Masupirdine (SUVN-502), 5-HT$_6$ Receptor Antagonist for Potential Treatment of Neuropsychiatric Symptoms in patients with Dementia of Alzheimer's Type

Phase-3 Study Initiation by Q3 2021

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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
Masupirdine: Pharmacological Characterization

- Pure 5-HT$_6$ receptor antagonist with >1200 fold selectivity over 5-HT$_{2A}$ 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-HT₆ 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

### 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

### 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 was 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.

Clinicaltrials.gov: NCT02580305
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

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=57)</th>
<th>Masupirdine 50 mg (n=53)</th>
<th>Masupirdine 100 mg (n=48)</th>
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</thead>
<tbody>
<tr>
<td>Point change from Placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 4</td>
<td>0.0</td>
<td>-1.2</td>
<td>-1.5</td>
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<tr>
<td>Week 13</td>
<td></td>
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<tr>
<td>Week 26</td>
<td></td>
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<td>p &lt; 0.001</td>
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</tbody>
</table>

p < 0.001
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

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<tr>
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<th>Placebo (n=57)</th>
<th>Masupirdine 50 mg (n=48)</th>
<th>Masupirdine 100 mg (n=50)</th>
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<tbody>
<tr>
<td>Week 4</td>
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<td>-0.3</td>
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<tr>
<td>Week 13</td>
<td>-1.5</td>
<td>-1.5</td>
<td>-1.0</td>
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<tr>
<td>Week 26</td>
<td>-0.9</td>
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<td>-1.4</td>
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**Significant changes**
- Masupirdine 50 mg: $p = 0.016$, $p = 0.03$
- Masupirdine 100 mg: $p = 0.091$, $p = 0.280$
**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

### Improvement

<table>
<thead>
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<th>Week 4</th>
<th>Week 13</th>
<th>Week 26</th>
</tr>
</thead>
<tbody>
<tr>
<td>Masupirdine 50 mg</td>
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<td>0.6</td>
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<tr>
<td>Masupirdine 100 mg</td>
<td>1.2</td>
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<td>-2.1</td>
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Masupirdine: Summary and Conclusions

- Masupirdine significantly reduced agitation/aggression in Alzheimer's 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 Alzheimer's patients