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

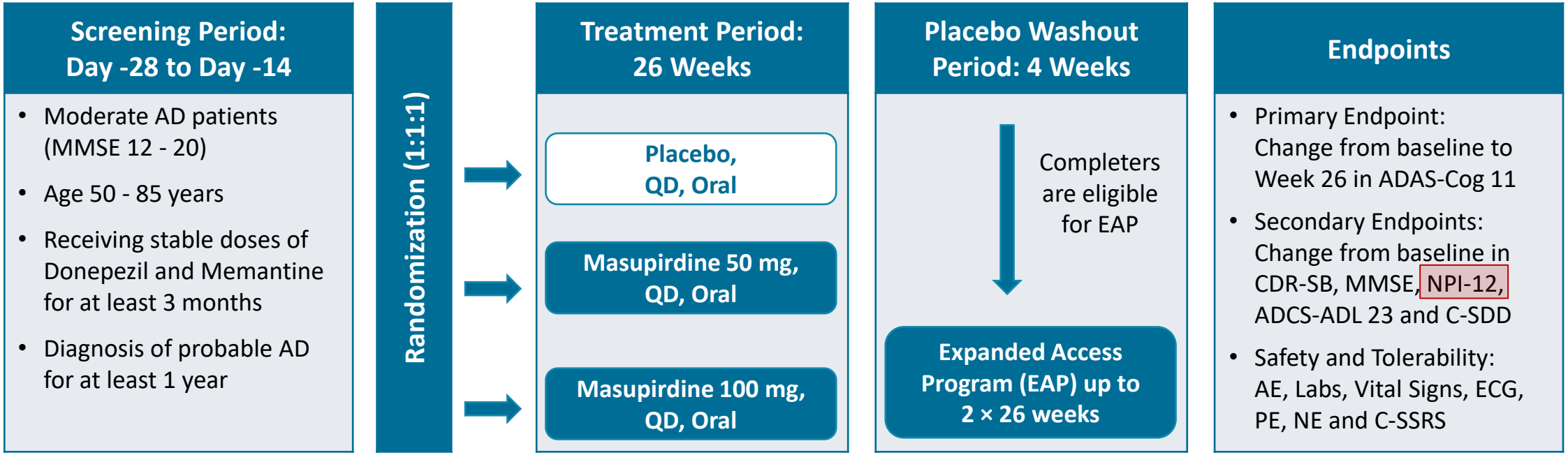
Clinicaltrials.gov: NCT02580305

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-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.

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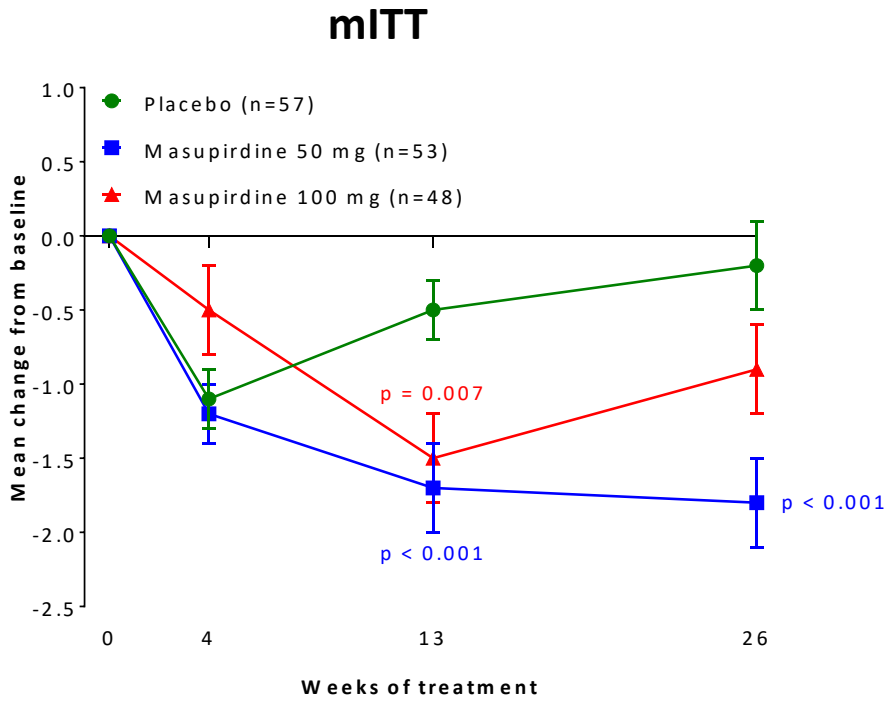
Study Endpoint Assessment

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)

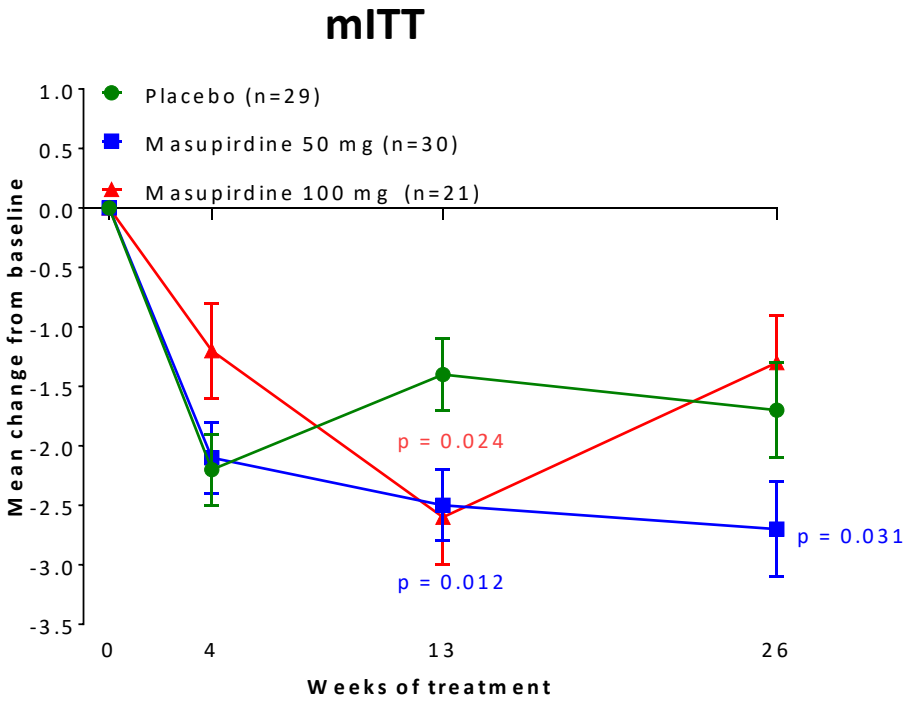
- Analysis population comprised of patients who had baseline NPI agitation/aggression score
- Mean baseline NPI agitation/aggression score was approximately 3
- Effects observed with masupirdine, 50 mg at week 13 & 26 is statistically significant compared to placebo
- Effect size (Cohen's *d*) observed 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



	Point change from Placebo		
	Week 4	Week 13	Week 26
Masupirdine 50 mg	0.0	-1.2	-1.5
Masupirdine 100 mg	0.7	-1.0	-0.6

Masupirdine: Agitation/Aggression (Baseline ≥ 3)

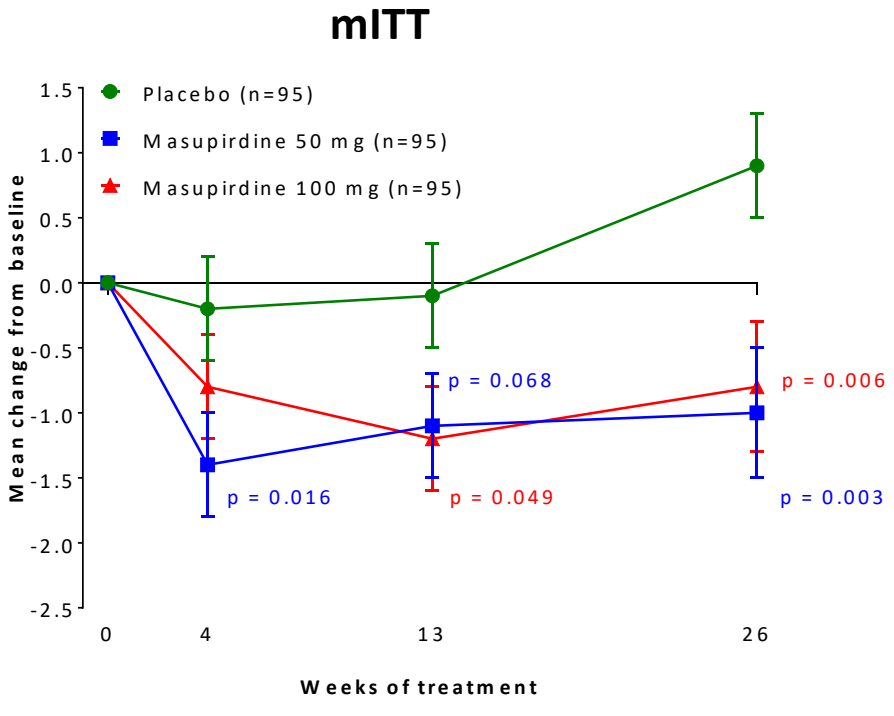
- Analysis population comprised of patients who had baseline NPI agitation/aggression score (≥ 3)
- Mean baseline NPI agitation/aggression score was approximately 4
- Significant effect of masupirdine 50 mg was observed from week 13
- Effect size (Cohen's *d*) observed in the masupirdine 50 mg treatment 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



	Point change from Placebo		
	Week 4	Week 13	Week 26
Masupirdine 50 mg	0.2	-1.2	-1.1
Masupirdine 100 mg	1.0	-1.2	0.3

Masupirdine: Agitation/Aggression (Composite Score)

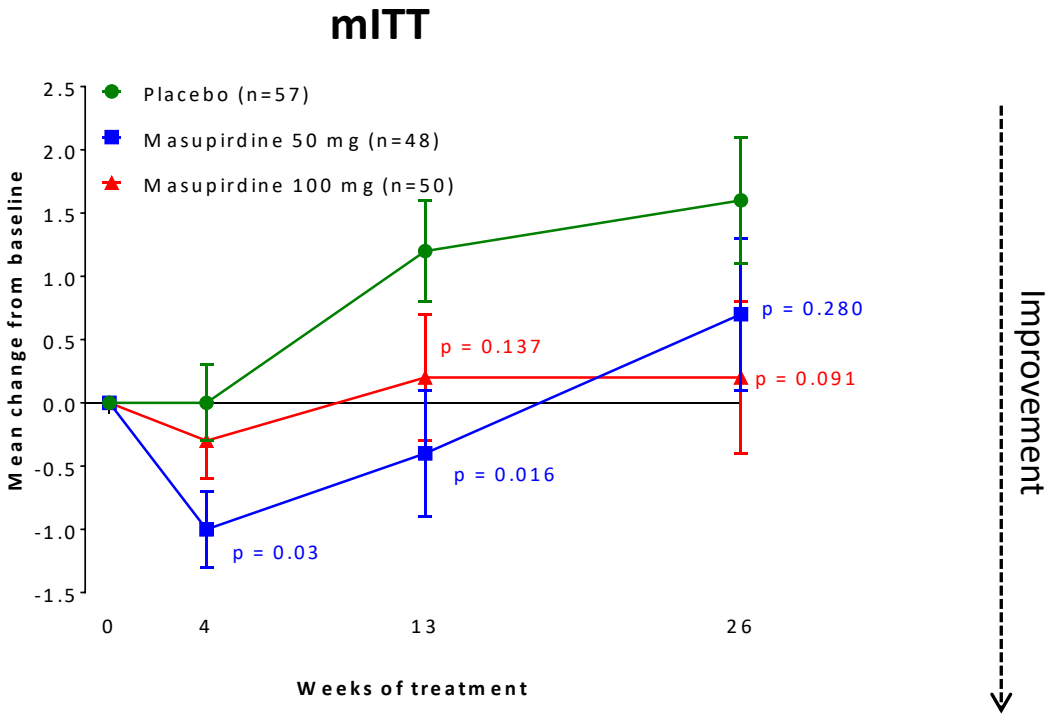
- Combined score of agitation/aggression, aberrant motor behavior and sleep and nighttime behavior disorders (baseline ≥ 1)
- Masupirdine attenuated symptoms in several domains which are commonly observed in patients with AD related to agitation/aggression
- Effect size (Cohen's *d*) observed with masupirdine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



	Point change from Placebo		
	Week 4	Week 13	Week 26
Masupirdine 50 mg	-1.2	-1.0	-1.9
Masupirdine 100 mg	0.6	-1.1	-1.7

Masupirdine: Delusions and/or Hallucinations

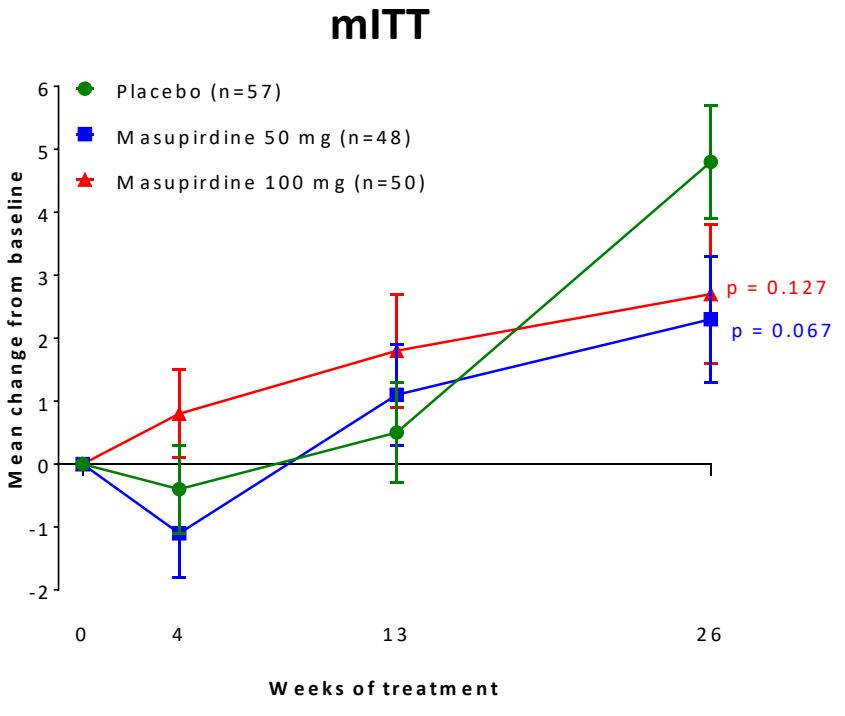
- Analysis population comprised of patients who had baseline delusions and/or hallucinations or symptom emergence
- Significant effect of masupirdine 50 mg was observed from week 4
- Effect size (Cohen's *d*) observed with masupirdine treatment is 0.31 - 0.58 and 0.24 - 0.35 at the end of 13 and 26 weeks,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



	Point change from Placebo		
	Week 4	Week 13	Week 26
Masupirdine 50 mg	-1.0	-1.5	-0.9
Masupirdine 100 mg	-0.3	-1.0	-1.4

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



	Point change from Placebo		
	Week 4	Week 13	Week 26
Masupirdine 50 mg	-0.7	0.6	-2.5
Masupirdine 100 mg	1.2	1.3	-2.1

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