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2 SYNOPSIS

Study identifier MRZ 92579/TI/3004

Title of study

An Open-Label, Long-Term Treatment Study to assess the Long-Term Safety and Tolerability and Efficacy of Neramexane in Patients with Subjective Tinnitus

Report type

This abbreviated report was generated according to ICH E3 CPMP/ICH/137/95. The content of the report was reduced by the efficacy results to a minimum due to premature termination of the study. However it provides the full safety evaluation as planned.

Co-ordinating investigator

[redacted]
Germany
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Study sites

This was a multi-center, multi-national study with 3 study sites in Austria, 10 in Belgium plus the Netherlands, 4 in Brazil, 8 in the Czech Republic, 9 in France, 22 in Germany, 12 in Mexico, 13 in Poland, 6 in South Africa, 8 in Spain plus Portugal, 9 in the United Kingdom and 30 in the United States (134 sites in all).

Publication (reference)

None at the time of reporting.

Study period First subject enrolled: 21-JAN-2009 **Phase: 3**
Last subject completed: 14-DEC-2011

Objectives

To evaluate the long-term safety and tolerability of daily doses of 50 or 75 mg (depending on fixed dose in the respective lead-in study) neramexane in the treatment of subjective tinnitus. The durability of treatment effects (long-term efficacy) was also to be investigated.

Study design and methodology

This clinical study was conducted as a multi-center, multi-national, open-label long-term extension treatment study at up to 225 centers where the studies MRZ 92579/TI/3001, MRZ 92579/TI/3002 and MRZ 92579/TI/3003 had been conducted.

Number of subjects planned

All subjects (a total of up to ca. 1200) who completed the three double-blind, placebo controlled phase 3 studies (above) and fulfilled the eligibility criteria for the present extension study were to be included. Study MRZ 92579/TI/3004 was terminated prematurely by the sponsor after the results of the double-blind phase 3 studies became available, not showing superior efficacy of neramexane as compared with placebo. The study termination procedure was performed according to study protocol. The safety and tolerability profile of neramexane remained unchanged favorable.

Diagnosis and main criteria for in- and exclusion

First-onset, persistent, uni- or bilateral subjective tinnitus, and successful completion of one of the lead-in studies (above; "successful" was defined as having attended all visits, with questionnaires answered and scale-based assessments performed, of the respective lead-in study without premature discontinuation) and who were deemed eligible by the investigator, on the basis of specific inclusion/exclusion criteria designed mainly to exclude subjects whose health might have been put at risk by their participation.

Test product

Neramexane mesylate 12.5 mg, 25 mg, and 37.5 mg immediate-release film-coated tablets for oral administration.

In the lead-in studies, subjects had received 50 mg neramexane daily (or matching placebo) if they had a body weight of <90 kg at study entry and 75 mg daily for those with a body weight of ≥90 kg; the higher dose could be reduced to 50 mg if there were tolerance problems. On migrating to the present study, subjects received the same neramexane dose as they had received at the end of the lead-in study (or: a neramexane dose corresponding to the placebo that they had received), again with the possibility of decrease from 75 to 50 mg daily if at any time the higher dose was poorly tolerated.

Reference product

None.

Duration of study treatment

The planned duration of the study for each subject was one year.

Criteria for evaluation

Efficacy

TBF-12 total and factorial scores, Tinnitus Rating Scale and Short Form-36 Health Survey.

Pharmacodynamics

Not applicable.

Pharmacokinetics

Not applicable.

Safety

Adverse events, clinical laboratory values, 12-lead resting electrocardiography, vital signs, body weight, concomitant medications and treatments.

Statistical methods

Safety and efficacy analyses were performed in a purely descriptive/ exploratory manner. No confirmatory statistical tests were performed. All efficacy analyses were based on the full analysis set (FAS). The complete time courses of all efficacy variables (values and, where applicable, changes) were analyzed descriptively. N, N_{miss}, mean, median, minimum, maximum, and confidence intervals were given for values and, where applicable, for changes in continuous variables. For safety variables, the analysis was performed on the safety evaluation set (SES). Incidences were calculated for treatment emergent adverse events (TEAE) at the 'system organ class' (SOC) and 'preferred term' levels on the basis of MedDRA coding. Listings and, where applicable, analyses of incidences of TEAEs leading to discontinuation, serious TEAEs and deaths were also provided. Laboratory, vital-sign and ECG variables were analyzed descriptively and screened for individual clinically relevant values and changes.

Interim analysis

No interim analysis was performed.

Summary of results

Study subjects

A total of 957 subjects from the three placebo controlled lead-in studies qualified to enter the present open-label study. Of these, 820 in fact entered the study and 819 of those were treated with neramexane. A total of 375 subjects completed the study. Most instances of failure to complete the study were due to adverse events, lack of efficacy, administrative reasons (i.e., premature termination of the study by the Sponsor) or withdrawal of the subject's consent.

The subject's baseline and demographic details were unremarkable in view of their recruitment from three earlier double-blind lead-in studies in which they received neramexane or matching placebo.

Compliance with dosing rules during the fixed-dose period was good.

Efficacy results

Only a descriptive efficacy analysis was performed, due to the premature study termination no efficacy results are being detailed in this abbreviated study report. ~~A brief summary is provided in chapter 11~~. Overall the data collected in this open-label study did not modify any of the conclusions drawn on the outcomes of the three controlled lead-in studies.

Pharmacodynamic results

Not applicable.

Pharmacokinetic results

Not applicable.

Safety results

A total of 819 subjects received study treatment (50 mg or 75 mg neramexane daily, as set out above). The median duration of exposure to neramexane was 311 days.

Treatment emergent adverse events were reported for 515 subjects (62.9%), and such events were considered to be related to the study treatment for 250 subjects (30.5%). Forty-five serious adverse events were reported, for a total of 33 (4.0%) subjects; seven of these events, affecting five subjects (0.6%), were considered related to the study treatment. No subjects died in this study.

The most frequent treatment emergent adverse event was dizziness, with a frequency of 15.8%. Other frequent adverse events were worsening of tinnitus (10.6%), headache (8.5%), nasopharyngitis (7.8%), and vertigo (6.8%). The SOCs 'nervous system disorders', 'ear and labyrinth disorders' and 'infections and infestations' were most frequently represented in the analysis of adverse events. All of these observations, and the pattern of adverse events as a whole, were comparable to those found in the lead-in studies.

Of the other safety assessments (laboratory values, vital signs, body weight, electrocardiography) none revealed any clear association with the active treatment, either in the total population or when subjects were grouped according to their treatment in the individual lead-in studies (neramexane without wash-out, neramexane with wash-out, or placebo), and none of the results led to any concern about the safety of the study treatment.

Conclusions

The long-term safety and tolerability profile of neramexane as revealed by this open-label study was in accordance with the safety and tolerability profile of the drug, known from the previously conducted controlled clinical trials during the development program. No new or unexpected safety risks have been identified.