Evaluation of the Safety, Tolerability and Pharmacokinetics of Tenaclidine (SUVN-I6107), A M1 PAM in Healthy Subjects

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Introduction:

Clinical, genetic, and preclinical evidence supports the potential of muscarinic M1 positive allosteric modulators (M1 PAMs) as a therapeutic approach for cognitive dysfunction associated with Alzheimer's disease, schizophrenia, and other CNS disorders. However, emerging data suggest that M1 PAMs differ in their pharmacological properties, with intrinsic agonistic activity potentially contributing to cholinergic adverse effects that may limit clinical development.

SUVN-I6107 is a novel, potent, and highly selective M1 PAM with minimal intrinsic agonistic activity, designed to enhance M1 receptor signaling while limiting direct receptor activation. In preclinical and IND-enabling studies, SUVN-I6107 demonstrated pro-cognitive effects without evidence of cholinergic side effects.

The Phase-1 first-in-human study (NCT06705088) evaluating the safety, tolerability and pharmacokinetics (PK) of SUVN-I6107 in healthy subjects following single and multiple oral administrations is completed in USA.

Objectives:

To evaluate the safety, tolerability and pharmacokinetic profile after single ascending oral administration of SUVN-I6107 in healthy subjects.

Methods:

Study Design:

The study consisted of two segments. Segment 1 evaluated single-dose administration and comprised five sequential cohorts, whereas Segment 2 evaluated repeated-dose administration over 14 days and comprised three sequential cohorts.

Results:

Demographics (Segment 1):

		Cohort 1 (n=3)	Cohort 2 (n=6)	Cohort 3a (n=6)	Cohort 4 (n=6)	Cohort 5 (n=6)	Placebo (n=10)	Overall (N=37)
Sex, N (%)	Female	3 (100)	3 (50)	4 (67)	3 (50)	1 (17)	4 (40)	18 (49)
	Male	0	3 (50)	2 (33)	3 (50)	5 (83)	6 (60)	19 (51)
Race, N (%)	White	2 (67)	3 (50)	5 (83)	3 (50)	5 (83)	7 (70)	25 (67)
	African American	0	2 (33)	1 (17)	3 (50)	1 (17)	3 (30)	10 (27)
	Asian	0	1 (17)	0	0	0	0	1 (3)
	Native American	1 (33)	0	0	0	0	0	1 (3)
Ethnicity, N (%)	Hispanic/ Latino	2 (67)	1 (17)	5 (83)	1 (17)	3 (50)	8 (80)	20 (54)
	Others	1 (33)	5 (83)	1 (17)	5 (83)	3 (50)	2 (20)	17 (46)
Age (years)*		33 ± 3.6	33 ± 9.3	26 ± 5.4	30 ± 6.0	33 ± 5.7	35 ± 6.8	32 ± 7.0
Weight (kg)*		66 ± 10.9	74 ± 3.1	62 ± 3.8	77 ± 11.2	79 ± 5.7	75 ± 10.2	73 ± 9.7
BMI (kg/m^2)*		26 ± 3.0	27 ± 1.8	23 ± 1.9	25 ± 2.2	26 ± 1.8	26 ± 2.3	26 ± 2.4

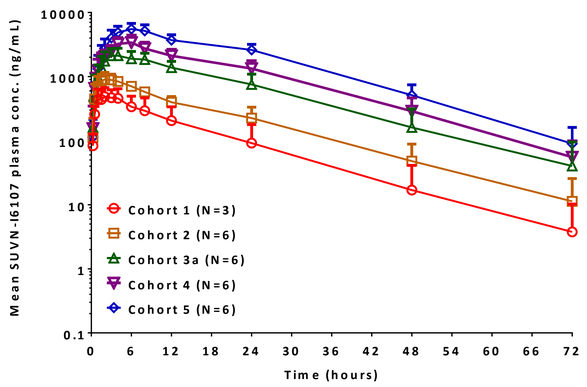
*Data are Mean ± SD

Safety and Tolerability (Segment 1):

- No predefined dose escalation stopping criteria were met.
- No Treatment-Emergent Adverse Events (TEAEs) led to study drug withdrawal or early termination.
- No deaths or Serious Adverse Events occurred across all the dose levels tested.
- All TEAEs were deemed recovered/resolved prior to study completion.

Pharmacokinetics (Segment 1):

SUVN-I6107 plasma concentration versus time profile:



Data are Mean ± SD.

	Cohort 1 (n=3)	Cohort 2 (n=6)	Cohort 3a (n=6)		Cohort 4 (n=6)	Cohort 5 (n=6)
Dose	Dose 1	Dose 2	Dose 3 (Fasted)	Dose 3 (Fed)	Dose 4	Dose 5
C_{max} (ng/mL)	494 ± 178	972 ± 211	2210 ± 673	2750 ± 382	3560 ± 996	5920 ± 1260
T_{max} (h)	2.0	2.0	3.6	6.0	5.2	6.0
$AUC_{0\text{-}inf}$ (h*ng/mL)	7100 ± 4800	14900 ± 4970	44200 ± 17100	50000 ± 15700	70700 ± 21400	124000 ± 30500
$T_{1/2}$ (h)	8.7 ± 2.9	10.5 ± 3.5	10.4 ± 2.4	10.7 ± 3.3	10.7 ± 2.1	10.2 ± 1.9

Data are Mean ± SD and T_{max} is expressed as Median. Crossover design was followed for Cohort 3a.

Conclusions:

- Tenaclidine (SUVN-I6107) was safe and well tolerated up to the highest dose tested.
- The C_{max} and AUC increased with increase in dose of SUVN-I6107.
- No notable differences in SUVN-I6107 pharmacokinetics observed between males and females at the tested doses.
- Food had no clinically meaningful effect on the SUVN-I6107 pharmacokinetics in healthy subjects.
- Results for the Segment 2 and pharmacodynamics parameters are being analyzed.
- The favorable pharmacokinetic (PK) properties and safety profile of SUVN-I6107 support its potential for further development as a therapeutic candidate.

A Phase-2 proof-of-concept study is currently being planned.