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

Phase-2 PoC study ongoing in USA with data readout estimated in early 2021
**SUVN-G3031: Overview**

- SUVN-G3031 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)
SUVM-G3031: 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
  - Clinical Global Impression of Severity (CGI-S); Epworth Sleepiness Scale (ESS)

Key Inclusion Criteria

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

ClinicalTrials.gov Identifier: NCT04072380
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)
### Assay Results

**Histamine H3 Binding**
- $K_i = 8.7 \text{ nM (human)} / 9.8 \text{ nM (rat)}$

**Functional – GTP$_\gamma$S IC$_{50}$**
- $20 \text{ nM}$

**Nature of Binding**
- Inverse agonist

**$I_{Kr}$ hERG Patch clamp assay (human)**
- IC$_{50} > 10 \muM$

**Selectivity**

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

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**Unlike competitor compounds no interspecies difference in binding to human or 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 \textit{in vivo} functional activity in rodents
  - Blocks RAMH induced dipsogenia in rats
  - Increases \textit{tele}-methyl histamine levels in rat and mice brain
- Neurochemistry studies demonstrating potential for the treatment of narcolepsy
  - Enhanced histamine and dopamine levels in cortex (role in treatment of narcolepsy)
  - Enhanced cortical norepinephrine levels (role in treatment of cataplexy)
- \textbf{Wake promoting effects} in wild-type, orexin-B SAP lesioned rats and orexin knockout mice
- \textbf{Decreased cataplectic episodes} in orexin knockout mice
- No effects on dopamine levels in striatum and nucleus accumbens and does not cause behavioral sensitization (\textbf{suggesting no abuse liability})
SUVN-G3031: 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 its use in narcoleptic patients
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 in long term toxicity studies
- SUVN-G3031 does not have genotoxic liability or teratogenic potential
- 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 $C_{\text{max}}$) increased in a dose proportional manner
- 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 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
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 as monotherapy is currently ongoing in narcoleptic subjects with and without cataplexy