AUT00206, a Novel Treatment for Schizophrenia, Improves Auditory Mismatch Negativity and Hearing Performance in Patients

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BACKGROUND

- Patients with schizophrenia show deficits in auditory information processing (Javitt et al. 2015), which manifest as abnormal tone matching, reduced auditory mismatch negativity, and reduced speech recognition when there is background noise.
- Auditory deficits likely impact social and cognitive function, and contribute to or exacerbate other symptom domains.
- Kv3.1 potassium channels expressed on principal neurons of the auditory brainstem and on parvalbumin positive interneurons in higher brain areas are critical for the function of auditory circuits. Indeed, positive modulation of Kv3 channels can rescue deficits in auditory temporal processing in rodents (Chambers et al. 2017).
- AUT00206 is a novel Kv3.1 and Kv3.2 channel positive modulator that reduced the impact of ketamine on BOLD responses in healthy volunteers, consistent with its ability to reduce the ketamine-induced BOLD signal changes in cortical and subcortical regions in rats (Deakin et al. 2019).
- Here, we investigated the ability of AUT00206 to improve auditory information processing at different levels of the auditory system in patients with recently diagnosed schizophrenia.

Methods

- This was a Phase Ib, double-blind, placebo-controlled, clinical trial (Clincaltrial.gov ID# NCT03164876) in patients with a recent (<5 years) diagnosis of schizophrenia.
- AUT00206 and placebo were randomized 2:1 and administered daily for 28 days. Patients were in-patient for the first week, and thereafter were outpatients.

Participants

- 24 males with schizophrenia; 18 – 50 yrs old
- Currently stable on up to 2 antipsychotic medications

AUT00206 Administration

- Taken orally after food
- Loading dose of 2000mg on Day 1
- Followed by 800 mg b.i.d. for 27 days

Trial Sequence

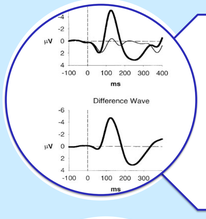
Day -28 to Day -2 Screening	Day -2 Admission	Day 1 – 6 AUT00206 or Placebo (in-patient)	Day 6 Discharge with IMP for Days 7 – 28	Day 14, 21, 28 Outpatient visits	Day 42 +/- 2 days Follow up
PANSS HADS CGI C-SSRS					

Optional MRI and PET at pre-dose and on treatment between Day 15 - 27

AIMS

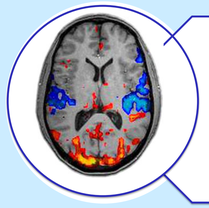
Primary Outcome:

- To assess the pharmacokinetics (PKs), safety and tolerability of repeated doses of AUT00206 for 28 days, as adjunctive therapy in patients with SZ.
- Laboratory assessments, Physical exam, ECG, vitals, adverse events, C-SSRS, VAS for Sedation
- Over 12 PK collections throughout study participation



Secondary Outcome:

- To assess the effects of repeated doses of AUT00206 on frequency and duration Mismatch Negativity (MMN) as a biomarker for SZ.
- Auditory-evoked MMN is reduced in patients with Schizophrenia
  - MMN is a usable biomarker
  - Presented at 75-dB SPL bilaterally
  - Standard tone (50 ms, 1000 Hz) compared to frequency (1050 Hz) & duration (100ms) deviants compared



Exploratory Outcomes:

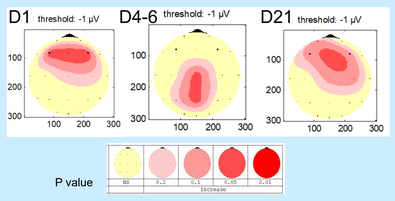
- To assess the effects of repeated doses of AUT00206 on clinical rating scales
- To explore pharmacodynamics of AUT00206 on putative biomarkers relevant to SZ.
- PANSS, CGI, fMRI, PET, additional EEGs (P300, qEEG, ASSR), and Hearing Outcomes

RESULTS - MMN

MMN Improvement:

- A consistent increase in frequency MMN was observed from Day 1 in the AUT00206 group. Whereas the placebo group showed mostly no change or worsening of MMN amplitude (Left Table)
- Due to the considerable numerical variability in the placebo group and the small overall number of subjects in this trial, the effect of AUT00206 was not significant in a group analysis.
- However, responder analysis showed a significant effect of AUT00206 across the trial (Right Figure)

Fz electrode	AUT00206 change from baseline (mV)	Placebo change from baseline (mV)
Day 1	-0.57	+0.80
Day 4-6	-0.66	-0.59
Day 14	-0.20	+0.04
Day 21	-0.49	+1.28
Day 28	-0.62	+0.15



The number of responders was compared between treatment groups using a Fisher's exact test, with an improvement of -1microV for a "response". Brain maps show regions of significance for AUT00206 vs Placebo on Day 1, Day 4-6, and Day 21.

RESULTS: Words in Noise test (WIN)

Words-In-Noise Improvement

- WIN was tested at Baseline, Day 1, Day 5 and Day 21. The standardized recordings were presented via headphones in a sound-treated booth at both a 70-dB HL presentation level and a more difficult 40-dB HL level. The speech to noise ratio systemically changed from +24 to 0 dB signal-to-noise ratio (SNR) and participants repeated back the words they recognized.
- We used the spearman-karber equation to quantify the SNR to recognize 50% of the words (SNR-50). The table shows WIN performance (SNR-50), at each test session, for the 40-dB HL presentation level, for each treatment group. There was a trend for improvement in the AUT00206 group on D5 (p=0.085), with a -1.4dB improvement by Day 21 versus a +0.8dB worsening on placebo.
- A Post-Hoc analysis with an outlier removed on D21 showed a significant difference between AUT00206 (-2.6dB improvement) and placebo (+0.8dB worsening) (p = 0.016).
- 70% (7/10) of the AUT00206 subjects showed an improvement in WIN performance by D21, with only 25% (1/4) showing an improvement on placebo.

SNR 50 post-hoc analysis	Baseline	Day 1	Day 5	Day 21	CfB D21
AUT00206	9.76	8.16	7.76	7.20	-2.56dB
Placebo	9.60	9.60	10.8	10.4	+0.8dB

SUMMARY FINDINGS

Summary of Primary, Secondary, and Exploratory Outcomes

- Administration of AUT00206 for 28 days was safe and well tolerated.
- Mean plasma concentration of AUT00206 was similar to the effective exposure in a previous clinical ketamine-challenge fMRI study (NCT02935725).
- There were consistent improvements in the MMN; but these failed to reach statistical significance due to the small sample size and notable variability in the placebo group.

Summary of Hearing Outcomes

- Audiology testing was optional; thus, only 11 participants dosed with AUT00206 and 4 on placebo completed the hearing outcomes.
- All participants had clinically normal hearing thresholds and performed within normal ranges on a few tests designed for listeners with hearing impairment (Audiometry, MLD, DD). Tests that indicated abnormal auditory processing at baseline (OAEs, WIN), showed an improvement with treatment.

CONCLUSIONS

Treatment with AUT00206 improved measures of auditory information processing at different levels of the auditory system in patients with schizophrenia, consistent with the assumption that Kv3.1 channels are critically involved in establishing high fidelity information processing and transfer. The size of improvements in WIN performance in the AUT00206 treated group at Day 21 was highly clinically relevant. Treatment of sensory deficits represents a novel, but long overdue approach that could lead to improvements in the quality of life of patients with schizophrenia. Auditory deficits may be associated with underlying pathology, and so targeting Kv3 channels may have a broader efficacy across symptom domains.

References

- Javitt, D.C., Freedman, R. 2015. Am J Psychiatry. 172(1): 17–31.
- Chambers, A.R., Pilati, N., Balaram, P., Large, C.H., Kaczmarek, L.K., Polley, D.B. 2017. Sci. Rep. 7(1), 17496.
- Deakin, B., Perini, F., Nazimek, J., McKie, S., Hutchison, J.B., McFarquhar, M., Turgut, T., Sajjala, A., Lovick, S., Alvaro, G., Dourish, C., Large, C.H. 2019. Sch. Bull., 45 (S2), S245–S246.