SYNOPSIS

Title of the study: Efficacy and safety of 2 mg/day M100907 on Sleep Maintenance Insomnia: a 6-week, multicenter, randomized, double-blind, placebo-controlled polysomnographic study (EFC6072).
Investigator(s): [redacted]
Study center(s): 64 sites - United States of America (36 centers), Canada (5 centers), Australia (5 centers), France (4 centers), Germany (10 centers), Austria (2 centers), and Russia (2 centers)
Publications (reference): None
Study period: Date first patient enrolled: 13 April 2007 Date last patient completed: 16 January 2008
Phase of development: 3
Objectives: **Primary**: To demonstrate efficacy of M100907 2mg/day in comparison to placebo for Sleep Maintenance Insomnia using change from baseline at 6 weeks of treatment of night polysomnography wake time after sleep onset (PSG-WASO). **Secondary**: ***Key Secondary objective***: • To evaluate patient's daytime functioning using items "22, 23, 24" and 1 and 2 (respectively desired activity level, concentration and remembering) of the functional outcomes of sleep questionnaire (FOSQ), with M100907 2mg/day as compared to placebo after 6 weeks of treatment. ***Other Secondary objectives***: • To evaluate the patient reported wake after sleep onset (pr-WASO) after 6 weeks of treatment with M100907 2mg/day as compared to placebo. • To evaluate the effects on sleep architecture of M100907 2mg/day compared to placebo. • To evaluate the clinical safety and tolerability of M100907 2mg/day compared to placebo. • To evaluate the residual effects (using patient's morning questionnaire and psychometric tests) that may be associated with M100907 2mg/day as compared to placebo during double-blind treatment period. • To compare the effect on sleep (pr-WASO and patient reported total sleep time [pr-TST]) during run-out period following abrupt discontinuation (after 42 nights) between M100907 2mg/day and placebo.
Methodology: This was an international, multicenter, randomized, double-blind, placebo-controlled study with two parallel groups of patients with sleep maintenance insomnia: 1 group received M100907 2 mg/day, and 1 group received placebo.

Number of patients: Planned: 580 (290 in each group)

Randomized: 604

Treated: 602

Evaluated:

Efficacy: Primary analysis – Placebo: 288 and M100907: 278; secondary efficacy – Placebo 287 and M100907 281.

Safety: M100907 290 exposed; placebo 298 exposed

Pharmacokinetics: 581

Diagnosis and criteria for inclusion:

Adult out-patient with primary insomnia based on criteria (Diagnostic and Statistical Manual of Mental Disorders [Fourth Edition]) with predominant complaints of difficulty in maintaining sleep prior to study visit.

Based on the PSG recordings during the screening nights (SN1 and SN2) the following criteria must be met:

- Mean PSG-WASO of SN1 and SN2 was to be ≥45 minutes and neither night was to be <30 minutes.
- PSG-TST ≤7 hours and ≥3 hours on both SN1 and SN2.
- Mean latency of persistent sleep (PSG-LPS) calculated on SN1 and SN2 ≤30 minutes.

Based on patient's information:

- patient must have complained of at least 1 hour of wakefulness after sleep onset for at least 4 or more nights per week over the preceding month
- patient must have spent at least 6.5 hours and no more than 9.0 hours in bed, each night over the preceding 2 weeks
- patient must have reported impact daytime functioning associated with sleep maintenance insomnia as measured by question 3 of Insomnia Severity Index at screening and randomization visits (the patient's answer should be either: 2 (somewhat interfering), or 3 (much), or 4 (very much interfering)

Investigational product:: M100907 (INN: volinanserin)

Dose: 2 mg/day

Administration: Oral tablet

Batch number: [redacted]

Duration of treatment: 6 week double-blind period

Duration of observation: 2 weeks

Reference therapy: Placebo

Dose: Not applicable

Administration: Oral tablet

Batch number(s): [redacted]

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Criteria for evaluation:

Efficacy:

Primary efficacy variables

The primary variable is the change from mean baseline (SN1/SN2) to the mean on (N41/N42) of PSG-WASO.

Key secondary variables

The key secondary endpoints were the change from baseline at Day 41 of the following variables:

- Change in desired activity level (mean of the questions 22, 23 and 24 of the FOSQ) from baseline to Week 6
- Change in concentration and remembering (mean of the questions 1 and 2 of the FOSQ) from baseline to Week 6

Other secondary variables

- From PSG recordings, the change from the mean baseline (SN1/SN2) to the mean Week 6 (N41/N42) of the following:
  - sleep efficiency index (PSG-TST/time in bed), completed PSG-TST, PSG-LPS, and number of nocturnal awakenings (PSG-NAW)
  - sleep architecture: % of time spent at each stage (stage 1, stage 2, stage 3, and stage 4) and during rapid eye movement (REM)
- From daily assessments from patient's morning questionnaire, the mean change from baseline to Week 1 up to Week 6 of the following:
  - pr-WASO, pr-TST, and patient reported number of nocturnal awakenings (pr-NAW)
  - Patient global impression at Visit 4 (Day 20) and at Visit 5 (Day 41).

Safety:

The occurrence of treatment-emergent adverse events (TEAEs), laboratory evaluations (hematology, blood chemistry, liver enzymes, and urinalysis), vital signs, body weight, electrocardiograms (ECGs) next day residual effect, rebound, and withdrawal effects.

Pharmacokinetics:

The pharmacokinetic samples were collected to describe the M100907 and MDL 105,725 plasma concentrations in the targeted population.

Pharmacokinetic sampling times and bioanalytical methods:

Sampling times*:*

Blood samples to determine M100907 and its metabolite (MDL105, 725) concentrations were collected at Visit 4 (Day 20) and at Visit 5 (Day 42) between 9 and 10 AM and between 6 and 7 PM.

For patients who signed the informed consent form, a single blood sample was collected for genotyping of the drug-metabolizing enzyme CYP2D6 at Visit 4 (Day 20).

Bioanalytical method*:*

Plasma: M100907 and MDL 105,725 plasma concentrations were determined using a validated liquid chromatography - tandem mass spectrometry method with a lower limit of quantification (LLOQ) of 0.02 ng/mL.

Genotyping: Deoxyribonucleic acid (DNA) was extracted from whole blood and assayed using validated TaqMan methods for different allelic variants of CYP2D6 genes.

Statistical methods:

Main analysis

As for the primary analysis, the comparison of the PSG-WASO (change from baseline) between M100907 versus placebo was performed at the planned end of double-blind treatment, on intent-to-treat population, with a mixed-effect model with repeated measures (MMRM) approach, assuming the missing at random framework. This model included the fixed categorical effects of treatment (2 levels: M100907 and placebo), visit (2 levels: mean of N20/N21 and mean of N41/N42), and treatment-by-visit interaction, as well as the centered baseline PSG-WASO (ie, baseline PSG-WASO after having centered baseline individual values on the grand baseline mean) as continuous fixed covariate.

Supportive analysis

To assess the sensitivity of the primary analysis, supportive analyses of covariance (ANCOVA) were conducted based on the two following strategies "last observation carried forward" providing estimates at last available visit during double-blind period and "observed cases" providing estimates at Week 6.

Safety:

All safety analyses were performed on all treated population.

Adverse events

Treatment-emergent adverse events were defined as adverse events that occurred during the double-blind study treatment exposure (including the day of the first double-blind intake) or within 5 half-lives (5 days) following the last double-blind intake of investigational product.

For summaries of all TEAEs, counts were provided by-treatment group for each preferred term within each system organ class concerned. Percentages were calculated with the number of patients from the exposed population in each group.

Laboratory, vital signs, and electrocardiogram parameters

The overall incidences of patients having at least 1 postbaseline potentially clinically significant abnormality (PCSA) in laboratory parameters, vital signs parameters, and ECG parameters during the double-blind period were summarized. For quantitative safety parameters, descriptive statistics were used to summarize results and changes from baseline values by treatment group.

Residual effects

The residual effects assessed in the sleep morning questionnaire (sleepiness in the morning and ability to concentrate in the morning) were analyzed through the double-blind treatment period, using all available weekly average of daily assessments from Week 1 to Week 6 as repeated measurements using MMRM analysis.

Psychometric tests assessing sedative, psychomotor and memory effects, digit symbol substitution test, and the Rey auditory verbal learning test were analyzed using MMRM model.

Rebound effect

Rebound effect was assessed by looking at the patients reported WASO: each time of the run-out (first day, mean of the first 3 days and mean of 7 days) was analyzed using ANCOVA with the baseline value as covariate, based on the observed cases strategy.

Withdrawal effect

Withdrawal analyses were performed on the total score of the Physician Withdrawal Checklist (PWC). The changes from Day 42 (evaluation under treatment) to Day 1, Day 2, Day 3, Day 4, Day 5, Day 6, and Day 7 after the last double-blind intake (run-out evaluations) on the total score of the PWC were summarized by descriptive statistics and using ANCOVA with the baseline value as covariate.

Pharmacokinetics:

Plasma concentrations of M100907 and MDL 105,725 were summarized using descriptive statistics [mean, geometric mean, standard deviation (SD), coefficient of variation, minimum, maximum, and median] according to the predefined time windows by visit.

Summary:

Efficacy results:

A total of 589 patients were randomized; 299 patients received placebo, and 289 received M100907 2 mg/day.

A statistically significant greater decrease in the PSG-WASO was observed after 6 weeks of treatment (primary efficacy criterion), the difference for PSG-WASO between groups in least square (LS) mean change from baseline was: -6:25 (minutes:seconds), 95% confidence interval (CI) (-12:38; -0:12) in favor of M100907.

This result is consistent with the analysis of the pr-WASO, which also showed an effect of M100907 with a difference between groups in LS mean change from baseline of -7:15 (minutes:seconds), 95% CI (-12:37; -1:53).

Polysomnography measurement of the PSG-NAW showed a greater reduction from baseline in the M100907 group over placebo (95% CI of the LS mean difference [-2.8;-1.5]); while there was only a trend in the pr-NAW at 6 weeks (95% CI of the LS mean difference [-0.36 ;0.02]).

No effect of M100907 as compared with placebo was observed on the other sleep parameters with PSG measures as TST, LPS, and sleep efficacy index; however, a significant improvement was observed on pr-TST.

Sleep architecture analyzed at N41/N42 showed a decrease in the percentage of time spent in stage 1 with the 95% CI of the LS mean difference from placebo (-2.2; -1.0); an increase in stage 3/4, 95% CI of the LS mean difference from placebo (0.7; 2.4), and no difference in time spent in stage 2 and in REM stage.

No difference was observed between M100907 and placebo on the main secondary parameter, ie, the desired activity level and the concentration/remembering domains assessed with the FOSQ.

Patient Global Impression rated at end of treatment showed an advantage of M100907 over placebo with more patients having a favorable opinion on the compound as an aid to sleep.

Safety results:

About one third of patients in both treatment groups had at least 1 TEAE: 33.2% in the placebo group and 35.2% in the M100907 group. In the M100907 group, the most frequently reported TEAEs with an incidence ≥1% (and at least 1% higher than the placebo group) were headache and fatigue. In the placebo group the most frequently reported TEAEs with an incidence ≥1% (and at least 1% higher than the M100907 group) were diarrhea and abnormal dreams. The majority of TEAEs were of mild to moderate intensity in both treatment groups.

Two patients (0.7%) reported treatment-emergent serious adverse events (TEAEs) (hypertensive crisis and cholecystitis acute) in the M100907 group and none in the placebo group; no particular pattern in the occurrence of these SAEs was detected. No deaths were reported in the study. Four patients in the placebo group and 5 in the M100907 group discontinued treatment due to TEAEs.

The percentage of patients with glucose level ≥11 mmol/L (unfasted) or ≥7 mmol/L (fasted), was higher in the M100907 group (7.1%) compared with the placebo group (3.8%). Sporadic PCSAs in other laboratory parameters and ECG values were observed in both treatment groups without clinical relevance.

The incidence of patients with PCSA for vital signs was slightly higher in the placebo group than in the M100907 group. In particular, PCSAs related to orthostatic decrease in diastolic blood pressure (≤-10mm Hg) were observed in 8.3% of patients in the placebo group versus 6.0% in M100907 group, PCSAs related to orthostatic decrease in systolic blood pressure (≤-20 mmHg): 7.3% in the placebo group versus 4.9% in the M1009007 group.

There was no evidence of symptoms related to residual effect (after each night of treatment) or rebound effect (collected from the run-out period) or withdrawal effect from M100907.

Pharmacokinetic results:

For M100907, the mean (SD) plasma concentration at Visit 5 (Day 41) was 0.62 (0.72) ng/mL at 9 to10 AM and the 0.37 (0.53) ng/mL at 6 to 7 PM. For MDL 105,725, the mean (SD) plasma concentration at Visit 5 (Day 41) was 0.02 (0.02) ng/mL at 9 to 10 AM and <LLOQ at 6 to 7 PM.

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Conclusions:

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