

SUVN-I6107, Muscarinic M1 True Positive Allosteric Modulator for Cognitive Disorders

Current Status: GLP Toxicity in Planning



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SUVN-I6107: Overview

- Novel, potent and selective muscarinic M1 positive allosteric modulator (M1 PAM) with no agonist like activity
- No affinity for muscarinic subtypes M2 to M5
- Excellent ADME properties
- Good brain penetration and high CSF concentrations in rats
- Robust efficacy in non-clinical models of cognition
- Potentiates the preclinical efficacy of current SOC for AD treatment (EEG)
- Dose dependent increase in the cortical sAPP α levels
- No cholinergic effects like salivation, emesis or diarrhea
- Excellent margin of safety in 28-day rat toxicity study
- Well protected intellectual property in all major markets

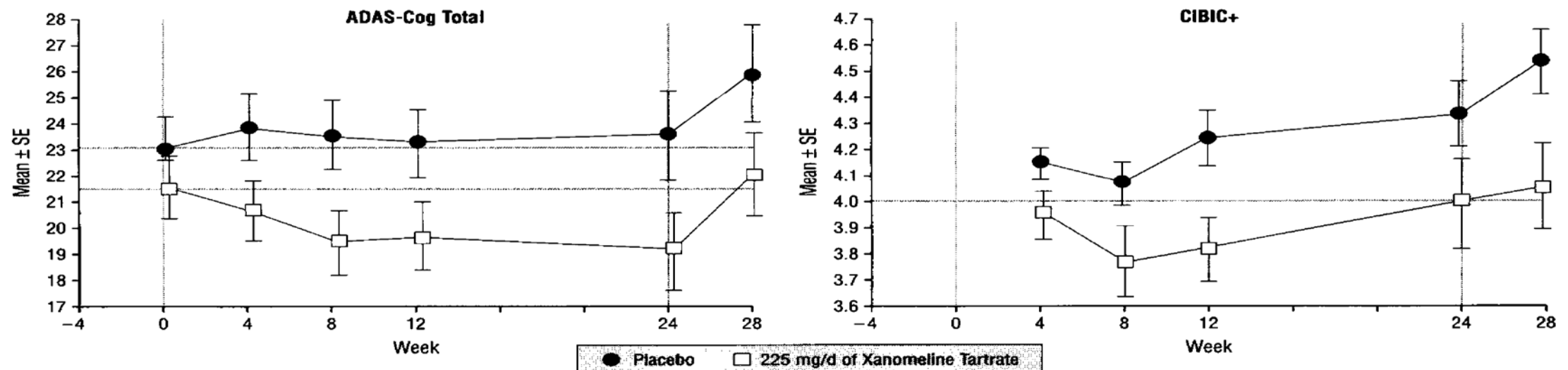


Muscarinic M1 for Dementia: Clinically Validated Target

Selective M1 agonist has been suggested as a therapeutic approach in dementia including Alzheimer's disease and age-associated memory impairment or cognitive impairment associated with schizophrenia¹

Xanomeline - M1 agonist (non-selective)

- Robust improvement in verbal learning and short-term memory associated with Xanomeline treatment.²
- Clinical development discontinued due to Cholinergic side effects like salivation and GI, and CV AEs – possibly mediated by M2 and M3 receptor.

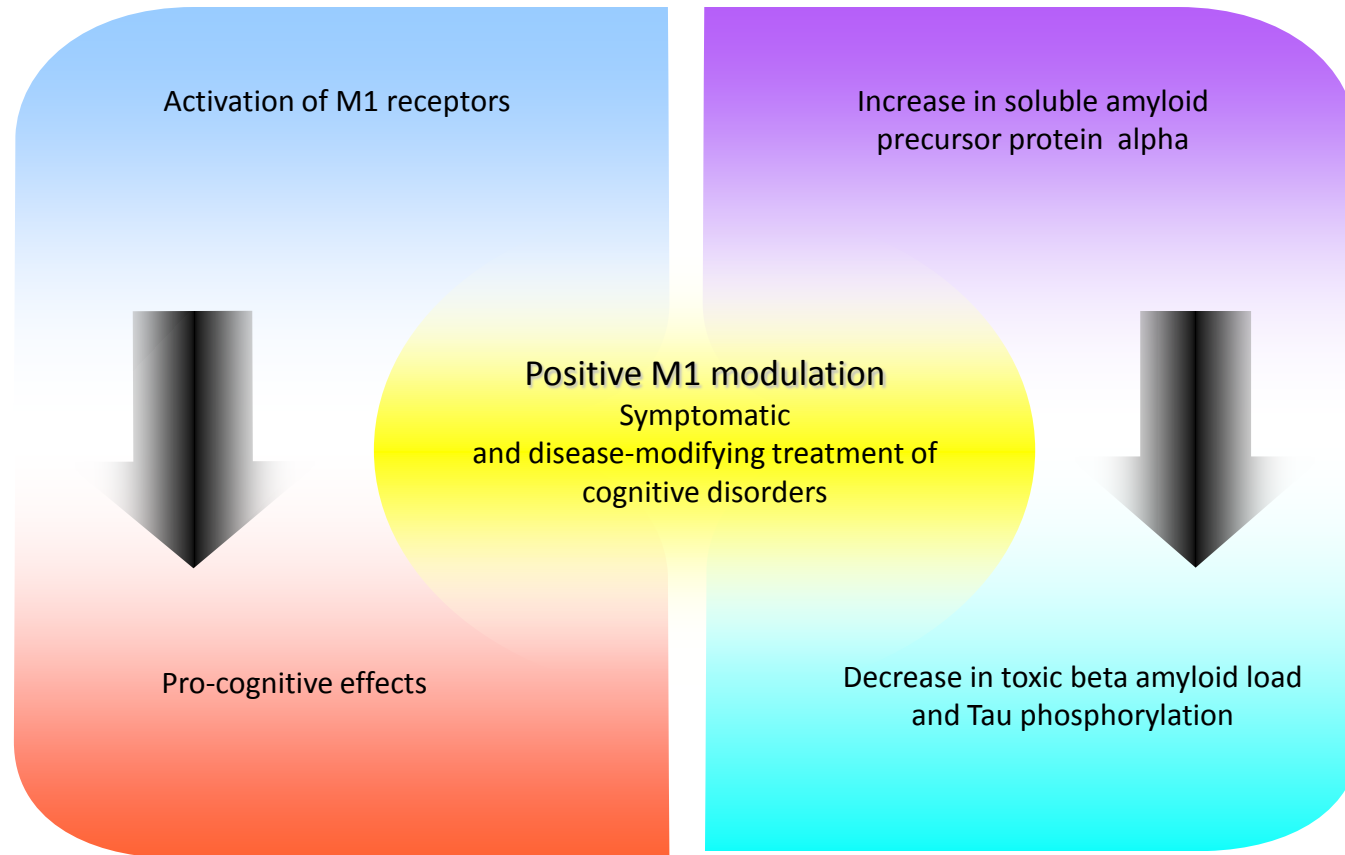


1. Fisher et. al. 2003

2. Bodick NC, Alzheimer Dis Assoc Disord. 1997;11 Suppl 4:S16-22.



Therapeutic Potential: Dual Mechanism of Action



Melancon et al., Drug Discov Today. **2013**, 18 (23-24), 1185-99.

Tarr, J.C. et al., ACS Chem.Neurosci. **2012**, 3, 884-95.



SUVN-I6107: Medicinal Chemistry & Intellectual Property

Medicinal Chemistry

SUVN-I6107 is a clinical candidate selected from a series of more than 200 synthesized compounds, which were innovatively designed using the combination of scaffold hopping and classical medicinal chemistry approaches.

- SUVN-I6107 is a crystalline compound with desirable physicochemical and pharmaceutical properties.

Intellectual Property

- Well protected intellectual property in all major markets



SUVN-I6107: *In Vitro* Efficacy Profile

In Vitro Potency and Selectivity

- SUVN-I6107 modulates the activity of endogenous ligand acetylcholine in G-protein dependent and independent signaling pathways.
- SUVN-I6107 displayed an ideal allosteric potency with no agonist activity favorable for cognitive effects and devoid of cholinergic side effects.
- SUVN-I6107 displayed no activity towards Muscarinic sub-types M2 – M5 (binding and functional), serotonin sub-types 5-HT1A, 5-HT2A, 5-HT2C, 5-HT3, 5-HT4B, Adrenergic α 1B, cannabinoid sub-types CB1 and CB2, Dopamine sub-types D2S and D3, Histamine H1 and H3, Monoamine transporters SERT, DAT (weak activity) and NET.



SUVN-I6107: ADME Profile

In Vitro ADME

- SUVN-I6107 is highly permeable and not a substrate for P-gp when tested in Caco-2 bi-directional permeability assay.
- Metabolism of SUVN-I6107 was found to be low or moderate in rat, dog, monkey and human liver microsomes.
- SUVN-I6107 is not an inhibitor at CYP2D6 and CYP3A4 enzymes.
- SUVN-I6107 is not CYP3A4 time dependent inhibitor.

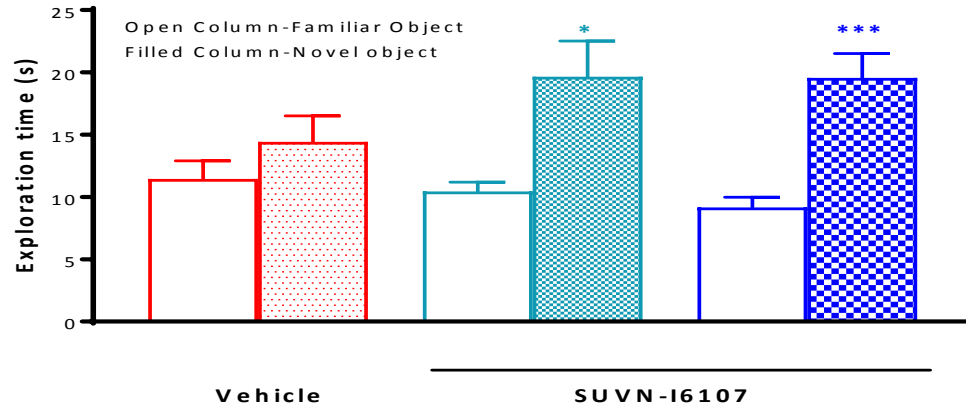
In Vivo Pharmacokinetics

- SUVN-I6107 was well absorbed into systemic circulation with high oral exposure and excellent bioavailability in rats. SUVN-I6107 clearance was low and has moderate volume of distribution.
- After oral administration at efficacious dose, SUVN-I6107 showed good brain penetration and high CSF concentrations in rats. Compound has good free fraction.
- SUVN-I6107 is well absorbed into systemic circulation with excellent oral bioavailability in dogs and monkeys.



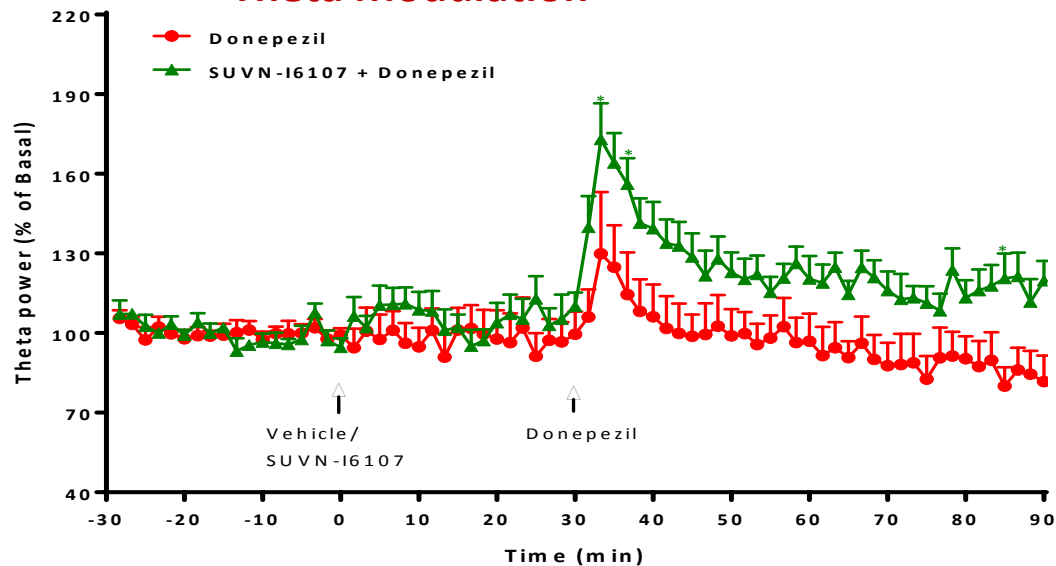
SUVN-I6107: Key Biology Results

Object Recognition Task



Robust efficacy in animal model of cognition

Theta Modulation

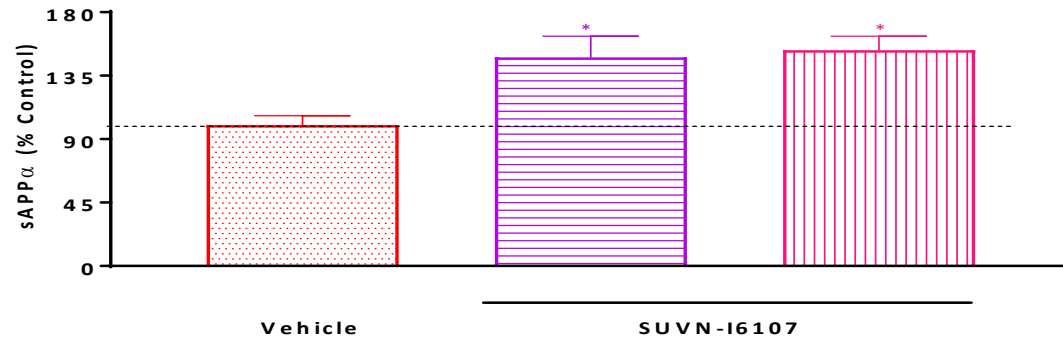


Potentiate the effects of donepezil



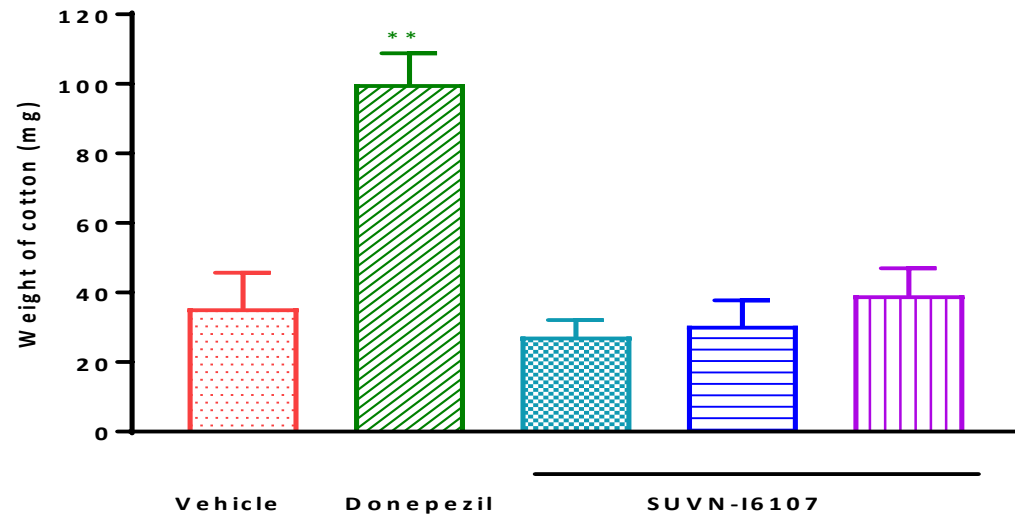
SUVN-I6107: Key Biology Results

sAPP α Modulation



Modulates soluble amyloid precursor protein levels in the brain

Salivation



No cholinergic side effects



SUVN-I6107: Safety Pharmacology

CNS Safety

- No seizure liability in rats up to the highest tested dose with wider margin of safety.

Cardiovascular Safety

- hERG channel: IC₅₀ value >10 μM in patch clamp assay.

Cholinergic side effects

- No effects of salivation in rats. Does not potentiate the side effects of donepezil.
- Cholinergic effects like salivation or diarrhea were not noticed in mice and rats.
- No cholinergic signs in Cynomolgus monkeys.

Gastrointestinal Safety

- No gastrointestinal side effects. Does not potentiate the side effects of donepezil.



SUVN-I6107: Non-Clinical Safety

Non-Clinical Toxicology

- Safety was evaluated in 28- day repeated dose toxicity study in rats for SUVN-I6107; no safety concerns for further development.
- Non mutagenic in bacterial reverse mutation (AMES) test.



SUVN-I6107: Chemistry, Manufacturing and Controls

Drug Substance

- Medicinal chemistry synthesis route is of 10 steps. Easy to scale up in production plant.
- All the required raw materials were commercially available.