Masupirdine (SUVN-502), 5-HT$_6$ Antagonist for Potential Treatment of Neuropsychiatric Symptoms in Alzheimer's disease

Phase-2 Study Initiation by Q4 2020

Suven Life Sciences Ltd
Serene Chambers, Road-5, Avenue-7, Banjara Hills,
Hyderabad-500 034, India.
Contacts: jasti@suven.com, nvsrk@suven.com
Masupirdine: Summary From Phase-2 Study

- Masupirdine significantly reduced agitation/aggression in patients with baseline symptoms
- Efficacy of masupirdine is independent of the severity of agitation/aggression at baseline
- Beneficial effects of masupirdine were observed in several NPI domains related to agitation/aggression
- Masupirdine significantly attenuated delusions and/or hallucinations in patients with dementia of the Alzheimer's type
- Masupirdine showed beneficial effects on cognition in patients with psychotic symptoms
- Masupirdine showed sustained and durable efficacy for the entire study duration of 26 weeks
- Masupirdine was generally safe and well tolerated

Clinicaltrials.gov: NCT02580305
Masupirdine: Pharmacological Characterization

- Pure 5-HT₆ receptor antagonist with >1200 fold selectivity over 5-HT₂A receptor
- Attenuates aggressive behavior in Swiss Albino mice
- Robust efficacy on cognition in animal models
- Elevates brain acetylcholine levels and neural oscillatory pattern of theta rhythm in animal models
- Wide margin of safety in all long-term animal studies
- Safe and well tolerated following single or repeated administration in healthy humans
- Food, gender and age has no effects on pharmacokinetics
- Human pharmacokinetics suitable for once a day treatment
Masupirdine: Phase-2 Proof of Concept Study Design

5-HT$_6$ receptor antagonist, Masupirdine in combination with Donepezil and Memantine (Triple Therapy)

**Screening Period:**
Day -28 to Day -14
- Moderate AD patients (MMSE 12 - 20)
- Age 50 - 85 years
- Receiving stable doses of Donepezil and Memantine for at least 3 months
- Diagnosis of probable AD for at least 1 year

**Randomization (1:1:1)**

**Treatment Period:**
26 Weeks
- Placebo, QD, Oral
- Masupirdine 50 mg, QD, Oral
- Masupirdine 100 mg, QD, Oral

**Placebo Washout Period:**
4 Weeks
- Completers are eligible for EAP
- Expanded Access Program (EAP) up to 2 x 26 weeks

**Endpoints**
- **Primary Endpoint:** Change from baseline to Week 26 in ADAS-Cog 11
- **Secondary Endpoints:** Change from baseline in CDR-SB, MMSE, NPI-12, ADCS-ADL 23 and C-SDD
- Safety and Tolerability: AE, Labs, Vital Signs, ECG, PE, NE and C-SSRS

Three dosage forms of Memantine: Memantine IR (10 mg, BID) or Namenda XR® (28 mg, QD) or Namzaric™ (28 mg, QD)

Planned subjects = 537; 179 per arm. Study is powered to detect a 2-point drug-placebo difference on ADAS-Cog 11 with a standard deviation of 6, assuming a 2-sided 5% significance level and a drop-out rate of 20% or less. All study sites were in USA.
Exploratory subgroup analysis was carried out to evaluate the efficacy of masupirdine on neuropsychiatric symptoms.

- Subgroup analyses of the twelve domains of NPI were carried out to understand the beneficial effects of masupirdine on the neuropsychiatric symptoms. Stratification was based on the baseline symptoms and/or symptom emergence.

- Responder analysis was also carried out for subgroup with baseline NPI agitation/aggression score ≥ 1. Responders were defined as patients having negative scores at Week 26 from baseline.
Masupirdine: Agitation/Aggression (Baseline ≥ 1)

- Analysis population comprised of patients who had baseline NPI agitation/aggression score
- Mean baseline NPI agitation/aggression score was approximately 3
- Effects observed with masupirdine, 50 mg at week 13 & 26 is statistically significant compared to placebo
- Effect size (Cohen's $d$) observed in the masupirdine, 50 mg treatment arm is 0.66 at the end of 26 weeks
- Responders: 45% (Placebo) & 75% (Masupirdine)
- Effect size in evaluable population is similar to mITT population

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<th>Placebo (n=57)</th>
<th>Masupirdine 50 mg (n=53)</th>
<th>Masupirdine 100 mg (n=48)</th>
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mITT
Masupirdine: Agitation/Aggression (Baseline ≥ 3)

- Analysis population comprised of patients who had baseline NPI agitation/aggression score (≥ 3)
- Mean baseline NPI agitation/aggression score was approximately 4
- Significant effect of masupirdine 50 mg was observed from week 13
- Effect size (Cohen's $d$) observed in the masupirdine 50 mg treatment arm is 0.60 at the end of 26 weeks
- Effect size in evaluable population is similar to mITT population
- Effects with masupirdine sustained for entire study duration of 26 weeks
Masupirdine: Agitation/Aggression (Composite Score)

- Combined score of agitation/aggression, aberrant motor behavior and sleep and nighttime behavior disorders (baseline ≥ 1)
- Masupirdine attenuated symptoms in several domains which are commonly observed in patients with AD related to agitation/aggression
- Effect size (Cohen's $d$) observed with masupirdine treatment is 0.34 – 0.35 at the end of 26 weeks
- Effects with masupirdine sustained for entire study duration of 26 weeks
Masupirdine: Delusions and/or Hallucinations

- Analysis population comprised of patients who had baseline delusions and/or hallucinations or symptom emergence
- Significant effect of masupirdine 50 mg was observed from week 4
- Effect size (Cohen's $d$) observed with masupirdine treatment is 0.31 - 0.58 and 0.24 - 0.35 at the end of 13 and 26 weeks, respectively
- Effects with masupirdine sustained for entire study duration of 26 weeks
- Effect was robust in the evaluable population

Improvement

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<td>Masupirdine 100 mg</td>
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Masupirdine: ADAS-Cog 11 (Delusions and/or Hallucinations)

- Analysis population comprised of patients who had a baseline delusions and/or hallucinations or symptom emergence
- Effect size (Cohen's $d$) observed with masupirdine treatment is 0.48 - 0.57 at the end of 26 weeks
- Effects with masupirdine on cognition is prominent at the end of 26 weeks and consistent in the evaluable population
- In addition to NPS, masupirdine has beneficial effects on cognition
Masupirdine: Summary and Conclusions

- Masupirdine significantly reduced agitation/aggression in patients having baseline symptoms
- Efficacy of masupirdine is independent of the severity of agitation/aggression at baseline
- Beneficial effects of masupirdine were observed in several NPI domains related to agitation/aggression
- Masupirdine significantly attenuated delusions and/or hallucinations in patients with dementia of the Alzheimer's type
- Masupirdine showed beneficial effects on cognition in patients with psychotic symptoms
- Masupirdine showed sustained and durable efficacy for the entire study duration of 26 weeks
- Masupirdine was generally safe and well tolerated
- Findings suggest further exploration of masupirdine for the treatment of neuropsychiatric symptoms in AD