Inhibition of the mechanistic target of rapamycin complex 1 signalling pathway for treatment of moderate-severe alcohol use disorder - an early phase safety and feasibility pilot study

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Introduction/Issues: Long-term effectiveness of current medications for moderate-severe alcohol use disorder (AUD) is limited. Pharmacotherapy development is expanding towards modifying underlying dysregulated neurobiology. Mechanistic target of rapamycin complex1 (mTORC1) signalling is involved in processes underpinning expression of addiction and relapse behaviours including drug-associated memory consolidation and maintenance. Preclinical evidence suggests inhibiting maladaptive mTORC1 signalling may reduce or prevent consumption and cue-induced relapse. mTORC1 inhibitors (e.g. everolimus) are used for other clinical indications and warrant trialling for AUD.

Method/Approach: An open-label early phase trial examining safety and feasibility of a 14-day course of everolimus (2.5 or 5mg daily) commenced during withdrawal in participants with moderate-severe AUD (N=12) will be undertaken. Safety (adverse events, symptom/side-effects), feasibility (proportion consented, time-point completion) and pilot efficacy [alcohol use (self-report and biochemical verification), cue-induced craving, withdrawal, mental health, wellbeing] outcomes will be assessed during, immediate-post and 28 days post-treatment. Pharmacokinetic analysis will be performed, and a neuroimaging sub-study implemented to examine neurobiological correlates involved in cue-elicited craving in people with AUD and the potential impact of treatment on dysregulated neural activity.

Key Findings: It is expected that treatment will be safe and tolerable, and the trial can be feasibly conducted in this population. Pilot efficacy outcome data will be obtained to power and inform larger multi-site randomised controlled trials. Pharmacokinetic profile will be established and underlying neuro-circuitry further understood.

Discussion and Conclusions: By targeting a brain pathway involved in the development and maintenance of addiction, in contrast to traditional treatments, mTORC1 inhibition is an innovative approach to medication development for AUD.

Implications for Translational Research: Early phase trials based on strong biological rationale are vital to ensure preclinical knowledge is successfully translated into clinical research. This study is an important contribution to the field and the goal of improving novel treatment options for people with AUD.

Disclosure of Interest Statement: There is no conflict of interest to disclose.