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

Phase-2 PoC Study in Planning
Samelisant: Overview

- Samelisant 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)
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.

## Samelisant: *In Vitro* Profile

<table>
<thead>
<tr>
<th>Assay</th>
<th>Results</th>
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</thead>
<tbody>
<tr>
<td>Histamine H3 Binding $K_i$</td>
<td>8.7 nM (human) / 9.8 nM (rat)</td>
</tr>
<tr>
<td>Functional – GTP$<em>{\gamma}$S IC$</em>{50}$</td>
<td>20 nM</td>
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<tr>
<td>Nature of Binding</td>
<td>Inverse agonist</td>
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<tr>
<td>$I_{Kr}$ hERG Patch clamp assay (human)</td>
<td>IC$_{50}$ &gt;10 μM</td>
</tr>
<tr>
<td>Selectivity (70 target sites including receptors-49, enzymes-5, peptides-5, ion channels-7, steroids, second messengers growth factors and prostaglandins-4)</td>
<td>&lt; 50% inhibition at 1 μM</td>
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</tbody>
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*Unlike competitor compounds no interspecies difference in binding to human and 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 concentrations are quantified in non-clinical efficacy and safety studies
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
- 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 propensity to induce abuse liability*)
No effects on sleep/ wake cycle at doses exhibiting procognitive effects; good separation between doses indicated for cognition and narcolepsy
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
- Samelisant does not have genotoxic liability
- 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 $C_{\text{max}}$) increased in a dose proportional manner across the tested dose range of 0.1 mg to 20 mg following single oral administration of Samelisant.
- Following multiple oral administration of Samelisant, the exposure increased in a dose proportional manner across the 1 to 6 mg dose range.
- 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 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
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 for treatment of cognitive disorders is in planning