Study Design and Rationale for a Phase-2 Study of Samelisant (SUVN-G3031) for the Treatment of Cataplexy In Patients with Narcolepsy Type 1

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Introduction:

Narcolepsy is a chronic neurological disorder categorized into narcolepsy type 1 (NT1) and narcolepsy type 2 (NT2) disorder. The hallmark feature of the NT1 patients is the cataplexy. Although several therapies have been approved for the management of cataplexy, there remains a void, specifically in terms of safety, such as abuse liability, drug interactions, and cardiovascular risks. Samelisant (SUVN-G3031) is a potent and selective histamine-3 receptor inverse agonist designed to modulate the histaminergic system, a key regulator of the brain's sleep–wake cycle. Preclinical studies in narcolepsy-relevant animal models have shown that Samelisant produces significant anticataplectic and wake-promoting effects, supporting its potential as a therapeutic option for NT1.

Objective:

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

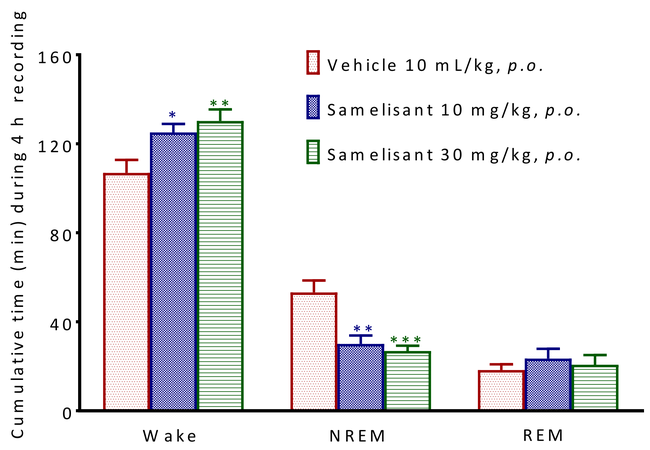
Methods and Results:

Non-clinical:

Electroencephalography for Evaluation of Sleep/ Wake Profile and Anticataplectic Effects:

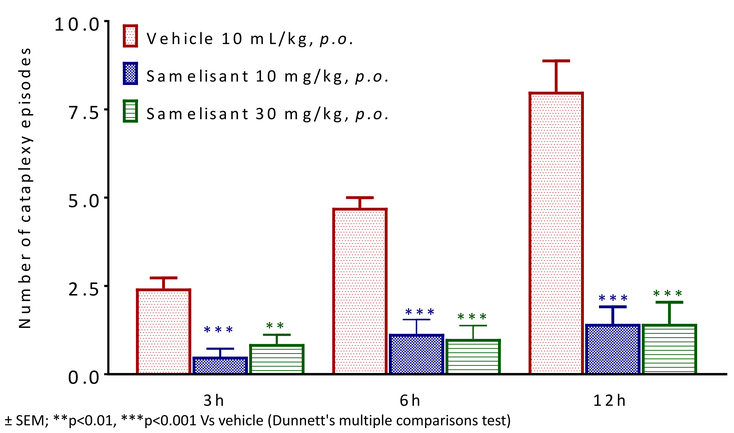
Samelisant was assessed in orexin knockout mice to evaluate its effects on sleep/ wake and cataplexy using electroencephalography (EEG). Orexin knockout mice were implanted with a telemetric transmitter (DSI, St. Paul, MN, USA) into the peritoneal cavity under isoflurane anesthesia. Pair of electrodes were implanted epidurally into the frontal cortex region using stainless steel screws (CMA Microdialysis, Stockholm, Sweden) for recording sleep EEG and the second pair of electrodes were implanted into the neck nuchal muscle to record electromyography (EMG). Animals were allowed a surgical recovery of minimum 3 weeks and were allowed free access to water and food. On the day of the study, recordings were continued for 24 hours post treatment. The treatments were given in a cross-over design by allowing a washout period of 1 week between treatments. The data was analyzed using NeuroScore software.

Fig 1. Effect of Samelisant on Cumulative Wake Time in Orexin Knockout Mice



Data represents Mean ± SEM; *p<0.05, **p<0.01, ***p<0.001 Vs vehicle (Dunnett's multiple comparisons test)

Fig 2. Effect of Samelisant on Cataplexy Episodes in Orexin Knockout Mice

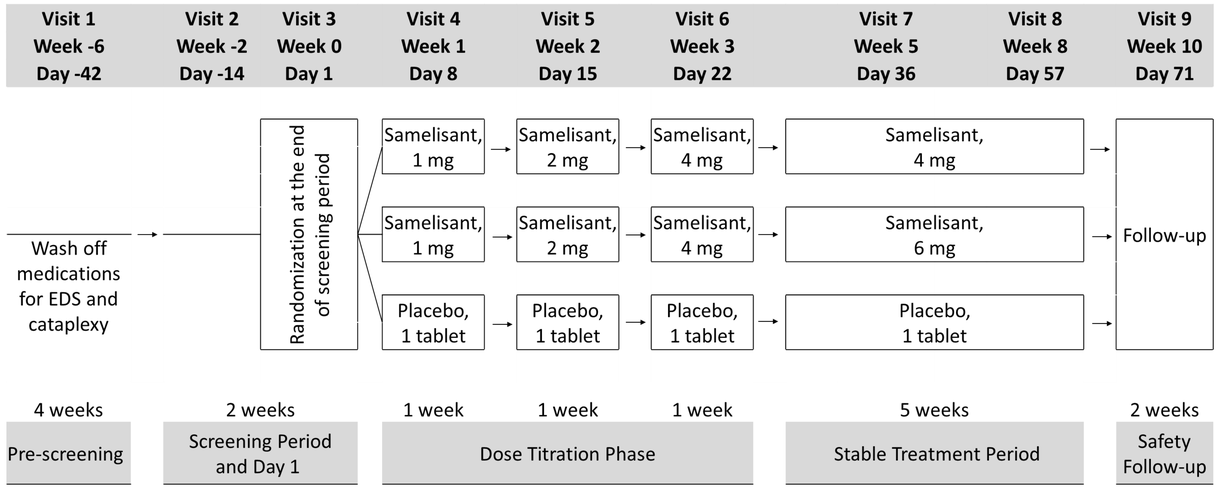


Data represents Mean ± SEM; **p<0.01, ***p<0.001 Vs vehicle (Dunnett's multiple comparisons test)

Samelisant produced significant increase in wake and decreased cataplectic episodes.

Clinical:

Fig 3. Phase-2 Study Design



Participants:

The study plans to randomize approximately 129 patients, using 1:1:1 treatment allocation, with 43 patients in each treatment group, Samelisant 4 mg, Samelisant 6 mg, and Placebo.

Endpoints:

Primary Endpoint	➢ Change in weekly cataplexy rate (WCR) between the 2-week baseline period and the last 4-week of stable dose period
Secondary Endpoints	➢ Change from Baseline in CGI-S score at Week 8 ➢ Change from Baseline in ESS total score at Week 8
Exploratory Endpoints	➢ Change from Baseline in CGI-C score at Week 8 ➢ Change from Baseline in PGI-C score at Week 8 ➢ Change from Baseline in NSS total score at Week 8
Safety Endpoints	➢ Physical examinations ➢ Laboratory assessments, including hematology, serum chemistry and urinalysis ➢ ECG parameters ➢ AEs ➢ Vital signs ➢ C-SSRS responses

Key Inclusion Criteria:

- Must be ≥18 years old.
- Have a primary diagnosis of NT1 that meets the ICSD-3 TR criteria or DSM-5 TR criteria.
- The patient must be positive for the human leukocyte antigen (HLA) genotype HLA-DQB1*06:02 or results from radioimmunoassay indicate the patient's cerebrospinal fluid (CSF) orexin (OX)/hypocretin-1 concentration is ≤110 picograms per milliliter (pg/mL).
- Have a history of ≥14 partial or complete episodes of cataplexy (typical cataplexy) as reported on the electronic cataplexy frequency diary during the 2-weeks baseline period.
- Has an ESS score ≥12 at Screening and Baseline visits.
- Able to show compliance with diary entries for at least 5 times/week in 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.
- Diagnosis of syndromes known to cause sleep disruption or any other cause of daytime sleepiness.
- Use of any investigational therapy within the 30-day period or 5 half-lives prior to screening, whichever is longer.
- Nicotine dependence that has an effect on sleep (i.e., a patient who routinely awakens at night to smoke).

Conclusions:

- Findings from animal models indicate that Samelisant may exert meaningful anticataplectic effects.
- In an earlier Phase-2 study, Samelisant was safe and well tolerated in narcolepsy patients.
- The results of the planned Phase-2 study will inform the therapeutic potential of Samelisant for the treatment of cataplexy in patients with NT1.