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Samelisant (SUVN-G3031), a histamine 3 receptor inverse agonist: Results from the phase 2 double-blind randomized placebo-controlled study for the treatment of excessive daytime sleepiness in adult patients with narcolepsy

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ABSTRACT

Narcolepsy is a rare, chronic neurological disorder characterized by a dysregulated sleep-wake cycle, with core clinical features including excessive daytime sleepiness (EDS), cataplexy, hypnopompic/hypnagogic hallucinations, and sleep paralysis. Several treatment options are available for the symptomatic management of narcolepsy, but they have limitations. Comorbidities of narcolepsy further limit the treatment choices. Blocking of histamine 3 (H3) receptors has been demonstrated to be a viable approach for the management of symptoms of narcolepsy. Samelisant (SUVN-G3031) is a new H3 receptor inverse agonist. The efficacy, safety, tolerability, and pharmacokinetics of Samelisant in narcolepsy patients were evaluated in a phase 2, double-blind, placebo-controlled study (ClinicalTrials.gov identifier: NCT04072380). Patients diagnosed with narcolepsy according to the International Classification of Sleep Disorders criteria and having an Epworth Sleepiness Scale (ESS) score of ≥12 and a mean Maintenance of Wakefulness Test (MWT) time of <12 min across the 4 sessions at baseline were enrolled. The total study duration was up to 7 weeks, which included a screening period of 4 weeks, a treatment period of 2 weeks, and a safety follow-up 1 week after the last study drug administration. The primary efficacy measure was the change in total ESS score compared to placebo. Secondary and exploratory assessments included the Clinical Global Impression of Severity, MWT, Clinical Global Impression of Change, Patient Global Impression of Change and cataplexy rate. Safety assessments included monitoring adverse events (AEs) and laboratory assessments. Of the 426 patients screened, 190 were randomized. The safety and intention-to-treat population included 188 and 164 patients, respectively. A statistically significant treatment effect of Samelisant was observed on the primary endpoint, indicating improvements in EDS. The treatment's impact on EDS was also evident on the other patients' and clinicians' perspectives scales. The AEs reported in ≥5 % patients in any treatment groups were insomnia, abnormal dreams, nausea, and hot flush. Global phase 3 studies and long-term safety and efficacy assessments of Samelisant are planned to reaffirm the current findings.

1. Introduction

Narcolepsy is a rare, chronic neurological disorder with core clinical features including excessive daytime sleepiness (EDS), hypnopompic/hypnagogic hallucinations, and sleep paralysis resulting from a dysregulated sleep-wake cycle. Narcolepsy patients are classified into two types: narcolepsy type-1 (NT1) and narcolepsy type-2 (NT2) based on orexin deficiency and symptoms of cataplexy [1,2]. The pathognomonic symptom of NT1 is cataplexy, characterized by a sudden and transient loss of voluntary muscle tone or strength triggered by strong emotions. Among the symptoms of narcolepsy, EDS is considered the most disabling disease burden [1,3–5]. Symptomatic treatments

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approved/prescribed for the management of EDS include stimulants (methylphenidates, Modafinil, Armodafinil, and amphetamines), oxybates, Solriamfetol, and Pitolisant. Management options for cataplexy, hallucinations and sleep paralysis include oxybates, Pitolisant, and antidepressants. Oxybates and antidepressants are prescribed for the symptomatic management of rapid eye movement (REM) sleep abnormalities [6–11]. Although several treatment options are available for the management of symptoms of narcolepsy, they have limitations, and persistent EDS is prevalent [9]. Narcolepsy can also be present with other sleep disorders like REM sleep behaviour disorder, restless legs syndrome, periodic limb movements during sleep, and obstructive sleep apnea [3]. Comorbidities of narcolepsy include dyslipidemia, obesity, diabetes, hypertension, depression, anxiety, psychosis, schizophrenia, and eating disorders [12–16]. Comorbid conditions and the presence of other sleep disorders further limit the treatment choices for narcolepsy. Thus, there is a need for newer pharmacological agents for the treatment of narcolepsy.

One of the options for addressing the symptoms of narcolepsy is targeting the brain histaminergic system. Histaminergic neurons, localized to tuberomammillary nucleus (TMN) within the posterior hypothalamus and projecting to alerting pathways of the brain [17,18], are implicated in the regulation of sleep–wake cycles [19,20]. TMN is considered to be one of the wake-promoting centers in the brain [21,22]. Histamine, a monoamine neurotransmitter localized in the histaminergic neurons, acts as a wake promoter agent by stimulating the post synaptic histamine 1 receptor located on the wake promoting neurons [17,23]. The release of histamine can be facilitated by blocking the presynaptic histamine 3 (H3) auto receptors. Additionally, the blockade of presynaptic H3 heteroreceptors can facilitate the release of non-histaminergic neurotransmitters like norepinephrine, serotonin, and dopamine which can also promote wakefulness and alleviate cataplexy [23,24]. Pitolisant, an H3 receptor inverse agonist/antagonist, is approved for treating EDS and cataplexy in narcolepsy patients. Its clinical profile includes a median half-life of approximately 20 h after a single dose of 35.6 mg, with median time to maximum plasma concentration (t_{max}) of 3.5 h. Renal clearance accounts for less than 2 % of the total clearance. Pitolisant is metabolized by CYP2D6 and CYP3A4 enzymes. Pitolisant has limitations regarding drug-drug interaction (DDI) liability and cardiovascular safety [25,26].

Samelisant (SUVN-G3031) is a new H3 receptor agent with potent affinity, functioning as an inverse agonist [27]. It was found to be orally bioavailable [27] and efficacious in animal models of sleep disorders, suggesting promise for the treatment of EDS and cataplexy [28]. Studies assessing its potential to induce or inhibit CYP enzymes suggested a low likelihood of causing drug-drug interactions, either as an inhibitor or inducer [29]. Evaluation using the hERG patch clamp assay and dog telemetry has suggested that Samelisant is unlikely to prolong the QT interval [27]. In phase 1 studies, Samelisant was well tolerated up to the highest tested single oral dose of 20 mg and repeated dose of 6 mg once daily for 2 weeks in healthy human volunteers. The half-life of Samelisant ranged from 23 to 34 h across the tested doses. Peak concentration was reached approximately 3 h after treatment. The primary route of elimination was renal excretion, which accounted for about 60 % of Samelisant. Safety parameters, including laboratory results, physical examinations, vital signs, fluid balance, suicidal ideation, and ECG parameters, showed no significant changes. The most commonly reported adverse events were dyssomnia, abnormal dreams and hot flushes. Food, gender, and age had no effects on the pharmacokinetics of Samelisant [30]. The non-clinical cardiovascular safety findings were corroborated by observations from phase 1 clinical studies. Based on the observed wake promoting effects in animal models and safety data from non-clinical models and healthy human volunteers, the present study aims to establish the proof-of-concept of Samelisant as a potential treatment option for EDS in narcolepsy patients. Doses of 2 mg and 4 mg of Samelisant were selected for evaluation based on receptor occupancy and efficacy data from non-clinical studies and outcomes from clinical trials in healthy human volunteers [27–30].

2. Methods

This study is a phase 2, double-blind, placebo-controlled, parallel-group, multicenter study aimed at evaluating efficacy, safety, tolerability, and pharmacokinetics (PK) of Samelisant compared with placebo in patients with NT1 or NT2 narcolepsy (ClinicalTrials.gov identifier: NCT04072380 [31]). The study was conducted across 44 centers in the USA and Canada. Prior to enrollment, the clinical study protocol, protocol amendments, informed consent form, and any other appropriate study-related documents were reviewed and approved by institutional review boards at each participating study center. The study adhered to ethical guidelines as outlined in the Declaration of Helsinki and ICH GCP guidelines, and it complied with local regulatory requirements of USA and Canada. Patients who provided written informed consent underwent screening up to 4 weeks prior to enrollment.

Patients diagnosed with narcolepsy (NT1 or NT2) according to the International Classification of Sleep Disorders (3rd Edition) criteria and aged between 18 and 65 years (both inclusive), were recruited. Patients also needed to have an Epworth Sleepiness Scale (ESS) score of $\geq$12 and a mean Maintenance of Wakefulness Test (MWT) time of <12 min across the 4 sessions at baseline. An ESS score of $\geq$12 for eligibility was only required at the baseline visit. Patients diagnosed with narcolepsy and treated for EDS were eligible for screening, and an ESS score of <12 at screening due to concomitant medications was subject to the investigator's discretion for eligibility. Eligible patients had to complete a washout period of $\geq$2 weeks for all agents targeting cataplexy and $\geq$1 week for all stimulants targeting EDS before baseline visit. Patients with a body mass index ranging from 18 to <45 kg/m^2 were eligible. Exclusion criteria included a current diagnosis or past treatment for syndromes known to cause sleep disruption or any other cause of daytime sleepiness, habitual wake-up time after 8 a.m. as assessed by a sleep diary, habitual sleep time of <6 h, and habitual bedtime past 1 a.m. as determined by sleep diary entries. Additionally, patients with an occupation requiring variable shift work, night shifts, or frequent overnight travel which could disrupt the sleep patterns were not eligible for the study.

At the end of screening period (up to 28 days), patients attended the clinic for randomization and baseline (Day 0) assessments. On Day 7 and Day 14, patients returned to the clinic for outpatient visits, during which efficacy, safety and PK assessments were conducted. A final safety follow-up visit was performed on Day 21. Overall, patients were enrolled in the study for a maximum of 49 days from the start of the screening period (Fig. 1).

2.1. Treatments

Patients were randomized to study treatment groups (Samelisant 2 mg or 4 mg or placebo) in a 1:1:1 ratio using an interactive response technology. Randomization was stratified based on whether they had NT1 or NT2 narcolepsy, ensuring at least 30 % representation for each type. Patients received oral tablet formulations that were identical in appearance and size. Tablets were provided in predispensed, blinded study kits, and a double-blind approach was followed. Patients were advised to take one tablet per day in the morning for 2 weeks, as soon as they woke up. Dosing could occur with or without food.

2.2. Efficacy outcomes

The primary objective of the study was to evaluate the effectiveness of Samelisant compared to placebo, measured by the change in total ESS score. The secondary objective of the study was to assess the effectiveness of Samelisant compared with placebo by improvements in the Clinical Global Impression of Severity (CGI-S) score related to EDS and the MWT score. Other exploratory efficacy objectives included

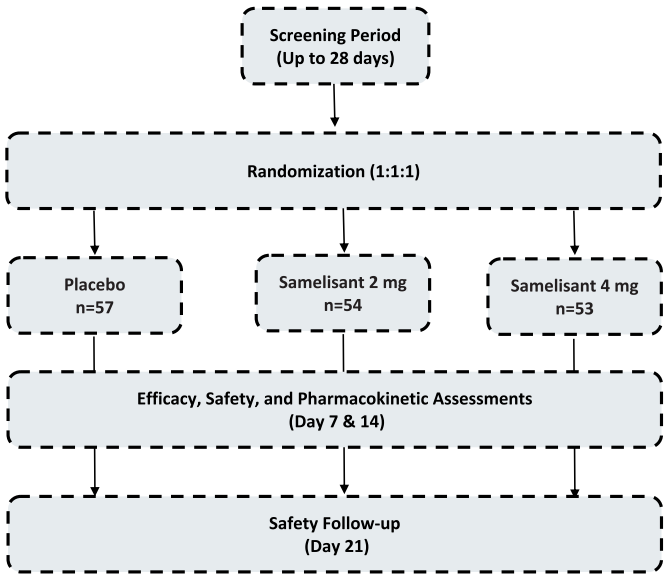

Fig. 1. Study design.

evaluating the changes in Clinical Global Impression of Change (CGI-C) score, Patient Global Impression of Change (PGI-C) score regarding EDS, and the daily cataplexy rate.

2.3. Safety outcomes

Safety endpoints assessed included physical examination, vital signs, laboratory assessments (hematology, serum chemistry and urinalysis), electrocardiogram (ECG), adverse event (AE), and the Columbia Suicide Severity Rating Scale (C-SSRS).

2.4. Pharmacokinetics

Blood samples for the measurement of Samelisant concentrations were collected just prior to dosing and at the estimated t_{max} (3 ± 0.5 h post dosing) on Day 7 and Day 14. Plasma concentrations of Samelisant were quantified using a method described previously [32].

2.5. Sample size

The sample size estimation was initially based on MWT. Considering standard deviation of 5.0, N = 38 randomized patients per group were to provide 80 % power to detect a treatment difference of 3.5 min or greater over placebo on the MWT at a 2-sided type 1 error level of 0.05, assuming a dropout rate of 10 %. Due to uncertainty in the underlying assumption supporting the power calculation for MWT, an unblinded interim analysis (IA) was planned when approximately 50 % of subjects completed 2 weeks of treatment (visit 3 completed). Based on the IA, the sample size was increased to 57 patients per group to enhance the likelihood of a positive study outcome. Evolving literature suggested that the ESS could be a more sensitive measure of EDS than MWT for H3 inverse agonist/antagonist [33], and thus, ESS was considered as the primary endpoint. Assuming a clinically relevant difference of −3 for ESS, standard deviation of 6, and type 1 error level of 0.05 for the two-sided test, with approximately 50 subjects per treatment group completing the study, the statistical power to detect the difference between the active group and placebo was only 69.7 %. However, combining Samelisant 2 and 4 mg treatment groups and testing versus placebo achieved a power of 81.8 %. Therefore, the Samelisant 2 and 4 mg treatment groups were combined for statistical analysis to meet the power requirements.

2.6. Statistical analysis

The statistical evaluation was performed using SAS® software version 9.4 (SAS Institute, Cary, NC). The primary testing approach for efficacy was the statistical comparison of the pooled active Samelisant dose groups of 2 mg and 4 mg (herein called as combined Samelisant group) versus placebo. Additionally, each active dose was tested against placebo and presented here for all efficacy parameters. The primary analysis approach was performed using a mixed model repeated measures (MMRM) analysis. This model incorporated all observed post-baseline assessments from Day 7 and Day 14. In the MMRM, all missing values were imputed using direct likelihood based on the assumption of missing at random.

All statistical tests were conducted at type 1 error level of 0.05 for the two-sided test. If the statistical comparison of combined Samelisant group versus placebo demonstrated superiority with p-values less than or equal to 5 %, then Samelisant was considered superior to placebo.

3. Results

Study patients were enrolled between September 2019 and May 2023. A total of 426 patients were screened, and 190 patients were randomized. Of the 190 randomized patients, 154 patients (81.1 %) completed the study. A total of 188 (98.94 %) and 164 (86.31 %) randomized patients were included in the safety and intention-to-treat population (ITT), respectively. Of the 35 patients (18.4 %) who discontinued the study, 12 patients (19.0 %) received Samelisant 2 mg, 14 patients (21.9 %) received Samelisant 4 mg, and 9 patients (14.3 %) received placebo. The most common reasons (>5 % of overall patients) for discontinuation from the study were AEs (10 patients, 28.6 %), withdrawal of consent (5 patients, 14.3 %), inclusion/exclusion criteria (3 patients, 8.6 %), investigator decision (2 patients, 5.7 %) and others (12 patients, 34.3 %). Detailed treatment-wise patient disposition is included in Fig. 2.

The demographic and baseline characteristics were well-balanced across the three treatment groups. Overall, the mean age of patients was 32.3 years (range 18–58 years). Most of the patients were female (70.7 %), White (68.3 %), and not Hispanic or Latino (88.4 %). Overall, the mean duration of narcolepsy was 6.4 years (range 1–31 years), with the majority of NT1 patients (52.4 %). The mean total ESS score was 17.4 (range 12–24), mean MWT score was 5.58 min (range 0–17.87), mean CGI-S score was 4.8 (range 3–7), and mean PGI-C score was 4.7 (range 3–7). Demographic and baseline characteristics for the ITT population are summarized in Table 1.

3.1. Efficacy

At Day 14, the least squares (LS) mean difference in ESS score was −1.841 (95 % CI: 3.445, −0.237) between the combined Samelisant group and the placebo group and the effect was statistically significant (p = 0.024) based on the weighted Cui, Hung, Wang test statistic, considering the combination of the data before and after IA. Additionally, a LS mean difference of −1.822 (95 % CI: 3.506, −0.139) and −1.853 (95 % CI: 3.551, −0.155) was observed between the Samelisant 2 mg group and 4 mg group, respectively, when compared against placebo, and these effects were also statistically significant (p = 0.034 and p = 0.032, respectively) (Fig. 3).

A statistically significant greater reduction in the CGI-S score at Day 14 was observed in the patients receiving Samelisant. The mean difference in CGI-S score between the combined Samelisant group and the placebo group was −0.459 (95 % CI: 0.801, −0.116 and p = 0.009). Similarly, the mean difference in CGI-S score was −0.415 (95 % CI: 0.781, −0.049) between the Samelisant 2 mg group and the placebo group and −0.503 (95 % CI: 0.870, −0.136) between the Samelisant 4 mg group and the placebo group, and these differences were statistically significant (p = 0.026 and p = 0.007, respectively).

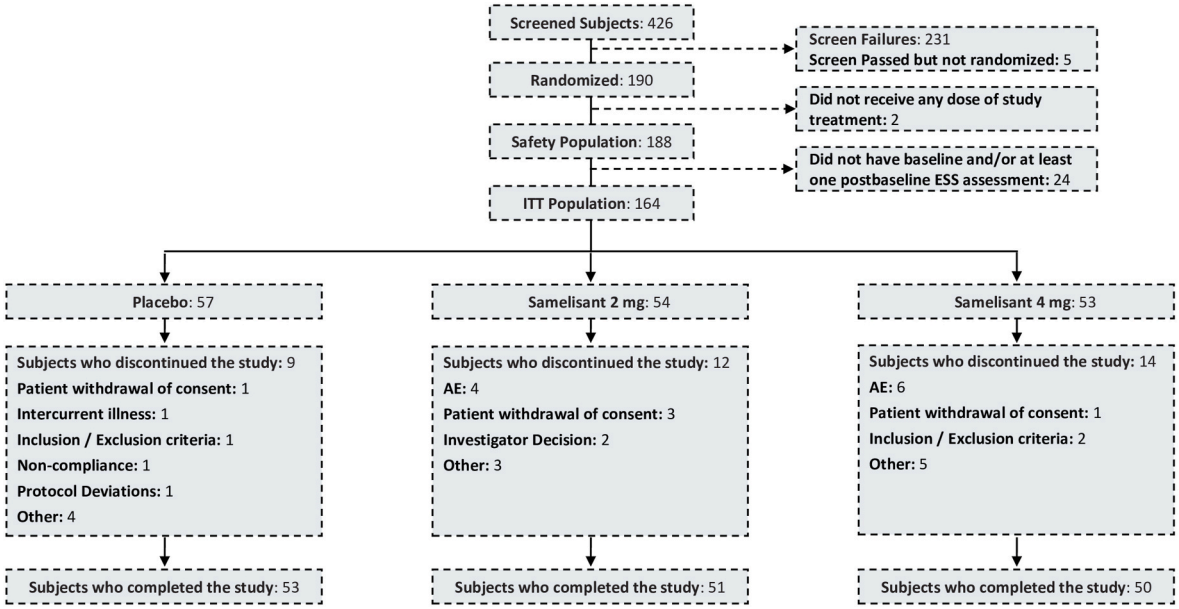

Fig. 2. Patient disposition.

At Week 2, the mean difference in MWT score was 0.002 (95 % CI: 2.219, 2.223) between the Samelisant 2 mg group and the placebo group, 0.683 (95 % CI: 1.522, 3.093) between the Samelisant 4 mg group and the placebo group, and 0.353 (95 % CI: 1.678, 2.383) between the combined Samelisant group and the placebo group, and the effect was not statistically significant ($p = 0.999$, $p = 0.550$, and $p = 0.734$, respectively).

The mean difference in CGI-C score between the combined Samelisant group and the placebo group was statistically significant ($p < 0.0001$ at Day 14). Similarly, the mean difference in CGI-C score between the Samelisant 2 mg group and the placebo group, as well as between the Samelisant 4 mg group and the placebo group, was also statistically significant ($p < 0.0001$ at Day 14).

At Day 14, the mean PGI-C score observed in the combined Samelisant group was 3.0. A larger decrease in mean PGI-C score was observed in the Samelisant 4 mg group (2.8) and the Samelisant 2 mg group (3.2) compared with the placebo group (3.7), with statistically significant mean difference in PGI-C score between the Samelisant 2 mg group and the placebo group ($p = 0.004$), the Samelisant 4 mg group and the placebo group ($p < 0.0001$), and the combined Samelisant group and the placebo group ($p < 0.001$).

At Week 2, the mean difference in the average number of cataplectic attacks between the Samelisant 2 mg group and the placebo group ($p = 0.283$), as well as between the Samelisant 4 mg group and the placebo group ($p = 0.334$), did not reach statistical significance. Efficacy outcomes are summarized in Table 2.

3.2. Pharmacokinetics

The PK population included all patients who received at least one dose of study treatment and had sufficient post-dose plasma concentration data ($N = 51$ for Samelisant 2 mg; $N = 53$ for Samelisant 4 mg). The geometric mean predose concentrations of Samelisant were 4.14 μg/L and 4.33 μg/L on Days 7 and 14, respectively, for the 2 mg dose, and 7.20 μg/L and 6.40 μg/L on Days 7 and 14, respectively, for the 4 mg dose. The geometric mean concentrations at 3 h post-dose were 9.15 μg/L and 8.80 μg/L on Days 7 and 14, respectively, for the 2 mg dose, and 16.63 μg/L and 15.48 μg/L on Days 7 and 14, respectively, for the 4 mg dose. Overall, Samelisant concentrations increased dose-proportionally on Days 7 and 14, with approximately a 2-fold greater concentration at predose and 3 h post-dose for the 4 mg dose compared to the 2 mg dose.

Possible accumulation of Samelisant may have occurred following once-daily administration of the 2 mg and 4 mg doses for 7 consecutive days as indicated by measurable predose concentrations on Day 7. However, no further accumulation in Samelisant concentrations was observed with daily doses from Day 7 to Day 14, as shown by similar concentrations at predose and 3 h post-dose, for both the 2 mg and 4 mg doses, suggesting steady state was reached by Day 7. The pharmacokinetic results are presented in Table 3.

3.3. Safety

Overview of treatment emergent adverse events (TEAEs) is summarized in Table 4. A total of 31 patients (49.2 %) each in the Samelisant 2 mg and 4 mg groups, and 14 patients (22.6 %) in the placebo group experienced at least one TEAE during the study. The majority of TEAEs reported across all the treatment groups were mild in severity. Treatment-related TEAEs occurred in a higher proportion of patients in the Samelisant 4 mg group (27 patients [42.9 %]) and Samelisant 2 mg group (23 patients [36.5 %]) compared to the placebo group (10 patients [16.1 %]). The most frequent TEAEs by patients (reported in ≥5 % patients in any of the treatment groups) were insomnia, abnormal dreams, nausea, and hot flush (see Table 5).

A total of 10 (5.3 %) patients discontinued the study, the most common reasons were insomnia (1 patient in 2 mg group, 4 patients in 4 mg group), anxiety (1 patient in 2 mg group, 2 patients in 4 mg group), and nausea (1 patient in 2 mg group, 2 patients in 4 mg group). A higher percentage of patients in the Samelisant 4 mg group (6 patients [9.5 %]) experienced TEAEs that led to treatment discontinuation compared with the Samelisant 2 mg group (4 patients [6.3 %]). None of the patients in the placebo group experienced a TEAE that led to treatment discontinuation.

No clinically meaningful differences across the treatment groups were observed for laboratory results, vital signs, ECG findings, physical examination, and C-SSRS. Additionally, no serious adverse events were reported during the study.

4. Discussion

Samelisant, a potent and selective H3 receptor inverse agonist, underwent evaluation for efficacy, safety, tolerability and PK in patients

Table 1
Demographics and baseline characteristics (ITT population).

Characteristic	Placebo (N = 57)	Samelisant 2 mg (N = 54)	Samelisant 4 mg (N = 53)	Total (N = 164)
Age (years)	32.9 (10.07)	29.5 (8.51)	34.6 (9.71)	32.3 (9.64)
Weight (kg)	82.10 (17.329)	82.19 (17.910)	79.02 (18.464)	81.14 (17.843)
Height (cm)	167.36 (9.735)	167.40 (10.904)	167.90 (9.417)	167.55 (9.979)
BMI (kg/m^2)	29.35 (6.062)	29.41 (6.391)	27.89 (5.587)	28.89 (6.029)
Sex [n (%)]				
Male	16 (28.1)	16 (29.6)	16 (30.2)	48 (29.3)
Female	41 (71.9)	38 (70.4)	37 (69.8)	116 (70.7)
Child-bearing potential [n (%)][a]				
Yes	32 (78.0)	35 (92.1)	30 (81.1)	97 (83.6)
No	9 (22.0)	3 (7.9)	7 (18.9)	19 (16.4)
Race [n (%)]				
American Indian or Alaska Native	1 (1.8)	0	1 (1.9)	2 (1.2)
Asian	1 (1.8)	3 (5.6)	5 (9.4)	9 (5.5)
Black or African American	14 (24.6)	12 (22.2)	13 (24.5)	39 (23.8)
NH or other Pacific Islander	1 (1.8)	0	0	1 (0.6)
White	39 (68.4)	39 (72.2)	34 (64.2)	112 (68.3)
Other	1 (1.8)	0	0	1 (0.6)
Ethnicity [n (%)]				
Hispanic or Latino	6 (10.5)	4 (7.4)	9 (17.0)	19 (11.6)
Not Hispanic or Latino	51 (89.5)	50 (92.6)	44 (83.0)	145 (88.4)
NT1 [n (%)]	32 (56.1)	27 (50.0)	27 (50.9)	86 (52.4)
NT2 [n (%)]	25 (43.9)	27 (50.0)	26 (49.1)	78 (47.6)
Duration of narcolepsy (years)	6.7 (6.34)	6.2 (5.77)	6.4 (6.53)	6.4 (6.19)
Total ESS score	17.1 (2.99)	17.4 (2.77)	17.6 (2.83)	17.4 (2.85)
CGI-S score	4.8 (0.79)	4.7 (0.77)	4.9 (0.82)	4.8 (0.79)
Mean MWT score	6.366 (3.953)	4.689 (3.392)	5.644 (3.376)	5.580 (3.638)
PGI-C score	4.8 (0.99)	4.6 (0.95)	4.7 (1.03)	4.7 (0.99)

[a] Percentage is based on number of female patients in each arm. Values are mean (±SD) unless specified; BMI = Body mass index; CGI-S = Clinical Global Impression of Severity; ESS = Epworth Sleepiness Scale; MWT = Maintenance of Wakefulness Test; NT1 = Narcolepsy type-1; NT2 = Narcolepsy type-2; PGI-C = Patient Global Impression of Change; ITT = Intent to treat.

with narcolepsy in a phase 2 study. The primary objective was to assess its effectiveness in reducing EDS symptoms. Following once-daily oral administration of Samelisant for 2 weeks, a significant reduction in EDS symptoms compared to placebo was observed, as measured by the ESS, a patient-reported outcome. The beneficial treatment effects were also evident in another patient-reported outcome, the PGI-C scale. Clinician assessments, reflected by changes from baseline in the CGI-S and CGI-C scores, similarly showed improvements compared to placebo. However, contrary to the observations in the ESS, PGI-C, CGI-C, and CGI-S, no notable treatment effects were observed in the MWT score when compared to placebo.

ESS is a subjective measure assessing self-reported sleepiness across various daily life situations, while the MWT provides an objective measure of wakefulness, influenced by motivation [34]. Both scales are widely used in assessing drug efficacy and routine clinical practice. Generally, the ESS is preferred in clinical settings due to its brevity and ease of administration whereas the MWT is valued in clinical research for its objectivity and lack of bias. Literature evidence suggests that the magnitudes of correlations between changes in ESS scores and measures of functioning are stronger than those between changes in MWT performance and measures of functioning [35]. Studies have consistently shown low to moderate correlation between ESS and MWT measures across different disorders of EDS [34–37]. Despite no notable treatment effects being observed in the MWT endpoint, significant effects of Samelisant treatment were observed in the CGI-S, PGI-C, and CGI-C endpoints, all anchored to the EDS. Therefore, the efficacy observed in ESS may reflect Samelisant's effectiveness in treating EDS in narcolepsy. Differences in the principles and aspects of sleepiness assessed by ESS and MWT may contribute to the discrepancies in outcomes observed with Samelisant, a phenomenon noted with other H3 receptor agents [33,38]. Despite criticism regarding the ESS as a self-reported questionnaire that includes hypothetical situations not experienced by all individuals (e.g., likelihood of falling asleep in a car while stopped in traffic) [39], it is generally considered more sensitive to treatment efficacy than the MWT [40].

The mean drug-placebo difference on the ESS scale in the Samelisant 4 mg treatment group was −2.3. While the clinical significance threshold for the ESS scale is typically a 2-point decrease [41], higher drug-placebo difference has been observed for agents used in treating EDS in narcolepsy [42–46]. However, the mean change from baseline scores in the ESS scale was −5.6-points, which compares favorably with outcomes seen in the pivotal studies of agents approved as treatments for narcolepsy: Pitolisant showed a −5.8-points change [42], Solriamfetol resulted in a −5.4-points change at 150 mg [43], modafinil showed a −5.7 to −6.9-points change at 400 mg [42,44], Sodium Oxybate demonstrated a −5.0-points change at 9 g [45,46] and once nightly Sodium Oxybate resulted in a −6.2-points change [47]. The lower drug placebo difference on the ESS scale observed in the current study could be attributed to the larger placebo effects. This observation extends to the PGI-C, CGI-S and CGI-C scales, where placebo effects also appeared larger. The study sites received training on placebo response mitigation during the initiation phase, which included education on factors contributing to placebo responses and site-specific strategies to minimize them. These strategies involved using neutral language in patient discussions, staggering appointments, and providing separate waiting rooms. Despite these efforts, placebo responses were still higher than anticipated. These enhanced placebo effects in our study may be due to the shorter treatment duration of two weeks.

In the current study, the daily baseline cataplexy rate ranged between 1 and 1.9, which aligns well with the studies that have evaluated treatment effects on cataplexy as a primary objective [45,47,48]. Considering the demonstrated effects of Samelisant in attenuating cataplexy-like effects in animal models [28], and the effects of Pitolisant in reducing cataplexy frequency in both narcolepsy patients and animal models [48,49], it was anticipated that Samelisant might also attenuate cataplexy in narcolepsy patients. However, compared with placebo, no significant effects of Samelisant on the daily cataplexy rate were observed in this study. Factors such as eligibility of NT1 patients not being based on positive HLA-DQB1*06:02 genotype or cerebrospinal fluid orexin/hypocretin-1 concentration, lack of baseline cataplexy

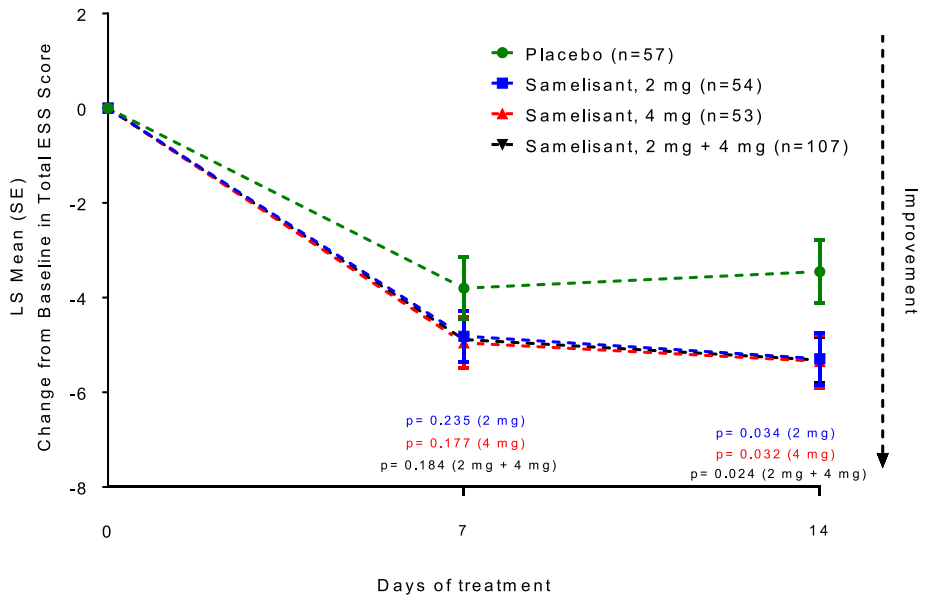

Fig. 3. Least squares mean change from baseline in total ESS score
ESS = Epworth Sleepiness Scale; LS = Least squares; SE = standard error.

Table 2
Summary of efficacy outcomes.

Efficacy Endpoints	N	Baseline Score, Mean (SD)	Change From Baseline at Day 14 or Day 14, Mean (SD)	Treatment Difference at Day 14 Versus Placebo		
				Mean Difference	Maximum Likelihood Estimate Difference (95 % CI)	p-value (MMRM analysis)
Primary Efficacy Endpoint						
ESS						
Placebo	57	17.1 (2.99)	−3.3 (4.61)	–	–	–
Samelisant 2 mg	54	17.4 (2.77)	−5.1 (5.00)	−1.8	−1.822 (−3.506, −0.139)	**0.034***
Samelisant 4 mg	53	17.6 (2.83)	−5.6 (5.46)	−2.3	−1.853 (−3.551, −0.155)	**0.032***
Samelisant 2 mg + 4 mg	107	17.5 (2.78)	−5.4 (5.21)	−2.1	−1.841 (−3.445, −0.237)	**0.024***
Secondary Efficacy Endpoints						
CGI-S						
Placebo	55	4.8 (0.79)	−0.8 (1.17)	–	–	–
Samelisant 2 mg	54	4.7 (0.77)	−1.2 (1.24)	−0.4	−0.415 (−0.781, −0.049)	**0.026**
Samelisant 4 mg	52	4.9 (0.82)	−1.4 (1.19)	−0.6	−0.503 (−0.870, −0.136)	**0.007**
Samelisant 2 mg + 4 mg	106	4.8 (0.80)	−1.3 (1.22)	−0.5	−0.459 (−0.801, −0.116)	**0.009**
MWT						
Placebo	57	6.59 (4.10)	2.73 (7.00)	–	–	–
Samelisant 2 mg	54	4.78 (3.45)	2.07 (4.68)	−0.7	0.002 (−2.219, 2.223)	0.999*
Samelisant 4 mg	52	5.77 (3.31)	4.25 (6.52)	1.5	0.683 (−1.555, 2.921)	0.55*
Samelisant 2 mg + 4 mg	106	5.27 (3.40)	3.15 (5.75)	0.4	0.353 (−1.678, 2.383)	0.734*
Exploratory Efficacy Endpoints						
PGI-C						
Placebo	54	4.8 (0.99)	3.7 (1.12)	–	–	–
Samelisant 2 mg	53	4.6 (0.95)	3.20 (1.16)	−0.54	−0.599 (−1.005, −0.192)	**0.004**
Samelisant 4 mg	51	4.7 (1.03)	2.8 (1.10)	−0.86	−0.835 (−1.244, −0.425)	**<0.0001**
Samelisant 2 mg + 4 mg	104	4.6 (0.98)	3.0 (1.14)	−0.70	−0.713 (−1.094, −0.332)	**<0.001**
CGI-C						
Placebo	57	–	3.5 (0.91)	–	–	–
Samelisant 2 mg	54	–	2.8 (1.01)	−0.70	−0.71 (−1.042, −0.379)	**<0.0001**
Samelisant 4 mg	53	–	2.6 (0.92)	−0.90	−0.797 (−1.129, −0.464)	**<0.0001**
Samelisant 2 mg + 4 mg	107	–	2.7 (0.97)	−0.80	−0.753 (−1.063, −0.443)	**<0.0001**
	Cataplexy (NT1 subjects)					
Placebo	31	1.0 (1.28)	−0.4 (1.02)	–	–	–
Samelisant 2 mg	27	1.9 (2.49)	−1.0 (1.85)	−0.6	−0.249 (−0.706, 0.208)	0.283
Samelisant 4 mg	27	1.8 (2.92)	−0.5 (0.92)	−0.1	0.223 (−0.231, 0.677)	0.334

*The Day 14 estimates are adjusted for the sample size increase after the interim analysis, and the p-value is for the weighted CHW test statistics of the data until interim analysis and after interim analysis; CGI-S = Clinical Global Impression of Severity; CGI-C = Clinical Global Impression of Change; ESS = Epworth Sleepiness Scale; MWT = Maintenance of Wakefulness Test; PGI-C = Patient Global Impression of Change; CHW = Cui, Hung, Wang.

Table 3
Summary of plasma concentrations of Samelisant (μg/L).

Treatment	Visit	Scheduled time point	n	GM	%GM CV
Samelisant 2 mg	Day 7	Predose	51	4.14	53.266
		3 h	50	9.15	34.663
	Day 14	Predose	48	4.33	52.957
		3 h	47	8.80	56.543
Samelisant 4 mg	Day 7	Predose	52	7.20	69.072
		3 h	51	16.63	40.857
	Day 14	Predose	49	6.40	80.965
		3 h	48	15.48	77.003

CV = coefficient of variation; GM = geometric mean.

criteria, randomization not based on the baseline cataplexy rates, shorter treatment duration, and the potential withdrawal effect due to washout of anticataplectic medications before baseline may have potentially masked the treatment effects of Samelisant. The effects of Samelisant on disrupted nighttime sleep, hypnagogic/hypnopompic hallucinations, and sleep paralysis could not be gauged due to the lower baseline rates in these symptoms.

Treatment-related TEAEs were in a higher proportion of patients in the Samelisant treatment arms compared with those in the placebo arm. The majority of TEAEs reported across the three treatment groups were mild in severity. No reports of suicidal ideation or behavior were noted on the C-SSRS. Sleep related side effects like insomnia, abnormal dreams/vivid dreams/nightmares, and hot flush were reported in the Samelisant treatment arms. Evaluation of H3 receptor inverse agonists/antagonists in patients has shown adverse events related to nighttime sleep disturbances resulting in higher discontinuation rates [33,38]. It could be assumed that these sleep related side effects might have also affected the performances in the MWT [38]. However, since treatment effects of Samelisant on EDS was also observed in other endpoints such as ESS, CGI-S, PGI-C, and CGI-C, sleep related side effects may not have confounded the effects of Samelisant treatment in the MWT scale. The safety profile of Samelisant is consistent with the other H3 receptor inverse agonist/antagonists [33,38,42,48]. In the present study, Samelisant was evaluated in fixed doses; a titration regimen may have resulted in better tolerability.

Several H3 receptor inverse agonists/antagonists have been evaluated for their potential effects on EDS. GSK-189254 was evaluated for its effectiveness in treating patients with narcolepsy; however, the study was terminated based on interim results of a futility test (NCT00366080 [50]). Enerisant underwent evaluation in two randomized, placebo-controlled trials in narcolepsy patients. Neither efficacy nor safety of Enerisant could be established due to large interindividual variability [33]. Bavisant was evaluated for its potential for the treatment of EDS in subjects with Parkinson's disease. At the tested doses of 0.5, 1 and 3 mg per day, no notable treatment effects were evident on the ESS scale when compared with placebo (NCT03194217 [51]). MK-0249 was evaluated to assess its effectiveness in the treatment of EDS in obstructive sleep apnea patients. Although no notable effects on EDS were observed as assessed by the MWT, treatment effects were noted on subjective endpoints like ESS and CGI-S compared with placebo [38]. There has been no further progress in the development of GSK-189254 or Enerisant or Bavisant or MK-0249. Currently, Pitolisant is the only H3 receptor ligand proven effective for treating both EDS and cataplexy, and it is approved for clinical use. Given that the efficacy and safety of Pitolisant have been established in phase 3 trials [42,48] and long-term follow-up studies [52], a direct comparison between Samelisant and Pitolisant is challenging since Samelisant was evaluated for only a 2-week duration compared to the extensive evaluation of Pitolisant. However, based on available data, Samelisant shows comparable efficacy and safety profiles to Pitolisant.

Pitolisant has notable limitations outlined in the US FDA and EMA label, including contraindications and warnings for inducing CYP3A4 enzymes, prolonging QT intervals, and drug interactions [25,26,53]. Inducers of CYP3A4 enzymes can reduce the effectiveness of preparations containing the hormones estrogen and progesterone and their derivatives [53]. Approximately one-quarter of the women aged between 15 and 44 use oral contraceptives as the method of choice [54]. Hormonal preparations are also used in conditions related to menstrual disorders. Narcolepsy prevalence is reported to be higher in females [55–57]. This higher prevalence may explain their increased participation in clinical trials [43,47,58], a pattern also noted in the current study. Given the potentially higher prevalence of narcolepsy in female population, there is a need for therapies without limitation for use in this population. The use of Pitolisant in female population using hormonal preparations can be limited due to these interactions. Pitolisant is metabolized by CYP2D6 enzyme. A drug interaction study with Paroxetine, a CYP2D6 inhibitor, resulted in a two-fold increase in Pitolisant exposures. Therefore, dose adjustment becomes essential for patients

Table 4
Overview of TEAE.

TEAE	Placebo (N = 62) n (%)	Samelisant		Total (N = 188) n (%)
		2 mg (N = 63) n (%)	4 mg (N = 63) n (%)	
Patients with at least 1 TEAE	14 (22.6)	31 (49.2)	31 (49.2)	76 (40.4)
Patients with at least 1 serious TEAE	0	0	0	0
Patients with at least 1 severe TEAE	0	1 (1.6)	1 (1.6)	2 (1.1)
Patients with at least 1 related TEAE	10 (16.1)	23 (36.5)	27 (42.9)	60 (31.9)
Patients with at least 1 TEAE leading to study drug discontinuation	0	4 (6.3)	6 (9.5)	10 (5.3)

TEAE = treatment-emergent adverse event. Notes: Percentages are based on the number of patients in each treatment group in the safety population.

Table 5
TEAEs reported in at least ≥5 % of patients in either treatment group.

System Organ Class Preferred Term	Placebo (N = 62)n (%)	Samelisant		Total (N = 188) n (%)
		2 mg (N = 63) n (%)	4 mg (N = 63) n (%)	
Number of patients with at least 1 TEAE	14 (22.6)	31 (49.2)	31 (49.2)	76 (40.4)
Psychiatric disorders				
Insomnia	2 (3.2)	6 (9.5)	11 (17.5)	19 (10.1)
Abnormal dreams	0	3 (4.8)	5 (7.9)	8 (4.3)
Gastrointestinal disorders				
Nausea	2 (3.2)	5 (7.9)	11 (17.5)	18 (9.6)
Vascular disorders				
Hot flush	1 (1.6)	3 (4.8)	7 (11.1)	11 (5.9)

TEAE = treatment-emergent adverse event. Percentages are based on the number of patients in each treatment group in the safety population.

taking CYP2D6 inhibitors or for CYP2D6 poor metabolizers. Pitolisant is also an inhibitor of CYP2D6 with moderate potency and may increase the exposures of CYP2D6 substrates like dextromethorphan. Furthermore, patients with narcolepsy often have comorbid disorders like obesity, diabetes, depression, and other sleep disorders, all of which are cardiovascular disease risk factors. QT interval prolongation by Pitolisant can further exacerbate cardiovascular challenges. In contrast, Samelisant demonstrates a more favorable profile concerning drug-drug interaction liability [27,29] and cardiovascular safety [27,30] based on available data. If subsequent evaluations reaffirm its efficacy and safety, Samelisant may have an advantage over Pitolisant. Currently, Pitolisant is the only non-controlled agent approved for use in the narcolepsy treatment landscape. Since Samelisant operates through a mechanism similar to that of Pitolisant, it is expected to remain unclassified as a controlled substance.

Given that our study was a phase 2 proof-of-concept trial, it naturally had some limitations. The efficacy and safety data were derived from a relatively short treatment duration of 2 weeks. Additionally, the study was conducted exclusively at sites in North America, which may limit the generalizability of the findings to broader populations. Consequently, the effects of Samelisant over a longer treatment duration and in diverse populations remain to be assessed in the context of chronic disorder. Despite these constraints, our findings indicate that Samelisant at doses of 2 and 4 mg significantly improved subjective sleepiness as assessed by both participant-reported and clinician-reported measures. The safety profile of Samelisant in narcolepsy patients aligns with observations from phase 1 studies in healthy human volunteers and with other H3 receptor inverse agonists/antagonists. Based on the available data, the efficacy and safety profile of Samelisant compares favorably with the agents approved for the treatment of EDS in narcolepsy. These data add to the growing body of evidence that H3 receptor inverse agonism/antagonism is a promising approach for treating EDS in narcolepsy. Global phase 3 studies are planned to further evaluate the efficacy and safety of Samelisant, along with studies to assess its long-term safety and maintenance of efficacy.

Agents like orexin agonists, which directly target the deficiency of orexin neurotransmitters, are in various stages of development. Additionally, several new strategies are being explored [9]. Ongoing research may unravel the potential of these agents and strategies. Since narcolepsy is a syndromic condition, a variety of options are needed for its management, highlighting the urgent need for newer, safe, and effective treatments.

CRediT authorship contribution statement

Ramakrishna Nirogi: Writing – review & editing, Visualization, Supervision, Resources, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Anil Shinde:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Vinod Kumar Goyal:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Jyothsna Ravula:** Writing – review & editing, Formal analysis, Data curation, Conceptualization. **Vijay Benade:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Satish Jetta:** Writing – review & editing, Formal analysis, Data curation, Conceptualization. **Santosh Kumar Pandey:** Writing – review & editing, Formal analysis, Data curation. **Ramkumar Subramanian:** Writing – review & editing, Formal analysis, Data curation. **Veera Raghava Chowdary Palacharla:** Writing – review & editing, Formal analysis, Data curation. **Abdul Rasheed Mohammed:** Writing – review & editing, Formal analysis, Data curation. **Renny Abraham:** Writing – review & editing, Formal analysis, Data curation. **Dhanunjay Kumar Dogiparti:** Writing – review & editing, Formal analysis, Data curation. **Ilayaraja Kalaikadhiban:** Writing – review & editing, Formal analysis, Data curation. **Pradeep Jayarajan:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Venkat Jasti:** Writing – review & editing, Formal analysis, Conceptualization. **Richard K. Bogan:** Writing – review & editing, Formal analysis.

Declaration of competing interest

Ramakrishna Nirogi, Anil Shinde, Vinod Kumar Goyal, Jyothsna Ravula, Vijay Benade, Satish Jetta, Veera Raghava Chowdary Palacharla, Dhanunjay Kumar Dogiparti, Ilayaraja Kalaikadhiban, Renny Abraham, Santosh Kumar Pandey, Ramkumar Subramanian, Abdul Rasheed Mohammed, Pradeep Jayarajan, and Venkat Jasti are full-time employees of Suven Life Sciences Ltd., India.

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