SUVN-L1101142: A Muscarinic 4 Positive Allosteric Modulator for the Treatment of Alzheimer's Disease and Schizophrenia

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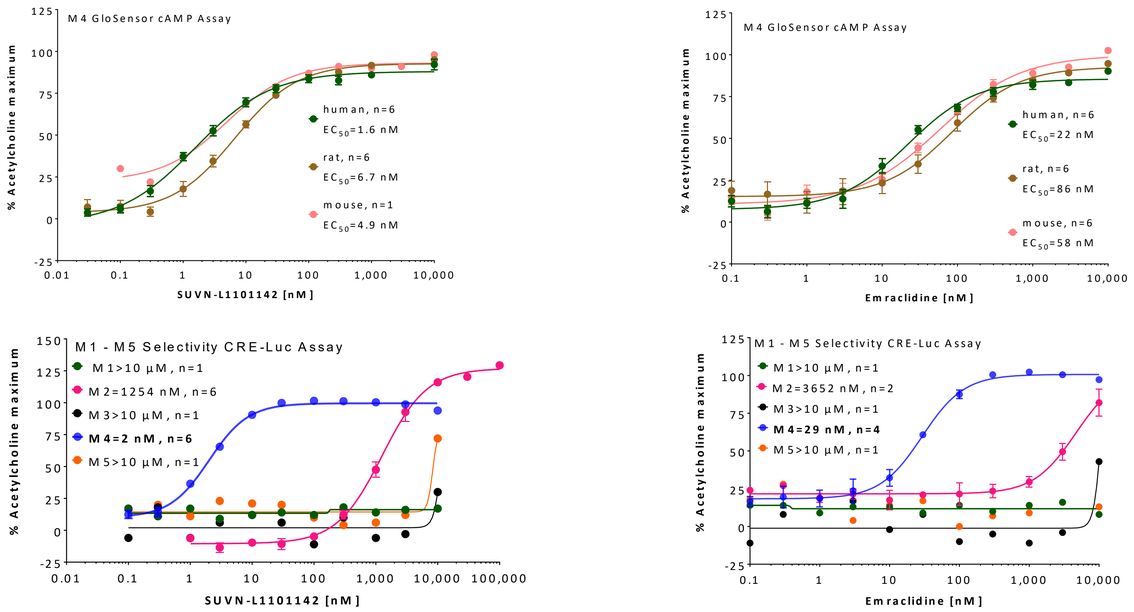
Introduction:

Traditional antipsychotics are effective in alleviating the positive symptoms of the schizophrenia, this approach frequently fails to provide substantial improvement. Muscarinic 4 Positive Allosteric Modulators (M4 PAMs) offer a novel approach to manage schizophrenia. M4 PAMs function by amplifying the receptor's response to endogenous acetylcholine, thereby selectively reducing hyperactive dopamine signalling while preserving motor function. We evaluated SUVN-L1101142, a novel, potent, and selective M4 PAM intended for the treatment of schizophrenia and Alzheimer's psychosis.

Methods and Results:

Potent and Selective Muscarinic M4 PAM:



Clean CYP Profile, Good Oral Exposure and Brain Penetration:

In-Vitro ADME Profile				
Parameters	Rat (Wistar)	Dog (Beagle)	Monkey (Cynomolgus)	Human
Metabolism, LM, %, 30min	15 ± 2.5	3.0 ± 2.5	51 ± 8.0	16 ± 4.1
Fu, Plasma, %	9 ± 0.001	25 ± 0.011	18 ± 0.005*	11 ± 0.011
Fu, Brain Homogenate, %	14 ± 0.005	NA	NA	NA
Fu, Liver Microsomes, %	82 ± 0.009	ND	70 ± 0.012	80 ± 0.027
CYP2D6 IC_{50}, µM	NA	NA	NA	>100
CYP3A4 IC_{50}, µM	NA	NA	NA	52

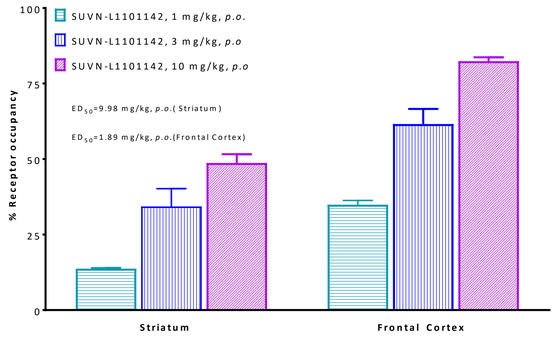
*Rhesus

Data are Mean ± SEM if error is specified; NA: Not Applicable; ND: Not Determined; Fu: Fraction Unbound; LM: Liver Microsomes.

Pharmacokinetic Profile			
Parameters	Rat (Wistar)	Dog (Beagle)	Monkey (Cynomolgus)
Dose (mg/kg)	3	1	3
C_{max} (ng/mL)	1572 ± 843	299 ± 249	1088 ± 573
T_{max} /$T_{1/2}$ (h)	1.75/5.95	1.75/5.42	2.67/10.10
AUC_{0-t} (ng·h/mL)	8155 ± 4093	2222 ± 1970	4534 ± 1450
F (%)	70 ± 35	55 ± 45	89 ± 37
C_{brain}/C_{plasma}	0.25	-	-

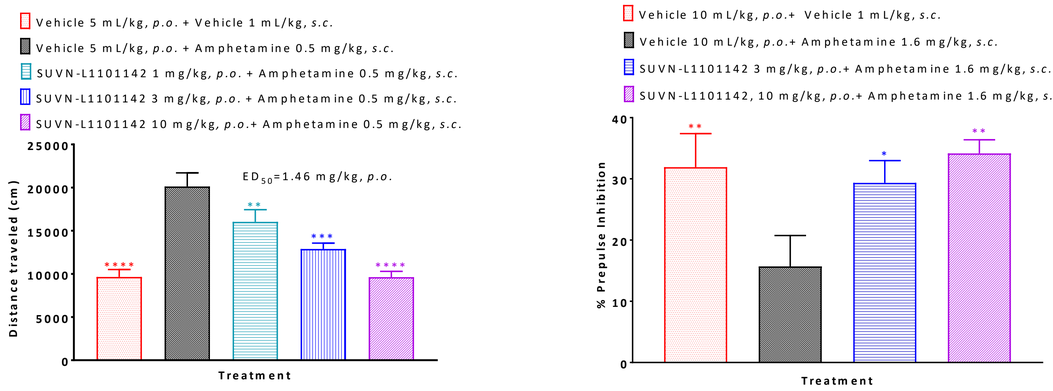
Data represents Mean ± SD; F: Bioavailability.

Dose Dependent M4 Receptor Occupancy in Rats:



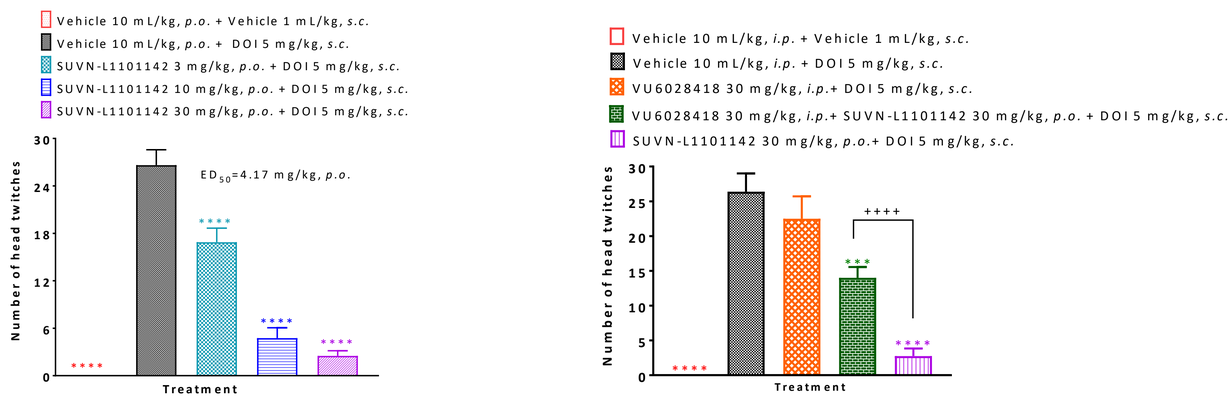
Data represents Mean ± SEM.

Attenuated Amphetamine Induced Hyperlocomotion and Prepulse Deficits in Rats:



Data represents Mean ± SEM. *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001 Vs. amphetamine.

Decreased DOI Induced Head Twitch Responses in Rats and the Effect is Attenuated by M4 Antagonist:



Data represents Mean ± SEM, ***p<0.001, ****p<0.0001 Vs. DOI, ++++p<0.0001 Vs. VU6028418.

Conclusions:

- SUVN-L1101142 is a novel, highly selective and potent PAM acting at muscarinic M4 receptors.
- It showed excellent oral pharmacokinetics and dose-dependent receptor occupancy in the cortex and striatum.
- SUVN-L1101142 exhibited dose dependent antipsychotic properties in diverse animal models which was attenuated by selective M4 antagonist.
- No safety concerns in preliminary rat toxicity studies.
- These results support the development of SUVN-L1101142 for the potential treatment of disorders such as schizophrenia and Alzheimer's psychosis.