Samelisant (SUVN-G3031), Histamine H3 Receptor Inverse Agonist for Potential Treatment of Narcolepsy (with and without cataplexy)

Phase-2 PoC study ongoing with data readout estimated in Q2 2022

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Samelisant: Overview

- Samelisant is potent and selective histamine H3 receptor inverse agonist
- Efficacy has been established in non-clinical sleep models
- Excellent ADME properties with no drug-drug interaction liability
- Non-clinical safety studies supports clinical development
- Safe and well tolerated in healthy humans
- Steady-state concentrations reached on day-6 after QD dosing
- Food, gender and age has no effect on pharmacokinetics (Phase-1 clinical study)

Samelisant: Phase-2 Study ongoing in USA

Phase-2 Proof-of-Concept Study as Monotherapy

- Double-blind, Placebo-controlled, Parallel-group, Multicentre Study
- Intervention/ treatment: One placebo and two active treatment arms
- Treatment duration: 14 days
- Estimated enrollment: 114 participants

Outcome Measures

- Primary outcome measures
  - Improvement in Maintenance of Wakefulness Test (MWT) score
- Secondary outcome measures
  - Epworth Sleepiness Scale (ESS); Clinical Global Impression of Severity (CGI-S)

Key Inclusion Criteria

- Subjects aged 18-50 years with a diagnosis of Narcolepsy

ClinicalTrials.gov Identifier: NCT04072380

Samelisant: Medicinal Chemistry & Intellectual Property

Medicinal Chemistry

Samelisant 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)

Samelisant: *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 or rat histamine H3 receptor

Samelisant: ADME Profile

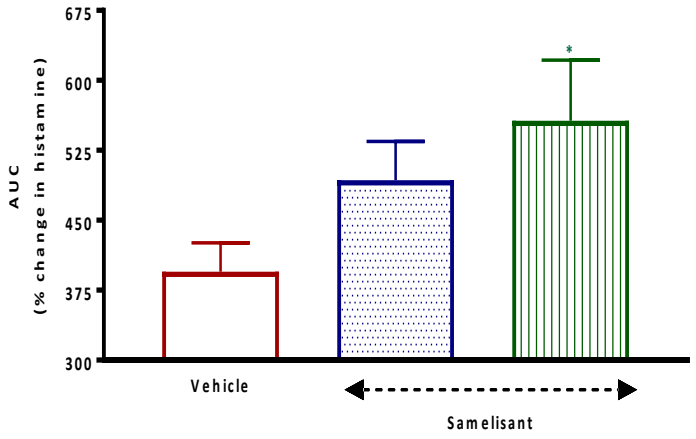
- Highly permeable
- Excellent oral exposure in non-clinical species
- Good brain penetrant and not a P-gp substrate
- High unbound fraction in plasma and brain
- Not an inducer or inhibitor of the CYP450 enzymes
- Metabolite profiles similar across species and with the largest metabolites in plasma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

Samelisant: Non-Clinical Efficacy Profile

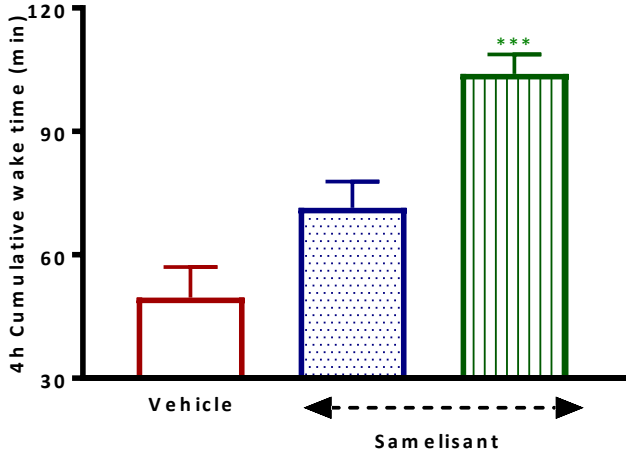
- Dose dependent **receptor occupancy** in the rat and mice brain
- Target engagement leading to **dose dependent *in vivo* functional activity** in rodents
  - ✓ Blocks RAMH induced dipsogenia in rats
  - ✓ Increases *tele*-methyl histamine levels in rat and mice brain
- Neurochemistry studies demonstrate **potential for the treatment of narcolepsy**
  - ✓ Enhanced histamine and dopamine levels in cortex (role in the treatment of narcolepsy)
  - ✓ Enhanced cortical norepinephrine levels (role in the treatment of cataplexy)
- **Wake promoting effects** in wild-type, orexin-B SAP lesioned rats and orexin knockout mice
- **Decreased cataplectic episodes** in orexin knockout mice
- No effects on dopamine levels in striatum and nucleus accumbens and does not cause behavioral sensitization (**suggesting no propensity to induce abuse liability**)

Samelisant: Non-Clinical Efficacy Profile

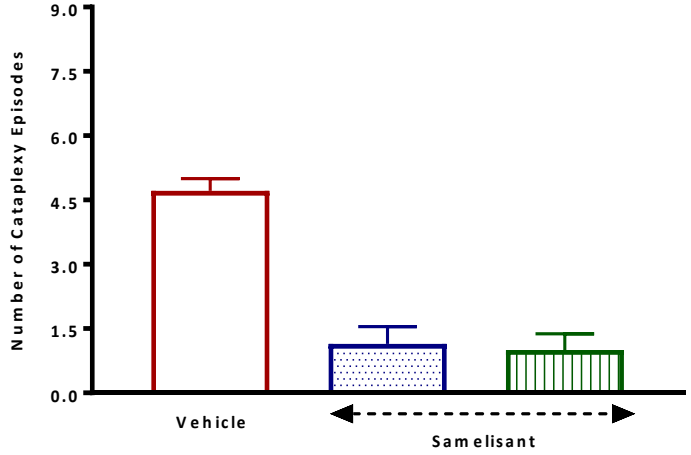
Histamine Modulation



Wake Promoting Effects



Anti-cataplectic Effects#



Data represents Mean ± SEM , *p<0.05,***p<0.001 Vs vehicle; # in orexin knockout mice

Dose-dependent increase in wakefulness in rats/mice, supporting a proof-of-concept for use in narcoleptic patients

Samelisant: Non-Clinical Safety

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

Samelisant: Clinical Overview (Phase-1)

Pharmacokinetic Summary:

- Samelisant exposures (AUC and C_{max}) increased in a dose proportional manner
- Following multiple administration of Samelisant, steady state was reached on Day 6
- Gender, Food and Age had no effects on the pharmacokinetics of Samelisant

Safety Summary:

- Samelisant 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

Samelisant: 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 and dose dependent increase in cortical histamine levels
- Elevates cortical levels of dopamine and norepinephrine demonstrating potential utility in the treatment of cataplexy in narcolepsy
- Exhibits robust wake promoting effects in wild-type, orexin-B saporin lesioned rats and orexin knockout mice
- Decreases cataplectic episodes in orexin knockout mice
- Does not affect dopamine levels in striatum and nucleus accumbens, suggesting no abuse and addiction liability

Samelisant: 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 Samelisant, steady state was reached on Day 6
- Gender, Food and Age had no effects on the pharmacokinetics of Samelisant
- **Phase-2 PoC study as monotherapy is currently ongoing in narcoleptic subjects with and without cataplexy**