SUVN-D1044, Non-brain Penetrant 5-HT_4 Receptor Agonist for GI Disorders

Current Status: GLP Toxicity Studies in Planning

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SUVN-D1044: Overview

- Potent and selective 5-HT₄ receptor agonist
- Excellent ADME properties with no drug-drug interaction liability
- No brain penetration
- Robust efficacy in non-clinical animal models of gastro-intestinal disorders
- No cardiovascular liability
- Excellent margin of safety in 7-day rat oral toxicity study
**SUVN-D1044: Mechanism of Action**

**Dorsal Root Ganglion**

- Inhibition

**Extrinsic primary afferent neurons**

**ECs**: Enterochromaffin cells

- 5-HT₄ receptor

**CNS**

**Serosa**

- Longitudinal muscle

**Myenteric plexus**

**Circular muscle**

**Submucosal plexus**

- Muscularis mucosae
- Lamina propria
- Epithelium

**Intrinsic primary afferent neurons**

**Excitatory motor neuron**

**Inhibitory motor neuron**

**Inhibition**

**Activation**

**Enterocytes**

**ECs**
SUVN-D1044: Medicinal Chemistry & Intellectual Property

Medicinal Chemistry

SUVN-D1044 is innovatively designed, best in class clinical candidate.

- Non-hygroscopic crystalline salt
- Favorable physicochemical and biopharmaceutical properties

Intellectual Property

- Series is patentable. Drafting of patent application is in progress.
SUVN-D1044: *In Vitro* Efficacy

- *In vitro* Efficacy
  - EC$_{50}$ of 3.5 nM towards 5-HT$_4$R, when tested in cell based reporter gene assay
SUVN-D1044: ADME Profile

**In Vitro**
- Low permeability across the Caco-2 monolayer and is a P-gp substrate \((B-A/A-B) = 49.6\)
- Stable in rat and human liver microsomes
- IC\(_{50}\) values are greater than 45 µM for CYP 2D6 and 3A4

**In Vivo**
- Good oral bioavailability both in rat and dogs
- No brain penetration with Cb/Cp = 0 in rats
SUVN-D1044: Key Biology Results

**Colonic Transit in Rats**

Enhances colonic transit
Dose dependently enhances colonic transit in mouse, rat and guinea pig colonic transit assay.

**Gastric Emptying in Beagle Dogs**

Clonidine-induced gastroparesis
Enhances gastric emptying in dogs
SUVN-D1044: Summary of Safety Pharmacology

• Safety Pharmacology
  o hERG patch clamp assay IC₅₀ = >10 µM
  o No effects on 5-HT₂B receptor (rat fundus)
  o No QT or QTc prolongation in dogs

• Pre-Clinical Toxicology
  o Demonstrated good margin of safety in repeat dose oral studies up to 7- day duration in rats
  o Did not show any side effects up to 10 mg/kg in single dose oral study in dogs
  o Non-mutagenic in AMES assay

• IPR Protection
  o Series is patentable. Drafting of patent application is in progress