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

Phase-2 Ready Clinical Candidate

SUVEN Life Sciences

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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

SUVN-911: Medicinal Chemistry & Intellectual Property

Medicinal Chemistry

SUVN-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

*Nirogi et al. , J. Med. Chem., 63, 2020, 2833-2853 (doi: 10.1021/acs.jmedchem.9b00790)

SUVN-911: *In Vitro* Efficacy

In Vitro Potency and Selectivity

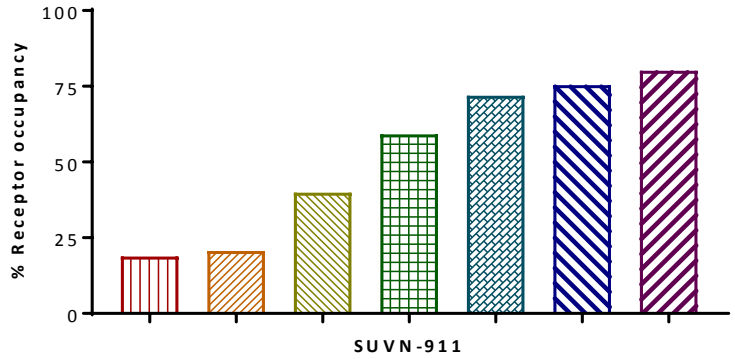
- Effectively binds at α4β2 ion channel with a Ki value of 31.1 nM
- Exhibited dose dependent blockade of nAChR α4β2 receptor currents induced by acetylcholine in whole cell patch clamp assay exhibiting antagonist property
- No inter species variation in binding to α4β2 receptor from mouse, rat and human
- 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

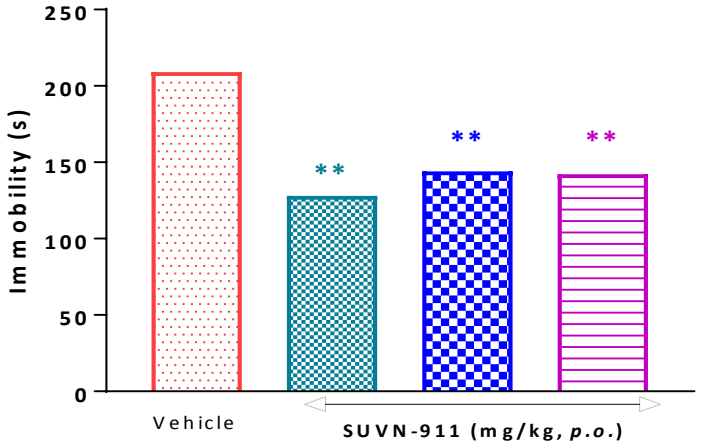
- Has high permeability and is not a P-gp substrate
- Good unbound fractions in plasma and brain
- Moderate metabolism in rat, dog, monkey and human liver microsomes
- Well absorbed into systemic circulation with excellent oral bioavailability
- Good brain penetration (brain to plasma ratio ~ 2.0)
- 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



In Vivo Efficacy



Dose-dependent receptor occupancy

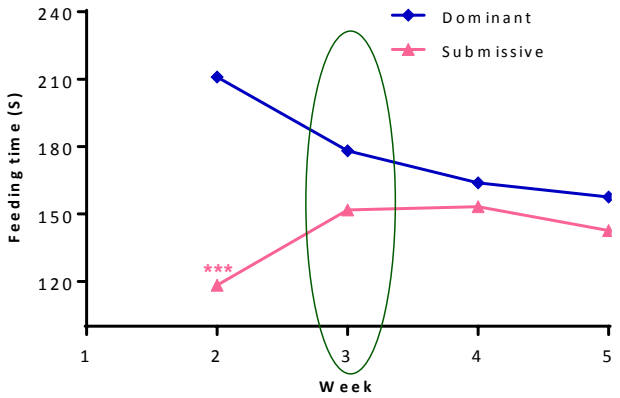
Good correlation with unbound concentrations at target site

Robust non-clinical efficacy

Marked antidepressant effects in forced swim test

SUVN-911: Key Biology Results

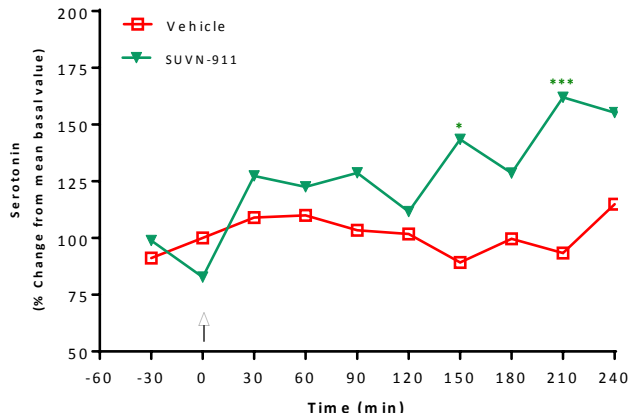
Dominant submissive assay



Faster onset of action

Antidepressant effects within a week of treatment

Serotonin Modulation

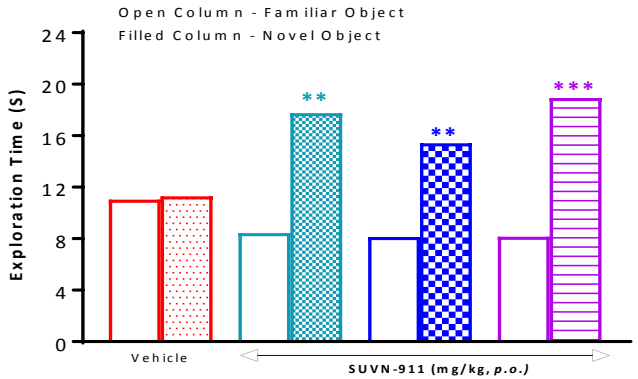


Basis for antidepressant effects

Modulation of cortical monoamines

SUVN-911: Key Biology Results

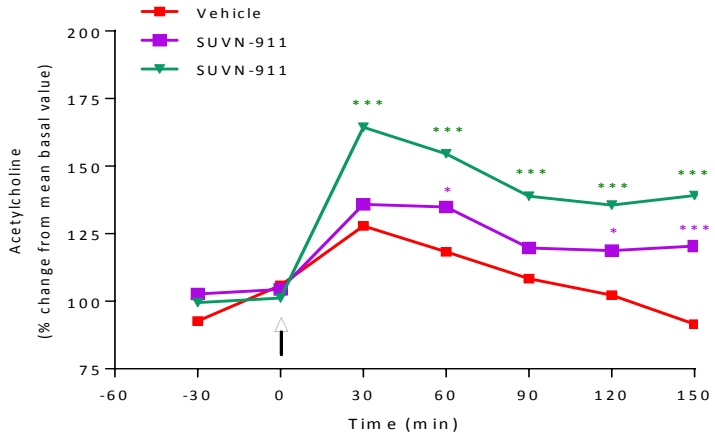
Procognitive Effects



Promotes cognition

A value addition in therapy for depressive disorders

Acetylcholine Modulation

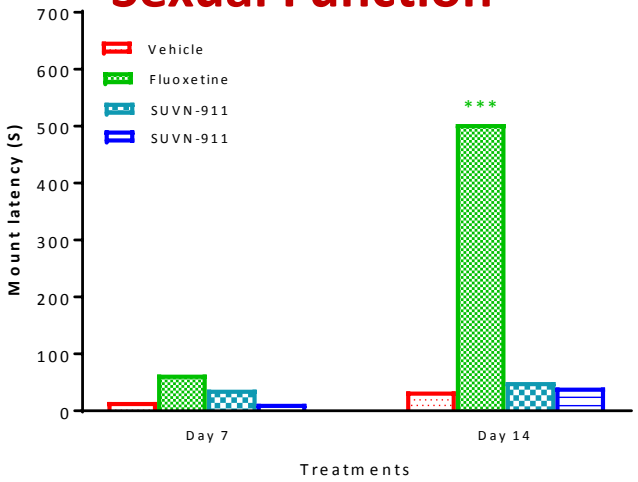


Basis for procognitive effects

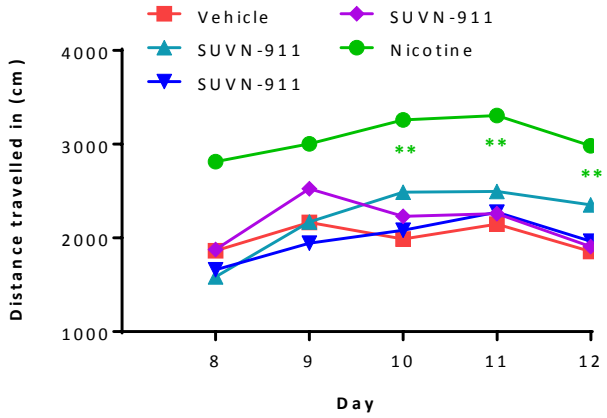
Modulation of cortical acetylcholine

SUVN-911: Key Biology Results

Sexual Function



Behavioral Sensitization



No effects on sexual functions

Differentiated from conventional antidepressants

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