AUT00206, a Novel Kv3.1/3.2 Positive Modulator, Normalizes Gamma Oscillations in Patients with Schizophrenia

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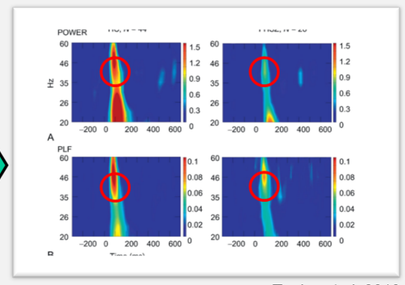
BACKGROUND

- Patients with schizophrenia show abnormalities in resting state and induced and evoked gamma oscillations including:
  - ❖ Increased resting state power
  - ❖ Decreased power and phase locking to 40 Hz auditory stimuli (ASSR)
  - ❖ Decreased power and phase locking to simple standard stimuli in 50 to 100 ms post-stimulus window (early auditory gamma response [EAGR])
  - ❖ The correlation between gamma synchrony and P300 amplitude is absent



Taylor et al. 2013

- These abnormalities implicate dysfunction of parvalbumin-expressing interneurons (PVINs) in cortical and subcortical circuits

❖ Kv3.1 channels expressed on PVINs are critical for their ability to establish and maintain fast firing activity and to support network synchronisation.

❖ Positive modulation of Kv3.1 channels highly expressed on PVINs is a potential therapeutic approach to counteract PVIN dysfunction.

❖ AUT00206 is a novel Kv3.1/Kv3.2 positive modulator that reduced the impact of ketamine on BOLD responses in healthy volunteers (Deakin et al. 2019) and rescued sub-chronic PCP-induced PVIN abnormalities in rodents.

- **Here, we test the hypothesis that treatment with AUT00206 will normalize resting state and induced gamma oscillations in patients with schizophrenia**

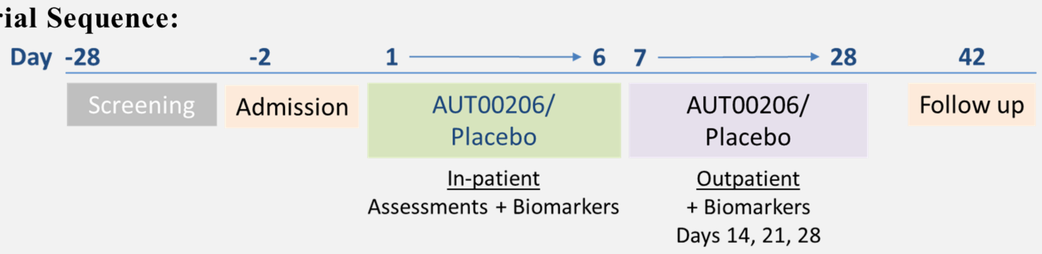
METHODS

- A randomised, double-blind, placebo-controlled study (NCT03164876)

Participants

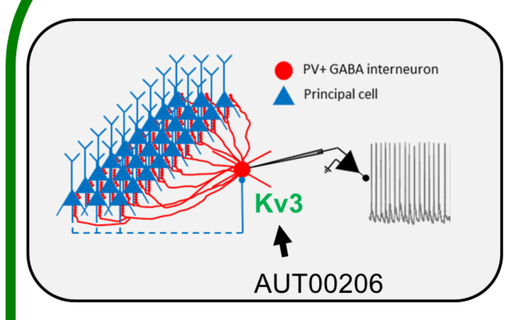
- 24 males with schizophrenia (< 5 years since diagnosis); 18 – 50 years old
- Currently stable on up to 2 antipsychotic medications
- Patients were randomised 2:1 to receive AUT00206 or placebo for 28 days.
- Loading dose of 2000mg Phase I formulation capsules on Day 1
- Followed by 800mg b.i.d. for 27 days

Trial Sequence:

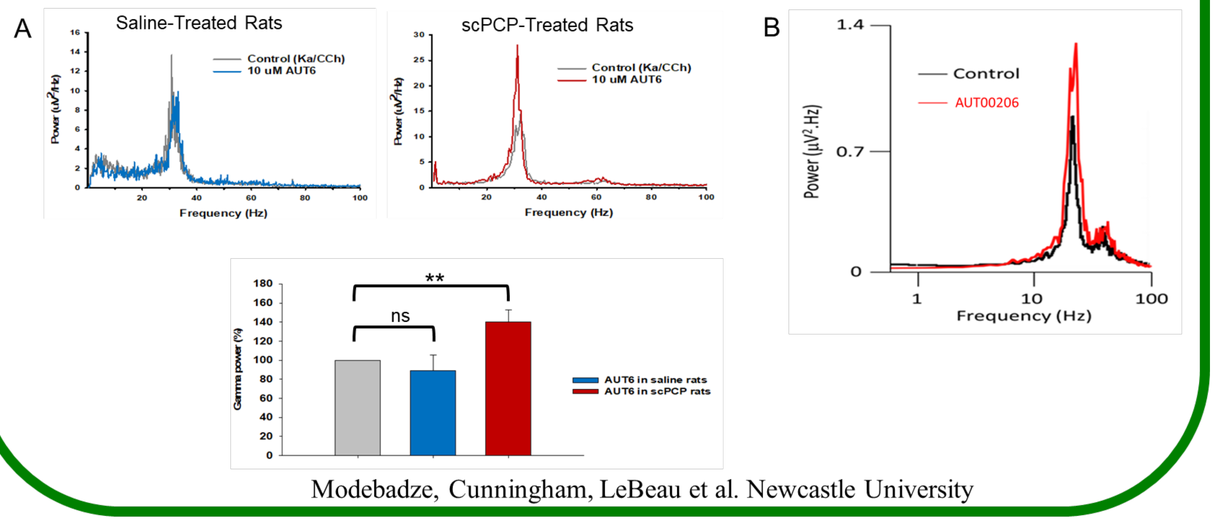


➢ Resting state and induced and evoked gamma oscillations were investigated in resting state EEG (eyes closed), 40 Hz auditory steady state response (ASSR), and in response to deviant and standard stimuli in an auditory oddball paradigm. Tests were conducted at baseline, day 1, and three further days over a 28-day period. Absolute power and phase locking factor (PLF) at midline electrodes and latencies to reach their peaks were the key dependent variables.

GAMMA OSCILLATIONS, *IN VITRO*

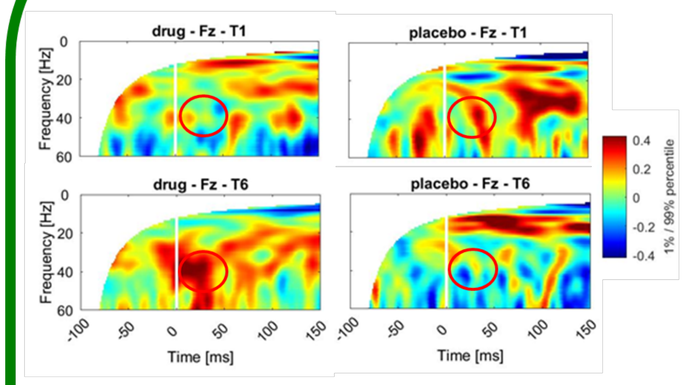


In previous studies, effects of AUT00206 were explored on Gamma Oscillations induced in cortical brain slices obtained from and from (A) a rat model of reduced PVIN function (Neill JC et al. (2014) Eur. Neuropsychopharm.) and (B) a human patient with schizophrenia during elective surgery for tumour removal



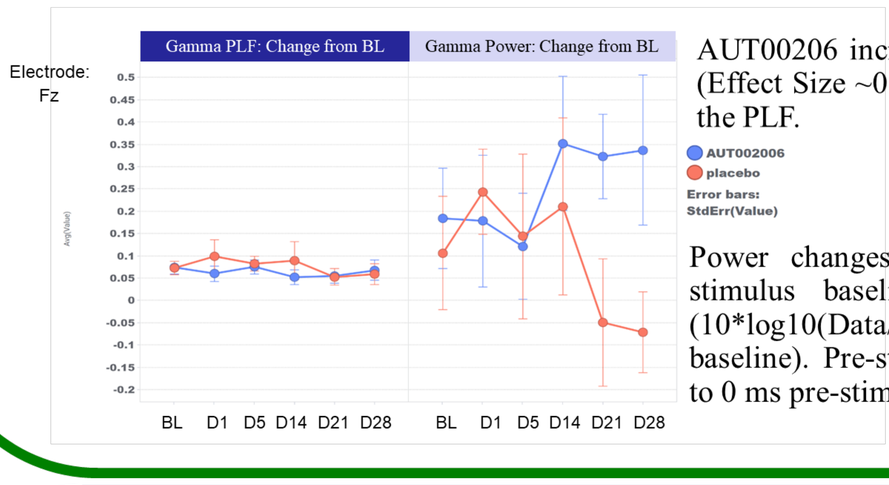
Modebadze, Cunningham, LeBeau et al. Newcastle University

EARLY AUDITORY GAMMA



Frequency-time plots show the gamma response ~50ms (EAGR) following auditory stimuli as part of a P300 paradigm.

The EAGR is increased in the AUT00206 group at Day 28 (n=16), but not in the placebo group (n=8)

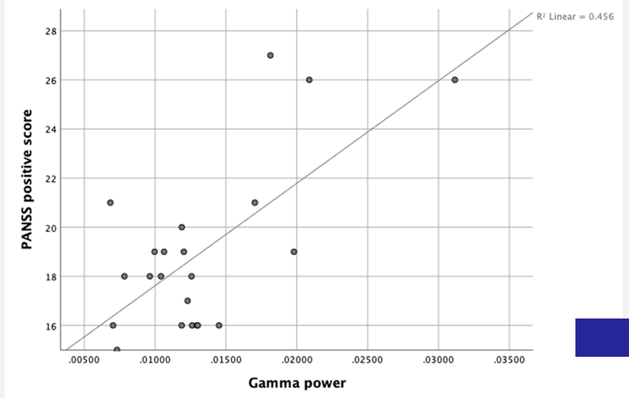


AUT00206 increased gamma power (Effect Size ~0.5), but did not affect the PLF.

Power changes compared to pre-stimulus baseline shown in dB (10*log10(Data/pre-stimulus baseline). Pre-stimulus baseline -75 to 0 ms pre-stimulus

RESTING STATE GAMMA

Baseline (All Patients)

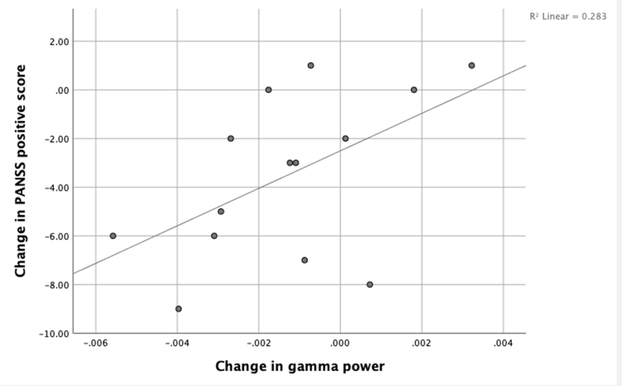


Positive correlation between frontal resting gamma power (mV/Hz) with baseline PANSS positive symptom severity score (n=22, r = 0.675 p < 0.001)

Change in PANSS positive score from baseline to day 28 in the AUT00206 group significantly correlated with a decrease in frontal resting gamma power (mV/Hz) (n = 14, r = 0.532, p = 0.05).

A change correlation was not observed in the placebo group, although this may be in part due to the low number of subject (n=8)

Change at Day 28 (AUT00206)



SUMMARY

Paradigm to elicit gamma oscillations	Power		PLF		Latency to Max Power		Latency to Max PLF	
	Schiz	AUT	Schiz	AUT	Schiz	AUT	Schiz	AUT
Resting State	↑	↓						
40-Hz ASSR	↓	=	↓	=	?	↓	=↓	↓
P300 Auditory Oddball Deviant	=	=	=	=				
P300 Auditory Oddball Standard (Early Auditory Gamma Response)	↓	↑	↓	=				

Treatment with AUT00206 improved measures of gamma oscillations in cortex of patients with schizophrenia, consistent with the hypothesis that positive modulation of Kv3.1/Kv3.2 channels would enhance the function of PVINs. A larger study will be required to confirm these findings, and explore efficacy versus clinical symptoms. However, these data suggest the utility of AUT00206 in the treatment of disorders associated with PVIN dysfunction, including schizophrenia, Fragile X Syndrome, and certain neurological diseases.

References

- 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.
- Neill JC et al. (2014) Eur. Neuropsychopharm. 24(5):822-35.
- Taylor, G. W., McCarley, R. W., & Salisbury, D. F. (2013). Supplements to Clinical Neurophysiology, 62, 131–145.

Disclosures: CL, GA, AS, ASh, JH are employees or shareholders in Autifony Therapeutics Limited. DU and VS are consultants to Autifony Therapeutics Limited.