SUVN-D4010, 5-HT$_4$ Receptor Partial Agonist for the Treatment of Cognitive Disorders

Phase-2 Ready Clinical Candidate
SUVN-D4010: 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
SUVN-D4010: 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 SUVN-D4010

Clinicaltrials.gov: NCT02575482 and NCT03031574
**SUVN-D4010: Medicinal Chemistry & Intellectual Property**

**Medicinal Chemistry**

SUVN-D4010 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.
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 ($E_{\text{max}}$: 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.
SUVN-D4010: 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

• SUVN-D4010 on oral administrations in rat and dog showed rapid absorption with oral bioavailability of 30 and 72 % respectively.
• Showed excellent brain to plasma ratio ($C_{\text{brain}}/C_{\text{plasma}} = 4.76$) with adequate CSF concentrations in rat.
**SUVN-D4010: Key Biology Results**

### Dose-dependent increase in acetylcholine levels

SUVN-D4010 increases neurotransmitter acetylcholine dose dependently; Neurochemical basis for pro-cognitive activity

### Dose-dependent increase in cortical sAPPα

SUVN-D4010 increases sAPPα dose dependently; Neurochemical basis for disease modifying effects in Alzheimer’s disease
Potentiation of current Standard Of Care (SOC)

Pro-cognitive effects of donepezil were potentiated dose dependently by SUVN-D4010 in behavioral animal models.

Potentiation of current SOC

SUVN-D4010 significantly increased effects of donepezil evoked acetylcholine levels.
**SUVN-D4010: 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
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
SUVN-D4010: Summary of Non-Clinical Safety

Non-Clinical Safety Evaluation

• SUVN-D4010 was well tolerated in 6 months rat and 9 months dog toxicity studies and demonstrated wide margin of safety.

• SUVN-D4010 is non-mutagenic in bacterial reverse mutation (AMES) test and non-clastogenic in *in vitro* chromosomal aberration test in human lymphocytes. SUVN-D4010 is also found to be negative in *in vivo* micronucleus test in mice.

• SUVN-D4010 did not show teratogenic potential when tested in rats and rabbits.
SUVN-D4010: 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)**

- SUVN-D4010, 15,000 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.
- SUVN-D4010 tablets disintegrate within 5 minutes. In dissolution testing, more than 80% of SUVN-D4010 was released within 15 minutes.
- SUVN-D4010 IR tablets are stable for up to tested 48 months at long term storage conditions.
SUVN-D4010 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 SUVN-D4010 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