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

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Abstract (4634 characters including spaces, limit=4700)

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 remain blinded at the time of writing, however somnolence was more common following high single doses, compared to lower doses in Part A, and headache was more prevalent at the higher dose levels 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 were no dropouts relating to treatment-emergent AEs. The PK analyses revealed a significant food effect, with Cmax and AUC_{0-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 dependant (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 is due to commence shortly in Manchester, UK. 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.

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