Early clinical evaluation of AUT00206, a novel and selective Kv3 channel modulator for the treatment of schizophrenia

John Hutchison[1], Anil Sajjala[1], Omair Saghal[2], Bill Deakin[3], Oliver Howes[4], Colin Dourish[5], Giuseppe Alvaro[1], Charles Large[1]

[1]Autifony Therapeutics Ltd, Imperial College Incubator, Imperial College, London, SW7 2AZ, UK; [2]Hammersmith Medicines Research, Cumberland Avenue, London, NW10 7EW ; [3]Neuroscience and Psychiatry Unit, University of Manchester, M13 9PT, UK; [4]King's College, Strand, London WC2R 2LS ; [5]P1Vital Ltd, Manor House, Howbery Park, Wallingford, Oxfordshire, OX10 8BA .

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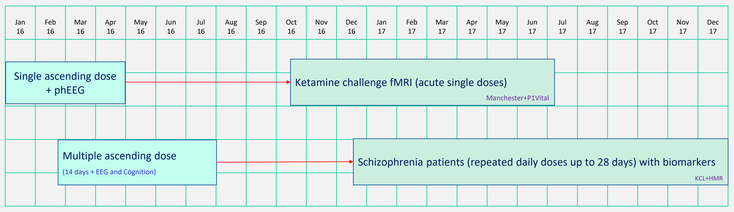
Background. It is universally acknowledged that there is a pressing need for novel treatments for schizophrenia, particularly in respect of negative and cognitive symptoms which are not well served by current therapeutic options (Keef *et al* Arch. Gen. Psychiatry 2007; 64:633-647). Here we present the first clinical data for AUT00206, a novel selective modulator of the Kv3 channel. We also describe the translational medicine approach we have adopted to bridge from preclinical studies to clinical trials in patients.

Methods. The first in human study was a randomised, double-blind, placebo-controlled study of single and multiple ascending oral doses of AUT00206 in healthy male volunteers, which also incorporated an evaluation of food effect. The primary objective was to explore the safety, tolerability (adverse events:AEs) and pharmacokinetics (PK) of AUT00206, with pharmacodynamic (PD) biomarkers as exploratory outcome measures. In Part A, 3 cohorts of 8 subjects participated in up to 5 dosing sessions, in which they received single oral doses of AUT00206 or placebo (6:2 ratio) in a dose escalating design. Progression from one dose level to the next was made after a medical review of the safety, tolerability and PK of the previous dose. The highest dose achieved by one cohort was repeated in the first dosing session of the next. The effect of food on the PK of AUT00206 was assessed in the first cohort – and all subsequent treatments were administered in the fed state. In Part B, 4 cohorts of 8 subjects (6:2 ratio) received multiple oral doses of AUT00206 once or twice daily for 14 days in the fed state. Pharmaco-EEG was performed in all subjects predose and at several timepoints post dosing. The 3 higher dose groups in Part B also involved cognitive function assessments (CANTAB battery) and Event-Related Potentials (ERPs). The ERPs included mismatch negativity (MMN), P300 oddball paradigm (P300), and gamma response to an auditory tone pre- and post- dosing, representing the exploratory biomarkers.

Results. AUT00206 was considered to be safe and well tolerated at all dose levels tested in Parts A and B of the study. The data indicate somnolence was more common following high single doses, compared to lower doses in Part A, and headache was more prevalent following AUT00206 compared to placebo in Part B. There were no deaths, serious AEs or severe AEs in either part of the study. Treatment-related AEs were more common in the Nervous System, compared to other system organ classes. There was one drop-out due to a Treatment-emergent AE in Part A; one subject's TSH blood level increased after a single dose of AUT00206 (50 mg; fasted), the subject was withdrawn by the Investigator and the AE resolved spontaneously. The PK analyses revealed a significant food effect, with Cmax and $AUC_{0\text{-}inf}$ increased 4 fold and 2 fold respectively in the presence of food. Following single doses in the fed state, exposure increased in a slightly less than dose proportional manner with low inter-individual variability.. Half-life ranged from 10-15 h, compatible with once daily dosing. The accumulation ratio (Racc) following multiple doses was approximately 1.5, with steady state achieved within 2-3 days in Part B. Data from the PhEEG, cognitive battery and ERPs are currently being analysed.

Conclusions and Next Steps. The first in human data both support and inform the continued development of AUT00206, as plasma exposure in the single and multiple dose parts of the study achieved levels in the range believed to be pharmacologically active, based on preclinical studies. Two dose levels from Part A have been chosen to explore the effects of AUT00206 on blood oxygen-level dependent (BOLD) fMRI and short term memory (N-Back) in human volunteers subjected to a low dose ketamine challenge, in a 4-way single dose crossover study in healthy human volunteers. This study will explore whether signals identified in a rodent ketamine challenge model can translate to humans and has commenced. The top dose level from Part B will be employed in an experimental study in patients diagnosed with schizophrenia within the last 5 years, who are taking no more than 2 recognised antipsychotics. This will be a randomised double-blind, placebo-controlled study (part inpatient, part outpatient) with daily dosing for 28 days. The study will be conducted jointly at King's College and Hammersmith Medicines Research, both in London, UK. In addition to clinical rating scales, cognitive function (CANTAB), ERPs (MMN, P300, ABRs) and imaging (18 F-DOPA PET, fMRI) will be performed at various timepoints to investigate PD effects in the target patient population. This study will commence later in the year.

Phase I Clinical Development Overview



Deliverables

- ❑ Human safety, tolerability, and PK data to support further clinical progression
- ❑ Ketamine challenge combined with fMRI in healthy volunteers to translate from preclinical studies and confirm central target engagement in relevant brain circuits
- ❑ Safety/tolerability and biomarker efficacy data in patients with schizophrenia

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AUT00206 First Time in Human Trial Design

A Phase 1, double blind, randomised, partial crossover study of the safety, tolerability, pharmacokinetics and pharmacodynamics of escalating single and multiple doses of AUT00206 in healthy adult men.

Part A- Single Ascending Doses (plus 800 mg BID)

- ❑ 3 groups of 8 subjects (6 active 2 placebo per session)
- ❑ 14 dosing sessions (up to 5 dosing sessions per individual)
- ❑ Doses tested: 50 to 2,400 mg
- ❑ Effect of food compared at 200 mg (fed/fasted)
- ❑ Safety, tolerability, pharmacokinetics and phEEG evaluated

Part B- Multiple Ascending Doses (14 days)

- ❑ 4 parallel groups of 8 subjects (6 active, 2 placebo per group)
- ❑ Doses tested: 200 mg OD, 400 mg OD, 800 mg OD, and 800 mg BID
- ❑ All administrations occurred with food
- ❑ Safety, tolerability, pharmacokinetics, cognition and ERPs evaluated
- ❑ ERPs included p300 oddball paradigm, MMN, resting phEEG

Summary of Drug-Related Treatment-Emergent Adverse Events

Part A

System Organ Class	Preferred Term	Placebo (fasted) (N=10) n %	Placebo (fed) (N=15) n %	Placebo bid (fed) (N=2) n %	AUT00206 (50 mg) fasted (N=6) n %	AUT00206 (100 mg) fasted (N=6) n %	AUT00206 (200 mg) fasted (N=6) n %	AUT00206 (200 mg) fed (N=6) n %	AUT00206 (400 mg) fasted (N=12) n %
Number of subjects with AEs		0	1 (6.7)	0	1 (16.7)	2 (33.3)	1 (16.7)	0	1 (8.3)
Nervous system disorders	Total number of subjects	0	1 (6.7)	0	1 (16.7)	1 (16.7)	1 (16.7)	0	1 (8.3)
	Headache	0	0	0	1 (16.7)	1 (16.7)	1 (16.7)	0	1 (8.3)
	Somnolence	0	1 (6.7)	0	0	0	0	0	0
Gastrointestinal disorders	Total number of subjects	0	0	0	0	1 (16.7)	0	0	0
	Abdominal pain	0	0	0	0	1 (16.7)	0	0	0
Psychiatric disorders	Total number of subjects	0	0	0	0	0	0	0	0
	Abnormal dreams	0	0	0	0	0	0	0	0
	Euphoric mood	0	0	0	0	0	0	0	0
General disorders and administration site conditions	Total number of subjects	0	0	0	0	0	0	0	0
	Fatigue	0	0	0	0	0	0	0	0
Investigations	Total number of subjects	0	0	0	1 (16.7)	0	0	0	0
	Blood thyroid stimulating hormone increased	0	0	0	1 (16.7)	0	0	0	0

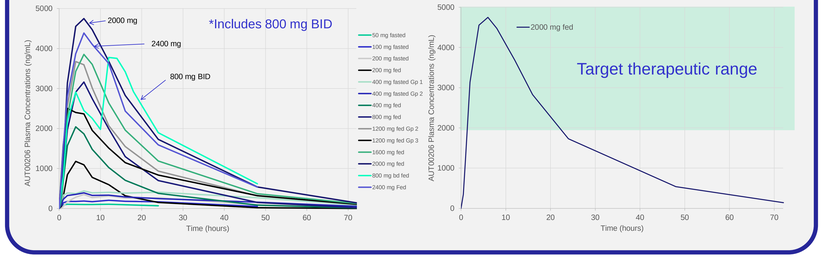
System Organ Class	Preferred Term	AUT00206 (400 mg) fed (N=6) n %	AUT00206 (800 mg) fed (N=7) n %	AUT00206 (800 mg) bid (fed) (N=6) n %	AUT00206 (1200 mg) fed (N=10) n %	AUT00206 (1600 mg) fed (N=6) n %	AUT00206 (2000 mg) fed (N=6) n %	AUT00206 (2400 mg) fed (N=6) n %
Number of subjects with AEs		1 (16.7)	0	0	0	1 (16.7)	2 (33.3)	3 (50.0)
Nervous system disorders	Total number of subjects	1 (16.7)	0	0	0	0	1 (16.7)	3 (50.0)
	Headache	1 (16.7)	0	0	0	0	0	0
	Somnolence	0	0	0	0	0	1 (16.7)	3 (50.0)
Gastrointestinal disorders	Total number of subjects	0	0	0	0	1 (16.7)	0	0
	Abdominal pain	0	0	0	0	1 (16.7)	0	0
Psychiatric disorders	Total number of subjects	0	0	0	0	0	1 (16.7)	0
	Abnormal dreams	0	0	0	0	0	1 (16.7)	0
	Euphoric mood	0	0	0	0	0	1 (16.7)	0
General disorders and administration site conditions	Total number of subjects	0	0	0	0	0	1 (16.7)	0
	Fatigue	0	0	0	0	0	1 (16.7)	0
Investigations	Total number of subjects	0	0	0	0	0	0	0
	Blood thyroid stimulating hormone increased	0	0	0	0	0	0	0

Part B

System Organ Class	Preferred Term	Placebo (N=6) n %	Placebo bid (N=2) n %	AUT00206 (200 mg) (N=6) n %	AUT00206 (400 mg) (N=6) n %	AUT00206 (800 mg) (N=6) n %	AUT00206 (800 mg) bid (N=6) n %
Number of subjects with AEs		1 (16.7)	1 (50.0)	4 (66.7)	1 (16.7)	1 (16.7)	2 (33.3)
Nervous system disorders	Total number of subjects	1 (16.7)	1 (50.0)	2 (33.3)	0	1 (16.7)	2 (33.3)
	Headache	1 (16.7)	1 (50.0)	2 (33.3)	0	0	2 (33.3)
	Dizziness	0	0	0	0	1 (16.7)	0
Skin and subcutaneous tissue disorders	Total number of subjects	0	0	3 (50.0)	0	0	0
	Erythema	0	0	1 (16.7)	0	0	0
	Pruritus	0	0	1 (16.7)	0	0	0
	Rash	0	0	1 (16.7)	0	0	0
Gastrointestinal disorders	Total number of subjects	0	0	0	1 (16.7)	0	0
	Abdominal distension	0	0	0	1 (16.7)	0	0

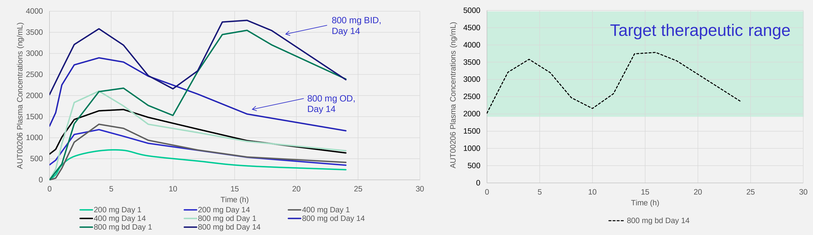
AUT00206 - Single Dose Pharmacokinetics*

AUT00206 2000mg covers the predicted therapeutic concentration range, based on preclinical data



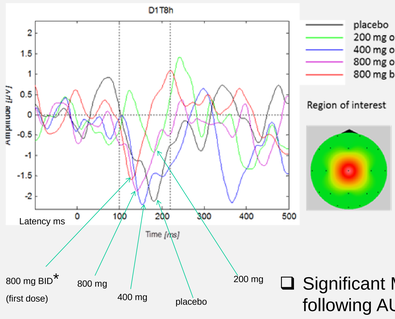
AUT00206 - Multiple Dose Pharmacokinetics

AUT00206 800mg BID achieves predicted therapeutic concentrations, based on preclinical data



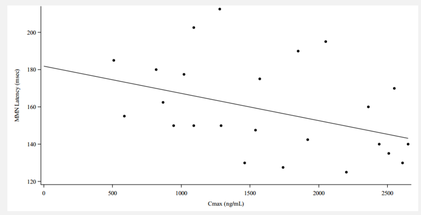
MMN Latency: Group mean data by dose and correlation with Cmax

Mismatch Negativity Latency: Dose dependent reduction 8 hours following AUT00206 on Day 1



* p<0.05

Correlation between individual Cmax values and MMN latency at 8 Hours on Day 1



Regression Equation: MMN Latency (msec) = 181.8 -0.015*Cmax (ng/mL)
P-value for Cmax (ng/mL): 0.063

- ❑ Significant MMN latency decrease observed in normal volunteers following AUT00206 on Day 1
- ❑ MMN latency increases are associated with cognitive deficits in patients[1,2]

Conclusions

- ❑ AUT00206 was safe and well tolerated following single oral doses up to 2400 mg, and following multiple doses of up to 800 mg BID for 14 days.
- ❑ Mild somnolence was present in 50% subjects at the highest single dose tested, whilst headache was more common following multiple doses of AUT00206 compared to placebo.
- ❑ Dose dependent increases in Cmax and AUC were observed which were just sub-proportional, and following multiple dosing the accumulation ratios were as predicted from single dose data. Half-life was consistent with once daily dosing and absorption was significantly enhanced in the presence of food.
- ❑ No drug-related effects were observed on phEEG, cognition or the P300 oddball paradigm auditory-evoked gamma responses, however dose and concentration dependent reductions were observed in Mismatch Negativity latency.
- ❑ Mismatch Negativity latency may be a novel biomarker for Kv3 activation, and hence is included in the forthcoming study of AUT00206 in patients with schizophrenia, as described above.

References

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2. Ji L-L, Zhang Y-Y, Zhang L, He B and Lu GH. (2015). Mismatch negativity latency as a biomarker of amnestic mild cognitive impairment in Chinese rural elders. Frontiers in Aging Neuroscience. doi: 10.3389/fnagi.2015.00022

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Declaration of interests: JH, AS, GA and CL are employees of Autifony Ltd. OS and CD are employees of companies contracted to perform clinical studies part-funded by Autifony Ltd. BD and OH have received expenses to attend conferences and fees for lecturing, consulting and attending advisory boards from different pharmaceutical companies.