SUVN-G3031, Histamine H3 Receptor Inverse Agonist for Potential Treatment of Cognitive Disorders

Phase-2 PoC Study in Planning

SUVEN Life Sciences

Suven Life Sciences Ltd
Serene Chambers, Road-5, Avenue-7, Banjara Hills,
Hyderabad-500 034, India.
Contacts: jasti@suven.com, nvsrk@suven.com

SUVN-G3031: Overview

- SUVN-G3031 is potent and selective histamine H3 receptor inverse agonist
- Efficacy has been established in non-clinical models related to cognition and neurochemistry
- Excellent ADME properties with no drug-drug interaction liability
- Neurochemistry and behavioral studies provide the support for therapeutic utility in the treatment of cognitive disorders
- Non-clinical safety studies supports clinical development
- Safe and well tolerated in healthy humans
- Steady-state concentrations reached on day-6 after QD dose
- Food, gender and age has no effect on pharmacokinetics (Phase-1 clinical study)

SUVN-G3031: Medicinal Chemistry & Intellectual Property

Medicinal Chemistry

SUVN-G3031 is innovatively designed, best in class clinical candidate.

- BCS class I non-hygroscopic crystalline dihydrochloride salt
- Favorable physicochemical and biopharmaceutical properties
- Log P, 2.2 and pKa, 5.1 and 8.7

Intellectual Property

- Patents have been granted in all major world markets.

*Nirogi et al. , J. Med. Chem. 2019, 62, 1203−1217 (DOI: 10.1021/acs.jmedchem.8b01280)

SUVN-G3031: *In Vitro* Profile

Assay	Results
Histamine H3 Binding K_i	8.7 nM (human) / 9.8 nM (rat)
Functional – $GTP_\gamma S$ IC_{50}	20 nM
Nature of Binding	Inverse agonist
I_{Kr} hERG Patch clamp assay (human)	IC_{50} >10 µM
Selectivity (70 target sites including receptors-49, enzymes-5, peptides-5, ion channels-7, steroids, second messengers growth factors and prostaglandins-4)	< 50% inhibition at 1 µM

Unlike competitor compounds no interspecies difference in binding to human and rat histamine H3 receptor

SUVN-G3031: ADME Profile

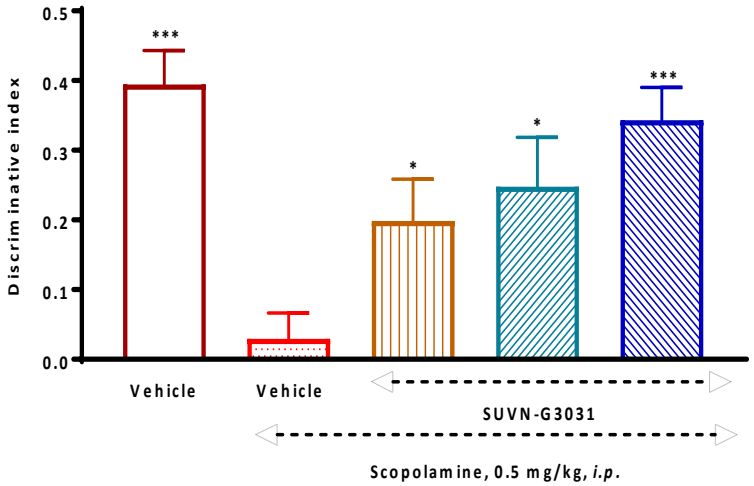
- Highly permeable
- Excellent oral exposure in non-clinical species
- Good brain penetrant and not a P-gp substrate
- High unbound fraction in plasma and brain
- Not an inducer or inhibitor of the CYP450 enzymes
- Metabolite profiles similar across species and with the largest metabolites in plasma and urine accounting for less than 10% of parent.
- SUVN-G3031 concentrations are quantified in non-clinical efficacy and safety studies

SUVN-G3031: Non-Clinical Efficacy Profile

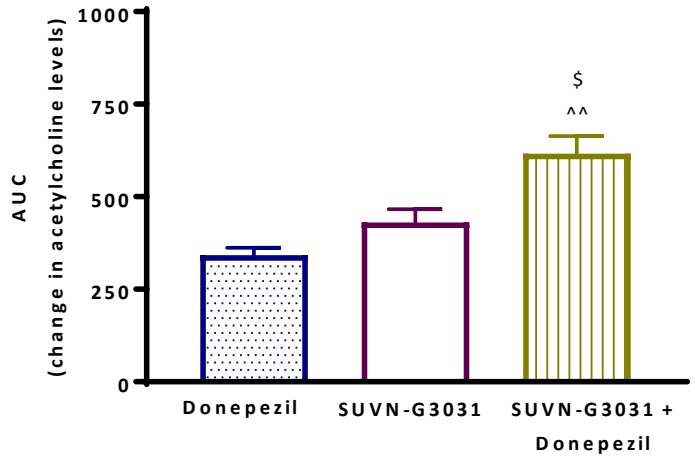
- Dose dependent **receptor occupancy** in the rat and mice brain
- Target engagement leading to **dose dependent *in vivo* functional activity** in rodents
  - ✓ Blocks RAMH induced dipsogenia in rats
  - ✓ Increases *tele*-methyl histamine levels in rat and mice brain
- Dose dependent **procognitive effects**
- **Elevates acetylcholine** levels in cortex (role in treatment of cognitive disorders)
- **Good separation between doses indicated for procognitive and wake promoting effects** in non-clinical species
- No effects on dopamine levels in striatum and nucleus accumbens and does not cause behavioral sensitization (**suggesting no abuse liability**) .

SUVN-G3031: Non-Clinical Efficacy Profile

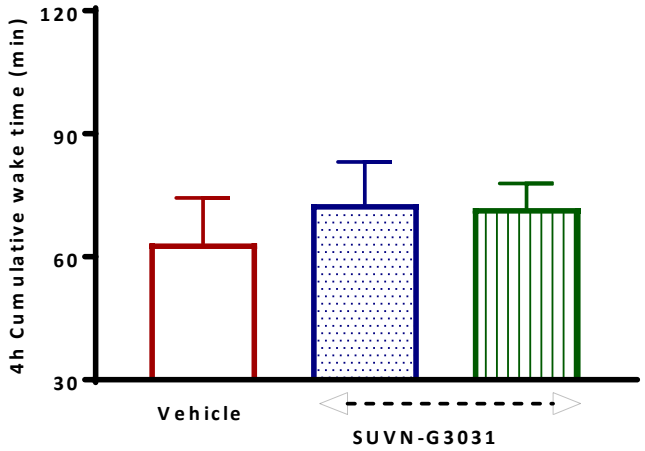
Procognitive Effects (Object recognition Task)



Potentiation of current SOC (Acetylcholine modulation)



Wake time (EEG)



Data represents Mean ± SEM , *p<0.05,***p<0.001 Vs scopolamine; $p<0.05 Vs SUVN-G3031; ^^p<0.01 Vs donepezil

No effects on sleep/ wake cycle at doses exhibiting procognitive effects; good separation between doses indicated for cognition and narcolepsy

SUVN-G3031: Non-clinical Safety

- No evidence of adverse effects in any of the safety pharmacology studies
- SUVN-G3031 is well tolerated with wide margin of safety
- SUVN-G3031 does not have genotoxic liability
- Non-clinical studies indicate no propensity to induce abuse liability, motor impairment or abnormal excitation

SUVN-G3031: Clinical Overview (Phase-1)

Pharmacokinetic Summary:

- SUVN-G3031 exposures (AUC and C_{max}) increased in a dose proportional manner across the tested dose range of 0.1 mg to 20 mg following single oral administration of SUVN-G3031.
- Following multiple oral administration of SUVN-G3031, the exposure increased in a dose proportional manner across the 1 to 6 mg dose range.
- Following multiple administration of SUVN-G3031, steady state was reached on Day 6
- Gender, Food and Age had no effects on the pharmacokinetics of SUVN-G3031

Safety Summary:

- SUVN-G3031 was well tolerated up to the highest tested single dose of 20 mg or 6 mg QD for 14 days.
- No significant changes were noticed in safety parameters including laboratory results, physical examinations, vital signs, fluid balance, suicidal ideation and ECG parameters.
- Most common adverse events reported were dyssomnia, abnormal dreams and hot flush; more incidences at higher doses.

Clinicaltrials.gov: NCT02342041 and NCT02881294

SUVN-G3031: Summary

- Potent, selective and orally bio-available histamine H3 receptor inverse agonist
- Good brain penetration with adequate CSF concentration
- Dose dependent receptor occupancy with good correlation to unbound concentrations at target site
- Good translation of *in vitro* functional activity into *in vivo* functional efficacy
- Significant increase in cortical acetylcholine levels
- Robust procognitive effects in non-clinical models
- Potentiates the activity of current standard-of-care for Alzheimer's disease
- No effects on sleep/ wake profile at doses indicated for pro-cognitive activity
- Does not affect dopamine levels in striatum and nucleus accumbens, suggesting no abuse and addiction liability

SUVN-G3031: Summary

- Shows excellent cardiovascular safety profile
- Exhibits wide margin of safety in all long term safety studies
- Devoid of genotoxicity, teratogenicity and effects on fertility
- Does not have drug-drug interaction liability
- Safe and well tolerated in single and multiple ascending dose studies in healthy human volunteers
- Following multiple administration of SUVN-G3031, steady state was reached on Day 6
- Gender, Food and Age had no effects on the pharmacokinetics of SUVN-G3031
- Phase-2 PoC study for treatment of cognitive disorders is in planning.