CLINICAL STUDY REPORT SYNOPSIS

<table>
<tr><td rowspan="3">Name of Sponsor/Company:
MDM S.p.A.
Via Volturno, 29/b
20052 Monza - Italy

Name of Finished Product:
NIMOBET

Name of Active Ingredient:
Nimodipine + Betahistine</td><td rowspan="3">Individual Study Table Referring to Part of the Dossier

Volume:

Page:</td><td rowspan="3">(For National Authority Use only)</td></tr>
<tr><td colspan="3">Title of Study:
“A phase II, randomized, double-blind, parallel groups study to assess the efficacy and safety of nimodipine 20 mg + betahistine 16 mg versus blacebo + betahistidine 16 mg in the treatment of vertigo”</td></tr>
<tr><td colspan="3">Investigators:
Prof. Daniele Monzani</td></tr>
<tr><td colspan="3">Study centre(s):

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41124, Modena, Italia</td></tr>
<tr><td colspan="3">Publication (reference):
none</td></tr>
<tr><td colspan="2">Studied period (years):
January 2015 – July 2015</td><td>Phase of development: II</td></tr>
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Objectives:

Primary Objectives

1. To evaluate the efficacy of Nimodipine 20 mg + Betahistine 16 mg (b.i.d) for the treatment of vertigo, compared to Betahistine 16 mg (b.i.d), as assessed by the Dizziness Handicap Inventory (DHI) after 4 weeks of treatment

Secondary Objectives

1. To evaluate the self-perceived vertigo disability as assessed by the change of Mean Vertigo Score (MVS), based on the sum of vertigo, dizziness, unsteadiness divided by three
2. To evaluate the quality of life in patients with vertigo, using the SF-12 questionnaire

Safety Objectives

1. To investigate the safety and tolerability of Nimodipine 20 mg + Betahistine 16 mg (b.i.d.)

Methodology:

Phase II, randomized, double-blind, single site, controlled study, with two parallel groups of patients.

Number of patients (planned and analysed):

Number patients planned: 80 evaluable patients, 40 per treatment group.
Number of patients analysed: 82, 43 in treatment group A (Nimodipine + Betahistine) and 39 in treatment group B (Palcebo + Betahistine).

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Diagnosis and main criteria for inclusion:

Inclusion Criteria

- Age > 20 years (both gender)
- Clinical and instrumental (vestibular examination) identification of labyrinthine vertigo, due to:
  - Ménière's disease (possible, probable, definite) as per the guidelines of the American Academy of Otolaryngology-Head and Neck Foundation
  - dysfunction of the inner ear of different origin with symptoms typical of Ménière's Syndrome (vertigo, hearing loss, tinnitus):
    - Lermoyez's syndrome
    - "delayed hydrops"
    - cochleo-labyrinthopathy in association with vascular disorders of the vertebro-basilar area

    all of them associated to otolith disorders or not
- Complaint of vertigo lasting more than three months
- Baseline total DHI score ≥ 40
- Negative pregnancy test for women of childbearing potential (to be performed at Visit 1) and use of an acceptable mean of contraception in the previous 2 months and for whole duration of the study
- Signed Informed Consent

Exclusion Criteria

- Cerebellopontine lesions, multiple sclerosis, vascular dementia, migraine associated vertigo, phobic vertigo, motion sickness, acoustic neuroma or other CNS tumor, as demonstrated by brain CT scan or NMR
- Patients treated with calcium channel blockers, antihistamines, rifampicin, phenobarbital, phenytoin or carbamazepine
- Known allergies, hypersensitivity, or intolerance to nimodipine or betahistine or any excipients used in their manufacture
- Patient with clinical gastrointestinal malabsorption
- Patients with blood pressure <100/70 mmHg
- Patients with hypertension, pharmacologically treated or not
- Patients with bronchial asthma
- Patients with a history of documented peptic ulcer
- Patients with urticaria, exanthema or allergic rhinitis
- Patients with phaeochromocytoma
- Pregnancy, breast feeding
- Use of vestibular suppressants drugs 7 days prior to study treatment start
- ALT > 1.5 upper normal limit (UNL), AST > 1.5 UNL, alkaline phosphatase > 1.5 UNL, total bilirubin > 2 UNL, creatinine > 1.5 UNL

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Diagnosis and main criteria for inclusion:

Exclusion Criteria

- Treatment with another investigational agent within the last 30 days
- Subjects with evidence of clinically unstable disease, as determined by medical history, physical examination, that, in the Investigator's opinion, preclude entry into the study
- Known or suspected history of alcohol or drug abuse based on medical history, physical examination, or the Investigator's clinical judgment

Test product , dose and mode of administration, batch number:

Group A - Betahistine dihydrochloride tablet (Betahistine ratiopharm 30 tablets, 16 mg) plus Nimodipine drops (Iskidrop, 25 ml, 30 mg/0.75 ml). Posology: 1 tablet twice in day plus 20 drops twice in day

Group B – Betahistine dihydrochloride tablet (Betahistine ratiopharm 30 tablets, 16 mg) plus Placebo drops (25 ml, 0 mg/0.75 ml). Posology: 1 tablet twice in day plus 20 drops twice in day

Duration of treatment:
4 weeks.

Reference therapy, dose and mode of administration, batch number:

IMP 1: Nimodipine drops: Iskidrop, 25 ml, 30 mg/0.75 ml.

Batch Number: NIMO01/14 *Expiry date 09/2016*

IMP 2 (PeIMP): Betahistine dihydrochloride: Betahistine ratiopharm 30 tablets, 16 mg.

Batch Number: N20143 *Expiry date 03/2016*

IMP 3: Placebo drops: 25 ml, 0 mg/0.75 ml.

Batch Number: NIMO01/14 *Expiry date 09/2016*

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Criteria for evaluation:

Primary efficacy endpoint

- Reduction of DHI after 4 weeks of treatment

Secondary Efficacy endpoints

- Reduction of MVS after 1 and 4 weeks of treatment and 4 weeks of follow-up
- Change in SF-12 scores after 4 weeks of treatment
- Reduction of DHI after 1 week of treatment and 4 weeks of follow-up

Safety Assessments

The safety profile of both treatment groups, A and B, was assessed through the recording, reporting and analyzing of baseline medical conditions, adverse events, physical examination findings including vital signs and laboratory tests.

Statistical methods:

Continuous variables were summarized by the number of patients, mean, standard deviation, median, minimum, maximum. Categorical variables were summarized by the number and the proportion of patients. The significance level of the statistical test was 0.05.

ANOVA was performed on normally distributed continuous variables. T-test was additionally performed for pairwise comparisons. Chi-square or Fisher's exact test was performed on discrete variables.

Efficacy results:

Primary endpoints:

Between day 1 and day 28, the DHI score improved of 13.41 points in the Betahistine+Placebo group and of 14.05 points in the Betahistine+Nimodipine group. Both the functional and physical subscale improved more in the Betahistine+Nimodipine group than in the Betahistine+Placebo group, but the improvement was slight and therefore not statistically significant. The adjustment for baseline values did not appreciably change the results. The analysis by gender revealed that among women the DHI scores improved more in the Betahistine+Placebo group than in the Betahistine+Nimodipine group. Among men, instead, the difference in the global DHI score was of 3.87 points in favor of the Betahistine+Nimodipine group, not statistically significant. The central vertigo patients had the greater difference between the two treatment groups (3.39 points), with 14.73 points of improvement in the Betahistine+Nimodipine and 11.33 points in the Betahistine+Placebo group. The difference was not statistically significant due to the lower number of patients (20 patients). At day seven, the difference between the two treatment groups was negligible. At end of study, the difference in the improvement between treatment groups was small (0.42 points).

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Efficacy results:

Secondary endpoints

The analysis of mean vertigo score (MVS) revealed a slight difference between the two treatment groups at the end of treatment, in favor of the Betahistine+Nimodipine group, both in the total MVS score and in each of its components (vertigo, dizziness and unsteadiness)) and the adjustment for baseline values did not change these results. Even the analysis by type of vertigo (central, peripheral or mixed) did not reveal any clear difference between the two treatment groups. In the analysis of central and mixed vertigo, the differences between the two treatment groups were only slightly increased. At the Day 7, the differences between the two treatment groups were negligible, and at end of study the differences were similar to those observed at end of treatment.

At end of treatment, both subscale of SF-12, i.e. PCS-12 and MCS-12, revealed an improvement slightly higher in the Betahistine+Nimodipine group (0.52 points higher for both subscales) and the adjustment for baseline values flattened these differences. An improvement in the Betahistine+Nimodipine group was observed among the patients with peripheral vertigo, where MCS-12 was 1.96 points higher than the Betahistine+Placebo group, while among patients with central or mixed vertigo, the improvement in MCS-12 was higher in the Betahistine+Placebo group.

Safety results:

Only three patient experienced an adverse event: two patients (ID 01-014 and 01-061) in the Betahistine+Placebo group and one patient (ID 01-056) in the Betahistine+Nimodipine group.

The patient treated with Betahistine+Nimodipine (ID 01-056) experienced a mild nausea that was resolved within four days with no other action than the permanent suspension of the treatment. This adverse event was considered related to the treatment taken.

The first patient treated with Betahistine+Placebo (ID 01-014) experienced a moderate wheal that was resolved within three days with no other action than the permanent suspension of the treatment. This adverse event was considered related to the treatment taken.

The first patient treated with Betahistine+Placebo (ID 01-061) experienced a mild persisting nausea that was resolved within five days with no other action than the permanent suspension of the treatment. This adverse event was considered related to the treatment taken.

The change between screening and end of treatment were evaluated as changes between normal values and abnormal values, and, when a value was abnormal, if it was clinically significant or not. Most of the patients had unchanged or improved clinical laboratory test results between the two visits. The few laboratory tests worsened during the study were considered not clinically significant.

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Conclusion:

Globally, both treatments were effective in the vertigo treatment, as both treatment groups had an improvement of symptomatology in the study period. The addition of Nimodipine to Betahistine seems to be slightly ameliorative even if never in a statistically significant way.
DHI score improved from day 1 to day 28 in both treatment groups, slightly more in the Betahistine+Nimodipine group. Both the functional and physical subscale improved more in the Betahistine+Nimodipine group than in the Betahistine+Placebo group.
The central vertigo had the greater difference between the two treatment groups, in favor of the Betahistine+Nimodipine, even if not clinically significant due to the low number of patients analysed (20 patients).
At end of study, DHI improvement from baseline was higher than that observed at end of treatment within both treatment groups, but the difference between treatment groups was Also mean vertigo score (MVS) data analysis revealed a slight, but not statistically significant, difference between the two treatment groups at the end of treatment, in favor of the Betahistine+Nimodipine group, both in the total MVS score and in each of its components (vertigo, dizziness and unsteadiness).
SF-12 data analysis at the end of treatment revealed an improvement slightly higher in the Betahistine+Nimodipine group, for both subscales of SF-12, i.e. PCS-12 and MCS-12. A difference in improvement was observed among the patients with peripheral vertigo in favor of the Betahistine+Nimodipine group, while among patients with central or mixed vertigo, the improvement in MCS-12 resulted higher in the Betahistine+Placebo group.
It must be noted that all the subjects included in this trial received a basal treatment, known to be an efficacious therapy for the disease under investigation.
In addition data dispersion due to the different typologies of vertigo included in the study (peripheral, central and mixed) and the consequent poor number of cases analysed per typology, as well as the subjective evaluation of the disease improvement, all these factors have possibly not allowed to detect a statistically significant additive effect by Nimodipine.

Only three mild to moderate adverse drug reactions occurred during the study, two in the group Betahistine+Placebo and one in the group Betahistine+Nimodipine. All the three events were resolved after study treatment interruption. No significant change in laboratory parameters or vital signs was reported. Therefore the association of Nimodipine to Betahistine is safe and generally very well tolerated.

Date of report: December 16th 2015