# SUVN-L1101142, a Muscarinic M4 Positive Allosteric Modulator (M4 PAM) for the Treatment of Psychosis-Related Disorders and Conditions

Ramakrishna Nirogi, Venkatesh Goura, Anil Shinde, Mayur Kumbhare, Rajesh Babu Medapati, Kumar Bojja, Aamer Shaikh, Rajesh kumar Badange, Ankit Das, Naga Sai Soma Chandra Sekhar Guduru, Keerthi Sai Bitra, Mary Praveena Nissankararao, Hima Bindhu Bobbili, and Anindita Jana

Suven Life Sciences Ltd., Hyderabad, India. E-mail: nvsrk@suven.com; jasti@suven.com

## Introduction

Traditional antipsychotics primarily focus on dopamine receptors, and although they are effective in alleviating the positive symptoms of the disorder, this method of treatment frequently fails to provide substantial improvement in negative and cognitive symptoms. In contrast to traditional antipsychotics, M4 Muscarinic Acetylcholine Receptor (M4 mAChR) Positive Allosteric Modulators (PAMs) offer a groundbreaking, non-dopaminergic approach to treating psychosis, especially in cases of schizophrenia. M4 PAMs function by amplifying the receptor's reaction to natural acetylcholine, thereby selectively diminishing hyperactive dopamine signaling in the brain areas associated with psychosis while preserving motor functions. In the present study, we assessed SUVN-L1101142, a novel, potent, and selective positive allosteric modulator (PAM) targeting the muscarinic M4 receptor.

## Methods

**In-vitro assay:** Muscarinic M4 receptor (human, rat and mice) activity was evaluated using GloSensor cAMP assay. Selectivity of compounds towards muscarinic receptor subtypes M1 to M5 was assessed using CRE-Luc cell-based reporter assays. Compound effects were expressed as a percentage of the response elicited by a saturating concentration of acetylcholine included on each plate. PAM activity was assessed in the presence of an $EC_{20}$ concentration of acetylcholine, determined individually for each cell line.

**Pharmacokinetic assessment:** Animals were fasted overnight before dosing, food was offered 2 hours post treatment. On the day of dosing, each animal was administered an intravenously (bolus) at 1 or 0.5 mg/kg and oral administration at 3 mg/ kg through gavage tube. Dose formulations for intravenous (IV) solution and oral suspensions were freshly prepared on the day of treatment using 5% pharmasolve + 45% Propylene glycol + 50% PEG mixture and 0.25% Tween 80 + 99.75% 1% HEC solutions as vehicles. At predetermined time-points, blood samples were collected.

**Receptor occupancy study:** Male Wistar rats were administered vehicle or SUVN-L1101142. Post 120 min of treatment, all rats were intravenously administered with non-radiolabelled tracer (MK-6884, 3 µg/Kg). Rats were sacrificed at 5 min post dose of tracer and two specific brain regions (striatum and frontal cortex) and one non-specific brain region (cerebellum) were isolated, transferred to pre-labeled centrifuge tubes and stored at -70 $^{o}$C until processed for analysis to quantify tracer using LC-MS/MS. Receptor occupancy of test compound was calculated in specific brain regions of rat using the change in binding ratio of tracer relative to vehicle treated animals.

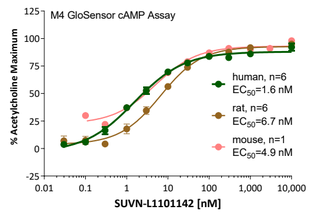
**Rat locomotor activity (LMA) assay:** Rats were acclimatized to the open field arenas for a duration of 20 minutes during which their locomotion was monitored. After this habituation period, vehicle/SUVN-L1101142 was administered, and locomotion was recorded for 10 minutes (T1 period). Following the T1 period, the rats were challenged with amphetamine, and their locomotion was recorded for 120 minutes (T2 period).

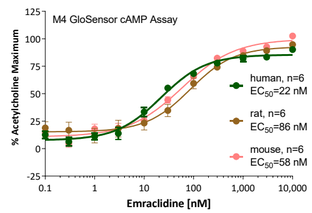
**Prepulse inhibition (PPI) assay:** Rats were acclimatized to the chambers for 10 minutes, with background white noise of 60db. Following day, the rats were subjected to PPI procedure. SUVN-L1101142 was administered, 60 minutes prior to the trial. Ten minutes prior to the trial amphetamine was administered. Then the rats were exposed to various prepulses in increments of 5 db. The pulse was 105 db. Reaction time was kept to 0.5 s.

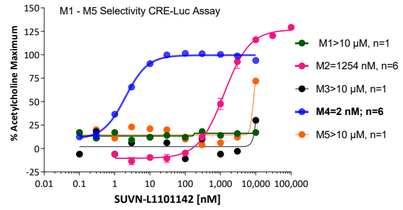
**DOI-induced head twitch:** On the habituation day (day-1), rats were acclimated to the arena for a duration of 15 minutes. On Day 2, vehicle/ VU6028418 (M4 antagonist)/SUVN-L1101142 was administered prior to the habituation in the arena. Following the habituation period (10 minutes), the rats were subjected to challenge with DOI (5 mg/kg, *s.c.* / Vehicle 1 mL/kg, *s.c.*). Subsequently, the rats were placed in the arena for 15 minutes, during which head twitches were observed.

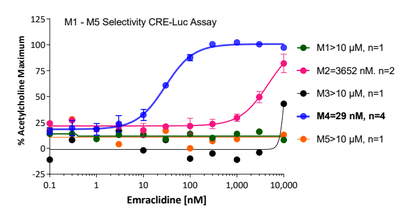
## Results

### Potent and selective muscarinic M4 PAM



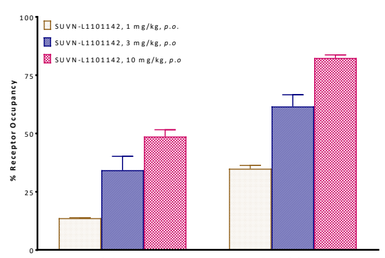




### Good oral exposure in rodent and non-rodents

| Pharmacokinetic Parameters | | | |
|---|---|---|---|
| **Parameters** | **Rat (Wistar)** | **Dog (Beagle)** | **Monkey (Cynomolgus)** |
| Dose (mg/kg) | 3 | 3 | 3 |
| Cmax (ng/mL) | 1572 ± 843 | 561 ± 99 | 1088 ± 573 |
| Tmax (h) | 1.75 | 2.25 | 2.67 |
| $AUC_{0-t}$ (ng·h/mL) | 8155 ± 4093 | 4335 ± 667 | 4534 ± 1450 |
| F (%) | 70 ± 35 | 34 ± 2 | 89 ± 37 |

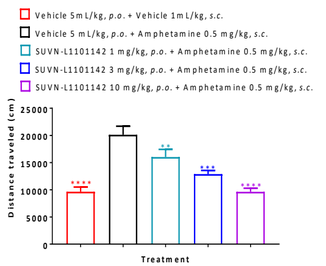
Data represents mean ± SD.

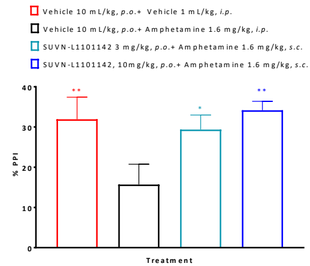
### Dose dependent receptor occupancy




Data represents Mean ± SEM.

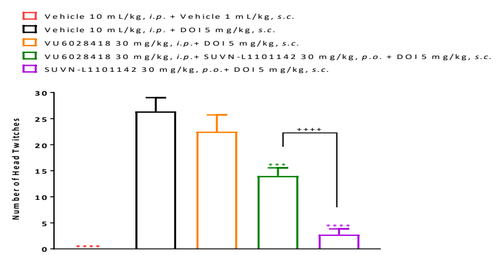
### Attenuated amphetamine induced hyperlocomotion and PPI deficits




Data represents Mean ± SEM. *p<0.05, **p<0.01, ***p<0.001, ***p<0.0001 (One way ANOVA followed by Dunnett's multiple comparisons test).

### Decreased DOI induced head twitch responses and the effect attenuated by M4 antagonist




Data represents Mean ± SEM, ***p<0.01, ****p<0.0001 Vs DOI (One-way ANOVA followed by Dunnett's multiple comparison test), ++++p<0.0001 Vs VU6028418 (Unpaired student t-Test), (n = 6-9).

### Clean safety profile

Toxicity and toxicokinetic profile of SUVN-L1101142 was assessed in female Wistar rats following 5-day repeated dose oral administration at 0, 30, 100, 300 and 500 mg/kg/day. Summary of Observations: There are no major safety findings in this study (MTD: 300 mg/kg/day NOAEL: 300 mg/kg/day).

## Conclusions

- SUVN-L1101142 is a novel and potent PAM acting at muscarinic M4 receptors
- Showed excellent oral pharmacokinetics in rat, dog and monkey
- Dose dependent M4 receptor occupancy in cortex and striatum
- Good correlation between doses exhibiting efficacy and receptor occupancy.
- SUVN-L1101142 showed dependent antipsychotic properties in diverse animal models, and the treatment effects were attenuated by selective M4 antagonist indicating specificity of SUVN-L1101142.
- Preliminary toxicity studies did not show any concern for development
- Results support the development of SUVN-L1101142 for the potential treatment of disorders like schizophrenia and Alzheimer's disease.