SUVN-911, α4β2 Receptor Antagonist for the Treatment of Major Depressive Disorders

Phase-2 Ready Clinical Candidate

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SUVN-911: Non-Clinical Overview

- Novel, potent and selective α4β2 nicotinic acetylcholine receptor (nAChR) antagonist
- Demonstrated excellent ADME properties with no drug-drug interaction liability
- Excellent oral bioavailability and brain penetration
- Shows robust efficacy in various animal models of depression
- Robust increase in serotonin levels in cortex which may partly explain the antidepressant property
- Addresses major limitations of existing MDD therapeutics by offering rapid onset of action, procognitive effects and no sexual dysfunction
- Demonstrated excellent safety margin in all long term toxicity studies
- Non-mutagenic and non-clastogenic
- Non-teratogenic
SUVN-911: Clinical Overview

- Safe and well tolerated in healthy adult male subjects with dose dependent pharmacokinetics
- Projected human efficacy concentrations achieved in Phase-1 study
- Predictive biomarker available for clinical evaluation
- Food, gender and age has no effect on pharmacokinetics

Clinicaltrials.gov: NCT03155503 and NCT03551288
**SUQN-911: Medicinal Chemistry & Intellectual Property**

**Medicinal Chemistry**

SUQN-911 is innovatively designed, best in class clinical candidate.*

- BCS class I non-hygroscopic crystalline hydrochloride salt and stable in all storage conditions
- Favorable physicochemical and biopharmaceutical properties
- Log P and pKa values of 1.9 and 8.9 respectively

**Intellectual Property**

- Patents have been granted in all major world markets

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**SUVN-911: In Vitro Efficacy**

**In Vitro Potency and Selectivity**

- Effectively binds at α4β2 ion channel with a Ki value of 31.1 nM

- Exhibited dose dependent blockade of nAChR α4β2 receptor currents induced by acetylcholine in whole cell patch clamp assay exhibiting antagonist property

- No inter species variation in binding to α4β2 receptor from mouse, rat and human

- Exhibited ~ 130 fold selectivity towards α3β4 and has a minimal binding against over 70 target sites (at 10 µM) comprising GPCRs, transporters, brain/gut peptides, enzymes, kinases, prostaglandins, ion channels including closely related α-Bungarotoxin sensitive neuronal nicotinic acetylcholine receptors (α7)
SUVN-911: ADME Profile

- Has high permeability and is not a P-gp substrate
- Good unbound fractions in plasma and brain
- Moderate metabolism in rat, dog, monkey and human liver microsomes
- Well absorbed into systemic circulation with excellent oral bioavailability
- Good brain penetration (brain to plasma ratio ~ 2.0)
- No drug-drug interaction liability
- Similar metabolites across species (rat, dog and human) and no unique metabolite observed
SUVN-911: Key Biology Results

Receptor Occupancy

Dose-dependent receptor occupancy
Good correlation with unbound concentrations at target site

In Vivo Efficacy

Robust non-clinical efficacy
Marked antidepressant effects in forced swim test
**SUVN-911: Key Biology Results**

### Faster onset of action
Antidepressant effects within a week of treatment

### Basis for antidepressant effects
Modulation of cortical monoamines

**Dominant submissive assay**

**Serotonin Modulation**
**SUVN-911: Key Biology Results**

**Procognitive Effects**

*Promotes cognition*

A value addition in therapy for depressive disorders

**Acetylcholine Modulation**

*Basis for procognitive effects*

Modulation of cortical acetylcholine
**SUVN-911: Key Biology Results**

**Sexual Function**

- **No effects on sexual functions**
- Differentiated from conventional antidepressants

**Behavioral Sensitization**

- **No abuse or addiction liabilities**
- Well differentiated from nicotine
SUVN-911: Summary of Safety Pharmacology

CNS Safety

- No CNS stimulant or depressant effects upon repeated administration (Open field assay).
- No addiction liability (Behavioral sensitization assay).
- No effect on skeletal muscles (Rota rod assay).
- No significant effect in rats at therapeutic dose range (Modified Irwin’s test).

Cardiovascular Safety

- hERG channel: IC$_{50}$ value >10 μM in patch clamp assay.
- ECG (QT / QTc) & Blood pressure: No significant effect on the cardiovascular parameters in conscious dogs.

Respiratory Safety

- No significant effect on respiratory parameters in rats at therapeutic dose range.

Gastrointestinal Safety

- No significant effect on gastrointestinal system.
SUVN-911: Summary of Non-Clinical Safety

Non-Clinical Safety Evaluation

- The safety of SUVN-911 has been well established following single and repeat dose oral administration up to 28-day, 6-month and 9-month duration in mice, rats, and dogs, respectively; SUVN-911 has a wide margin of safety.

- SUVN-911 was found to be non-mutagenic and non-clastogenic in in-vitro/in-vivo genotoxicity studies.

- SUVN-911 did not show teratogenic potential when tested in rats and rabbits.
**SUVN-911: Clinical Profile (Phase-1)**

SUVN-911 has been evaluated for its safety, tolerability, and pharmacokinetics under US-IND (NCT03155503) following single and multiple oral administration in healthy subjects.

Effect of food, gender and age on the pharmacokinetics of SUVN-911 in healthy subjects has also been evaluated (NCT03551288).

- Well tolerated after single and multiple oral administrations up to 14 days
- No serious adverse events reported by any subject and no subject withdrawn from the study due to the treatment
- Rapid oral absorption
- Exposures in healthy subjects are more than dose proportional at tested doses
- Projected efficacious concentrations achieved in Phase-1 study
- Food, gender and age has no effects on human pharmacokinetics of SUVN-911
- Active IND at US FDA