Usmarapride (SUVN-D4010), 5-HT_4 Receptor Partial Agonist for the Treatment of Cognitive Disorders

Phase-2 Ready Clinical Candidate

SUVEN Life Sciences

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Usmarapride: Non-Clinical Overview

- Orally bioavailable with good brain penetration
- Good correlation between affinity, free fraction and efficacy
- Clean in hERG and phospholipidosis assays
- No adverse effects on ECG in dog telemetry study
- Robust efficacy in animal models of cognition and depression
- Increases neuro-protective sAPP levels in rat brain showing disease modifying potential for Alzheimer's disease (AD)
- Increases acetylcholine levels in the brain demonstrating neurochemical basis for symptomatic benefits in disorders associated with cognitive deficits
- Well tolerated in 6 months rat and 9 months dog toxicity studies with wide margin of safety
- No genotoxic or teratogenicity liability

Usmarapride: Clinical Overview (Phase-1)

- Safe and well tolerated in healthy subjects (adult male, female, and elderly)
- Excellent human pharmacokinetics suitable for once a day oral treatment
- Dose proportional increase in exposures at steady state
- Steady state concentrations were attained on the third day after once a day oral dosing
- Food, gender and age has no effects on human pharmacokinetics of Usmarapride

Clinicaltrials.gov: NCT02575482 and NCT03031574

Usmarapride: Medicinal Chemistry & Intellectual Property

Medicinal Chemistry

Usmarapride is innovatively designed, best in class clinical candidate

- BCS class I non-hygroscopic crystalline oxalate salt
- Favorable physicochemical and biopharmaceutical properties
- Log P, 2.9 and pKa, 8.4

Intellectual Property

- Patents have been granted in all major world markets

Usmarapride: *In Vitro* Efficacy

In Vitro Potency and Selectivity

- Showed binding affinity (K_i) of 23.9 nM in radioligand binding assay with EC_{50} of 32.0 nM (E_{max}: 69%) towards 5-HT_4 receptor when tested in cell based reporter gene assay
- Devoid of species difference in *in vitro* functional activity (EC_{50}) between rat and human
- No significant difference in *in vitro* functional activity between 5-HT_4 isoforms A, D and E
- Showed minimal binding at 1 µM for over 70 target sites including GPCRs, transporters, ion channels, peptides, steroids, second messengers, growth factors and prostaglandins

Usmarapride: ADME Profile

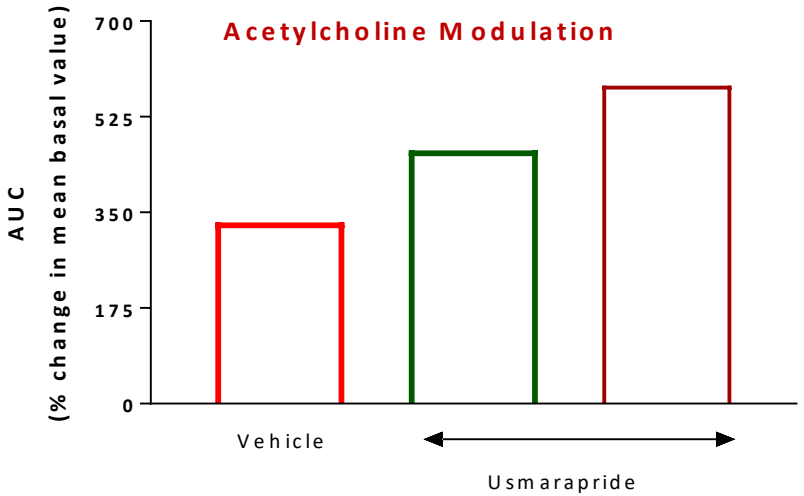
In Vitro

- Highly permeable across the Caco-2 monolayer and is not a P-gp substrate
- Moderately bound to plasma proteins. Metabolism low in human, moderate in rat and dog, high in monkey.
- Does not inhibit CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4 enzymes in pooled human liver microsomes
- Metabolism is mediated through CYP3A4 enzyme
- Does not induce enzymes CYP1A2, CYP2B6 and CYP3A4 at tested concentrations
- Likelihood of drug-drug interaction potential of SUVN-D4010 as an inhibitor/ inducer is remote
- Metabolites observed in plasma and urine collected from a phase-1 clinical trial were comparable with circulatory metabolites in rat and dog suggesting "No unique metabolite formation in humans"

In Vivo

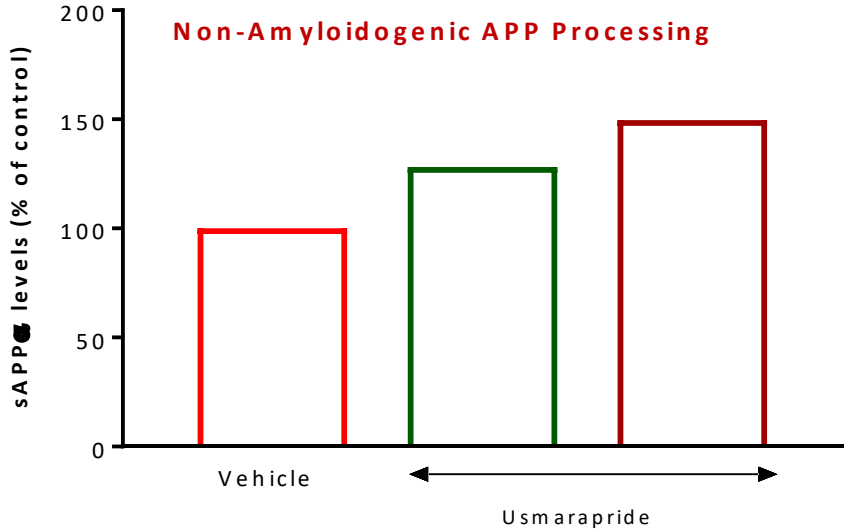
- Usmarapride on oral administrations in rat and dog showed rapid absorption with oral bioavailability of 30 and 72 % respectively
- Showed excellent brain to plasma ratio (C_{brain}/C_{plasma} = 4.76) with adequate CSF concentrations in rat

Usmarapride: Key Biology Results



Dose-dependent increase in acetylcholine levels

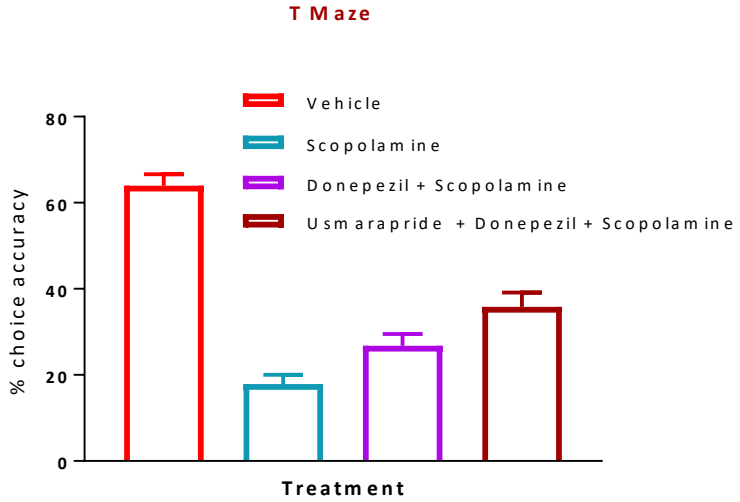
Usmarapride increases neurotransmitter acetylcholine dose dependently; Neurochemical basis for pro-cognitive activity



Dose-dependent increase in cortical sAPPα

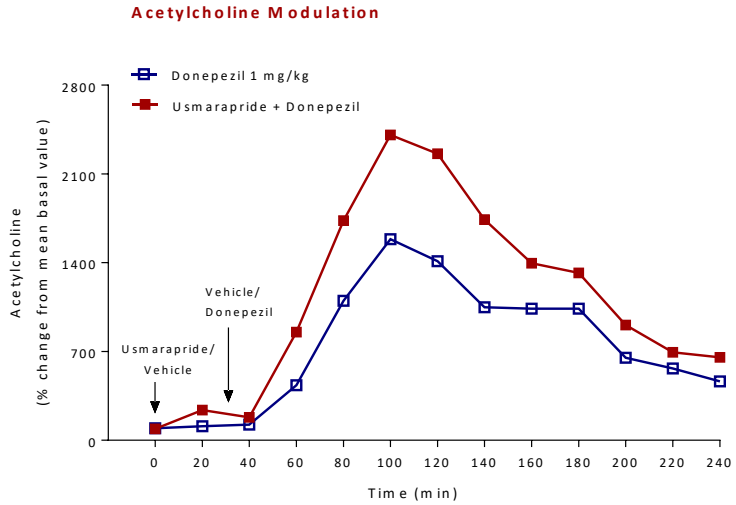
Usmarapride increases sAPPα dose dependently; Neurochemical basis for disease modifying effects in Alzheimer's disease

Usmarapride: Key Biology Results



Potentiation of current Standard Of Care (SOC)

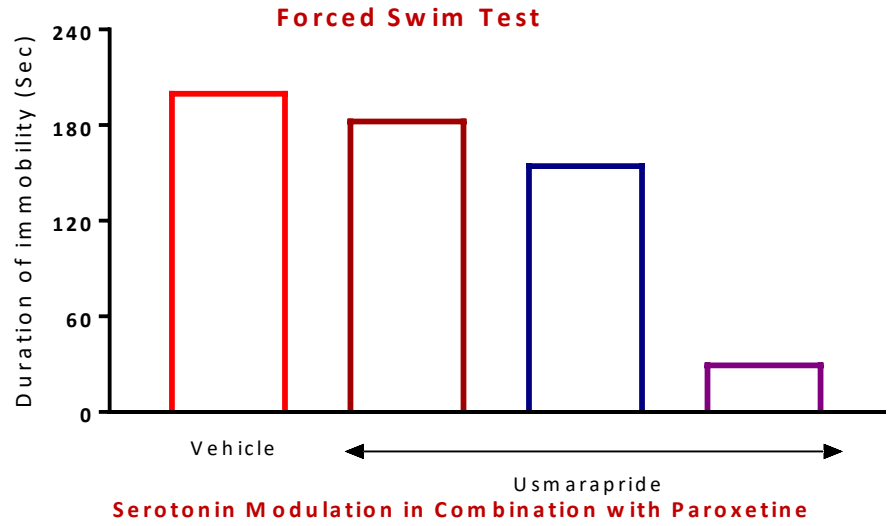
Pro-cognitive effects of **donepezil** were potentiated dose dependently by Usmarapride in behavioral animal models

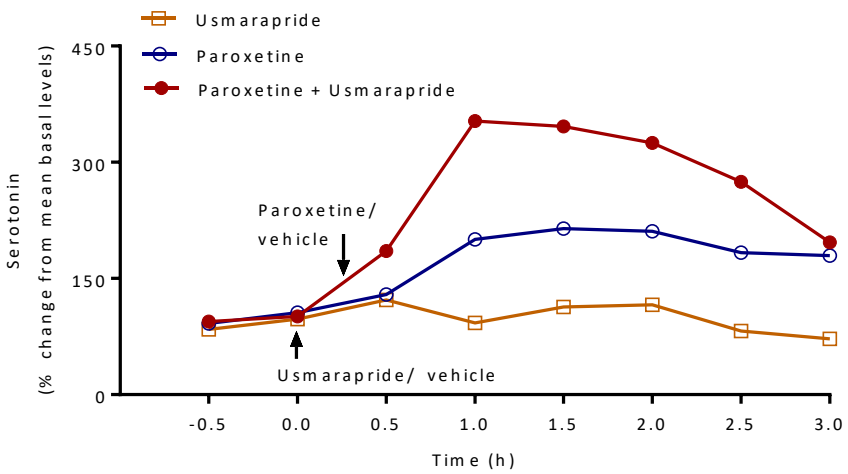


Potentiation of current SOC

Usmarapride significantly increased effects of **donepezil** evoked acetylcholine levels

Usmarapride: Key Biology Results





Antidepressant like effects in preclinical models

A value addition in therapy for Alzheimer's disease

Potentiation in effects of current antidepressants

May address the co-morbid depressive symptoms in AD patients

Usmarapride: Summary of Safety Pharmacology

CNS Safety

- No neurotoxic effects in rats (modified Irwin's test)
- No CNS stimulant or depressant effects in rats (Open field assay)
- No effect on motor co-ordination in rats (Rotarod test)
- No effect on sensory motor gating in rats (Acoustic startle response)

Cardiovascular Safety

- No QT/QTc prolongation up to highest tested dose in freely moving conscious dogs
- Blood pressure (Mean arterial, systolic and diastolic): No effects in conscious dogs or, in anaesthetized guinea pigs

Respiratory Safety

- No significant effect on respiratory parameters in rats

Gastrointestinal Safety

- No significant effect on gastrointestinal system

Usmarapride: Summary of Non-Clinical Safety

Non-Clinical Safety Evaluation

- Usmarapride was well tolerated in 6 months rat and 9 months dog toxicity studies and demonstrated wide margin of safety
- Usmarapride is non-mutagenic in bacterial reverse mutation (AMES) test and non-clastogenic in *in vitro* chromosomal aberration test in human lymphocytes. Usmarapride is also found to be negative in *in vivo* micronucleus test in mice
- Usmarapride did not show teratogenic potential when tested in rats and rabbits

Usmarapride: Chemistry, Manufacturing and Controls (CMC)

Drug Substance (DS)

- Well optimized six step scale up process with cost effective commercially available raw materials.
- Manufactured in 5 kg and 10 kg batches in a class 100,000 area for stability , Phase-1 clinical studies and long term animal safety evaluations.
- DS is stable for 6 months under accelerated conditions, 1 year under intermediate conditions, and 5 years under long term storage conditions.

Drug Product (DP)

- Usmarapride IR tablets were developed and manufactured for in cGMP facility for clinical studies. A batch size of more than 100,000 tablets can be manufactured with no change in process for Phase-2 POC study.
- Usmarapride tablets disintegrate within 5 minutes. In dissolution testing, more than 80% of Usmarapride was released within 15 minutes.
- Usmarapride IR tablets are stable for up to tested 48 months at long term storage conditions.

Usmarapride: Clinical Profile (Phase-1)

Usmarapride has been evaluated in Phase-1 clinical studies for its safety, tolerability, and pharmacokinetics evaluation (US-IND; NCT02575482) following single or multiple oral administrations in healthy subjects.

Effect of food, gender and age on the pharmacokinetics of Usmarapride was also evaluated in healthy subjects (US-IND; NCT03031574)

- Well tolerated in young male/ female and elderly subjects. There were neither treatment emergent serious adverse events (SAEs) reported by any subject nor any subject withdrawn from the study
- Excellent human pharmacokinetics for once a day oral dosing
- Attained steady state within 3 days on repeated administrations
- No significant accumulation upon multiple administrations
- Projected human efficacy concentrations are achieved
- Food, gender and age has no effect of on human pharmacokinetics
- Active IND at US FDA