# A multi-center, double-blind, randomized, parallel design study to compare the effectiveness of suvorexant versus placebo on sleep pressure and circadian rhythm in hypertensives with insomnia: The Super 1 study

## (To compare the effectiveness of suvorexant vs placebo on sleep pressure in hypertensives with insomnia: Super 1)

# Study Protocol and Statistical Analysis Plan

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Study duration ：2016/6/16～2018/9/30

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| Study Title: | A multi-center, double-blind, randomized, parallel design study to compare the effectiveness of suvorexant versus placebo on sleep pressure and circadian rhythm in hypertensives with insomnia: The Super 1 study |
| Objectives: | The purpose of this study is to compare the effectiveness and safety of suvorexant versus placebo on sleep blood pressure and circadian rhythm in hypertensives with insomnia. |
| Study Subjects: | Patients with hypertension and insomnia |
| Inclusion criteria: | (1) At pre-enrollment<br>Patients who meet the following criteria are eligible for the study:<br>1. Patients who give written consent of agreement to voluntarily participation in the clinical study<br>2. Age 20 years or older<br>3. Sex: Male or female<br>4. Treatment classification: Outpatient<br>5. Hypertensive patients who meet at least one of the following:<br>- Clinic systolic blood pressure (SBP) <160 mmHg<br>- Under antihypertensive medications<br>6. Patients with insomnia who meet at least one of the following:<br>- Patients with any one of the following symptoms twice a week and at least 1 month-continuation: difficulty initiating sleep (time to sleep onset ≥2 hours longer than usual), difficulty maintaining sleep (awakening ≥twice in the night), difficulty sleeping deeply (no soundly asleep feeling at the time of awakening in the morning), early morning awakening (awakening ≥2 hours earlier in the morning than usual)<br>- Patients with interference with social or occupational function due to the above insomnia symptoms<br><br>(2) At enrollment<br>Patients who meet the following criteria at the end of run-in period are eligible for the study:<br>1. Stable unchanged antihypertensive medication for run-in period<br>2. Average morning home SBP ≥135 mmHg during 5 days before the end of run-in period |
| Exclusion criteria: | Patients who meet any of the following criteria are not eligible for the study:<br>-Patients with serious liver and respiratory disease<br>-Patients with secondary hypertension<br>-Patients with sleep apnea syndrome<br>-Patients with history of narcolepsy or cataplexy<br>-Patients with history of organic cerebral disorders<br>-Patients with history of hypersensitivity to suvorexant<br>- Patients received CYP3A strongly-inhibitors including itraconazole, clarithromycin, ritonavir, saquinavir, nelfinavir, indinavir, telaprevir and voriconazole at the start of the run-in period<br>-Patients received suvorexant and other hypnotic at the start of the run-in period<br>-Patients with average clinic SBP of ≥160 mmHg at the start of the run-in period<br>-Patients who are breast-feeding, pregnant, possibly pregnant, or plan to become pregnant |

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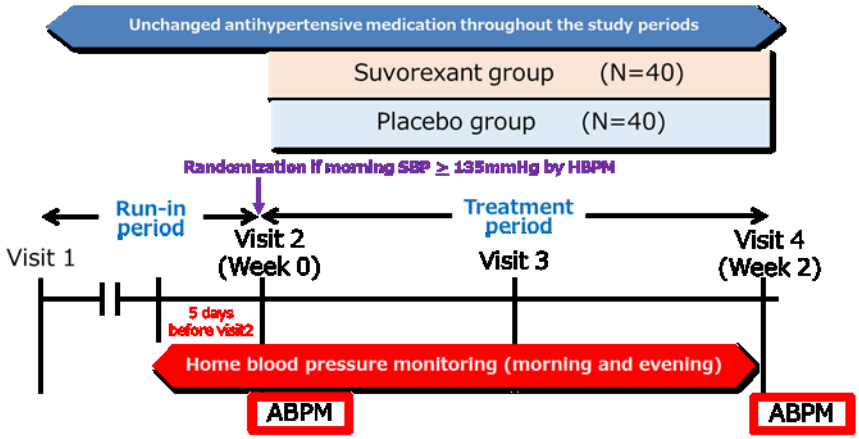
| | -Patients who are considered not to be eligible for this study by their investigator or sub-investigator |
| Study drug: | (1)Dosage Form：Film coat tablet<br>Suvorexant 15mg tablet/20mg tablet, Placebo 15mg tablet/20 mg tablet<br><br>(2)Package：<br>Suvorexant 15mg tablet: 21 tablets in a plastic bottle<br>Suvorexant 20mg tablet: 21 tablets in a plastic bottle<br>Placebo 15mg tablet: 21 tablets in a plastic bottle<br>Placebo 20mg tablet: 21 tablets in a plastic bottle<br><br>(3)Storage：Investigational products are to be stored at room temperature. Store in the bottle just before taking to protect from light and moisture. |
| Study design: | This study is a multi-center, double blind, randomized, parallel design.<br>  |
| Outcomes | Primary Outcome：<br>- Change in sleep systolic blood pressure (BP) at week 2 from week 0 by ambulatory blood pressure monitoring (ABPM)<br><br>Secondary Outcomes：<br>- Percent of patients changed from the non-dipper to the dipper during the treatment period<br>- Change in morning SBP at week 2 from week 0 by ABPM and home blood pressure monitoring (HBPM)<br>- Change in standard deviation (SD) and coefficient of variation (CV) of sleep SBP at week 2 from week 0 by ABPM<br>- Change in the total sleep time<br>- Change in the time to sleep onset<br>- Correlation of changes in nighttime BP parameters with changes in sleep quality parameters<br>- Correlation of changes in urinary albumin-to creatinine ratio (UACR)/NT-proBNP |
| Study size: | 80 patients in total |

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| Statistical Analysis: | Study size calculation:<br>At 80% power and assuming adjusted mean differences in the change from baseline in mean nighttime SBP with suvorexant vs placebo of −5.0 mm Hg with a standard deviation (SD) of 7.5 mm Hg in both groups, it was calculated that 36 patients in each group would be required (72 in total). The target enrollment was set at 80 patients to allow for a 10% withdrawal rate.<br><br>Statistical analysis methods:<br>All analyses will be conducted in the full analysis set (FAS), which included all enrolled participants who received their assigned therapy at least once after randomization and who had made 24‐hour ABPM recordings at least once. The safety analysis set (SAS) included all randomized participants who had received the assigned therapy at least once during the study period. Efficacy analyses for BP values will be conducted in the FAS, and safety will be determined in the SAS. Intergroup comparisons will be tested with a t-test for continuous variables, and Pearson's chi-squared test or Fisher's exact test will be used for dichotomous data. Mixed‐effects model repeated measures (MMRM) analysis will be used to compare the changes in SBP. MMRM included the randomized study group, the time points (baseline, week 2), the interaction between the study group and time points as fixed effects, and age and sex as covariates. P‐values for interactions between baseline SBP and the change from baseline in SBP will be determined using the general linear model, adjusted for age and sex. All statistical analyses will be performed with SAS version 9.4 software (SAS Institute Inc, Cary, NC, USA). P‐value is two‐tailed, and its <0.05 is considered statistically significant. |

## Schedule of examination, observation and assessment

| | Run-in period※1 | Treatment period | | | Termination |
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| | Visit 1 | Visit 2 | Visit 3 | Visit 4 | |
| | - 4 week | Week 0 | Week 1 | Week 2 | |
| Informed consent | ○ | | | | |
| Pre-enrollment※2 | ○ | | | | |
| Enrollment※2 | | ○ | | | |
| Randomization | | ○ | | | |
| Administration of study drug※3 | | ← | — | → | |
| Study drug adherence | | | | ○ | ○ |
| Concomitant medications | ○ | ○ | ○ | ○ | ○ |
| Demographic characteristics | ○ | | | | |
| Subjective symptoms, Objective findings | ○ | ○ | ○ | ○ | ○ |
| Height, Weight, Abdominal circumference※4 | ○ | ○ | | ○ | ○ |
| Home blood pressure monitoring (morning, evening) ※5 | ← | — | — | → | |
| Clinic blood pressure monitoring | ○ | ○ | ○ | ○ | ○ |
| Ambulatory blood pressure monitoring (ABPM)※6 | | ○ | | ○ | ○※9 |
| Blood test：NT-proBNP | | ○ | | ○ | ○ |
| Urinalysis: Albumin | | ○ | | ○ | ○ |
| Urinalysis: Creatinine | | ○ | | ○ | ○ |
| Adverse events※7 | ← | — | — | — | → |
| Sleep diary※8 | ← | — | — | — | → |

※1 At least 3 weeks for the run-in period

※2 Pre-enrollment and enrollment will be registered on web system.

※3 Patients will orally receive study drug once daily before bedtime during the treatment period (from the next day of week 0 to the day of Week 2).

※4 Height will be measured at the start of run-in period (Visit 1).

※5 Home blood pressure monitoring (morning, evening) should be performed every day from 5 days before week 0 to the next day of week 2.

※6 ABPM will be performed at the start of treatment (Week 0) and the end of treatment (Week 2) for 26 hours until the following day.

※7 Adverse events will be collected from the start of run-in period (Visit 1) to completion of this study (the next day of visit 4).

※8 Patients will be asked to record “Sleep diary” from the start of run-in period (Visit 1) to completion of this study (the next day of visit 4).

※9 ABPM will be performed as much as possible at the termination.