Ropanicant (SUVN-911), an α4β2 nAChR Antagonist: A Phase 2b, Randomized, Double-blind, Placebo-controlled, Parallel-group Study, Evaluating the Efficacy and Safety of Ropanicant in Patients with Major Depressive Disorder

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Introduction

Ropanicant (SUVN-911) is a potent and selective α4β2 nicotinic acetylcholine receptor (nAChR) antagonist that is being developed for the treatment of major depressive disorder (MDD). Ropanicant has demonstrated more than 100-fold selectivity against over 70 receptors which include closely related α3β4 nAChR receptors. Ropanicant displayed good oral bioavailability in rats, mice, and dogs. Good brain exposure upon oral administration in rats was observed along with dose-dependent receptor occupancy at α4β2 receptors. Ropanicant showed robust antidepressant-like effects in animal models relevant to depression. It showed faster onset of antidepressant activity, enhanced cognitive function and did not cause sexual dysfunctions in animal models, thus addresses major limitations of the currently used antidepressants. Non-clinical safety of Ropanicant has been established in a battery of safety pharmacology, genotoxicity, general toxicity, and reproductive and developmental toxicity studies.

Ropanicant was well tolerated and safe up to the highest tested dose of 60 mg single dose and 45 mg once daily (qd) for 14 days in healthy subjects. An open-label parallel-group Phase 2a study evaluated the safety and efficacy of Ropanicant in patients with moderate to severe MDD patients across multiple centres in the USA (NCT06126497). A total of 41 patients were randomized to receive Ropanicant either 45 mg qd, 30 mg twice a day (bid), or 45 mg bid in a ratio of 1:1:1, for duration of 14 days. Of the 41 randomized patients, 14 received Ropanicant 45 mg qd, 14 received 30 mg bid, and 13 received 45 mg bid. On Day 14, the Montgomery-Asberg Depression Rating Scale (MADRS) total score had changed significantly from baseline for the 30 mg bid group (-12.7), followed by the 45 mg qd (-10.5), and 45 mg bid (-10.4) groups. Day 14 MADRS total score showed a statistically significant improvement from baseline ($p < 0.0001$) across Ropanicant treatment arms. Ropanicant was found to be safe and well tolerated in patients with moderate to severe MDD across tested doses.

Salient Features of Ropanicant

- Rapid onset of action as demonstrated in animal models of depression
- Improved side effect profile (No sexual dysfunction and cognitive dulling)
- No CYP mediated drug-drug interaction liability

Methods

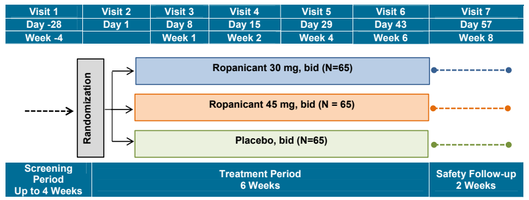
Study Design

A Phase 2b, randomized, double-blind, placebo-controlled, parallel-group, multicenter trial is ongoing (NCT06836063) in the United States (USA). The study is evaluating the efficacy and safety of Ropanicant 30 and 45 mg bid compared to placebo bid. The study is planned to randomize 195 patients in a 1:1:1 ratio to receive either 30 or 45 mg bid of Ropanicant or placebo bid (65 per treatment group) for a duration of 6 weeks.

The study consists of 4-weeks screening period, 6-weeks treatment period, and a 2-weeks follow-up period. The study design is depicted in Figure 1.

The primary objective of the study is to evaluate the efficacy of Ropanicant compared to placebo in reducing the depressive symptoms. The secondary objectives are efficacy of Ropanicant compared to placebo based on clinician reported outcome, functional impairment, and safety.

Figure 1: Study Design of Ropanicant Phase 2b Study



Endpoints

Primary Endpoint	• Change from Baseline in Montgomery-Asberg Depression Rating Scale (MADRS) total score at Week 6
Secondary Endpoints	• Change from Baseline in Clinical Global Impression-Severity (CGI-S) score at Week 6 • Change from Baseline in Sheehan Disability Scale (SDS) score at Week 6 • Adverse events (AEs), AEs indicative of abuse potential, Physical examination, Vital signs, Laboratory assessments (blood and urine), Electrocardiogram (ECG), Columbia-Suicide Severity Rating Scale (C-SSRS), Discontinuation-Emergent Signs and Symptoms (DESS)
Exploratory Endpoints	• Change from Baseline in Quality of Life in Depression Scale (QLDS) score at Week 6 • Change from Baseline in Snaith-Hamilton Pleasure Scale (SHAPS) score at Week 6 • Change from Baseline in Patient Health Questionnaire-9 (PHQ-9) score at Week 6

Key Inclusion Criteria

- Male or female patients between 18 and 65 years of age (inclusive) at the screening visit.
- Patients must have a body mass index between 18.5 and 40 kg/m^2 (inclusive) at the screening visit.
- Patients must meet the DSM-5-TR criteria for MDD without psychotic features based on the MINI with a current major depressive episode of at least 4 weeks of duration but no longer than 12 months prior to the screening visit.
- Patients must have a Structured Interview Guide for the Hamilton Depression Rating Scale (SIGH-D) score of ≥20 at the screening and Baseline visits, a CGI-S score of ≥4 at the screening and Baseline visits, and a SHAPS score of ≥20 at the screening and Baseline visits.

Key Exclusion Criteria

- Patients with an improvement in SIGH-D score of ≥25% between the screening and Baseline visits
- Patients who meet criteria for TRD during the current major depressive episode, which is defined as being non-responders (<50% of improvement) to 2 or more depression treatment periods of adequate dose and duration as defined by the MGH ATRQ.
- Patients taking antidepressant treatment (SSRIs or SNRIs) or any medication that is contraindicated with the use of Ropanicant within 2 weeks (or 5 half-lives, whichever is longer) prior to Baseline and until the follow-up visit

Results

Demographics and Baseline Characteristics (Enrolled Set)

Variable	Placebo bid (N=71)	Ropanicant 30 mg bid (N=73)	Ropanicant 45 mg bid (N=70)	Total (N=214)
Age (years)	45.1 (13.88)	45.8 (12.17)	46.4 (12.15)	45.7 (12.71)
Sex, n (%)				
Female	43 (60.6)	45 (61.6)	44 (62.9)	132 (61.7)
Race, n (%)				
American Indian or Alaska Native	0	0	3 (4.3)	3 (1.4)
Asian	4 (5.6)	5 (6.8)	2 (2.9)	11 (5.1)
Black or African American	20 (28.2)	31 (42.5)	28 (40.0)	79 (36.9)
Native Hawaiian or Other Pacific Islander	1 (1.4)	0	0	1 (0.5)
White	41 (57.7)	35 (47.9)	35 (50.0)	111 (51.9)
Other	5 (7.0)	2 (2.7)	2 (2.9)	9 (4.2)
Ethnicity, n (%)				
Hispanic or Latino	13 (18.3)	11 (15.1)	12 (17.1)	36 (16.8)
Not Hispanic or Latino	58 (81.7)	62 (84.9)	58 (82.9)	178 (83.2)
BMI (kg/m^2)	28.8 (5.28)	29.0 (5.90)	31.4 (5.04)	29.7 (5.52)
MADRS Total score	31.4 (4.84)	30.8 (4.85)	31.0 (4.68)	31.1 (4.78)
CGI-SD	4.5 (0.53)	4.4 (0.49)	4.3 (0.47)	4.4 (0.50)
SDS Total score	19.6 (6.05)	20.3 (5.68)	21.2 (6.50)	20.3 (6.08)
QLDS Total score	22.4 (7.71)	21.7 (6.84)	21.9 (8.28)	22.0 (7.58)
SHAPS Total score	39.6 (6.46)	39.4 (6.96)	39.6 (5.96)	39.5 (6.45)
PHQ-9 Total score	16.7 (4.61)	16.7 (4.15)	16.7 (5.17)	16.7 (4.63)

*values are mean (SD) unless specified

Conclusion

- The demographics and baseline characteristics are consistent with other MDD studies and are representative of MDD population.

The results from the double-blind, randomized, placebo-controlled Phase 2b clinical study in MDD patients will inform the clinical utility of Ropanicant.