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

SIRS April 2021

Charles Large, CEO

Disclosures

CL is a founder and shareholder in Autifony Therapeutics Limited

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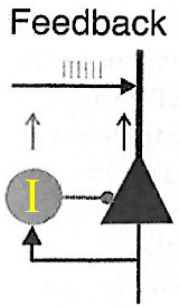
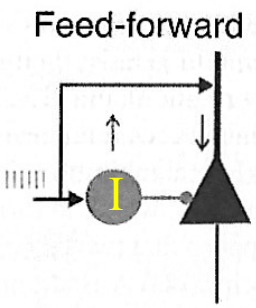
Rhythms of the Brain
Structure drives Function

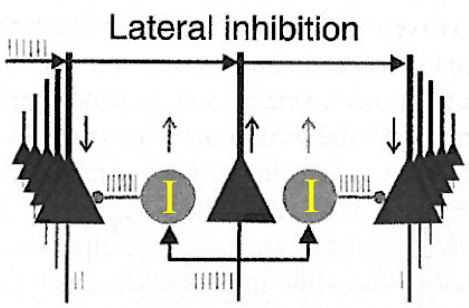
Circuit Stability



Input Filtering



Segregation of Activity



Inhibitory networks provide the building blocks for neural processing and oscillatory behaviour that underpins **Synchrony** and **Information Transfer**

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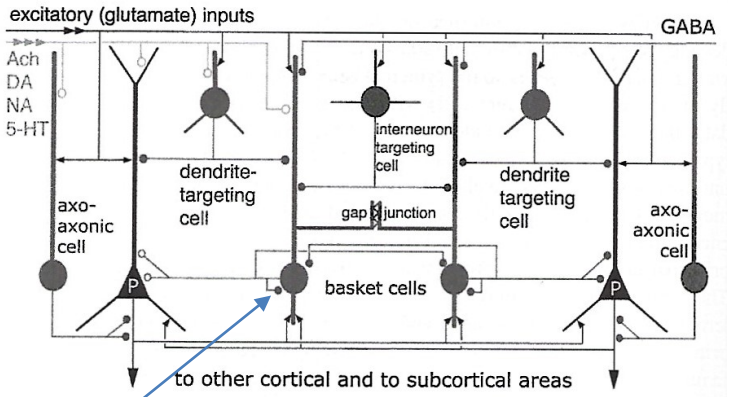
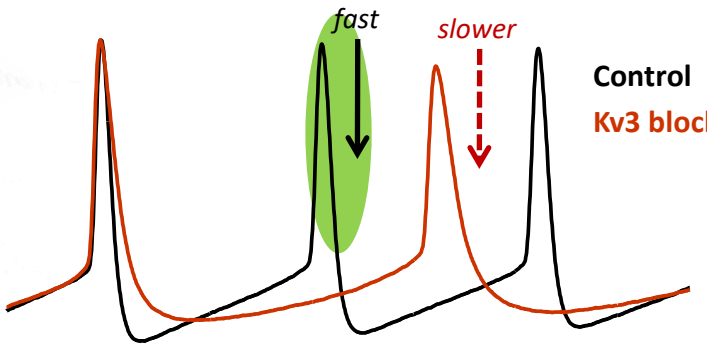
Kv3 Channels are critical to the precise firing of key interneurons that underpin network function

GABA neurons



Kv3

Parvalbumin +ve GABA neuron (basket cell)



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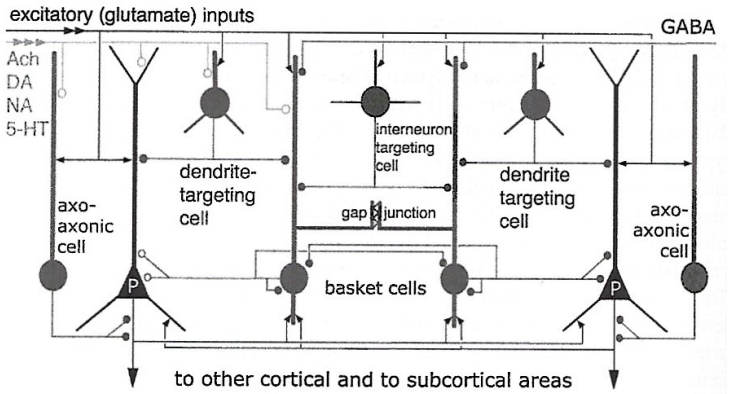
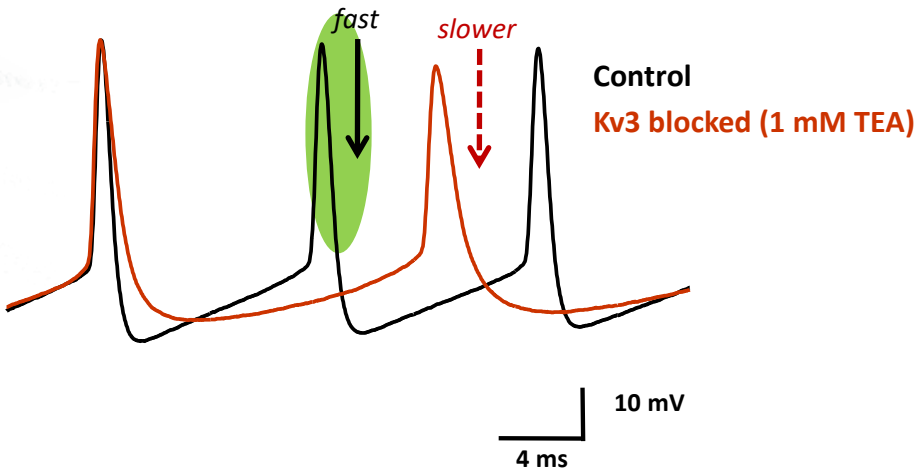


↓Parvalbumin GABA neuron

↓Kv3



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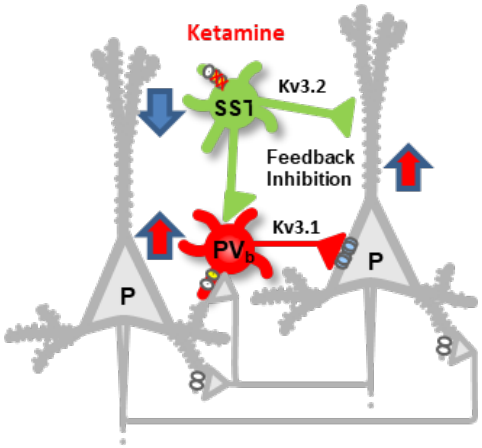
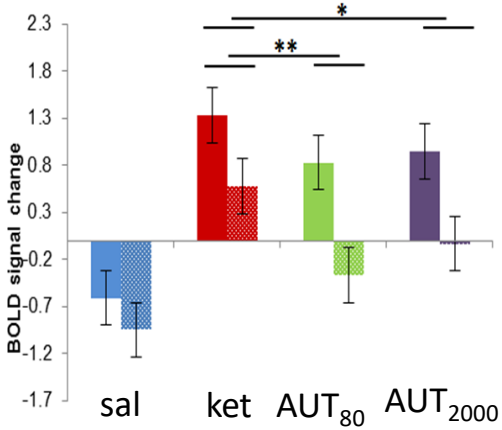
Pathophysiology in Schizophrenia
Efficacy of Kv3 Positive Modulators (PAMS)

Corticolimbic Circuit Dysfunction



Ketamine-induced BOLD response in humans



Kv3 PAMs reduced the ketamine response

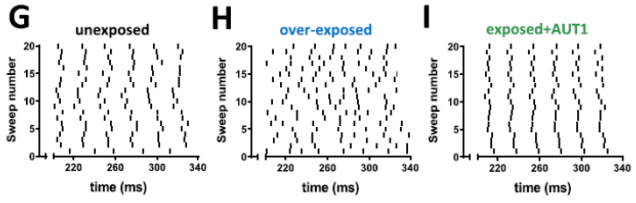
Deakin et al. 2019, SIRS

Auditory Processing

Dan Javitt, Nathan Kline Institute, New York

"Patients had a lot of difficulty processing tone of voice, which leads to having significant deficits in social cognition and in interacting normally with other people. That's a major feature of schizophrenia, and our findings are suggesting that these very low-level bottom-up deficits are cascading up the system to produce more complex dysfunction"

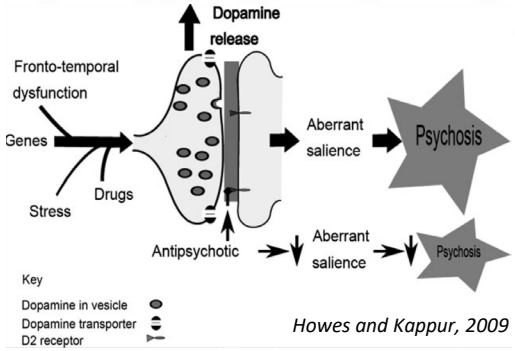
Noise impacts auditory brainstem firing



Kv3 PAMs improve firing and auditory temporal resolution

Olsen et al. 2018, Neuropharmacology

Dopamine Transmission

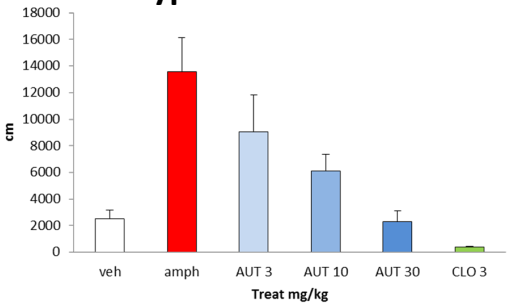


Howes and Kappur, 2009

Multiple hits interact to result in striatal dopamine dysregulation

Current antipsychotic drugs all act through blockade of dopamine transmission

Rodent amphetamine-induced Hyperlocomotion

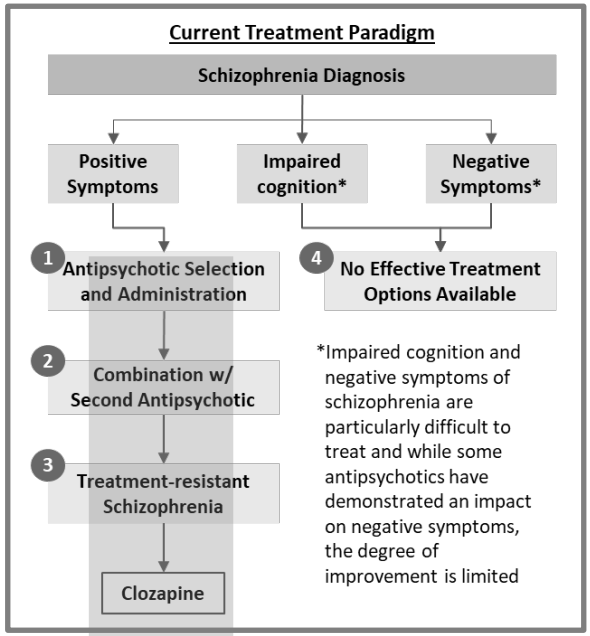


Kv3 PAMs reduce amphetamine-induced hyperactivity

Parekh, McClung et al. 2017, Neuropsychopharm

Kv3 Channel Modulation represents a paradigm shift in the treatment of schizophrenia

Transmitter-focused Intervention



Dampening of dopamine (via D2 block) and glutamate (via 5HT2a block) may reduce aberrant information flow

Circuit-focused Intervention

Kv3 Positive Modulator

Normalise information transfer across cortical and subcortical brain areas to target symptoms that cross the canonical +ve, -ve and cognitive domains

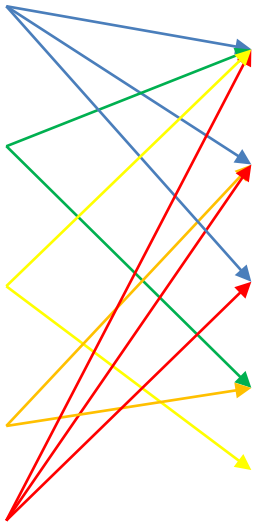
Cortical functional connectivity and local circuit synchronisation

Hippocampal encoding and plasticity

Thalamic pattern generation (slow wave/spindles)

Striatal processing and regulation of output

Auditory processing



Cognitive & Perceptual disturbance

Auditory Hallucinations

Reduced Social interaction

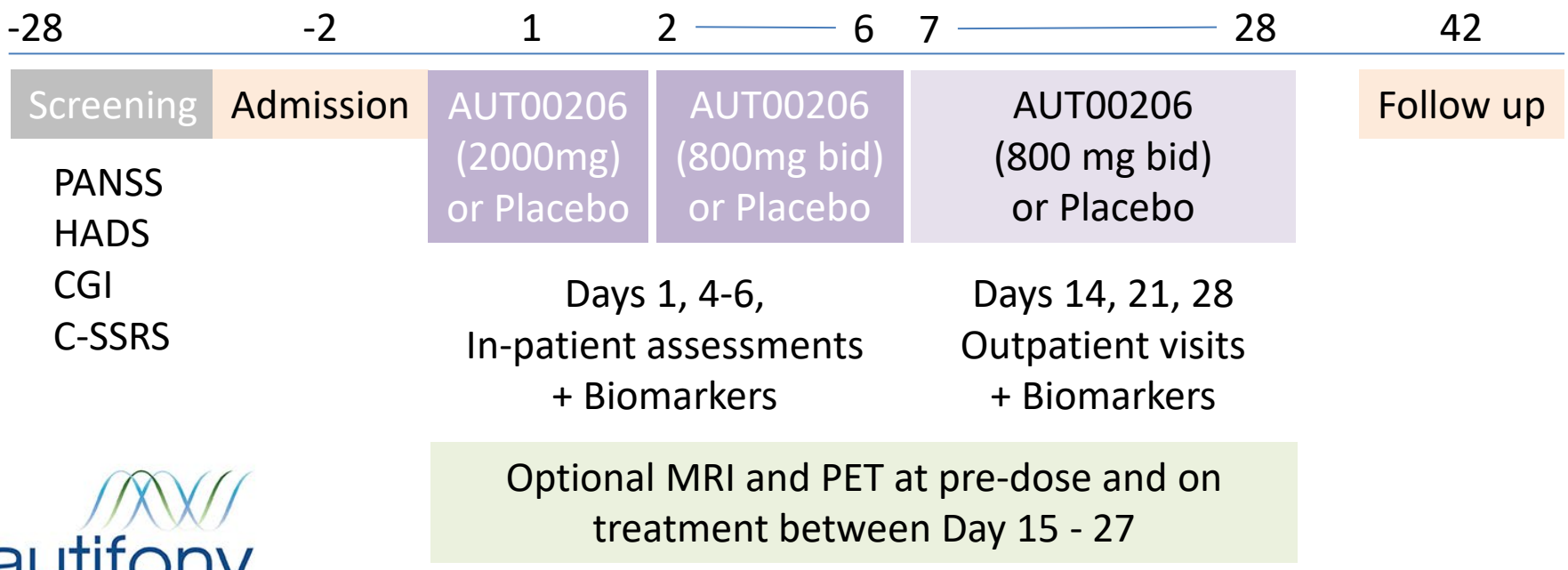
Disturbed Reward & motivation

Sleep disturbance

AUT00206
Phase Ib Study in 24 Patients with Schizophrenia

A randomised, double-blind, placebo-controlled study of the safety, pharmacokinetics and exploratory pharmacodynamics of AUT00206 for 28 days as adjunctive therapy in patients with recently diagnosed schizophrenia

- 24 male subjects, aged 18 - 50 years
- Schizophrenia - first diagnosis within last 5 years
- Taking 1 or 2 antipsychotics (excluding clozapine)
- Baseline PANSS: ~78
- 2:1 randomisation (AUT00206 : placebo)



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(Clincaltrial.gov ID# NCT03164876)

Safety/Tolerability

AUT00206 has shown excellent safety and tolerability at multiple dose levels across three Phase 1 studies, with no severe AEs or other safety signals

Primary safety and tolerability variables of the study include the following:

Vital signs, ECG, physical examination, laboratory safety tests, VAS for sedation, C-SSRS, AES

Summary of Treatment Emergent Adverse Events (TEAEs) in Patients with Schizophrenia

	Number (%) of subjects		
Severity	**Placebo (N=8)**	**AUT00206 (N=16)**	**Overall (N=24)**
Mild	2 (25)	7 (44)	9 (38)
Moderate	4 (50)	6 (38)	10 (42)
Severe	0	0	0
Total	6 (75)	13 (81)	19 (80)

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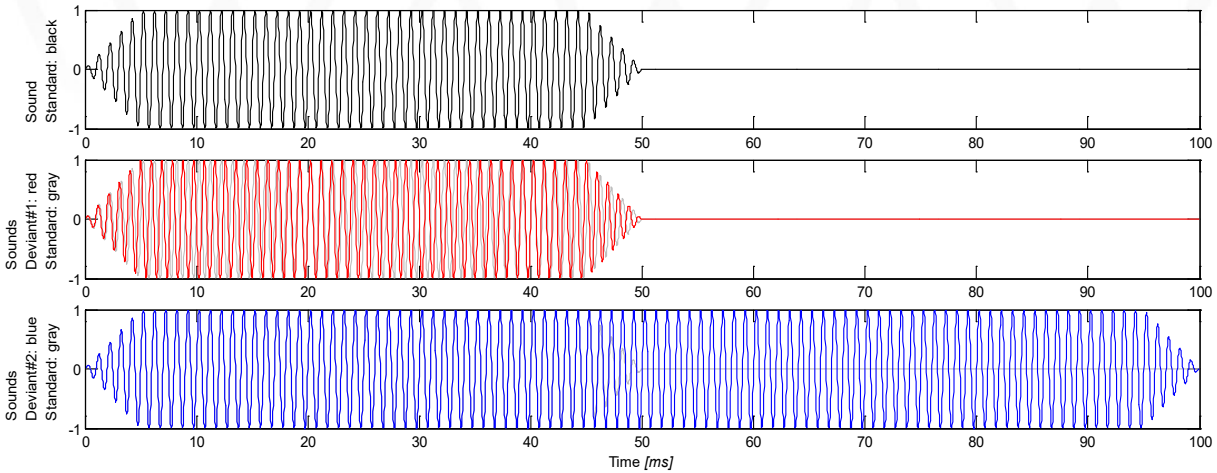
Auditory Mismatch Negativity

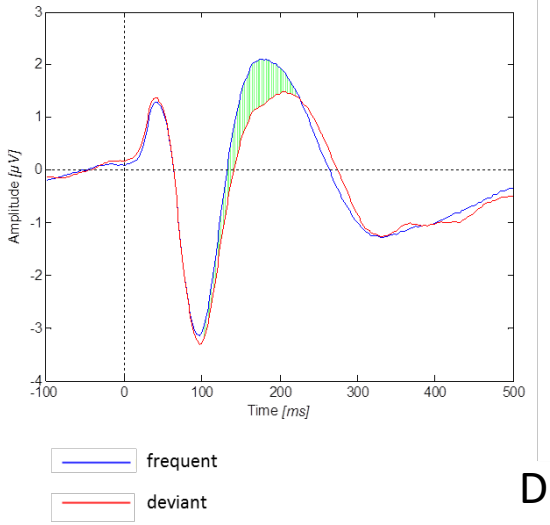
"Normal"
1000Hz, 50ms

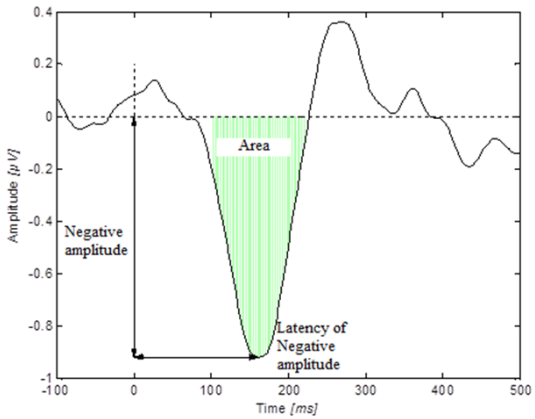
Freq. Deviant
1050Hz

Duration dev.
100ms



- Tones were presented at 75 dB SPL
- Deviants occurred 20% of the time
- Intervals between tones were randomised





Difference = "mismatch negativity"

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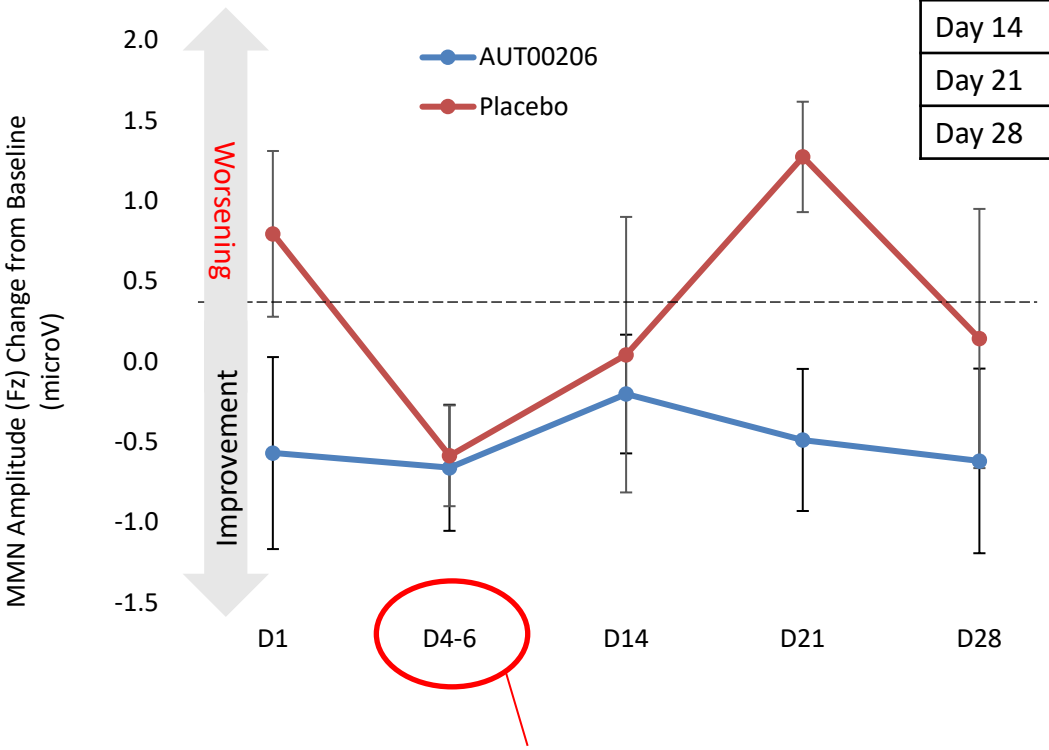
Frequency Mismatch Negativity

Change from Baseline at the FZ Electrode

Fz electrode	AUT00206 change from baseline (μV)	Placebo change from baseline (μV)
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



Pre-specified outcome measure

Consistent improvement over days was observed in the AUT00206 group (n=16)

Considerable test-test variability was seen in the placebo group (n=8)

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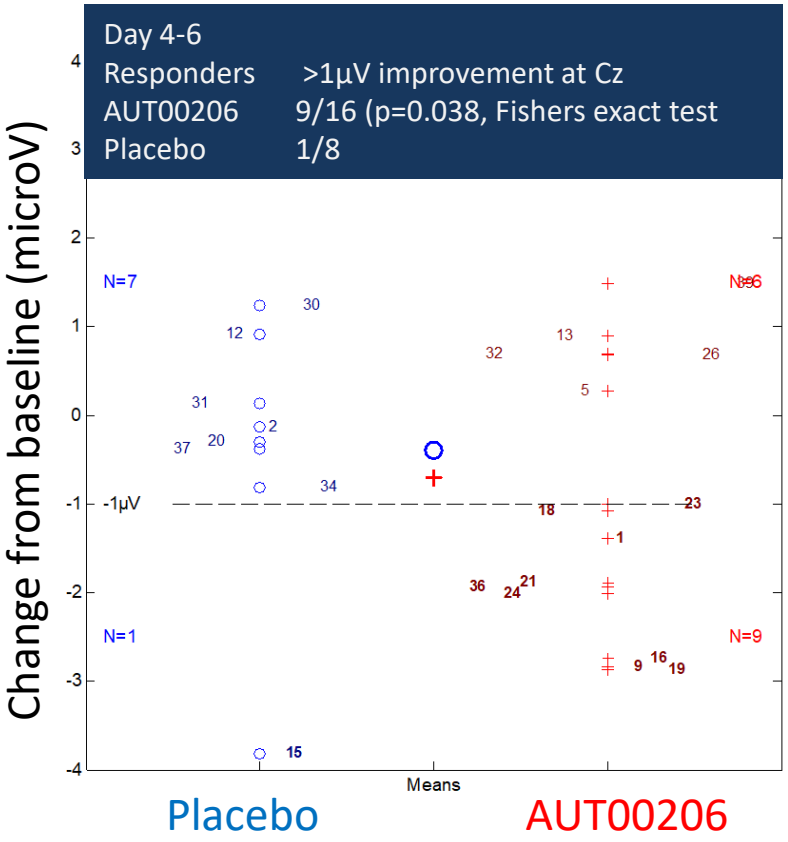
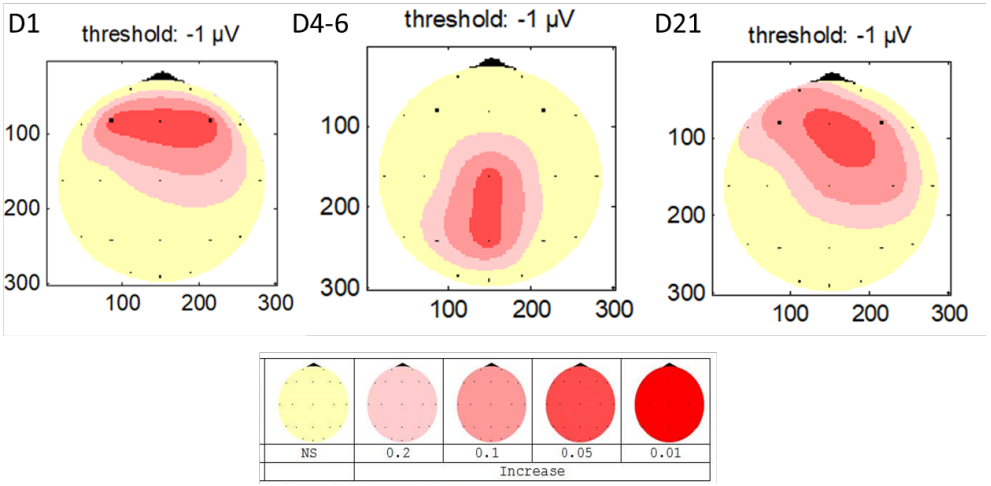
Frequency Mismatch Negativity
Responder Analysis

A post-hoc non-parametric analysis was performed to explore signals on each test day





P values (Fishers exact test)

Assessment across days observed a significant difference between AUT00206 and placebo where response was defined as a >1µV improvement from baseline

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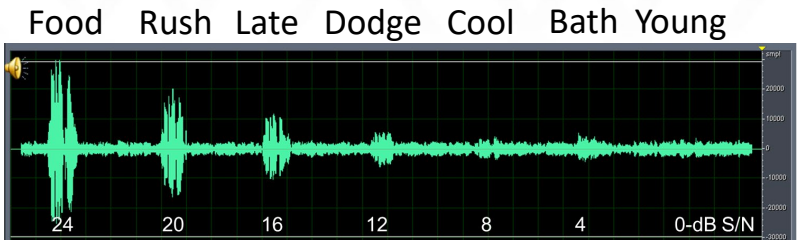
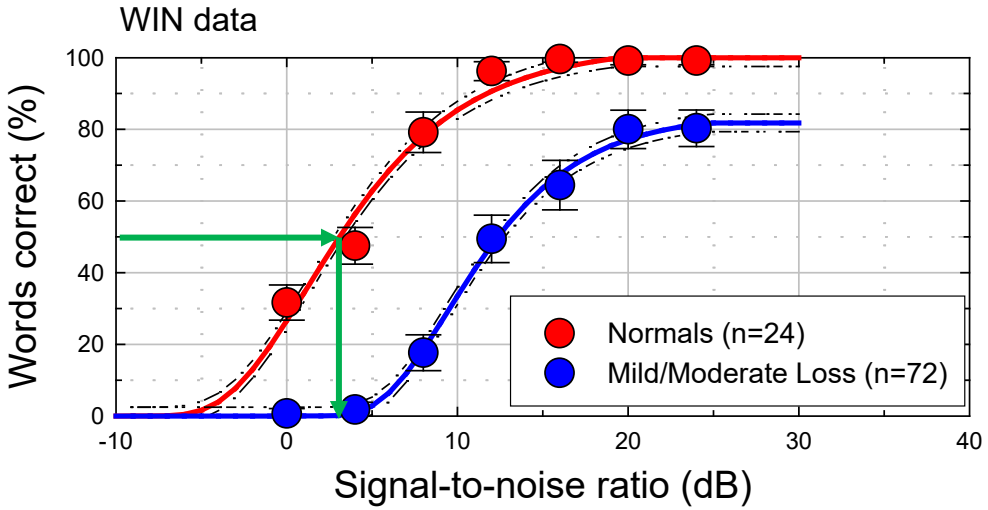
Words in Noise Test



- 35 monosyllabic words (female speaker)
  - 5 words per signal-to-noise ratio
  - Presented at 70dB and then 40db HL level
- Multi-talker babble – Varied sound level
- Scored in terms of signal-to-noise ratio at the 50% correct point (Spearman-Kärber equation)

Typical WIN data for normal hearing subjects and people with mild/moderate hearing loss (70dB presentation)



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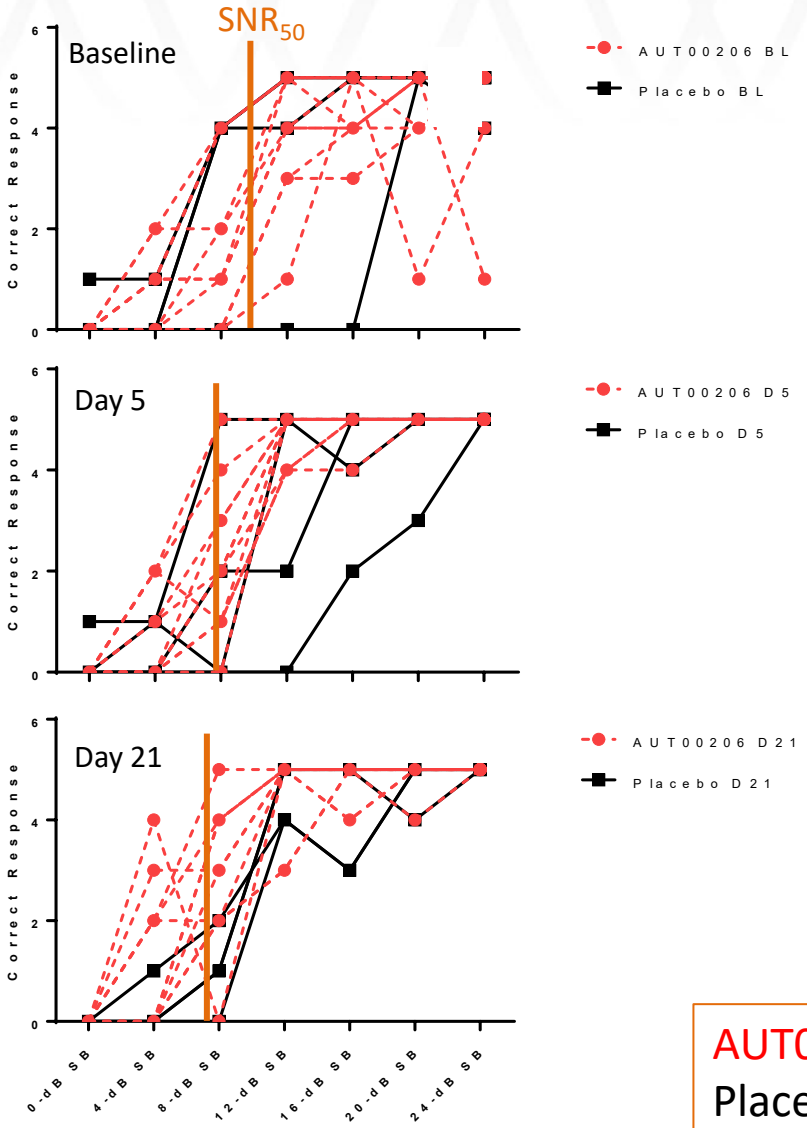
Words in Noise Test

AUT00206 improved performance of Patients with Schizophrenia

Words presented at 40dB HL



9.76 dB SNR
9.60 dB SNR

Healthy controls ~6dB on this more difficult 40dB HL presentation

7.76 dB SNR
10.80 dB SNR
P=0.085

7.20 dB SNR
10.4 dB SNR
P=0.016

AUT00206 -2.56 dB improvement
Placebo +0.8 dB worsening

Excludes S018 on D21

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Words in Noise Test

AUT00206 improved performance of Patients with Schizophrenia

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

- 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.
- 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).
- 7/10 of the AUT00206 subjects showed an improvement in WIN performance by D21
- 1/4 of the placebo subjects showed an improvement by D21
- These results are encouraging, although require replication with larger groups

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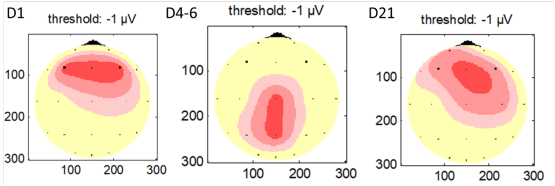
Kv3 Channel Modulation represents a paradigm shift in the treatment of schizophrenia

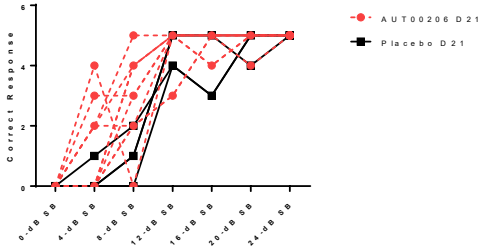
Improved information transfer will impact cognitive, negative, and perhaps positive symptom domains

Studies to date have shown clear effects on auditory information processing

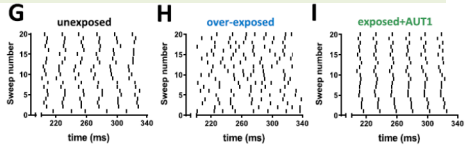
AUT00206 improved auditory MMN

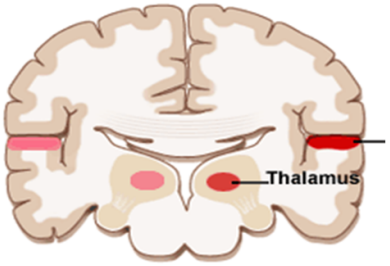


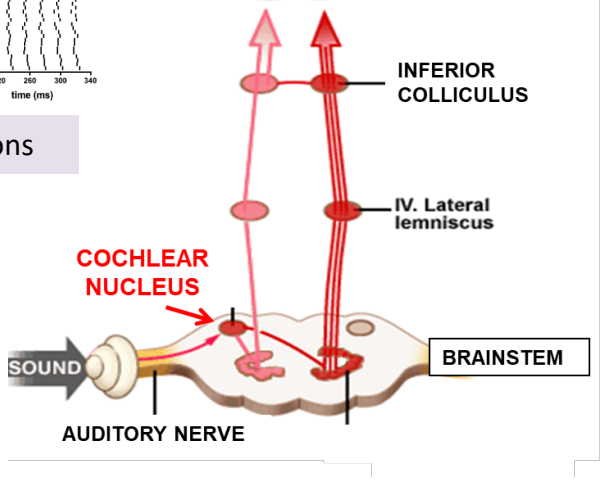
AUT00206 improved WIN performance



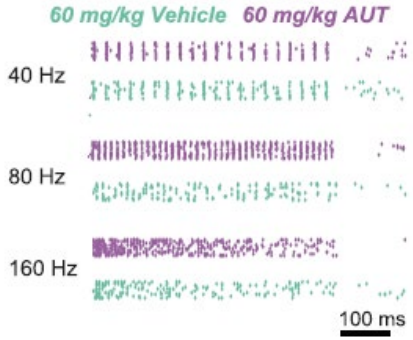
Kv3 PAMS improve cochlear nucleus firing



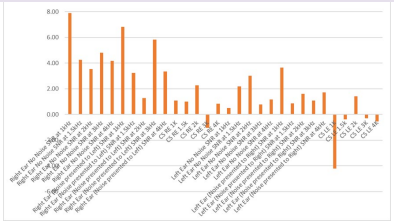




Kv3 PAMS improved Inferior Colliculus firing



AUT00206 improved otoacoustic emissions



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AUT00206 is an exciting potential treatment for patients with schizophrenia

Acknowledgements

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Additional Information

AUT031206
Patient Demographics

	Placebo	AUT00206
Age (range)	28.8 (24-38)	28.4 (21-45)
Race		
Caucasian	2	2
Black	5	12
Asian	0	1
Other	1	1
BMI (mean)	29.7	27.3
HADS-A	5.5	3.1
HADS-D	6.4	3.8
Baseline PANSS	76.9 (SD 5.67)	78.2 (SD 10.84)
Time since Diagnosis (yrs)*	1.25	0.91
Treatment Compliance (%)		
Inpatient	100	100
Outpatient	96.5	95.5

* Likely to be an underestimate

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Sources: AUT031206 CSR 25 March 2020 v1

AUT031206
Concomitant Medications

Antipsychotics (stable ≥ 3 months)	Placebo (n=8)	AUT00206 (n=16)
Aripiprazole	3	6
Paliperidone	2	1
Olanzapine	3	7
Zuclopenthixol	0	2
Flupenthixol	0	1
Amisulpiride	0	1

Other con-meds	Placebo (n=8)	AUT00206 (n=16)
Paracetamol	2	3
Procyclidine	1	3
Promethazine	0	3
Ibuprofen	1	2
Valproate	0	2

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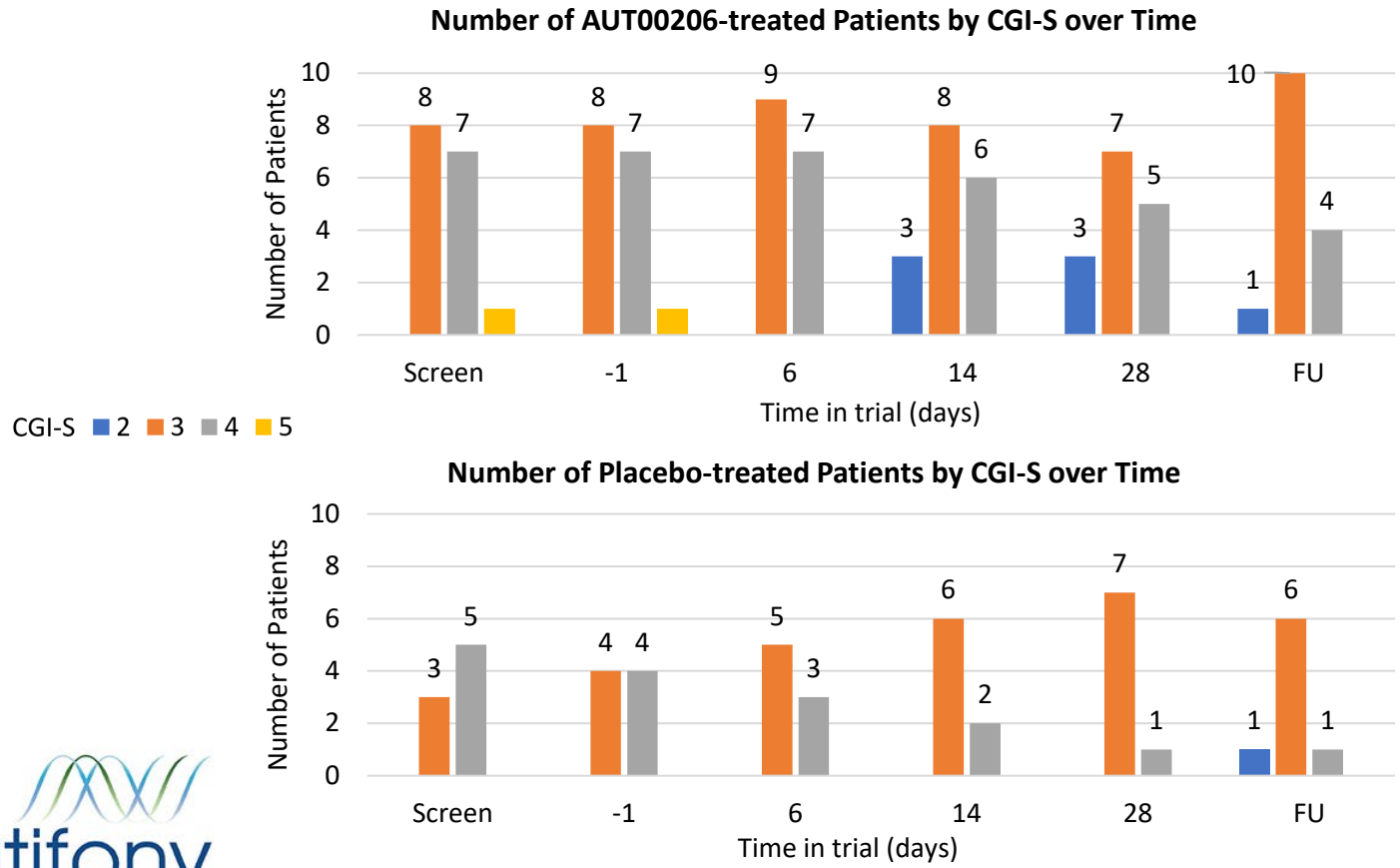
Sources: AUT031206 CSR 25 March 2020 v1

AUT031206
Clinical Effects

The study was not powered to explore efficacy on standard clinical measures (PANSS, CGI); there was no evidence of worsening of symptoms, and some signals for improvement on AUT00206

Early, Encouraging Evidence of AUT00206 for Tx of SZ Cont.

- **Clinical Global Impression (CGI): A general improvement was seen over the course of the trial in both groups, with a slight rebound at follow-up; 3 subjects achieved a CGI-S of 2 in the AUT00206 group compared to none in the placebo group**



Sources: Back Bay analysis; Autifony internal documents