SYNOPSIS

Title of the study: Efficacy and safety of 2 mg per day of M100907 on sleep maintenance insomnia with a sub-study of the effect of M100907 on stable Type 2 diabetes mellitus: a 12-week, multi-center, randomized, double-blind, placebo-controlled study (LTE6672).

Investigator(s): [redacted]

Study center(s): The study was conducted in 114 active centers in Brazil, Canada, Colombia, Czech Republic, Finland, France, Greece, Italy, Malaysia, Netherlands, Russian Federation, South Africa, Taiwan, Turkey, and the United States of America.

Publications (reference): Not applicable

Study period:

Date first patient enrolled: 20 June 2007

Date last patient completed: 30 October 2008

Phase of development: 3

Objectives:

- The primary objective of the study was to demonstrate efficacy of M100907 2 mg/day in comparison to placebo for sleep maintenance insomnia using change from baseline to 12 weeks of patient reported wake time after sleep onset (pr-WASO).
- The key secondary objective (modified according to the amended statistical analysis plan, dated 18 November 2008) was to evaluate the patient's daytime functioning using the mean of questions 1 (concentration) and 2 (memory), and the mean of the questions 22, 23, and 24 (desired activity level) of the Functional Outcomes of Sleep Questionnaire (FOSQ) with M100907 2 mg/day as compared to placebo after 12 weeks of treatment.

Other secondary objectives included:

- To assess efficacy of M100907 2 mg/day in comparison to placebo as change from baseline to 12 weeks on other parameters of patient's sleep questionnaire.
- To evaluate the clinical safety and tolerability of M100907 2 mg/day in comparison to placebo during the 12 weeks of treatment.
- To evaluate subjective next morning residual effects associated with M100907 2 mg/day as compared to placebo at 12 weeks of treatment.
- To evaluate the effect on sleep (pr-WASO, and patient reported total sleep time [pr-TST]), following abrupt discontinuation after 12 weeks of study treatment with M100907 2 mg/day in comparison to placebo during the 1-week run-out period.
- To measure the M100907 and the metabolite MDL105,725 plasma concentrations.

The objectives for the substudy of patients with type 2 diabetes mellitus and sleep maintenance insomnia were:

- To assess the glycemic control in patients with type 2 diabetes mellitus and sleep maintenance insomnia using change from baseline of HbA_{1C} at 12 weeks.
- To evaluate efficacy through reduction in dose of medicine(s) required for adequate diabetes control after 12 weeks of treatment with M100907.
- To assess the glycemic control in patients with type 2 diabetes mellitus and sleep maintenance insomnia using change from baseline of fructosamine at 12 weeks.

Methodology: This was an international, multicenter, randomized, 12-week, double-blind, placebo-controlled study with 2 parallel groups of patients with sleep maintenance insomnia to evaluate M100907 2 mg/day versus placebo. A substudy population diagnosed with type 2 diabetes was also included in the study.

Number of patients: Planned: 840 (420 per treatment arm)

Randomized: 848

Treated: 847 including 1 patient not randomized

Efficacy: Placebo: 410, M100907 435

Safety: Placebo 410, M100907 436

Pharmacokinetics: 809

Diagnosis and criteria for inclusion: Patients aged ≥18 years diagnosed with primary insomnia based on the criteria described in the Diagnostic and Statistical Manual of Mental Disorders 4th edition text revision, with predominant complaints of difficulty maintaining sleep, for at least 1month preceding the study visit, and having clinically significant distress or impairment in social occupational or other important areas of functioning.

In addition, based on the patient's information:

- The patient must complain of at least 1 hour of wakefulness after sleep onset for at least 4 nights per week over the preceding month
- The patient must spent at least 6.5 hours and not more than 9.0 hours, in bed, each night, over the preceding 2 weeks
- The patient must report impact on daytime functioning associated with sleep maintenance insomnia as measured by question 3 of Insomnia Severity Index at screening and randomization visits. To be included patient's answer should be either: 2 (= some what interfering), or 3 (= much), or 4 (= very much interfering) at both visits
- The patient must report during the screening week:
  - WASO ≥60 min in more than half of nights
  - TST ≤7 hours and ≥ 3 hours on 3-worst nights
  - Excluding 1 night with the highest Sleep Onset Latency (SOL) value, the mean SOL must be ≤30 min

To be included in a substudy population, patients with sleep maintenance insomnia and type 2 diabetes must have been on an oral hypoglycemic agent and/or insulin for at least 3 months prior to the screening visit (stable regimen for at least 1 month).

Investigational product: M100907/INN: volinanserin tablets

Dose: 2 mg

Administration: oral, once daily around bedtime

Batch number: [redacted]

Duration of treatment: 12 weeks

Duration of observation: Approximately 14 weeks including Segment A (run-in period, 5 to 10 days), Segment B (double-blind treatment period, 12 weeks), and Segment C (run-out period, 1 week).

Reference therapy: placebo tablets

Dose: not applicable

Administration: oral, once daily around bedtime

Batch number: [redacted]

Criteria for evaluation:

Efficacy:

Primary efficacy variable:

The primary efficacy variable was the change from baseline to Week 12 (Visit 6) of the mean pr-WASO measured by patient's sleep questionnaire recorded at Week 9 through Week 12 double-blind visit.

Secondary efficacy variables:

The key secondary variables were the change from baseline to Week 12 of the following variables derived from the FOSQ collected in the evening prior to each visit:

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

Other secondary efficacy variables:

The other secondary efficacy endpoints were:

- pr-WASO at other timepoint than primary endpoint
- pr-NAW (patient reported number of nocturnal awakenings), pr-TST (patient reported total sleep time), pr-SOL (patient reported sleep onset latency), pr-sleep quality and pr-refreshing sleep quality
- Sub-score for the 5 domains (general productivity, activity level, vigilance, intimacy and sexual relationships, social outcome) and total score of the FOSQ
- Patient Global Impression (PGI) consisting of 4 questions (aid to sleep, sleep induction, sleep duration and medication strength) with 3-category codification.

Substudy efficacy variables for the population of patients with diagnosis of sleep maintenance insomnia and type 2 diabetes mellitus were:

- Change from baseline at Week 12 (Visit 6) for HbA1c
- Change from baseline at Week 12 (Visit 6) for fructosamine
- Reduction in dose of medicine(s) required for adequate diabetes control at Week 12 (Visit 6) or last double-blind intake compared to baseline.

Statistical methods:

Efficacy

Main analysis

For the primary efficacy analysis, the comparison of the change from baseline in the mean of pr-WASO between M100907 and placebo was performed at the planned end of double-blind treatment, on the intent-to-treat (ITT) population using a mixed-effect model with repeated measures (MMRM) approach, assuming a missing at random mechanism.

The model included the fixed categorical effects of treatment (2 levels: M100907 and placebo), visit (4 levels: Week 1 to Week 2, Week 3 to Week 4, Week 5 to Week 8 and Week 9 to Week 12), and treatment-by-visit interaction, as well as the continuous fixed covariate of centered baseline mean pr-WASO (ie, baseline mean pr-WASO after centered baseline individual values on the grand mean baseline).

Supportive analysis

To assess the sensitivity of the primary analysis, supportive analyses of covariance (ANCOVA) were conducted based on the last observation carried forward (LOCF) providing estimates at the last available visit in the double-blind period and observed cases (OC) strategies providing estimates at Week 12.

Secondary analyses

Analyses of the secondary efficacy variables were performed in the same way as for the primary efficacy variable.

Substudy of type 2 diabetes mellitus

The change from baseline of HbA1C and fructosamine at Week 12 (Visit 6), or at the last available postbaseline assessment before Visit 6, was analyzed using a 1-way LOCF ANCOVA using treatment factor as fixed effect with 2 levels (M100907 and placebo) and the baseline value as covariate. No interaction was included in the model.

Safety

All safety analyses were performed on the all treated population.

Adverse events

Treatment-emergent adverse events (TEAEs) were defined as AEs that developed, worsened, or became serious during the on-treatment period, ie, from the day of the first dose intake of double-blind study drug up to 5 days (5 half-lives) after the last administration of the double-blind study drug.

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 all treated population in each group.

Laboratory, vital signs, and electrocardiogram parameters

Summary tables of patients with at least 1 postbaseline PCSA by treatment group, at any postbaseline time point during the on-treatment period for each laboratory, vital sign, and ECG parameter were provided. For quantitative safety parameters, descriptive statistics were used to summarize results and changes from baseline values by treatment group

Residual effect

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 the mean change from baseline to each assessed visit with the same model assuming a missing at random mechanism as for primary analysis (MMRM with centered baseline value as the covariate), on the all treated population.

Rebound effect

The mean change from baseline of pr-WASO and pr-TST at each time point of the run-out period (first day, mean of the first 3 days, and mean of the 7 days) were analyzed using an ANCOVA with the baseline value as covariate, based on observed cases strategy. No interaction was included in the model.

Withdrawal effect

The change from baseline (collected within 1 day following the end of double-blind study treatment) to Day 1, Day 2, Day 3, Day 4, Day 5, Day 6, and Day 7 after the last double-blind study drug intake (run-out period) on each of the 20 symptoms and on the total score of physician withdrawal checklist (PWC) were analyzed using an ANCOVA with the baseline value as covariate, based on observed cases strategy.

Pharmacokinetics

Plasma concentration of M100907 and MDL 105,725 were listed for all patients.

Summary:

Efficacy results:

The primary efficacy analysis did not show a significant difference between volinanserin 2 mg/day and placebo on the change from baseline of pr-WASO after 12 weeks of treatment (LSmeans change from baseline of -42:39 min:sec and -45:20 min:sec for placebo and volinanserin respectively, LSmean difference of -2:41 min:sec, p-value=0.3437).

The results on the key secondary endpoints from the FOSQ scale at week 12 (mean of items 22, 23, and 24 desired activity level and mean of items 1 and 2 concentration/remembering) did not show any difference between the 2 treatment groups.

No difference was shown for any of the secondary efficacy parameters from the Patient's Sleep questionnaire (analyzed as exploratory).

Safety results:

Approximately half of the patients experienced at least 1 TEAE (45.6% in placebo versus 50% in volinanserin). The most frequently reported TEAEs in the volinanserin group (≥1% and with a difference of ≥1% compared to the placebo group) during the study were upper respiratory tract infection, dizziness, dry mouth, disturbance in attention, fatigue, and asthenia. The percentage of patients who discontinued treatment due to a TEAE was higher in the volinanserin group (2.2% in placebo versus 3.7% in volinanserin). The percentage of serious TEAEs was similar in the 2 treatment groups (0.5% in placebo versus 0.7% in volinanserin).

Four cases of elevated ALT to 3 to 5 x ULN were observed in the volinanserin group. None of them were associated with increased bilirubin. Analysis of PCSAs for all other laboratory parameters showed similar results between groups. Analysis of PCSAs for vital sign and ECG parameters showed similar results between the 2 treatment groups.

No residual effect was observed with volinanserin. Rebound effect was observed in volinanserin compared to placebo at each time point of the run-out period. No difference was detected on withdrawal symptoms (PWC) during the run-out period from the end of treatment.

Conclusions: [redacted]

Date of report: 30-Jun-2009