

Neramexane plasma levels measured after 11, 17 and 29 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.

Safety results

Of the 225 neramexane-treated subjects, 165 were assigned to receive 50 mg neramexane daily as their body weight was <90 kg. The remaining 60 subjects initially received 75 mg neramexane daily. Of these, 51 maintained this dose level throughout the study and 9 had dose reduction to 50 mg because of poor tolerance. 229 subjects have been exposed to placebo. The mean duration of overall exposure was 158.5 days (neramexane) and 170.1 days (placebo).

The number of subjects with treatment emergent adverse events (TEAEs) was approximately the same in the neramexane group (65.3%) and the placebo group (64.6%). However, the number with TEAEs considered by the investigator to be related to the study treatment was greater among the subjects treated with neramexane (35.1%, compared with 21.8% in the placebo group). The numbers of subjects with serious treatment emergent adverse events were equal in each group, 4 subjects each with a total of 6 such events in the neramexane group and 5 in the placebo group; none of these events was considered by the investigator to be related to the study treatment. No subject died in this study. Among adverse events predefined as being of special interest, eye disorders did not differ substantially in frequency between the treatment groups

(neramexane group, 3.6%; placebo group, 2.6%), while psychiatric disorders occurred exclusively in the neramexane group (1.3%).

The most frequent treatment emergent adverse event was dizziness, with a higher incidence among the actively treated subjects (21.5% compared with 5.7% under placebo). A similar though smaller difference was found for headache, somnolence, fatigue, pain and especially for the mutually related events decreased libido and sexual and erectile dysfunction. Impaired hearing was recorded for noticeably more subjects in the placebo than in the verum group. There was no indication of systematic differences between the incidence rates, severities or relationship to the study treatment of adverse events among the subpopulation of AHL subjects compared with the total population.

Of the other safety assessments (laboratory values, vital signs, body weight, electrocardiography, ophthalmological examination, inquiry about sexual dysfunction) none revealed any clear association with the active treatment, either in the total population or among the AHL subjects, and none of the results led to any concern about the safety of the study treatment.

Conclusions

In both treatment groups clinically meaningful improvements were seen. However the efficacy analysis showed no statistically significant or clinically relevant differences in the effect of neramexane and placebo in the study population. This was the case both for the subgroup of subjects whose tinnitus was reported in the context with an acute hearing loss event and for the total study population. The safety and tolerability profile of neramexane as demonstrated by this study was in accordance with the known safety profile of the drug. There were no new safety concerns identified in this controlled clinical trial.