Improvement in Otoacoustic Emissions and Speech-in-Noise Performance Among Patients with Schizophrenia treated with AUT00206

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BACKGROUND

- **Schizophrenia** (SZ) is a chronic and severe mental disorder. SZ symptoms include:
  - Positive Symptoms (e.g., hallucinations, delusions),
  - Negative (e.g., decreased feelings of pleasure, social isolation, decreased emotional expression),
  - Cognitive Deficits (e.g., poor attention span, decreased working memory, impaired sensory processing).
- Current treatments target positive symptoms, but do not affect cognitive deficits or negative symptoms. There is an urgent need for novel therapies with improved efficacy across all symptom domains
- **Parvalbumin-positive (PV+) GABA interneurons** play a key role in the synchronization of cortical circuits, and in the generation of rhythms that underpin attention, sensory processing, and cognition. **Kv3 channels** expressed on these neurons are critical for establishing normal synchrony by allowing rapid repolarization of the neuronal action potential, which permits neurons to fire more accurately and consistently.
- In schizophrenia abnormalities in PV+ interneurons are implicated in abnormal synchrony. Reduced expression of Kv3.1 in the cortex of patients with schizophrenia may contribute to PV+ interneuron dysfunction, reduced gamma activity, and deficits in connectivity and cognition.
- These abnormalities may contribute to impairments in central auditory processing as evidenced in abnormal mismatch negativity (MMN) and difficulty understanding speech in a noisy environment.
- **AUT00206 is** a potent and selective small molecule modulator of Kv3.1 and Kv3.2 voltage-gated potassium channels. Its effects on Kv3 may help to synchronize the activity of cortical networks and thus address a key abnormality underlying various symptoms of schizophrenia.
- Here we present the its effects on auditory sensory processing in schizophrenia.

TRIAL DESIGN

- This was a Phase Ib, double-blind, placebo-controlled, and randomized 2:1, clinical trial (Clincaltrial.gov ID# NCT03164876)

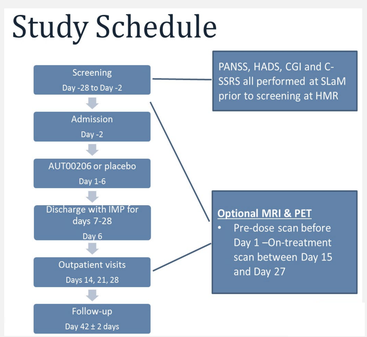
Participants

- 24 males with SZ; 18 – 50 yrs old
- Current stable antipsychotic

AUT00206 Administration

- Taken orally after food
- Loading dose of 2000mg on Day 1
- Twice-daily dose of 800 mg for 28 days

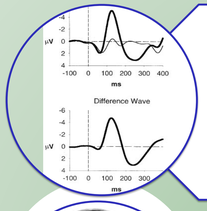
Study Schedule



TRIAL OBJECTIVES

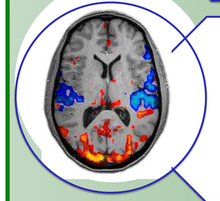
Primary Outcome:

- 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 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 of target engagement and efficacy relevant to SZ.
- PANSS, CGI, fMRI, PET, additional EEGs (P300, qEEG, ASSR), and ***Hearing Outcomes***

Hearing Outcomes Methods

- At Baseline, Day 1, and three further testing timepoints, subjects completed a comprehensive audiologic test battery that probed different levels of the auditory information processing chain including otoacoustic emissions (OAEs), pure-tone and speech audiometry, masking-level difference (MLD), mismatch negativity, the Words-in-Noise test (WIN), and a dichotic digits test (DD).

RESULTS

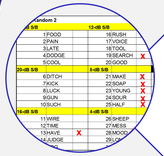
Summary of Primary, Secondary, and Exploratory Outcomes

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

Summary of Hearing Outcomes

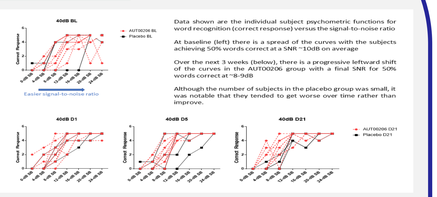
- Audiology testing was optional; thus, only 11 participants dosed with AUT00206 and 4 on placebo completed the hearing outcomes.
- All participants had clinically normal hearing thresholds and performed within normal ranges on a few tests designed for listeners with hearing impairment (Audiometry, MLD,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

IMPROVED HEARING OUTCOMES



Words in Noise (WIN)

- Monosyllabic words presented in multi-talker babble ranging from 24 – 0 dB SNR
- Presented at standard 70-dB HL and more difficult 40-dB HL level



Data shown are the individual subject psychometric functions for word recognition (correct response) versus the signal-to-noise ratio

At baseline (left) there is a spread of the curves with the subjects achieving 50% words correct at a SNR ~10dB on average

Over the next 3 weeks (below), there is a progressive leftward shift of the curves in the AUT00206 group with a final SNR for 50% words correct at ~8-9dB

Although the number of subjects in the placebo group was small, it was notable that they tended to get worse over time rather than improve.

WIN Improvement

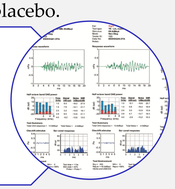
- WIN was tested at Baseline, Day 1, Day 5 and Day 21. Performance was quantified as the signal-to-noise required for 50% correct word recognition. The **Figures** display the WIN performance at 40dB HL as a function of the signal-to-noise ratio levels.
- There was a trend for improvement in the AUT00206 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 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.

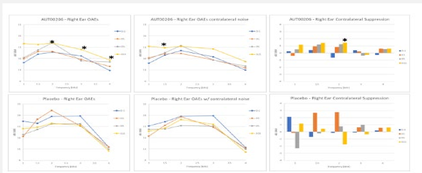
OAE Improvements:

- A consistent increase in OAEs and contralateral suppression of OAEs was observed in the AUT00206 group that reached statistical significance at several frequencies.
- Data shown are the right-ear emissions for both treatment and placebo groups and contralateral suppression induced by noise applied to the left ear. Statistical significant ($p<0.05$) is indicated with * shows increases in the change from baseline in the AUT00206 group compared to placebo.

Otoacoustic Emissions (OAEs)

- **Active response of the hair cells and MOC efferent track**
- **Transient Evoked (TE)**
- **TE w/ contra-lateral suppression**





CONCLUSION, NEXT STEPS

- Clinically meaning and statistically significant improvement with AUT00206 (800 b.i.d.) over 3 weeks compared to Placebo were seen in several hearing outcomes in patients with schizophrenia. The improvement in WIN performance in the AUT00206 treated group at Day 21 (-2.6dB) would equate to a noticeable improvement in ability to hear in challenging listening environments.
- The hearing improvement observed as early as Day 5 in the WIN test is consistent with expectation for a Kv3 ion channel modulator, with effects occurring soon after the initiation of treatment. However, a longer and larger trial will be required to confirm these results.
- Treatment of sensory deficits represents a novel, but long overdue approach to managing and improving the quality of life of patients with SZ. Central auditory deficits may be associated with underlying SZ pathology; thus, targeting Kv3 channels may have a broader efficacy.
- Additional studies are underway to evaluate Kv3 channel modulation on central auditory processing.