Clinical Study Report Synopsis for Public Disclosure

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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 Title	**Efficacy and safety of neramexane mesylate in congenital idiopathic nystagmus and acquired nystagmus: a randomized, double-blind, placebo-controlled, single center, proof of concept study using a two-period cross-over design**
Name of finished product	Neramexane
Name of active ingredient	Neramexane mesylate
Principal Investigator	[redacted] UK
Total number of study centers	1
Publication (reference)	None to date
Study period	Date of first enrolment: 18-JUN–2008 Date when the last subject completed the study: 06-NOV-2009
Phase of development	Clinical Phase II
Objective(s)	The primary objective was to investigate the safety and efficacy of neramexane mesylate at daily doses of up to 75 mg (target dose; reduction to 50 mg was allowed) in the treatment of congenital acquired nystagmus (CIN) in comparison with placebo. No secondary objective was defined in the study protocol. However, in addition to the primary objective, a subgroup of up to 20 multiple sclerosis (MS) patients (or fewer patients, if 28 patients with CIN had already been randomized) suffering from acquired nystagmus were to be included and analyzed in an exploratory manner.
Methodology	Randomized, double-blind, placebo-controlled, single-center study with a two-period cross-over design.

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Number of subjects (planned and analyzed)	Planned: 28 patients diagnosed with CIN (population for primary analysis), and also Up to 20 MS patients with acquired nystagmus (exploratory analysis). Analyzed: 28 patients with CIN, and 7 MS patients with acquired nystagmus
Diagnosis and main criteria for inclusion	CIN or acquired nystagmus (see above); 18–80 years old; nystagmus-related, best-corrected, reduced metric visual acuity (VA) of 6/9 or worse; no relevant abnormal laboratory or electrocardiography findings; normal results of ophthalmological examination; no history of (specified) disorders that might have compromised the patient's safety or the study result. For CIN patients, normal electroretinography and visually evoked potential; for MS patients, neurologically stable with no evidence of acute relapse.
Investigational Product	Dose: Neramexane mesylate modified release (MR) tablets (25 mg), 25-75 mg per day (individual dose adjustment with 75 mg as target dose or at least 50 mg) Mode of administration: Oral, once daily Batch number: 0711023074
Reference Product (placebo)	Dose: (no active substance) Mode of administration: As verum Batch number: 0711023074

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Duration of treatment	In cross-over design: One dosing period with verum comprising 3 weeks' up-titration followed by 4 weeks' treatment at 75 or 50 mg/day; one identical dosing period with placebo treatment. Including screening (up to 8 weeks), between-period wash-out (4–5 weeks) and follow-up (4 weeks) the total duration was up to 31 weeks.
Criteria for evaluation **Efficacy:**	*Primary response variable:* • Mean best corrected VA after 7 weeks of treatment performed at null point at distance (4m) using the LogMAR VA charts and with both eyes open. *Secondary response variables:* • Mean best corrected VA as above, separate tests for left and right eye; results of the best eye or the predominantly fixing eye were used for analysis. • Mean best corrected VA measured at null point at near (0.4 m) using LogMAR VA charts with both eyes open. • Mean best corrected VA measured at null point at near (0.4 m) using LogMAR VA charts, (separate tests for left and right eye; results of the best eye or the predominantly fixing eye were used for analysis). • Number/frequency of patients with an improvement in distance LogMAR VA by at least 0.2 score points. • Mean VA at different gaze eccentricity. • Mean nystagmus intensity (amplitude times frequency) at primary position of gaze at 1.2m and 0.33m (near fixation) for null region and over the entire fixation range. • Mean expanded NAFX at 1.2m at the different fixation points used during the measurement of nystagmus intensity. • Mean reading speed and reading acuity (LogRAD), at near (0.4m), test with both eyes opened (as based on Radner reading charts©). • Investigator's assessment of change in nystagmus

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	intensity, based on a verbal rating scale (VRS). • Patient's subjective change of oscillopsia (MS patients) or nystagmus intensity (CIN patients) based on a VRS. • Overall patient satisfaction with treatment, based on a VRS. • Patient's self-assessment of visual disability (disease-related quality of life) based on the Visual Function questionnaire (VF-14).
Safety:	• Adverse events. • Standard clinical chemistry, hematology, coagulation, and urinalysis. • Intraocular pressure. • Peripheral visual field measurement. • Vital signs (systolic and diastolic blood pressure, pulse rate). • Body weight and body mass index. • Digital 12-lead resting electrocardiogram. *Ancillary variables:* • Plasma levels of study drug for determination of population kinetics (PopPK; PK/PD modelling).
Statistical methods	Primary analysis population (CIN patients): All efficacy analyses were performed on the Full Analysis Set (FAS), i.e. all randomized patients who completed both periods of the study. Descriptive analyses were performed for both the Per Protocol Set (PPS) and the FAS. The PPS was defined as the subset of all patients in the FAS without major protocol deviations. The primary efficacy parameter and all other secondary efficacy parameters relating to VA were be analyzed by using an ANOVA approach to accommodate between- and within-patient factors, with treatment, period and sequence as fixed effects, and patient as random effect. The same statistical model was used for the analysis of mean nystagmus intensity, NAFX, reading speed, and visual disability measured by the VF-14 questionnaire. For nystagmus intensity and NAFX, the area under the

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	curve (AUC) was calculated for the null region ±6° left and right to the minimum intensity value using the trapezoidal rule and analyzed with the model described above. Furthermore, the AUC of a graph of nystagmus intensity plotted against eccentricity was calculated for the entire curve. For categorical variables, tests for treatment effects were performed by using a Prescott test, with non-binary variables (e.g. investigator assessment of change in nystagmus intensity) appropriately dichotomized. For MS patients all efficacy analyses were performed in a descriptive manner only. Safety parameters were analyzed for the Safety Evaluation Set (SES), i.e. for the subset of all randomized patients who received at least one dose of the randomized study medication. For continuous variables (e.g. vital signs and laboratory parameters) analyses were performed using descriptive statistics. For categorical data (e.g. adverse events, laboratory parameters with respect to normal ranges) frequency tables and shift tables were presented where applicable.
Summary / Conclusions	
Study population	Forty-one CIN and 7 MS patients were screened, of whom respectively 28 (14 to each treatment sequence) and 7 (3 to the treatment sequence neramexane-placebo and 4 to the treatment sequence placebo-neramexane) were randomized and treated; 1 CIN and 2 MS patients withdrew prematurely from the study. Reasons for withdrawal were adverse events, withdrawal of consent and loss to follow-up.
Efficacy results	The principal conclusions were to be drawn from the FAS. The variable for the primary efficacy analysis was the mean best corrected central VA at 4 m, measured by LogMAR with both eyes open. Comparison between treatment periods used a mixed-model ANOVA approach with 'treatment', 'period', and 'sequence' as fixed effects, and with 'patient' as random effect; all

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	randomized CIN patients in the FAS were included in an 'observed cases' approach. For the CIN patients, in the primary analysis, the LogMAR after seven weeks of treatment was 0.230 ± 0.089 with neramexane and 0.240 ± 0.087 with placebo. The difference was –0.010, with a confidence interval from –0.031 to 0.011 and with $p = 0.3399$ for the influence of the variable 'treatment'. Thus, the very small relative improvement associated with the active treatment was without statistical significance. A similar result was obtained for the MS patients and for the supporting PPS analysis. In the secondary analyses, most variables showed no relevant difference between the treatments with verum and placebo; where there was a slight trend in favor of the active treatment, this was without statistical significance except for the case of the patients' overall satisfaction with treatment, where there was a preference for the active treatment with $p = 0.0146$ for the CIN patients. In an exploratory *ad hoc* analysis, the collective of eight patients who expressed a greater satisfaction with the active treatment than with the placebo was examined in order to detect any possible factors that might have differentiated these patients from the others in the study; this analysis did not reveal any such factors.
Safety results	The incidence rate of adverse events was higher during treatment with verum group than during treatment with placebo, among both the CIN and the MS patients. Events considered related to the study treatment were likewise more frequent among patients receiving neramexane than among those receiving placebo. One MS patient was withdrawn from the study because of adverse events (including a serious adverse event, hypomania/mania, which was rated as being related to the treatment and which was recorded as two serious adverse events at the same time). Only one serious adverse event occurred in one MS patient that was recorded as two serious adverse events at the same time (mania and hypomania). No patient died during the study. Severe adverse events occurred in two CIN

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	patients ('dizziness' and 'disturbance in attention') and one MS patient ('fatigue', 'feeling drunk', 'dissociation', 'hypomania' and 'mania'; this was the same patient who experienced the serious adverse event) during treatment with neramexane, and no severe adverse events occurred among patients receiving placebo. Adverse events assessed as being related to the study treatment were likewise more frequent in the periods of treatment with neramexane than those of treatment with placebo. In the CIN group there was a preponderance of such events for almost all event types (preferred terms) during the neramexane treatment relative to the placebo treatment. Laboratory values, vital signs, electrocardiography, body weight and peripheral field measurement all showed no relevant differences between the verum and placebo treatments. Intra-ocular pressure was slightly higher at the end of the treatment with placebo than after treatment with neramexane.
Conclusion	In both study indications (congenital idiopathic nystagmus and nystagmus associated with multiple sclerosis), the treatment with neramexane showed only a very slight beneficial effect; this effect was neither clinically nor statistically significant. The safety analysis revealed a pattern of adverse events that accorded with the results of earlier studies. The modified release formulation and the once-daily regimen for intake of neramexane mesylate combined with the three-week up-titration period and the obligatory target dose of 75 mg showed no relevant change in tolerability compared with the 75 mg immediate-release formulation and four-week up-titration used in earlier clinical studies.