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

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Sponsor: Carol Tamminga

Results: This is the first clinical trial for AUT00206, performed in patients with drug-resistant positive and negative schizotypal symptoms, who are not being treated with current antipsychotic medications (Olanzapine, Clozapine, Paliperidone, Quetiapine, Ziprasidone). In part A, receptor occupancy, plasma and brain concentrations were measured in 12 subjects receiving 3 doses (50, 200, and 400 mg) administered orally to healthy volunteers. In part B, there were 4 groups (Gp1-Gp4) of 6 subjects each, who were administered AUT00206 in a double-blind, randomised, placebo-controlled, multiple ascending dose design (i.e. single ascending dose followed by 4 ascending doses). AUT00206 was administered orally at 50, 200, and 400 mg for a total of 21 days after an initial single ascending dose of 50 mg. Each dose was administered to all subjects as a single dose followed by a repetition of all four doses on day 21. The study was conducted at 2 sites, (UK and USA) using the same protocol in all subjects. A significant drug related increase in mean plasma level of AUT00206 was observed. A significant drug related increase in mean plasma level of AUT00206 was also observed at 50 mg (p<0.05). Plasma concentrations were below the LOQ level at 200 mg. A significant reduction in mean plasma level of AUT00206 was observed at 400 mg (p<0.05).

Conclusions: This programme is supported by non-dilutive funding from Innovate UK/MRC.

References:

Sources of financial sponsorship: The work was supported by Innovate UK and Autifony Theraputics Limited.

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

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 in 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 pEEG, 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.

Conclusions
- Significant MMN latency decrease observed in normal volunteers following AUT00206 on Day 1
- MMN latency increases are associated with cognitive deficits in patients

SUMMARY OF DRUG-RELATED TREATMENT-EMERGENT ADVERSE EVENTS

AUT00206 First Time in Human Trial Design

A Phase 1, double blind, randomised, parallel 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 2400 mg
- Effect of food compared at 200 mg (fed/fasted)
- Safety, tolerability, pharmacokinetics and pEEG 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 pEEG

AUT00206 - Single Dose Pharmacokinetics

AUT00206 Plasma Concentrations (ng/mL)

AUT00206 - Multiple Dose Pharmacokinetics

Significant MMN latency decrease observed in normal volunteers following AUT00206 on Day 1
MMN latency increases are associated with cognitive deficits in patients

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Declarations of interest: John Hutchison, Anil Sajjala, Omar Haghighi, Bill Deakin, Oliver Howes, Colin Dourish, Giuseppe Alvaro and Charles Large are employees of companies contracted to perform clinical studies part funded by Autifony Ltd. CS and DH have received expenses to attend meetings and fees for lecturing, consulting and attending advisory boards from different pharmaceutical companies.