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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12th Clinical Trials on Alzheimer's Disease (CTAD)
December 4-7, 2019

SUVEN Life Sciences

Presenter Disclosures

Dr. Cummings has provided consultation to Acadia, Actinogen, AgeneBio, Alkahest, Alzheon, Avanir, Axsome, Biogen, Cassava, Cerecin, Cerevel, Cognoptix, Cortexyme, EIP Pharma, Eisai, Foresight, Green Valley, Grifols, Hisun, Idorsia, Karuna, Nutricia, Orion, Otsuka, Probiodrug, QR, ReMYND, Resverlogix, Roche, Samumed, Samus, Signant 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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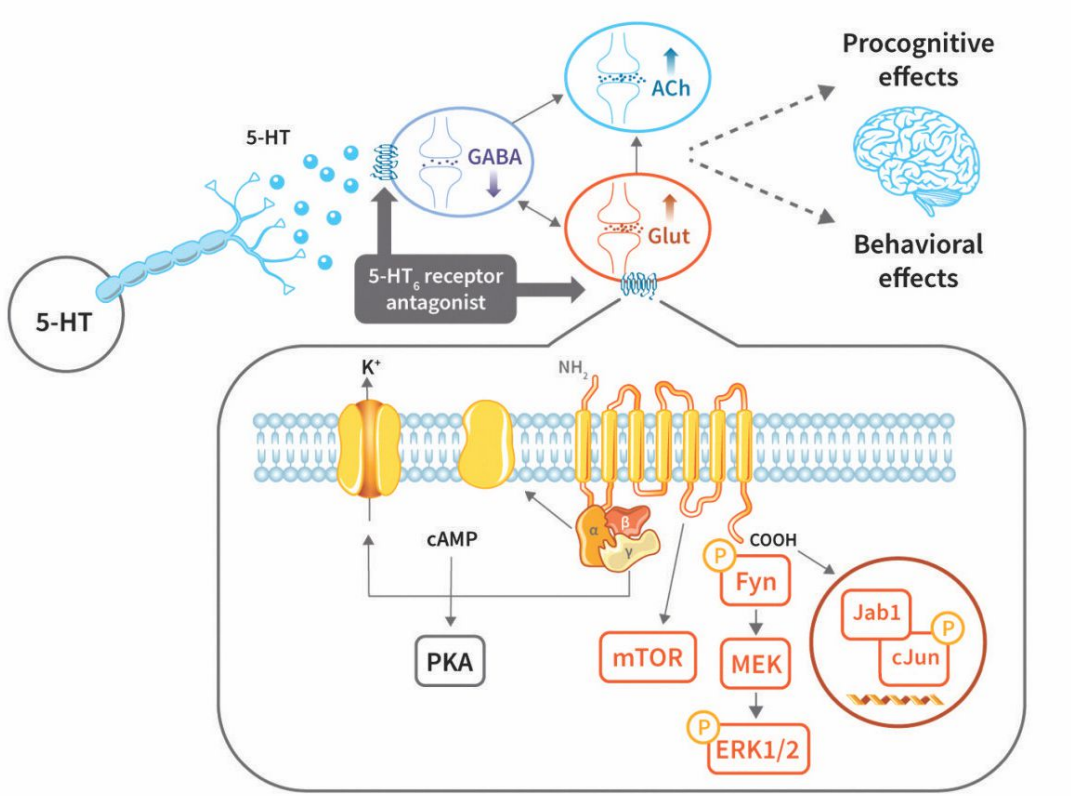
Dr. Cummings is supported by KMA; NIGMS grant P20GM109025; NINDS grant U01NS093334; and NIA grant R01AG053798.

This talk will include reference to unapproved medications and diagnostics.

5-HT_6 Receptor: Cognition and Behavior

- 5-HT_6 receptor is a G-protein coupled receptor mediating its effects through cAMP pathways; Ca^{2+} 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-HT_6 receptors modulate the release of neurotransmitters like acetylcholine, glutamate, GABA, dopamine and norepinephrine.[4,5]
- Non-clinical evidence for the potential role of 5-HT_6 receptor antagonists in reversing cognitive impairment.[6]



[1]Grimaldi *et al*., 1998; [2]Monsma *et al*., 1993; [3]Hirst *et al*., 2003; [4]Riemer *et al.,* 2003; [5]Dawson *et al.,* 2000; [6]Upton *et al.,* 2008

Masupirdine: Overview

Non-clinical

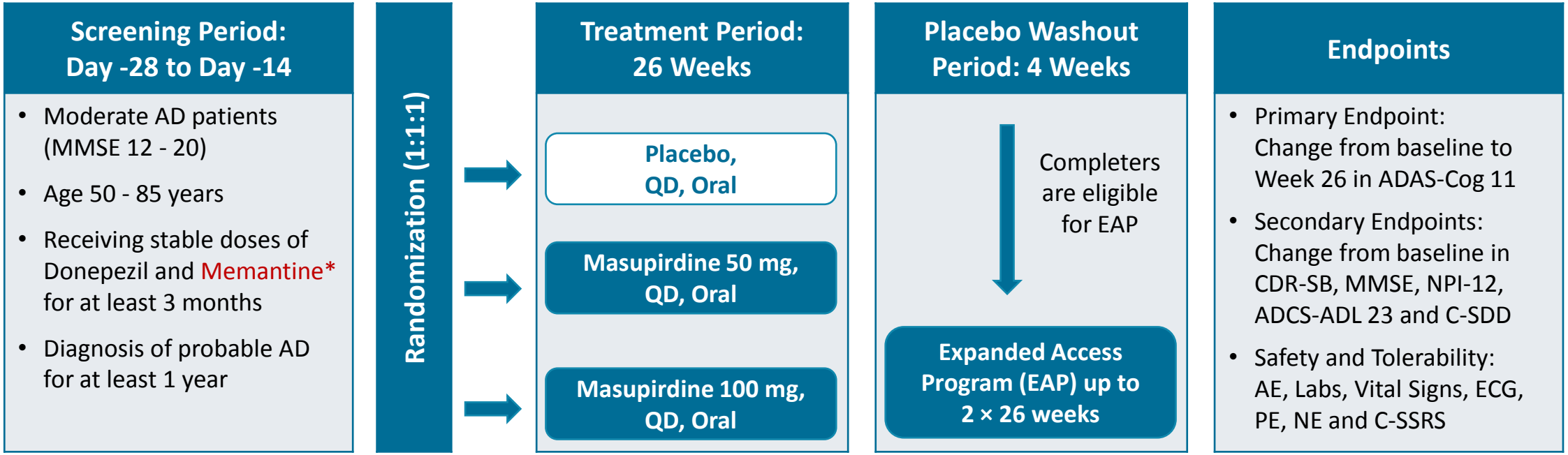
- Masupirdine is a pure 5-HT_6 receptor antagonist (>1200 fold selectivity over 5-HT_{2A} receptor)
- Robust efficacy for cognition in animal models
- Elevates brain acetylcholine levels and neural oscillatory pattern of theta rhythm
- Attenuates aggressive behavior in an animal model
- Wide margin of 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-HT_6 receptor antagonist, Masupirdine in combination with Donepezil and Memantine (Triple Therapy)



*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

Variables	Placebo	Masupirdine 50 mg	Masupirdine 100 mg	Total
Study Population				
Randomized with intent to treat, n	188	187	183	558
Safety Population, n (%)	188 (100)	187 (100)	181 (98.9)	556 (99.6)
Modified Intent to Treat, n (%)	183 (97.3)	184 (98.4)	176 (96.2)	543 (97.3)
Evaluable Population, n (%)	141 (75.0)	134 (71.7)	122 (66.7)	397 (71.1)
Demographics*				
Age in Years, Mean (SD)	72.9 (7.2)	73.4 (8.1)	74.4 (7.0)	73.6 (7.5)
BMI in Kg/m^2, Mean (SD)	26.4 (5.0)	26.6 (5.0)	26.9 (5.4)	26.6 (5.1)
Male, n (%)	77 (42.1)	89 (48.4)	80 (45.5)	246 (45.3)
White, n (%)	168 (91.8)	171 (92.9)	162 (92.0)	501 (92.3)
APO-E4 Carrier, n (%)	119 (65.0)	101 (54.8)	110 (62.5)	330 (60.8)

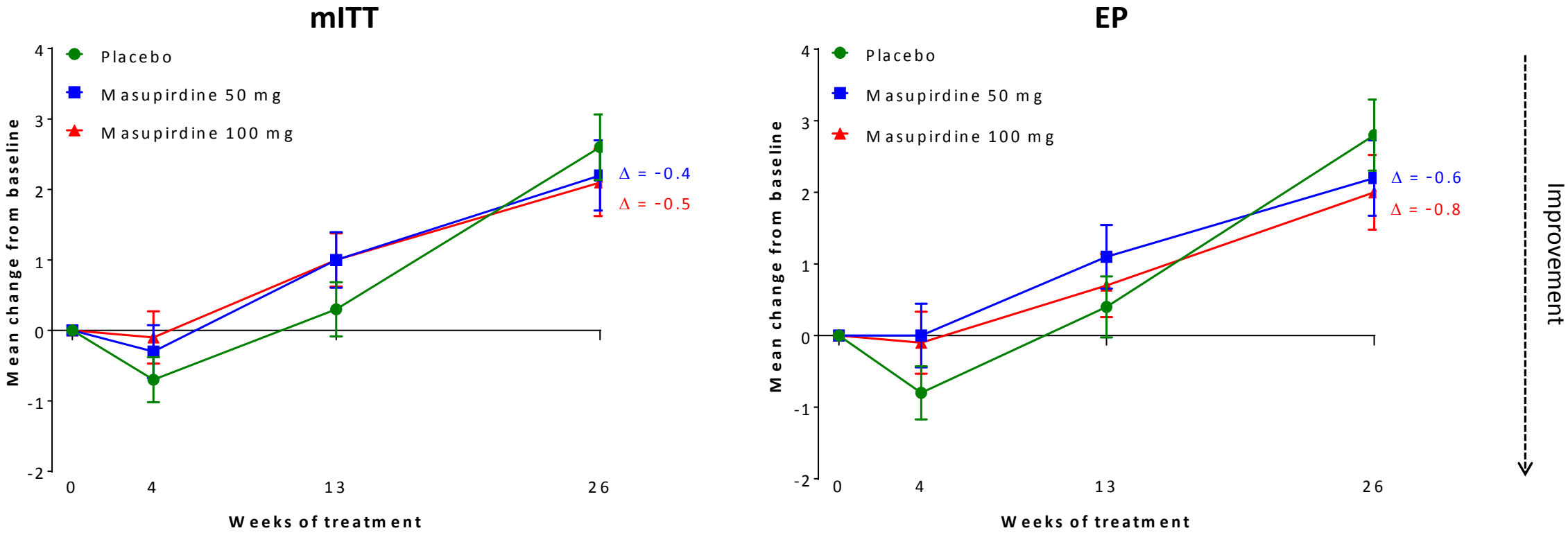
*Based on mITT (Modified Intent to Treat) population

Masupirdine: Baseline Characteristics

Variables*	Placebo	Masupirdine 50 mg	Masupirdine 100 mg	Total
	n=183	n=184	n=176	n=543
ADAS-Cog 11, Mean (SD)	28.4 (8.2)	27.7 (6.9)	27.9 (8.6)	28.0 (7.9)
MMSE, Mean (SD)	16.5 (2.5)	16.9 (2.2)	17.0 (2.5)	16.8 (2.4)
Memantine Regimen				
Memantine IR 10 mg, BID, n (%)	114 (62.3)	126 (68.5)	117 (66.5)	357 (65.7)
Namenda XR® 28 mg, QD, n (%)	38 (20.8)	27 (14.7)	32 (18.2)	97 (17.9)
Namzaric™ 28 mg, QD, n (%)	31 (16.9)	31 (16.8)	27 (15.3)	89 (16.4)
Memantine Use Duration				
> 3 Years, n (%)	36 (19.7)	32 (17.4)	29 (16.5)	97 (17.9)
> 4 Years, n (%)	21 (11.5)	18 (9.8)	21 (11.9)	60 (11.0)
AD Diagnosis Duration				
> 3 Years, n (%)	95 (51.9)	92 (50.0)	82 (46.6)	269 (49.5)
> 4 Years, n (%)	65 (35.5)	59 (32.1)	49 (27.8)	173 (31.9)

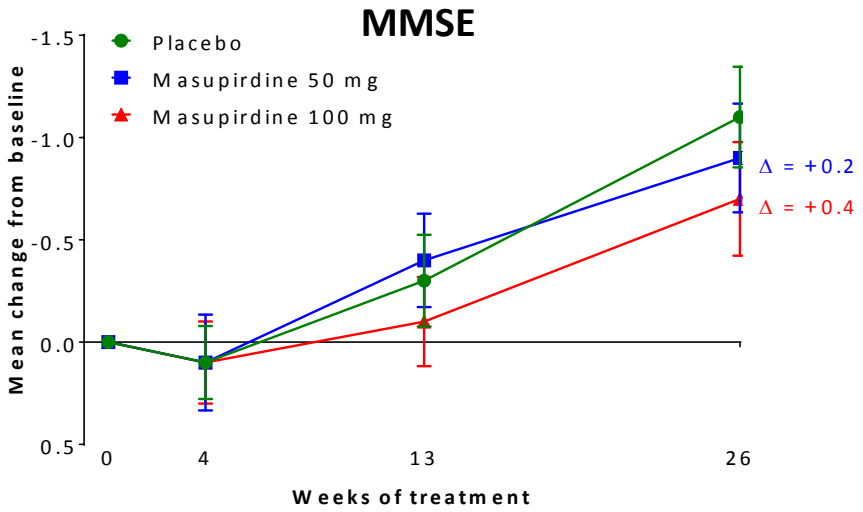
*Based on mITT population

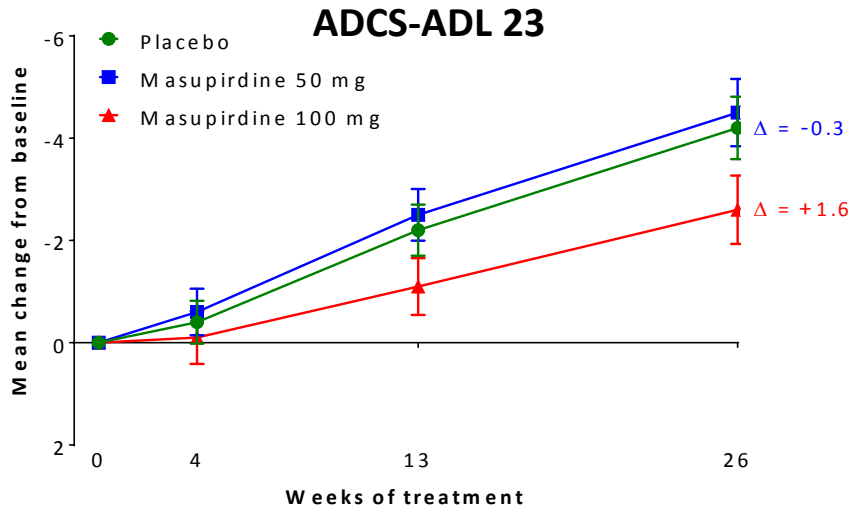
Masupirdine: Primary Outcome, ADAS-Cog 11

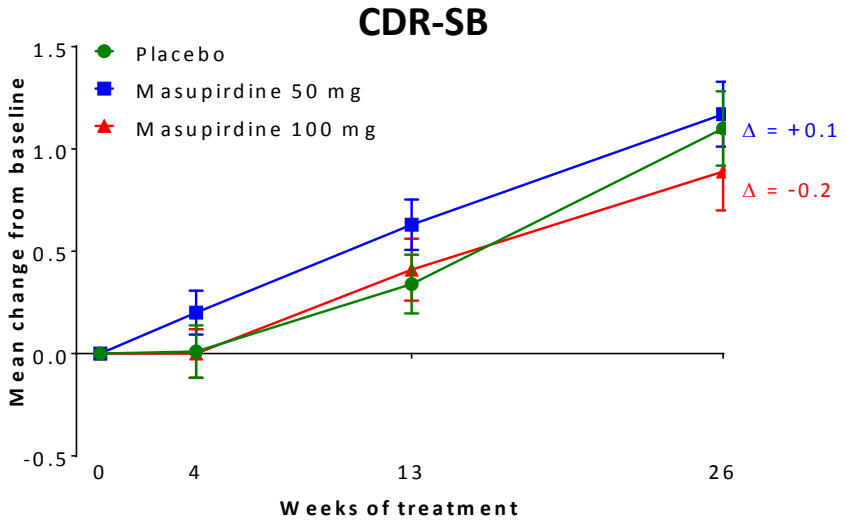


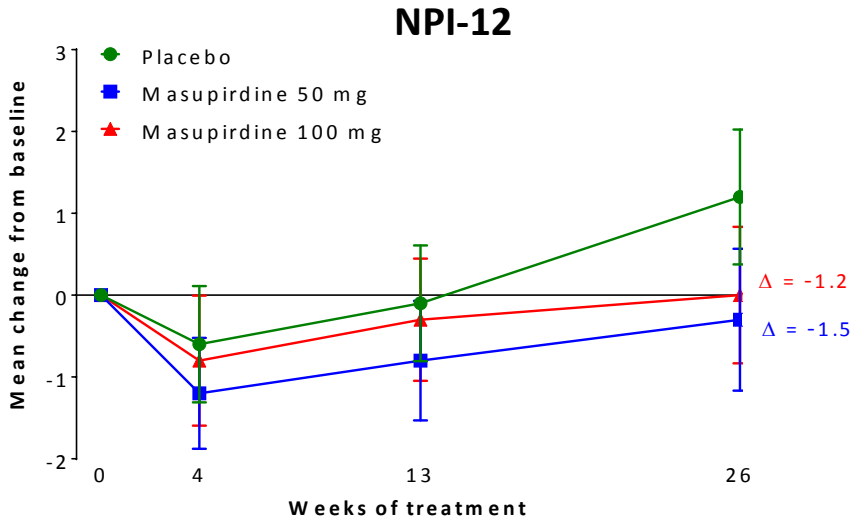
p > 0.05; mITT: Modified Intent to Treat; EP: Evaluable Population

Masupirdine: Secondary Outcomes









Improvement

p > 0.05; Evaluable Population

Masupirdine: Safety and Tolerability

	Number (%) of Subjects			
	Placebo	Masupirdine 50 mg	Masupirdine 100 mg	Total
Any TEAE	108 (57.4)	101 (54.0)	107 (59.1)	316 (56.8)
Any Treatment Related AE	21 (11.2)	29 (15.5)	38 (21.0)	88 (15.8)
Any Serious TEAE	12 (6.4)	10 (5.3)	14 (7.7)	36 (6.5)
Any Treatment Related SAE	0	1 (0.5)	1 (0.6)	2 (0.4)
Any TEAE Leading to Study Discontinuation	10 (5.3)	14 (7.5)	19 (10.5)	43 (7.7)

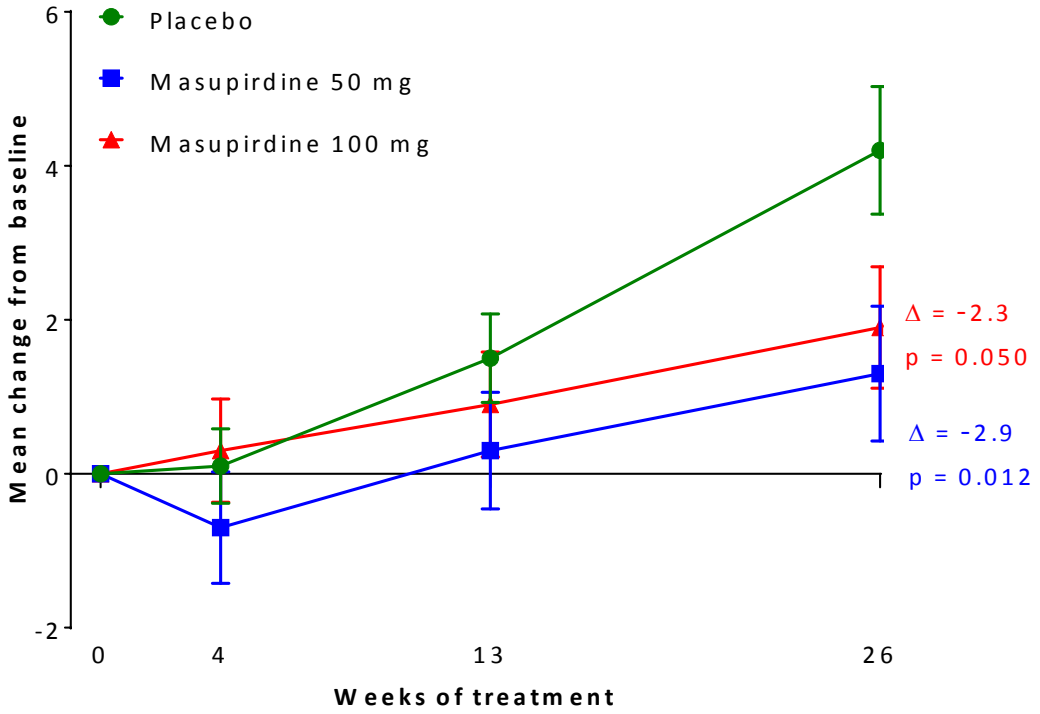
The most common treatment emergent AEs are urinary tract infection, headache, diarrhea and fall; occurred in more than 5% of subjects in any of the treatment arm.

Masupirdine is safe and well tolerated in moderate AD patients

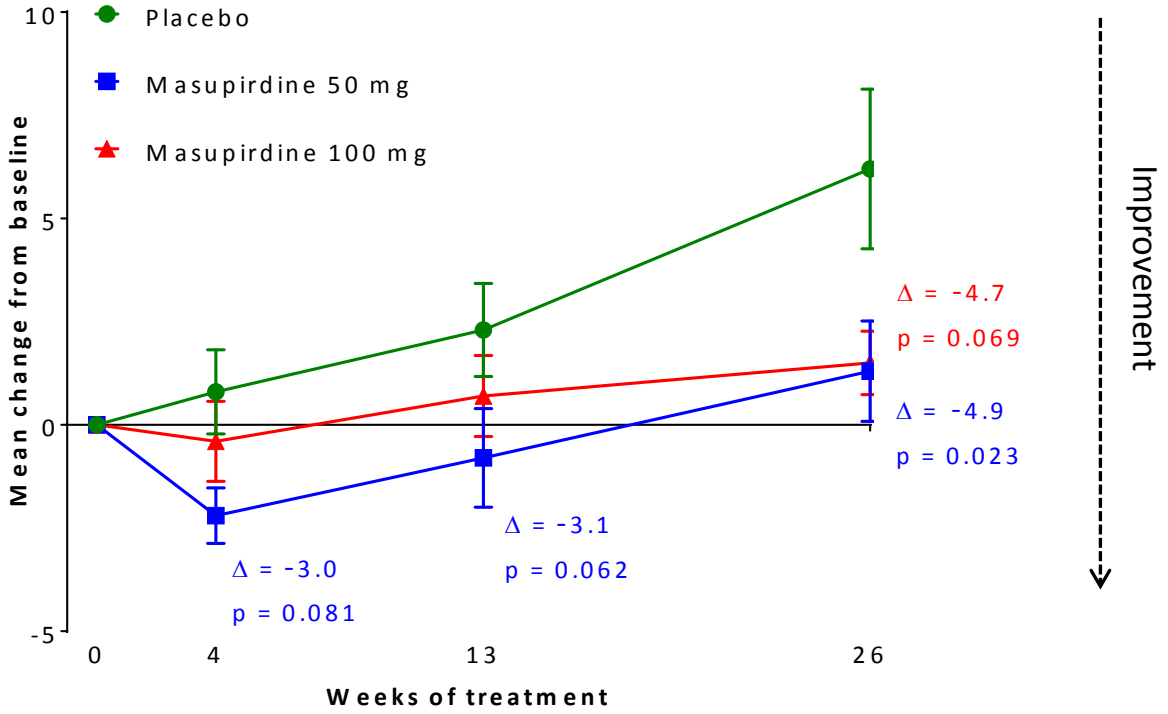
Hypothesis-Generating Subgroup Analyses

Masupirdine: Effect on Cognition, ADAS-Cog 11

Memantine plasma concentrations ≤ 100 ng/mL



Memantine use > 4 years



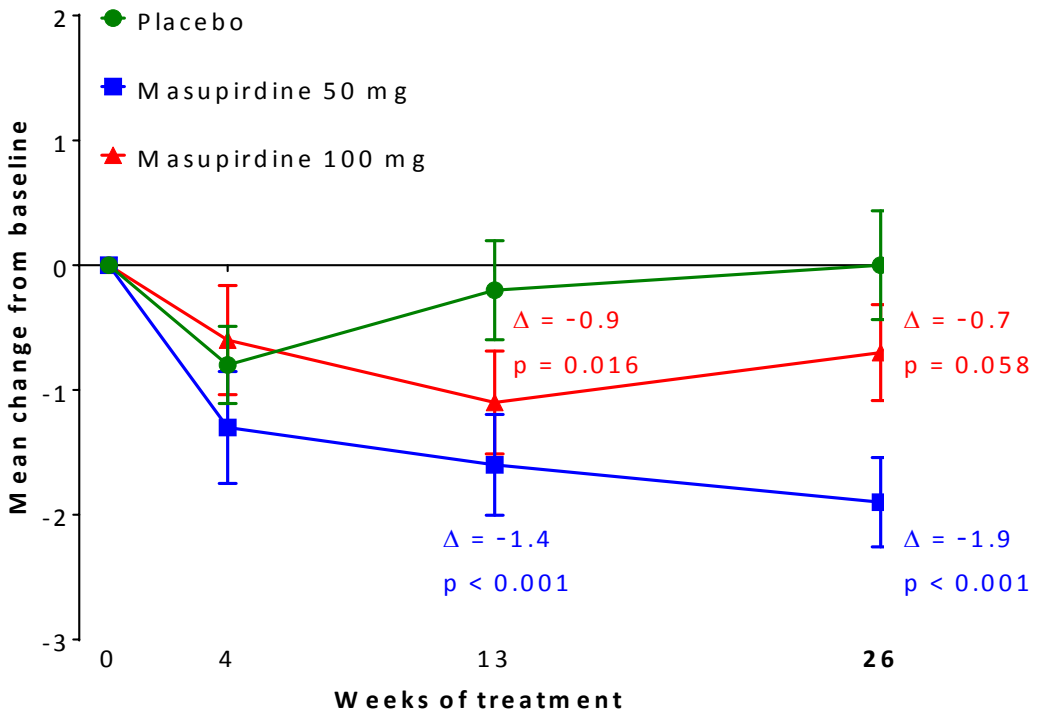
Findings suggest exploration of Masupirdine for the treatment of cognitive disorders in the absence of memantine treatment

Evaluable Population

Hypothesis-Generating Subgroup Analyses

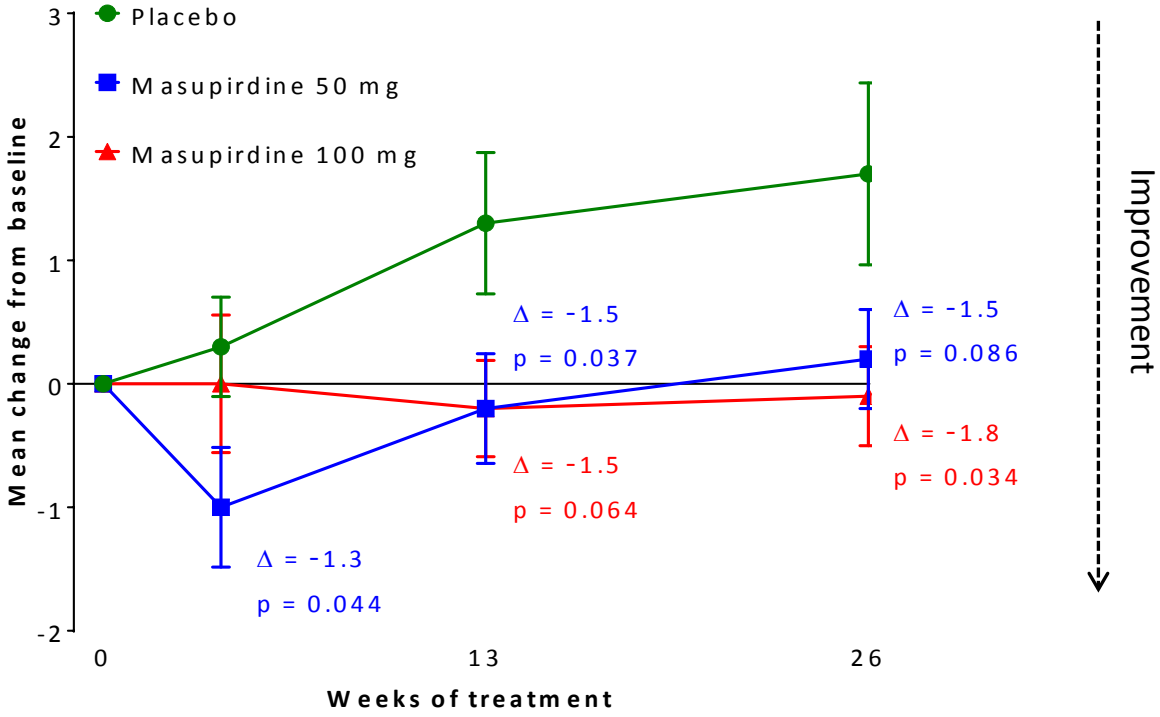
Masupirdine: Effect on NPI Domains

Agitation/Aggression



Subjects with baseline agitation/aggression

Delusions and Hallucinations



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.

Masupirdine: 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 masupirdine 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