Phase-3 Clinical Development of Samelisant: Rationale and Study Design for Treating Excessive Daytime Sleepiness In Patients with Narcolepsy (AWAKE STUDY)

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Introduction:

Samelisant is a novel, selective and orally active inverse agonist at the histamine receptor, subtype 3 (H3Rs), intended for the treatment of disorders related to sleep like narcolepsy with or without cataplexy, idiopathic hypersomnia, obstructive sleep apnea, etc. In orexin knockout mice, Samelisant demonstrated significant wake-promoting and anticataplectic effects, supporting its therapeutic potential. The Samelisant Phase-1 program included 72 healthy humans and provided preliminary clinical safety and pharmacokinetic (PK) data. Samelisant was well tolerated in both single-dose (up to 20 mg oral [PO]) and multiple-dose administrations (up to 6 mg PO for 14 days). Food, gender, and age had no appreciable effect on the PK profile of Samelisant. In a Phase-2 double-blind, randomized study, Samelisant produced a statistically significant and clinically meaningful reduction in excessive daytime sleepiness (EDS), as measured by the Epworth Sleepiness Scale (ESS) total score ($p < 0.024$). Improvements in ESS total score were consistent with favorable changes in Clinical Global Impression–Severity (CGI-S), Patient Global Impression of Change (PGI-C), and Clinical Global Impression of Change (CGI-C) scores. Samelisant was well tolerated, with a favorable safety profile. Based on the encouraging results from the Phase-2 study, a Phase-3 study has been initiated.

Objective:

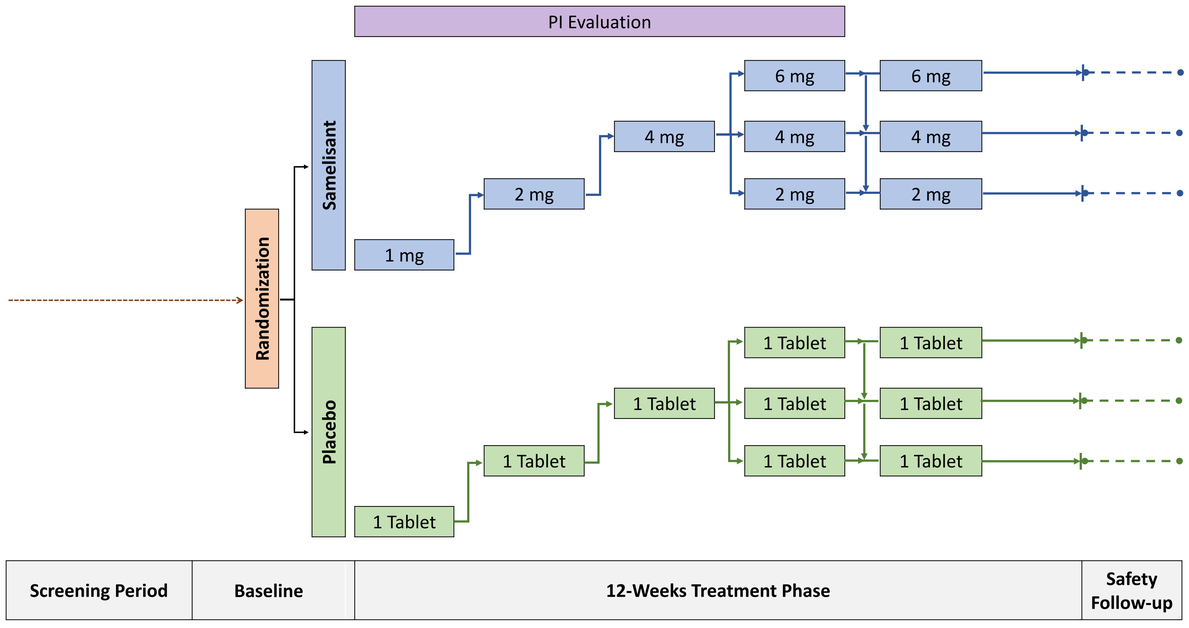
To evaluate the efficacy and safety of Samelisant for treatment of EDS in narcolepsy patients.

Methods:

This study will be conducted at approximately 80 centers in North America and Europe. After a screening period of up to 4 weeks, approximately 240 participants will be randomized in a 2:1 ratio to receive either Samelisant or Placebo (160 participants in Samelisant and 80 participants in Placebo group) for 12 weeks (4-week dose adjustment phase followed by an 8-week stable dose phase), and will then be followed up for another 4 weeks for safety evaluation. It is anticipated that 192 participants will complete the study (128 and 64 for Samelisant and placebo, respectively).

Fig 1. Phase-3 Study Design

Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
Day -28 to Day-1	Day 1	Day 8	Day 15	Day 22	Day 29	Day 57	Day 85	Day 113
Week -4 to Week -1	-	Week 1	Week 2	Week 3	Week 4	Week 8	Week 12	Week 16



Visits:

After the screening period, participants will come to site visits at Day 1 (Baseline), Day 8, Day 15, Day 22, Day 29, Day 57, and Day 85 during the treatment period. A safety follow-up visit will be performed at the study site on Day 113.

Endpoints:

Primary Endpoint	➢ Changes from Baseline in ESS total score at Week 12
Secondary Endpoints	➢ Change from Baseline for MWT score at Week 12 ➢ Change from Baseline in the CGI-S score as related to EDS at Week 12 ➢ Change from Baseline in Weekly Cataplexy Rate (WCR) for NT1 at Week 12 ➢ Change from Baseline in NSS-CT score for NT1 at Week 12
Safety Endpoints	➢ Physical examinations ➢ Laboratory assessments, including hematology, serum chemistry and urinalysis ➢ ECG parameters ➢ AEs ➢ Vital signs ➢ C-SSRS responses

Key Inclusion Criteria:

- Participants must be male or female of ≥18 years of age.
- Narcolepsy with or without cataplexy (NT1) or (NT2) based on the International Classification of Sleep Disorders 3-TR/Diagnostic and Statistical Manual of Mental Disorders (DSM-5-TR) criteria for the diagnosis of narcolepsy.
- For narcolepsy type 1 (NT1) only, current continuing presence of cataplexy as defined by participant report for the last 3 months and have average of ≥4 weekly cataplexy events during the last 2 weeks of the washout period.
- At the Screening visit and the Baseline visit, participants who are not on treatment for EDS must have ESS score ≥12 (as assessed with a look-back period of 1 week).
- A mean MWT time of <12 minutes across the first 4 sessions at Baseline visit.
- Able to show compliance with sleep diary entries for at least 5 times per week in the final 2 weeks of the screening period.

Key Exclusion Criteria:

- Median habitual wake-up time after 9 AM as assessed by sleep diary, habitual sleep time of <6 h and median habitual bedtime past 1 AM, as determined by sleep diary entries.
- Use of any investigational therapy within the 30-day period (or 5 half-lives, whichever is longer) prior to enrollment.
- History of (within past 3 months) or current substance use disorder involving illicit drugs, alcohol, or marijuana, as per DSM-5-TR criteria.
- Excessive caffeine (defined as >600 mg/day) use at least 1 week prior to baseline assessments and during the study.
- Nicotine dependence that affects sleep (eg, a participant who routinely awakens at night to smoke).
- If receiving stimulants, modafinil, oxybates, pitolisant, solriamfetol, bupropion or other treatments for narcolepsy, and unwilling or unable to complete weaning 2 weeks prior to Baseline visit (Day 1).
- Concurrent use of hypnotics, tranquilizers, centrally acting H1 receptor antagonists, benzodiazepines, anticonvulsants, or clonidine, tricyclic antidepressants that have H1-antihistamine properties (clomipramine and protriptyline).
- Adjunctive pharmacotherapy directed against cataplexy (including but not limited to venlafaxine, fluoxetine and gamma hydroxybutyrate) is prohibited.

Recruiting Across the United States, Canada, France, Germany, Italy and Spain
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