Identification of Brain/Behavior-based Pro-cognitive Pharmacodynamic Effects for ALTO-101 in Healthy Volunteers: Results from a Randomized, Double-blind Phase 1 Study and a PK/Tolerability Phase 1 Study

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1. Introduction

- Cognitive impairment is prevalent in schizophrenia (SCZ) and predicts long-term functional outcomes. There is currently no approved treatment for cognitive impairment associated with schizophrenia (CIAS)
- Drugs that increase intracellular cyclic adenosine monophosphate (cAMP) signaling have shown promise as pro-cognitive agents in animal models and early-stage trials in humans
- ALTO-101 is a subtype non-selective brain penetrant phosphodiesterase-4 (PDE4) inhibitor shown to increase cAMP in brain regions critical for cognition
- To limit peaks and troughs associated with adverse events (AE) and reduced efficacy, respectively, ALTO-101 was developed into a transdermal delivery system (TDS)
- The first focus of this research was to evaluate pharmacodynamic (PD) markers of ALTO-101's effects in humans. The second focus was to compare the pharmacokinetics (PK) and tolerability of ALTO-101 administered orally versus via the TDS

2. Study Design

- Data from a dose-response study and a PK/tolerability study contributed to analyses of PD markers and AEs, and PK and AEs, respectively
- Both studies were conducted in healthy volunteers aged 40-64 and included a 7-day washout period between doses

	Dose-response study	PK/tolerability study
Study design	placebo-controlled, double-blind, 3-way crossover	open-label, 2-way crossover
ALTO-101 doses	0.5 mg, 1.5 mg	1.0 mg, 18 mg (TDS)*
Sequence	randomized, counterbalanced	fixed
Sample size	40 (PD), 44 (AE)	15, 14 (TDS)
Age (mean ± SD)	50.5 ± 7.6	52.2 ± 8.0
Gender (M/F)	20/20	9/6

SD: standard deviation; M: male; F: female; * - TDS dosing occurred for 2 days

PD outcomes and their rationale:

- Theta inter-trial coherence (ITC)
  - Passive auditory oddball task (standard trials)
  - Blunted in SCZ, related to cognition
- Mismatch negativity (MMN)
  - Blunted in SCZ, related to cognition
- Resting relative theta power
  - Individuals SCZ have elevated theta power
  - Pro-cognitive drugs (AChEI, memantine, AZD3480) decrease theta power
- Processing speed
  - Composite score: flanker incongruent reaction time, choice reaction time, and simple reaction time

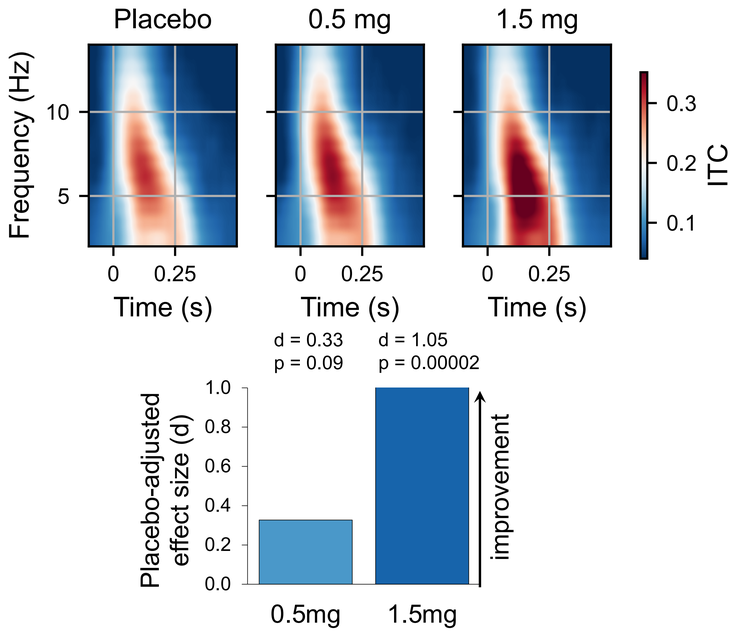
3. Data Analysis

- Mixed-effects models were used to evaluate the effects of ALTO-101 vs placebo in the PD marker analyses

Dose-Response Study

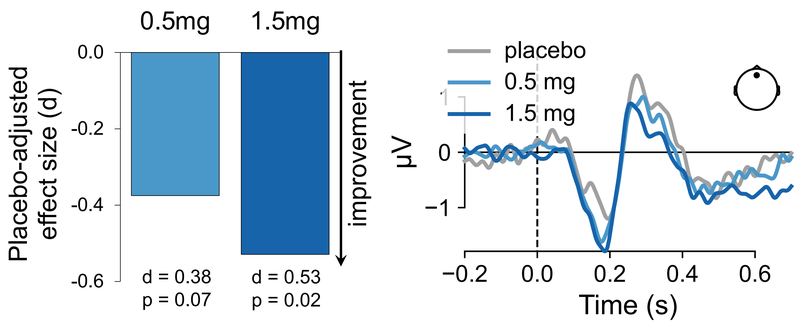
4. Theta Inter-trial Coherence

Dose-dependent increase in ITC in the theta band (Cz)



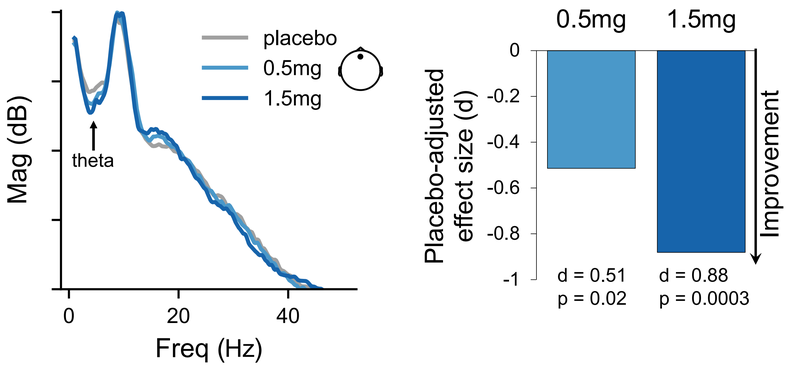
5. Mismatch Negativity

Dose-dependent increase in MMN amplitude (Fz)



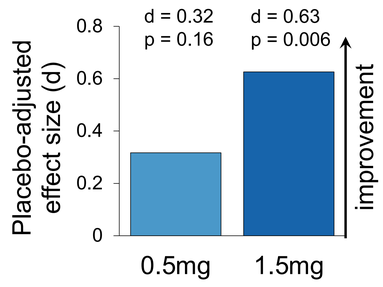
6. Resting Theta Power

Dose-dependent decrease in relative theta power (Fz)



7. Processing Speed

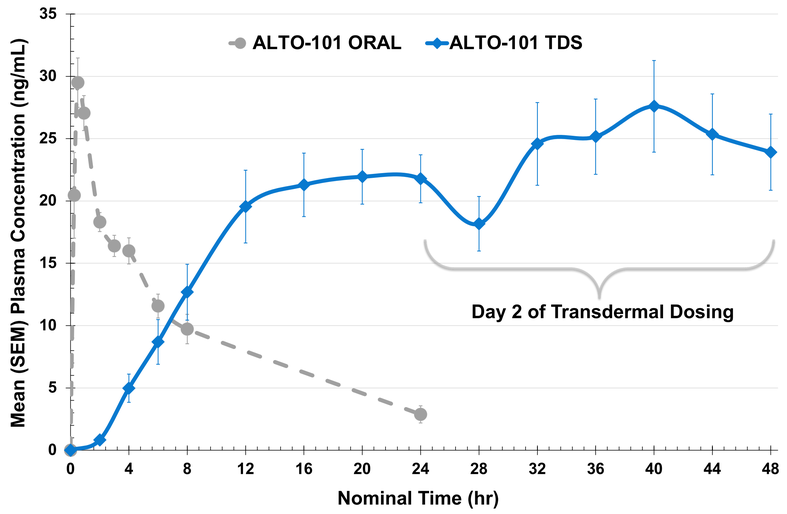
Dose-dependent improvement in processing speed



PK/Tolerability Study

8. Pharmacokinetics of Oral vs TDS ALTO-101

- TDS achieved similar C_{max} as oral but for longer and more consistently
- AUC 62% and 170% greater for TDS on day 1 and 2, respectively (day 1 p=0.01; day 2 p<0.001) versus oral
- TDS adhered well and had no application site reactions leading to patch removal or intolerance.



9. Adverse Events

Related TEAEs > 5% by preferred term and dose by study

Related adverse events > 5% n (%)	Dose-response study			PK/tolerability study	
	Oral			Oral	TDS
	Placebo (N = 40)	0.5 mg (N = 42)	1.5 mg (N = 43)	1.0 mg (N = 15)	18 mg (N = 14)
PDE-4i Class-Related AEs					
Dizziness	1 (2.5)	3 (7.1)	16 (37.2)	6 (40.0)	1 (7.1)
Nausea	0	1 (2.4)	12 (27.9)	3 (20.0)	0
Diarrhea	0	0	1 (2.3)	1 (6.7)	0
Dyspepsia	0	0	0	1 (6.7)	0
Vertigo	0	0	0	1 (6.7)	0
Other Aes					
Headache	1 (2.5)	1 (2.4)	2 (4.7)	2 (13.3)	5 (35.7)
Administration site pruritus	NA	NA	NA	0	2 (14.3)
Asthenia	0	0	0	1 (6.7)	0

10. Conclusions

- Strong SCZ and cognition-related PD effects of ALTO-101 as measured by EEG and neurocognitive tasks
- Consistent dose response to ALTO-101 across multiple PD markers
- TDS produced greater drug exposure and demonstrated an improved tolerability profile
- Phase 2 proof of concept study of ALTO-101 in CIAS expected to be launched in the first half of 2024

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