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

Current Status: GLP Toxicity Studies in Planning

SUVEN Life Sciences

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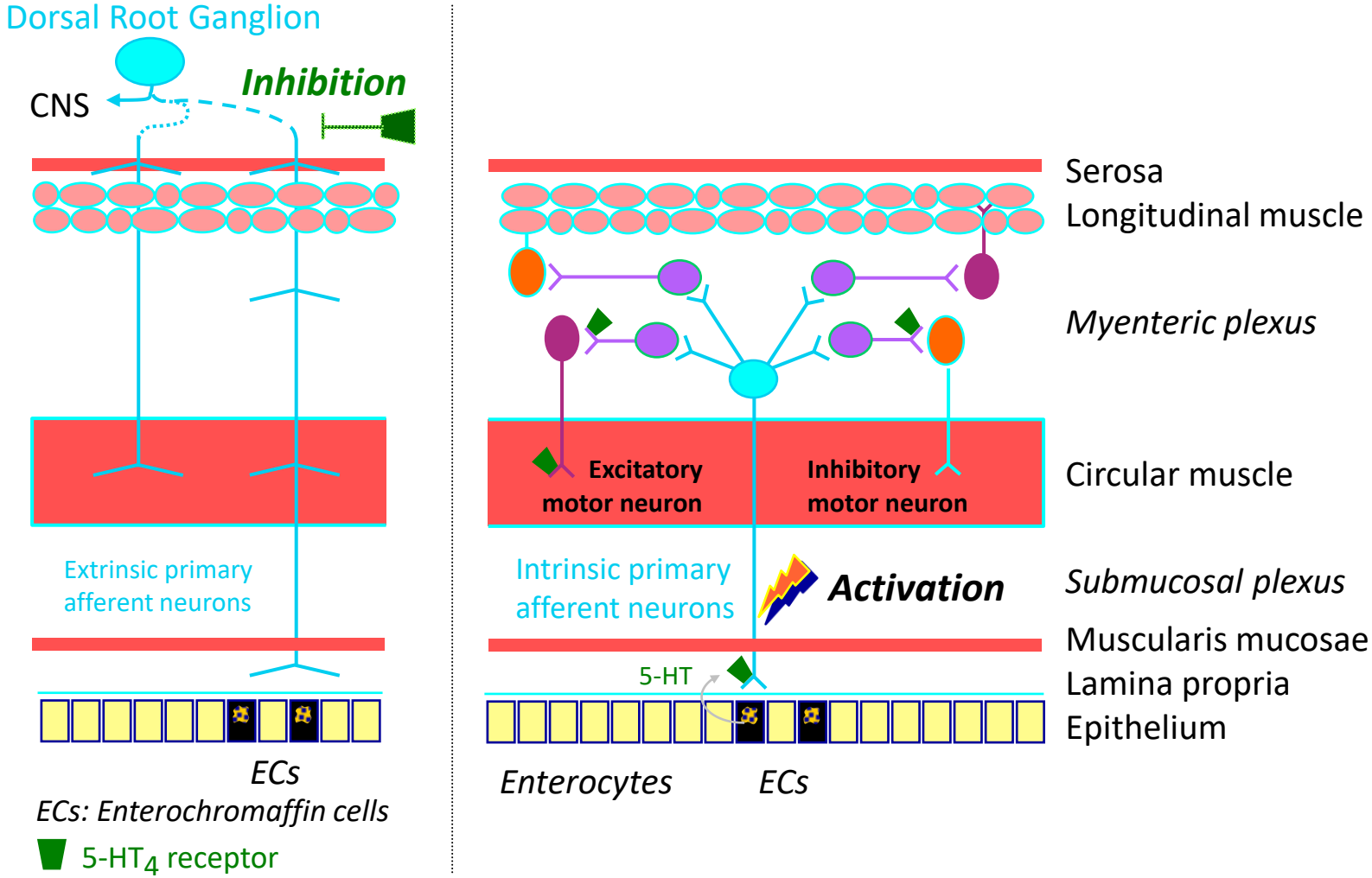
SUVN-D1044: Overview

- Potent and selective 5-HT_4 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



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_4R, when tested in cell based reporter gene assay

SUVN-D1044: ADME Profile

In Vitro

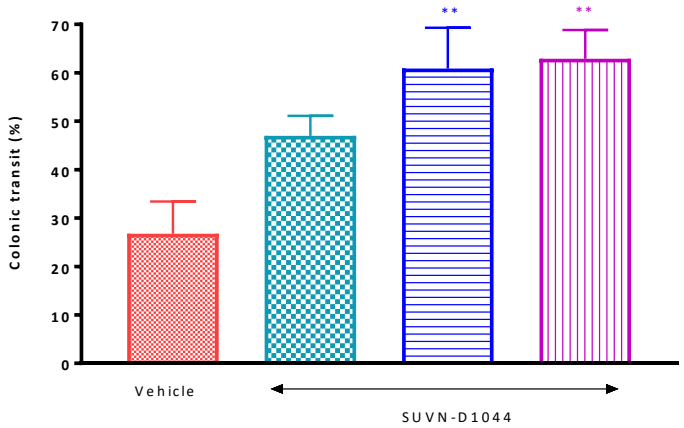
- Low permeability across the Caco-2 monolayer and is a P-gp substrate [(B-A/A-B) = 49.6]
- Stable in rat and human liver microsomes
- IC_{50} values are greater than 45 µM for CYP 2D6 and 3A4

In Vivo

- Good oral bioavailability both in rat and dogs
- No brain penetration with Cb/Cp = 0 in rats

SUVN-D1044: Key Biology Results

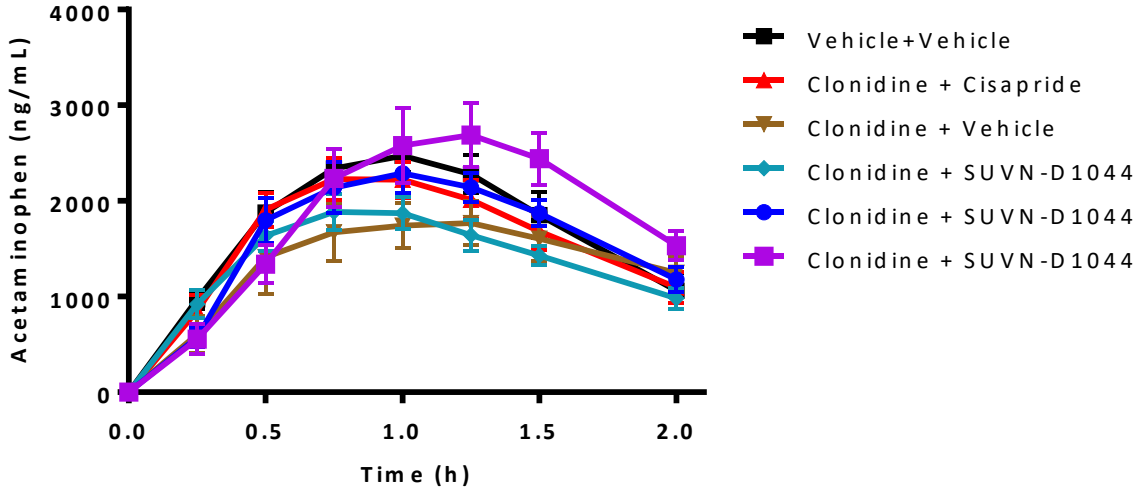
Colonic Transit in Rats



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**
  - hERG patch clamp assay IC_{50} = >10 µM
  - No effects on 5-HT_{2B} receptor (rat fundus)
  - No QT or QTc prolongation in dogs

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