Masupirdine (SUVN-502), 5-HT_6 Receptor Antagonist for the Potential Treatment of Cognitive Deficits in Alzheimer's Disease

Additional Clinical Study in Planning

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Masupirdine: Summary From Phase-2 Study

- ✓ **First trial where 5-HT_6 antagonist was tested in combination with donepezil and memantine as triple therapy.**
- ✓ Exploratory analysis of primary and secondary outcomes to assess potential effects of memantine regimen and memantine plasma concentrations suggested several interesting potential signals for differential effects favoring masupirdine treatment.
- ✓ In participants whose memantine plasma concentrations were ≤100 ng/mL at Week 26, there was lesser cognitive decline in participants taking masupirdine than in those on placebo. In participants taking masupirdine daily, there were congruent signals of benefit for masupirdine on cognition and behavioral symptoms of AD.

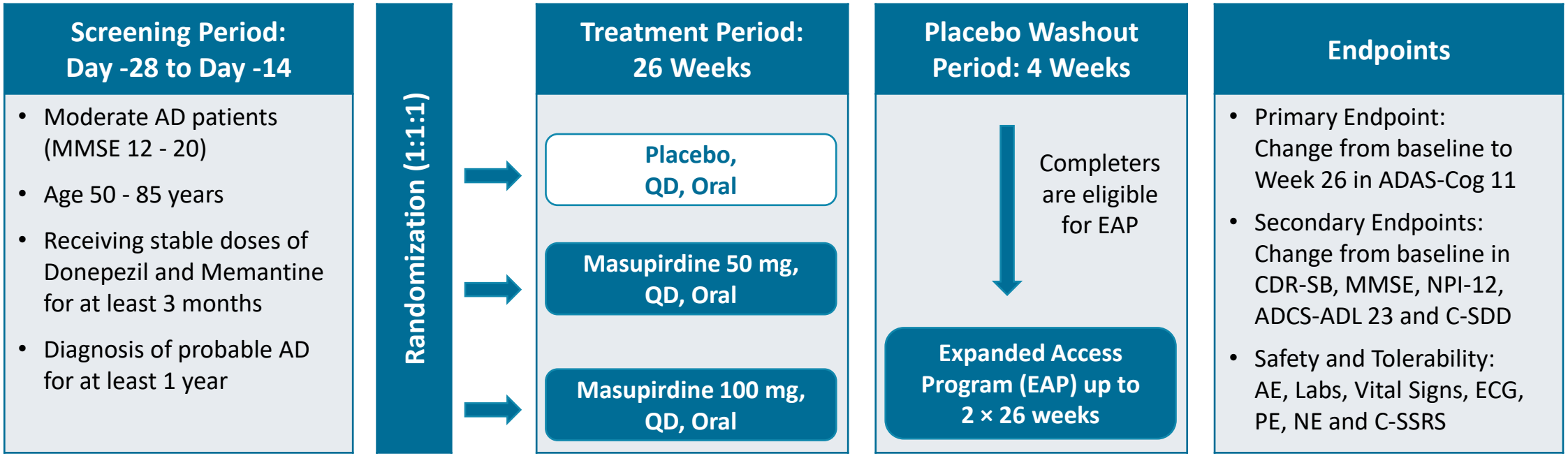
Clinicaltrials.gov: NCT02580305

Masupirdine: Pharmacological Characterization

- A Pure 5-HT_6 receptor antagonist with >1200 fold selectivity over 5-HT_{2A} receptor
- Robust efficacy on cognition in animal models
- Elevates brain acetylcholine levels and neural oscillatory pattern of theta rhythm
- Has a wide margin of safety in long-term animal studies
- Good safety and tolerability profile following single or repeated administration in healthy humans
- Food, gender and age has no effects on human pharmacokinetics
- Has suitable pharmacokinetics 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 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

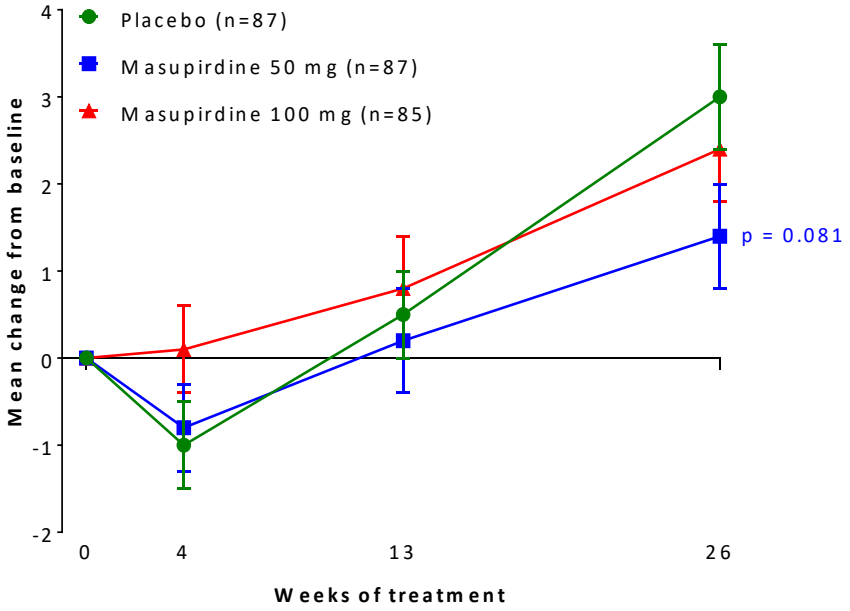
Study End Point Assessment

Assessment of the impact of memantine background therapy on efficacy of masupirdine, based on primary (ADAS-Cog 11) and secondary (ADCS-ADL 23, MMSE, CDR-SB and NPI-12) outcome measures from Phase-2 PoC study was carried out.

Phase-2 PoC study has been completed in patients with moderate Alzheimer's disease (AD). Masupirdine Phase-2 study was an unique triple-therapy design, first of its kind, focused on moderate AD patients who were on background treatment with donepezil and memantine.

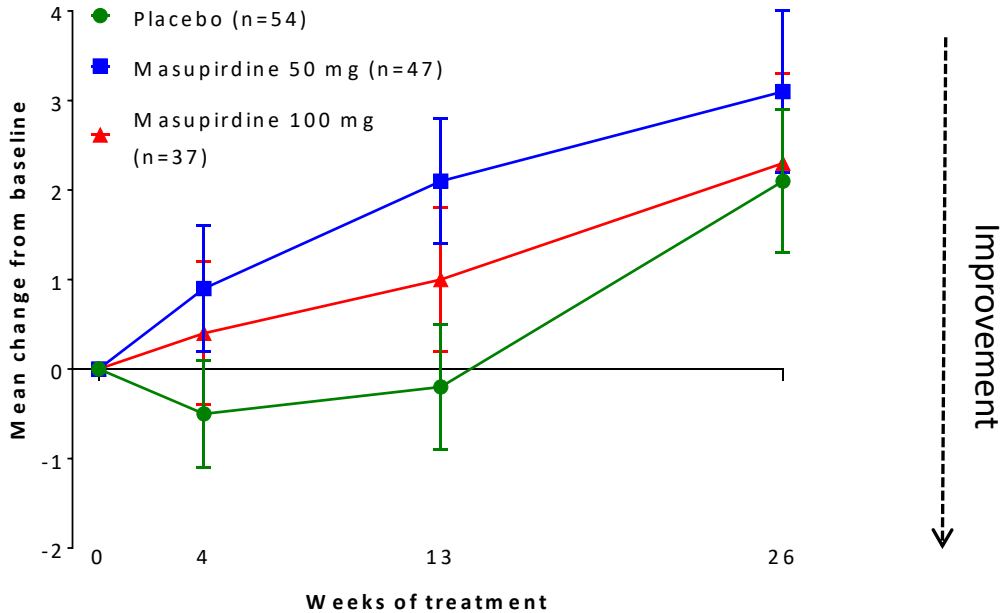
Masupirdine: ADAS-Cog 11 Scores by *Concomitant Medication*

Memantine IR (10 mg, BID)*



	Point change from Placebo		
	Week 4	Week 13	Week 26
Masupirdine 50 mg	0.2	-0.2	-1.5 (Cohen's *d* = 0.21)
Masupirdine 100 mg	1.0	0.4	-0.6 (Cohen's *d* = 0.16)

Namenda XR* or Namzaric (28 mg, QD)

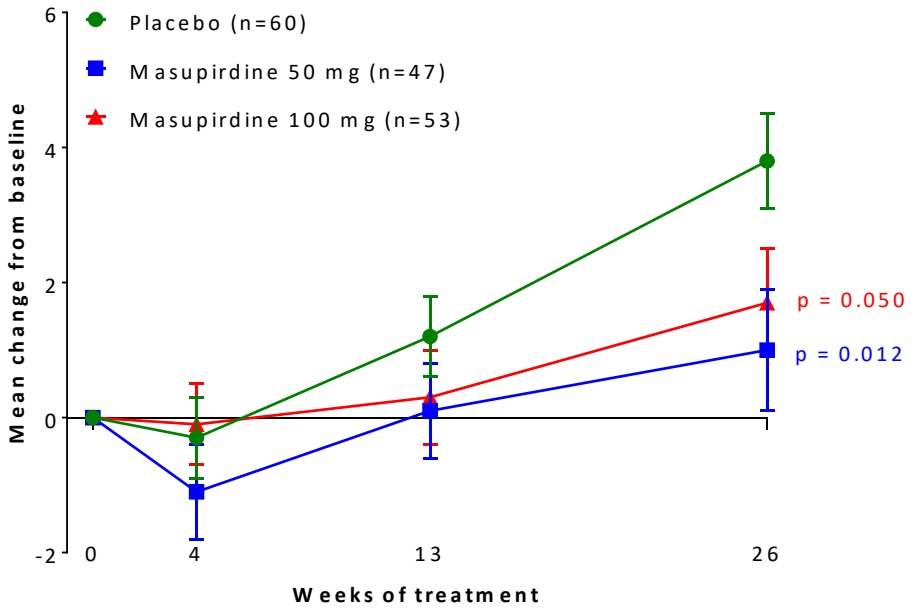


	Point change from Placebo		
	Week 4	Week 13	Week 26
Masupirdine 50 mg	1.5	2.3	1.0
Masupirdine 100 mg	0.9	1.3	0.1

Evaluable Population; * In combination with donepezil

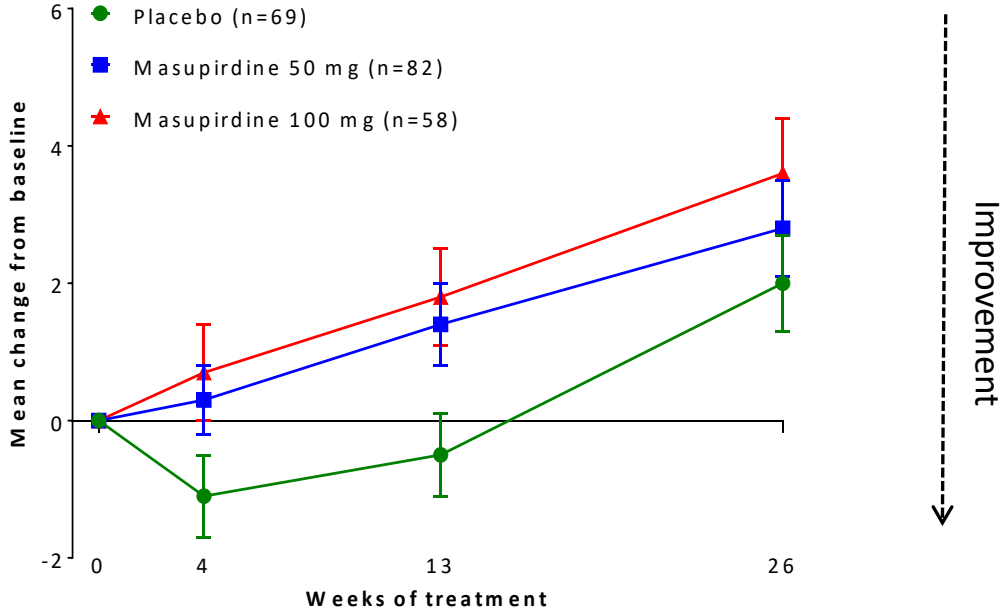
Masupirdine: ADAS-Cog 11 Scores by *Memantine Concentrations*

Memantine plasma concentrations ≤ 100 ng/mL



	Point change from Placebo		
	Week 4	Week 13	Week 26
Masupirdine 50 mg	-0.9	-1.1	-2.8 (Cohen's *d* = 0.47)
Masupirdine 100 mg	0.2	-0.9	-2.1 (Cohen's *d* = 0.38)

Memantine plasma concentrations >100 ng/mL



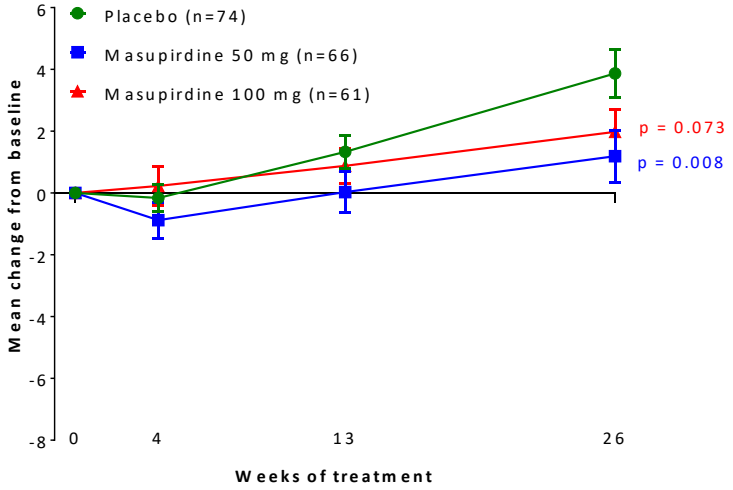
	Point change from Placebo		
	Week 4	Week 13	Week 26
Masupirdine 50 mg	1.4	1.9	0.8
Masupirdine 100 mg	1.8	2.2	1.6

Evaluable Population

Masupirdine: ADAS-Cog 11 Scores by *Memantine Concentrations*

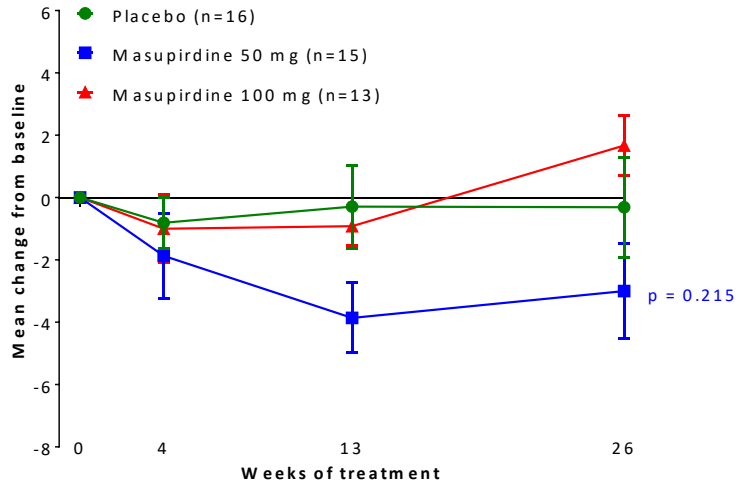
Memantine plasma concentrations at Week 26

≤ 100 ng/mL



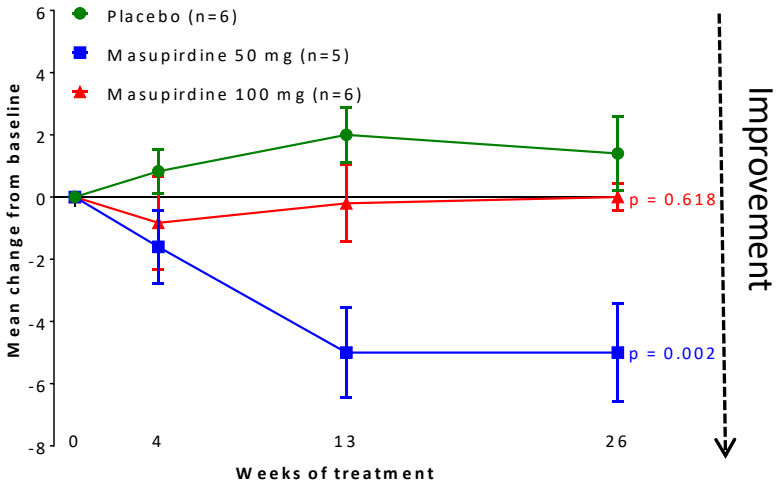
	Point change from Placebo		
	Week 4	Week 13	Week 26
Masupirdine 50 mg	-0.7	-1.3	-2.7 (Cohen's *d* = 0.42)
Masupirdine 100 mg	0.4	-0.5	-1.9 (Cohen's *d* = 0.31)

≤ 50 ng/mL



	Point change from Placebo		
	Week 4	Week 13	Week 26
Masupirdine 50 mg	-1.1	-3.6	-2.7 (Cohen's *d* = 0.48)
Masupirdine 100 mg	-0.19	-0.63	2.0

≤ 25 ng/mL

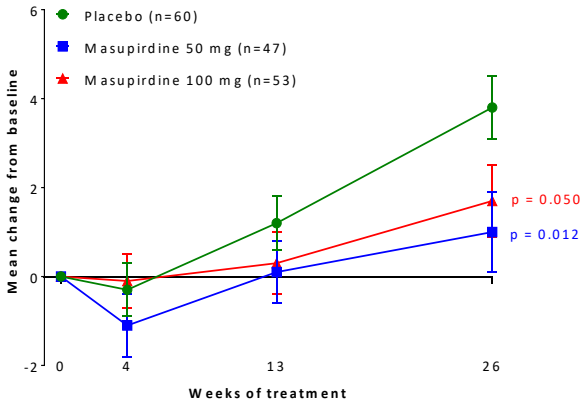


	Point change from Placebo		
	Week 4	Week 13	Week 26
Masupirdine 50 mg	-2.4	-7.0	-6.4 (Cohen's *d* = 2.18)
Masupirdine 100 mg	-1.7	-2.2	-1.4 (Cohen's *d* = 0.69)

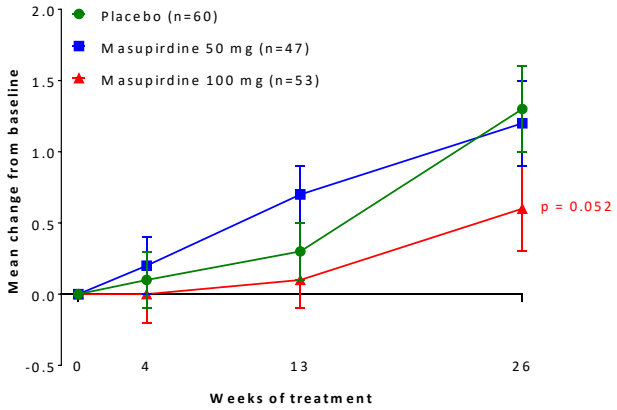
Effect of masupirdine increased with decreasing memantine concentrations

Masupirdine: Outcomes with *Memantine Concentrations**

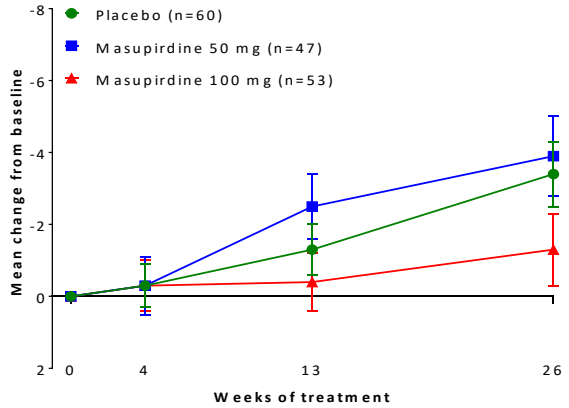
ADAS-Cog 11



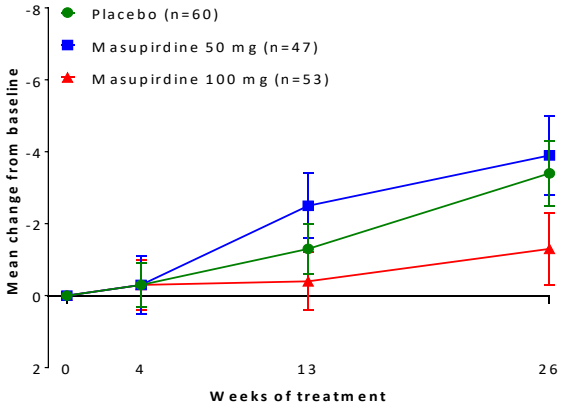
MMSE



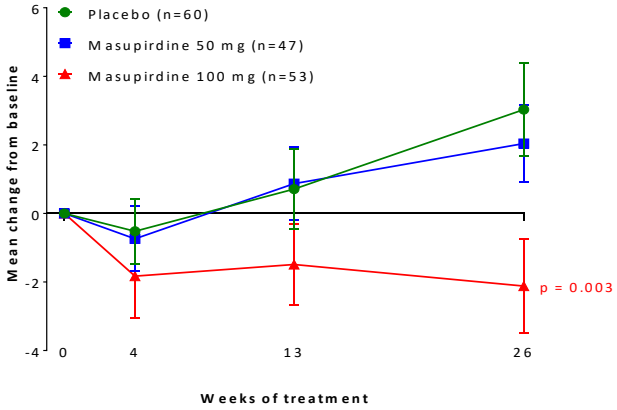
CDR-SB



ADCS-ADL



NPI-12



Improvement

Beneficial effects of masupirdine on cognition and behavioral symptoms of AD

* Subject with Memantine Concentration ≤ 100 ng/mL at Week 26

Masupirdine: ADAS-Cog 11 Scores by *Memantine Concentrations*

Responder Analysis[#] (Subject with Memantine Concentration ≤ 100 ng/mL at Week 26)

Treatment	Week 4		Week 13		Week 26	
	% Responder	p- value*	% Responder	p- value*	% Responder	p- value*
Placebo	62	-	40	-	25	-
Masupirdine 50 mg	70	0.356	53	0.174	49	**0.010**
Masupirdine 100 mg	55	0.455	47	0.443	47	**0.014**
Masupirdine 50 mg + 100 mg	62	0.967	50	0.307	48	**0.004**

[#] Subjects who did not deteriorate on ADAS-Cog 11 at Week 26 are considered as responders

*Chi-square test

Masupirdine: Summary and Conclusions

- ✓ **First trial where 5-HT_6 antagonist was tested in combination with donepezil and memantine as add-on triple therapy.**
- ✓ Exploratory analysis of primary and secondary outcomes to assess potential effects of memantine regimen and memantine plasma concentrations suggested the possibility for several interesting potential signals for differential effects favoring masupirdine treatment.
- ✓ In participants whose memantine plasma concentrations were ≤100 ng/mL at Week 26, there was lesser cognitive decline in participants taking masupirdine than in those on placebo. In participants taking masupirdine daily, there were congruent signals of benefit for masupirdine on cognition and behavioral symptoms of AD.
- ✓ These exploratory and thought provoking observations merit better understanding and further possible investigations of masupirdine effects and its role as a potential future drug in the AD pharmaceutical armamentarium.