Masupirdine (SUVN-502), a 5-HT$_6$ Receptor Antagonist in Combination with Donepezil and Memantine in Moderate Alzheimer's Patients: Study Outcomes from a Phase 2 Study

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Presenter Disclosures

Dr. Cummings has provided consultation to Acadia, Actinogen, AgeneBio, Alkahest, Alzheon, Avanir, Axsome, Biogen, Cassava, Cerecoin, Cerevel, Cognoptix, Cortexyme, EIP Pharma, Eisai, Foresight, Green Valley, Grifols, Hisun, Idorsia, Karuna, Nutricia, Orion, Otsuka, Probiodrug, QR, ReMYND, Resverlogix, Roche, Samumed, Samus, Sigmant Health, Sunovion, Suven, Third Rock, and United Neuroscience pharmaceutical and assessment companies.

Dr. Cummings has stock options in ADAMAS, MedAvante, QR pharma, BiOasis, and United Neuroscience.

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This talk will include reference to unapproved medications and diagnostics.
5-HT₆ Receptor: Cognition and Behavior

- 5-HT₆ receptor is a G-protein coupled receptor mediating its effects through cAMP pathways; Ca²⁺ signaling, and ERK1/2 pathway.¹

- Highest density of the receptor is found in cortex, dorsal hippocampus and striatum; brain areas primarily involved in cognition and behavior.²,³

- Blockade of central 5-HT₆ receptors modulate the release of neurotransmitters like acetylcholine, glutamate, GABA, dopamine and norepinephrine.⁴,⁵

- Non-clinical evidence for the potential role of 5-HT₆ receptor antagonists in reversing cognitive impairment.⁶

¹Grimaldi et al., 1998; ²Monsma et al., 1993; ³Hirst et al., 2003; ⁴Riemer et al., 2003; ⁵Dawson et al., 2000; ⁶Upton et al., 2008
Masupirdine: Overview

Non-clinical

- Masupirdine is a pure 5-HT₆ receptor antagonist (>1200 fold selectivity over 5-HT₂A receptor)
- Robust efficacy for cognition in animal models
- Elevates brain acetylcholine levels and neural oscillatory pattern of theta rhythm
- Attenuates aggressive behavior in an animal model
- Wide margin of safety in all long-term animal studies

Clinical: Phase 1

- Safe and well tolerated following single or repeated administration
- 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

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 are in USA.

Clinicaltrials.gov: NCT02580305
# Masupirdine: Study Population and Demographics

## Study Population

<table>
<thead>
<tr>
<th>Variables</th>
<th>Placebo</th>
<th>Masupirdine 50 mg</th>
<th>Masupirdine 100 mg</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized with intent to treat, n</td>
<td>188</td>
<td>187</td>
<td>183</td>
<td>558</td>
</tr>
<tr>
<td>Safety Population, n (%)</td>
<td>188 (100)</td>
<td>187 (100)</td>
<td>181 (98.9)</td>
<td>556 (99.6)</td>
</tr>
<tr>
<td>Modified Intent to Treat, n (%)</td>
<td>183 (97.3)</td>
<td>184 (98.4)</td>
<td>176 (96.2)</td>
<td>543 (97.3)</td>
</tr>
<tr>
<td>Evaluable Population, n (%)</td>
<td>141 (75.0)</td>
<td>134 (71.7)</td>
<td>122 (66.7)</td>
<td>397 (71.1)</td>
</tr>
</tbody>
</table>

## Demographics*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Placebo</th>
<th>Masupirdine 50 mg</th>
<th>Masupirdine 100 mg</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in Years, Mean (SD)</td>
<td>72.9 (7.2)</td>
<td>73.4 (8.1)</td>
<td>74.4 (7.0)</td>
<td>73.6 (7.5)</td>
</tr>
<tr>
<td>BMI in Kg/m², Mean (SD)</td>
<td>26.4 (5.0)</td>
<td>26.6 (5.0)</td>
<td>26.9 (5.4)</td>
<td>26.6 (5.1)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>77 (42.1)</td>
<td>89 (48.4)</td>
<td>80 (45.5)</td>
<td>246 (45.3)</td>
</tr>
<tr>
<td>White, n (%)</td>
<td>168 (91.8)</td>
<td>171 (92.9)</td>
<td>162 (92.0)</td>
<td>501 (92.3)</td>
</tr>
<tr>
<td>APO-E4 Carrier, n (%)</td>
<td>119 (65.0)</td>
<td>101 (54.8)</td>
<td>110 (62.5)</td>
<td>330 (60.8)</td>
</tr>
</tbody>
</table>

*Based on mITT (Modified Intent to Treat) population
# Masupirdine: Baseline Characteristics

<table>
<thead>
<tr>
<th>Variables*</th>
<th>Placebo</th>
<th>Masupirdine 50 mg</th>
<th>Masupirdine 100 mg</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=183</td>
<td>n=184</td>
<td>n=176</td>
<td>n=543</td>
</tr>
<tr>
<td>ADAS-Cog 11, Mean (SD)</td>
<td>28.4 (8.2)</td>
<td>27.7 (6.9)</td>
<td>27.9 (8.6)</td>
<td>28.0 (7.9)</td>
</tr>
<tr>
<td>MMSE, Mean (SD)</td>
<td>16.5 (2.5)</td>
<td>16.9 (2.2)</td>
<td>17.0 (2.5)</td>
<td>16.8 (2.4)</td>
</tr>
</tbody>
</table>

**Memantine Regimen**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Masupirdine 50 mg</th>
<th>Masupirdine 100 mg</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memantine IR 10 mg, BID, n (%)</td>
<td>114 (62.3)</td>
<td>126 (68.5)</td>
<td>117 (66.5)</td>
<td>357 (65.7)</td>
</tr>
<tr>
<td>Namenda XR® 28 mg, QD, n (%)</td>
<td>38 (20.8)</td>
<td>27 (14.7)</td>
<td>32 (18.2)</td>
<td>97 (17.9)</td>
</tr>
<tr>
<td>Namzaric™ 28 mg, QD, n (%)</td>
<td>31 (16.9)</td>
<td>31 (16.8)</td>
<td>27 (15.3)</td>
<td>89 (16.4)</td>
</tr>
</tbody>
</table>

**Memantine Use Duration**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Masupirdine 50 mg</th>
<th>Masupirdine 100 mg</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 3 Years, n (%)</td>
<td>36 (19.7)</td>
<td>32 (17.4)</td>
<td>29 (16.5)</td>
<td>97 (17.9)</td>
</tr>
<tr>
<td>&gt; 4 Years, n (%)</td>
<td>21 (11.5)</td>
<td>18 (9.8)</td>
<td>21 (11.9)</td>
<td>60 (11.0)</td>
</tr>
</tbody>
</table>

**AD Diagnosis Duration**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Masupirdine 50 mg</th>
<th>Masupirdine 100 mg</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 3 Years, n (%)</td>
<td>95 (51.9)</td>
<td>92 (50.0)</td>
<td>82 (46.6)</td>
<td>269 (49.5)</td>
</tr>
<tr>
<td>&gt; 4 Years, n (%)</td>
<td>65 (35.5)</td>
<td>59 (32.1)</td>
<td>49 (27.8)</td>
<td>173 (31.9)</td>
</tr>
</tbody>
</table>

*Based on mITT population
Masupirdine: Primary Outcome, ADAS-Cog 11

p > 0.05; mITT: Modified Intent to Treat; EP: Evaluable Population
Masupirdine: Secondary Outcomes

**MMSE**
- Placebo: Mean change from baseline = 0.0
- Masupirdine 50 mg: Mean change from baseline = +0.2
- Masupirdine 100 mg: Mean change from baseline = +0.4

**ADCS-ADL 23**
- Placebo: Mean change from baseline = 0.0
- Masupirdine 50 mg: Mean change from baseline = -0.3
- Masupirdine 100 mg: Mean change from baseline = +1.6

**CDR-SB**
- Placebo: Mean change from baseline = 0.0
- Masupirdine 50 mg: Mean change from baseline = +0.1
- Masupirdine 100 mg: Mean change from baseline = -0.2

**NPI-12**
- Placebo: Mean change from baseline = 0.0
- Masupirdine 50 mg: Mean change from baseline = -1.2
- Masupirdine 100 mg: Mean change from baseline = -1.5

*p > 0.05; Evaluable Population*
Masupirdine: Safety and Tolerability

<table>
<thead>
<tr>
<th></th>
<th>Number (%) of Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
</tr>
<tr>
<td>Any TEAE</td>
<td>108 (57.4)</td>
</tr>
<tr>
<td>Any Treatment Related AE</td>
<td>21 (11.2)</td>
</tr>
<tr>
<td>Any Serious TEAE</td>
<td>12 (6.4)</td>
</tr>
<tr>
<td>Any Treatment Related SAE</td>
<td>0</td>
</tr>
<tr>
<td>Any TEAE Leading to Study Discontinuation</td>
<td>10 (5.3)</td>
</tr>
</tbody>
</table>

The most common treatment emergent AEs are urinary tract infection, headache, diarrhea and fall; occurred in more than 5% of subjects in any of the treatment arm.

Masupirdine is safe and well tolerated in moderate AD patients
Hypothesis-Generating Subgroup Analyses

Masupirdine: Effect on Cognition, ADAS-Cog 11

Memantine plasma concentrations ≤ 100 ng/mL

- Placebo
- Masupirdine 50 mg
- Masupirdine 100 mg

Findings suggest exploration of Masupirdine for the treatment of cognitive disorders in the absence of memantine treatment

Memantine use > 4 years

- Placebo
- Masupirdine 50 mg
- Masupirdine 100 mg

Evaluable Population
Hypothesis-Generating Subgroup Analyses

Masupirdine: Effect on NPI Domains

**Agitation/Aggression**

- **Placebo**
- **Masupirdine 50 mg**
- **Masupirdine 100 mg**

![Graph showing mean change from baseline for Agitation/Aggression](image)

<table>
<thead>
<tr>
<th>Weeks of treatment</th>
<th>Mean change from baseline</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>-1.3</td>
<td>0.034</td>
</tr>
<tr>
<td>13</td>
<td>-1.5</td>
<td>0.037</td>
</tr>
<tr>
<td>26</td>
<td>-1.5</td>
<td>0.064</td>
</tr>
</tbody>
</table>

Subjects with baseline agitation/aggression

**Delusions and Hallucinations**

- **Placebo**
- **Masupirdine 50 mg**
- **Masupirdine 100 mg**

![Graph showing mean change from baseline for Delusions and Hallucinations](image)

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</tr>
<tr>
<td>13</td>
<td>-1.5</td>
<td>0.086</td>
</tr>
<tr>
<td>26</td>
<td>-1.8</td>
<td>0.034</td>
</tr>
</tbody>
</table>

Subjects with baseline delusions and/or hallucinations or symptom emergence

Findings suggest exploration of Masupirdine in Behavioral and Psychological Symptoms of Dementia (BPSD)

Evaluable Population
Masupirdine: Summary and Conclusions

- First trial where 5-HT$_6$ antagonist was tested in combination with standard of care, donepezil and memantine.

- Masupirdine is safe and well tolerated.

- Masupirdine in combination with donepezil and memantine missed its primary endpoint.

- Hypothesis-generating observations emerged from the subgroup analyses of cognition and behavior assessment scales.
  - Potential beneficial effects of masupirdine on cognition emerged upon considering age, AD duration; memantine plasma concentrations and memantine regimen.
  - Beneficial effects of masupirdine were observed on several neuropsychiatric symptoms.
Acknowledgements

Sponsor wishes to thank all subjects, their family members and investigators participated in this masupirdine phase 2 POC study.
Masupiridine: Posters on Subgroup Analyses

Dec 4 - 5, 2019

P37: Subgroup analyses of memantine regimen, concentrations and duration of treatment

P38: Potential benefits on Behavioral and Psychological Symptoms (BPSD) in patients with moderate Alzheimer's disease

Dec 6 - 7, 2019

P180: Effect of AD duration since diagnosis on efficacy endpoints

P181: AD diagnosis duration in combination with memantine concentrations on masupiridine efficacy

P182: Subgroup analyses based on patient’s age and its effect on cognitive endpoints

P183: Baseline ADAS-Cog 11 scores and its effect on cognitive endpoints