Clinical Study Protocol

Protocol Title: An Open-Label Study Evaluating the Safety and Efficacy of Ropanicant in Participants with Moderate to Severe Major Depressive Disorder

Protocol Number: CTP2S1911A4B2

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1 Protocol Summary

1.1 Protocol Synopsis

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Title: An Open-Label Study Evaluating the Safety and Efficacy of Ropanicant in Participants with Moderate to Severe Major Depressive Disorder

Sponsor: Suven Life Sciences Ltd., 6th Floor, Serene Chambers, Road – 5, Avenue – 7, Banjara Hills, Hyderabad-500034, Telangana, India

Indication: MDD

Study Phase: Phase 2a

Study Sites: The study will be conducted at study center(s) located in the US.

Rationale:

Though there are many approved antidepressants available for treatment of MDD, there is still an unmet medical need for new medicines with novel mechanisms, better efficacy, faster onset of action, higher response and remission rates, and improved safety profile.

Ropanicant (SUVN-911) is a novel and orally active α4β2 nicotinic acetylcholine receptor (nAChR) antagonist intended for the treatment of MDD. The novel mechanism of action, robust efficacy, and rapid onset of action in animal models of depression, and good safety, and tolerability in FIH studies make ropanicant a potential clinical candidate to evaluate its safety and efficacy in MDD participants in the proposed Phase 2a study.

Objectives and Endpoints:

Objective(s)	Endpoints
Primary	
To evaluate the safety and tolerability of ropanicant in participants with MDD	• Incidence of AEs. • Incidence of SAEs. • [redacted] • Absolute values and change from baseline in laboratory assessments. • Absolute values and change from baseline in vital signs. • Absolute values and change from baseline in ECG assessments. • C-SSRS scores during the study.
Secondary	
To evaluate the efficacy of ropanicant in participants with MDD	• Absolute values and change from baseline in MADRS total score at Day 14. • Proportion of participants with CGI-S score <3 at Day 14. • Proportion of participants with ≥2 points decrease from baseline on CGI-S scale at Day 14.
To evaluate the PK of ropanicant in participants with MDD	PK parameters of ropanicant including, but not limited to, C_{max}, T_{max}, C_{trough}, C_{avg}, $AUC_{0\text{-}tau}$, $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, $t_{½}$, CL/F, Vz/F, R_{ac} for C_{max}, and R_{ac} for AUC.
Exploratory	
To further evaluate the efficacy of ropanicant in participants with MDD	• Absolute values and change from baseline in MADRS total score at Days 7 and 21. • Proportion of participants with reduction of ≥50% from baseline in MADRS total score at Day 14. • Proportion of participants who achieved an MADRS total score ≤9 at Day 14. • Proportion of participants with CGI-S score <3 at Day 7. • Proportion of participants with ≥2 points decrease from baseline on CGI-S scale at Day 7. • Absolute values and change from baseline in CGI-S score at Days 7 and 14.
[redacted]	[redacted]

Diagnosis and Main Criteria for Inclusion and Exclusion:

Adult participants fulfilling the DSM-5 criteria for MDD without psychotic features and diagnosis confirmed by the MINI will be eligible for the study. The current major depressive episode must be at least 4 weeks of duration prior to the screening visit. The participants must have an MADRS score of ≥25 at the screening visit and the baseline visit (Day 1).

Participants who meet criteria for TRD during the current major depressive episode, which will be defined as being non-responders (less than 50% of symptom improvement) to 2 or more depression treatment periods of adequate dose and duration as defined by the MGH ATRQ, will be excluded from the study. Participants with a diagnosis of schizophrenia, bipolar disorder, or any Axis I psychotic disorder at the screening visit will be excluded from the study.

Study Design:

This is an open-label, parallel-group study to evaluate the safety and efficacy of ropanicant in participants with moderate to severe MDD. Approximately 36 participants will be randomly assigned to receive ropanicant either [redacted] for 2 weeks, in a ratio of 1:1:1 (12 participants in each treatment group). Following a screening period of up to 4 weeks, the participants will be treated for 2 weeks. The screening period may be extended up to 5 weeks in case of washout of compounds with longer $t_{1/2}$.

On the day of the study visits, participants will be instructed not to take their study drug at home, as it will be administered at the study site. On days with no scheduled study visits, at about the same time every day, the participant will take 1 tablet/day in the morning (for qd dosing) or 2 tablets/day (~12 hours apart for bid dosing). Tablets are to be taken with a glass of water (with or without food).

A participant is considered to have completed the study if he/she has completed the 2-week open-label treatment period, the EOT visit, and the follow-up visit.

Duration of Treatment:

The duration of treatment with ropanicant in the study will be 2 weeks.

Safety Assessments:

Safety assessments will include AEs, physical examination, vital signs, ECGs, clinical laboratory tests, and SIB risk monitoring (C-SSRS).

Efficacy Assessments:

The efficacy assessments included in the study will be based on MADRS and CGI-S.

PK and PD Assessments:

Blood samples for PK will be collected at the site on Day 1 and Day 14 for full PK sampling for the participants receiving bid dosing of ropanicant only. No PK sampling will be performed for participants receiving qd dosing of ropanicant.

[redacted]

Description of Study Drug:

Study Drug/IMP	Ropanicant
Dose Formulation	Tablet
[redacted]	[redacted]
[redacted]	[redacted]
Route of Administration	Oral

Sample Size:

The study will randomize approximately 36 participants to either [redacted] ropanicant in a 1:1:1 ratio (12 participants in each treatment group). No prospective calculations of statistical power have been made and the sample size has been selected based on clinical reasoning to provide information on safety, tolerability, and reduction in depressive symptoms following either qd or bid dosing of ropanicant.

Statistical Methods:

No formal significance testing will be performed.

Data collected in this study will be presented using summary tables, figures, and participant data listings. Continuous variables will be summarized using the mean, SD, median, minimum value, and maximum value. Categorical variables will be summarized using frequency counts and percentages.

No interim analysis will be performed.

Analysis of primary endpoints:

The incidence of AEs for the safety population will be descriptively summarized by treatment group. AEs will also be summarized by severity, seriousness, and relationship to treatment for each treatment group.

The incidence of laboratory abnormalities by type, frequency, and severity will be descriptively summarized by treatment groups. Change from baseline in continuous laboratory variables will be summarized by visit and treatment groups.

All other safety variables (including vital signs, ECG assessments and C-SSRS) will be descriptively summarized by treatment group and visit. This will include absolute and change from baseline value summaries for vital signs and ECG assessments.

Analysis of secondary endpoints:

The absolute values and change from baseline in MADRS total score at Day 14 will be descriptively summarized by treatment group using the mFAS. Additionally, change from baseline in MADRS total score at Day 14 will be analyzed using an ANCOVA model including terms for treatment, gender, and baseline MADRS (as a covariate).

The proportion of participants with CGI-S score <3 at Day 14 and proportion of participants with ≥2 points decrease from baseline on CGI-S scale at Day 14 will be analyzed using a logistic regression model including factors for treatment group, gender, and the measures recorded at baseline using the mFAS. The odds ratio and its 95% confidence interval will be estimated.

Individual and mean plasma PK concentrations of ropanicant versus time profiles will be plotted by treatment and day in both linear and semi-logarithmic scales. Plasma PK concentration data of ropanicant will be listed by individual participant and summarized using descriptive statistics by treatment and day.

Plasma PK parameters of ropanicant will be derived from plasma concentration versus time data using noncompartmental analysis with Phoenix WinNonlin (Certara USA, Inc., Princeton, New Jersey) Version 8.0 or higher. PK parameters will also be listed by individual participant and summarized using descriptive statistics by treatment and day.

Dose proportionality of PK parameters (C_{max}, $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}tau}$) will be assessed using a power model if data permit.

Analysis of exploratory endpoints:

The absolute values and change from baseline in MADRS total score at Days 7 and 21 and CGI-S score at Days 7 and 14 will be descriptively summarized by visit and treatment group using the mFAS.

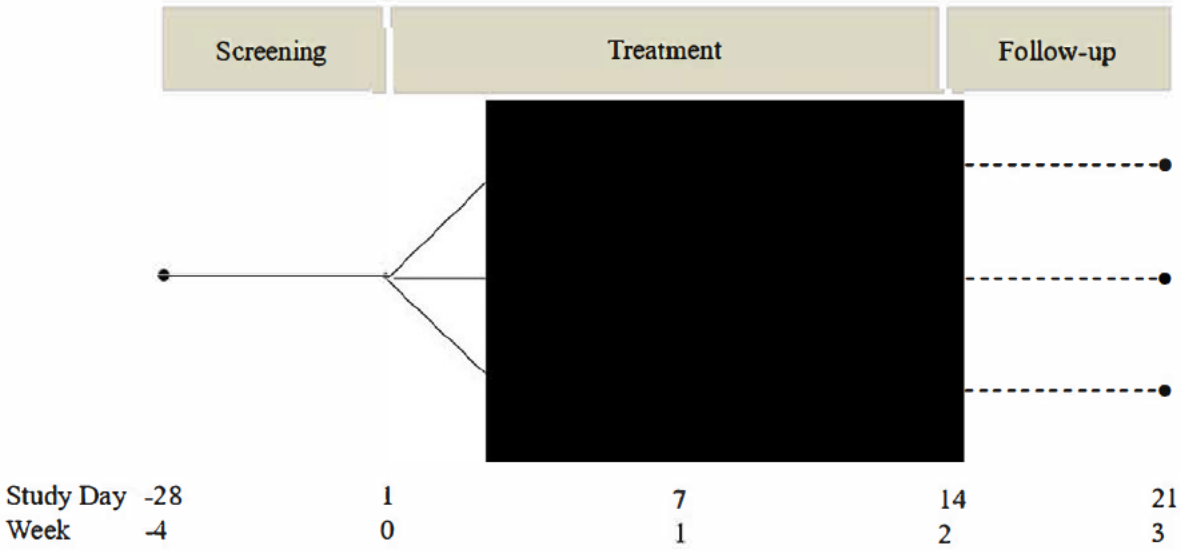
The proportion of participants with reduction of ≥50% from baseline in MADRS total score at Day 14, proportion of participants who achieved an MADRS total score ≤9 at Day 14, proportion of participants with CGI-S score <3 at Day 7, and proportion of participants with ≥2 points decrease from baseline on CGI-S scale at Day 7 will be analyzed using a logistic regression model including factors for treatment group, gender, and the measures recorded at baseline using the mFAS. The odds ratio and its 95% confidence interval will be estimated.

[redacted]

[redacted]

1.2 Study Schema

Figure 1-1 Study Design



1.3 Schedule of Assessments

Table 1-1 Schedule of Assessments

	Screening	Open-Label Treatment			Follow-Up	
Visit	**Visit 1 (Screening)**	**Visit 2 (Baseline)**	**Visit 3**	**Visit 4[a] (EOT)**	**Visit 5 (EOS)**	**ET[a]**
Days from Randomization	**Day -28 to -1[b]**	**Day 1[b]**	**Day 7**	**Day 14**	**Day 21**	
Clinic Visit Window (days)	**NA**	**NA**	**±1 day**	**±3 days**	**±3 days**	
Weeks from Randomization	**Week -4 to -1**	**Week 0**	**Week 1**	**Week 2**	**Week 3**	
Informed consent	X					
Inclusion/exclusion criteria	X	X				
Demographics	X					
Medical history	X					
MINI	X					
MGH ATRQ	X					
Physical examination	X	X[c]		X		X
Height	X					
Body weight	X	X	X	X	X	X
BMI	X					
Laboratory assessments[d]	X	X	X	X	X	X
Urine drug screen[d]	X	X[c]	X	X		X
Pregnancy test[e]	X	X[c]	X	X	X	X
Vital signs	X	X[c]	X[f]	X[f]	X	X
12-Lead ECG	X[l]	X[c, l]	X[f]	X[f]		X
C-SSRS	X	X[c]	X	X	X	X
CGI-S	X	X[c]	X[f]	X[f]		X
MADRS	X	X[c]	X[f]	X[f]	X	X
PK sample[g]		X		X[h]		

	Screening	Open-Label Treatment			Follow-Up	
Visit	**Visit 1 (Screening)**	**Visit 2 (Baseline)**	**Visit 3**	**Visit 4[a] (EOT)**	**Visit 5 (EOS)**	**ET[a]**
Days from Randomization	**Day -28 to -1[b]**	**Day 1[b]**	**Day 7**	**Day 14**	**Day 21**	
Clinic Visit Window (days)	**NA**	**NA**	**±1 day**	**±3 days**	**±3 days**	
Weeks from Randomization	**Week -4 to -1**	**Week 0**	**Week 1**	**Week 2**	**Week 3**	
[redacted]		X		X	X	
Study drug administration[j]		X	X	X		
Study drug dispensation		X	X			
Compliance check			X	X		X
AEs	X	X[c]	X	X	X	X
Concomitant medications	X[k]	X[c]	X	X	X	X

a) In the event a participant discontinues study drug prematurely, every effort will be made to continue the participant in the study and have all planned assessments completed until the EOT visit. If a participant withdraws from the study prematurely for any reason, the participant will be encouraged where possible to return to the study site for an ET visit.

b) Screening period may be extended up to 5 weeks in case of washout of compounds with longer $t_{1/2}$. Assessments included in inclusion/exclusion criteria at the screening visit and the baseline visit (Day 1) should be performed in order to exclude noneligible participants as quickly as possible and minimize inconvenience for them, therefore, assessments should be performed in the order as follows: MINI *(at the screening visit only)*, MGH ATRQ (*at the screening visit only*), MADRS, CGI-S, C-SSRS, vital signs, ECG, pregnancy test (for WOCBP), and laboratory tests (The baseline visit [Day 1] laboratory samples should only be collected after randomization).

c) To be collected prior to randomization to ensure the participant is still eligible to participate in the study.

d) Clinical laboratory tests will be performed at a central laboratory. [redacted]

e) At the screening visit, a serum hCG pregnancy test will be done for WOCBP. At all other visits, a urine pregnancy test will be done.

f) Vital signs and ECGs on Day 7 and Day 14 will be performed 1 hour after administration of the study drug (T_{max} of ropanicant). *For participants on bid dosing of ropanicant:* Vital signs and ECGs will be performed 1 hour after administration of the morning dose of study drug only.
MADRS and CGI-S will be collected prior to dosing.

g) Full PK sampling will be performed at the site on Day 1 and Day 14 for the participants receiving bid dosing of ropanicant only. On Day 1 and Day 14, participants from bid dosing group will stay at the study center for 24 hours after the morning dose. PK samples will be collected prior to the administration of the study drug and at 0.5, 1, 2, 4, 6, and 12 hours after the first dose (morning dose) and at 0.5, 1, 2, 4, 6, and 12 hours after the second dose (evening dose) at the baseline visit (Day 1) and Day 14. The sample at 12 hours after the first dose will be collected prior to the administration of the second dose. The sample at 12 hours after the second dose on Day 1 will be collected prior to the administration of the first dose on Day 2.

h) On Day 14, the 1-hour postdose PK sample will be collected after the 1-hour postdose vital signs and ECG assessments.

i) [redacted]

j) Participants will receive ropanicant either [redacted], for 2 weeks. On the day of the study visits, participants will be instructed NOT to take their dose of study drug at home, as it will be administered at the study site.

k) Includes history of all medications used in the past year.

l) ECG will be performed in triplicates at the screening and baseline visits and the average of the 3 readings will be reported and used for interpretation. A triplicate ECG reading is considered more reliable than a single reading.