Conclusions: The results provide support for a larger scale efficacy trial that is currently in progress. A description of the randomized controlled trial will be provided in conjunction with the lessons learned from the pilot project that informed adaptations to the I-CAT model.

32. ADDRESSING METHODOLOGICAL CHALLENGES IN CIAS TO ENHANCE CLINICAL TRIAL SUCCESS

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Cognitive impairment is common in patients with schizophrenia, with deficits frequently observed across both neurocognitive and social cognitive tasks. Cognitive dysfunction is among the strongest determinants of poor social and occupational functioning in this population, indicating that these deficits represent an important unmet target for therapeutic intervention. Despite considerable efforts by pharmaceutical companies, there are currently no drugs that have been approved for the amelioration of these deficits in schizophrenia. A series of compounds have demonstrated early promise, only to have failed at the later stages of development. It remains a matter of debate whether this is truly due to the compounds being ineffective, or whether trial methodology itself has been a limiting factor in successfully demonstrating the efficacy of these agents.

Key methodological limitations of existing trials, to be discussed, include a multitude of factors around patient selection, such as level of cognitive impairment, age, symptom severity and current plus existing medical history and medication. Product-specific data is gradually becoming available, to build an evidence base which suggests not all patients meeting the DSM-V diagnostic criterion for schizophrenia should be included in trials targeting cognitive impairment associated with schizophrenia (CIAS). Several stakeholders, including regulatory agencies and payers, are increasingly interested in exploring and understanding ways to enhance the outcome of CIAS trials to see the approval of an effective pharmacological agent reach the market.

This symposia will hear from four presenters to discuss 1) a brief history of CIAS trials and the current consensus on patient selection (Dr Jack Cotter); 2) lessons learnt from the successes and failures in these trials, including regulatory considerations (Dr Steve Brannan, Karuna Pharmaceuticals); 3) a post-hoc analysis of a large Phase II multi-national trial (Dr Kiri Granger, on behalf of Boehringer Ingelheim); 4) a novel compound entity currently in development & methodological/statistical adaptations made to this drug development program (Dr Charles Large, Autifony Therapeutics). Chief Scientific Officer at Cambridge Cognition, Dr Jenny Barnett, will be the discussant for this symposia panel to summarize, what we have learnt so far in CIAS trials, the status of the current evidence base to guide decision making and what the future of drug development and post-marketing approval for CIAS potentially holds.

We hope this symposia will be both educational and thought provoking by providing useful, evidence-based, considerations for the design of future studies to enhance CIAS trial success. Advances in this area are likely to hold direct 'real world' benefits for patients and their families, while also reducing the financial burden of the disorder on society. The lessons learned and recommendations discussed here could also improve the efficacy and outcome of clinical trials for other serious mental health illnesses in which cognitive dysfunction is a core and debilitating feature.

32.1 PHARMACOTHERAPY TRIALS FOR CIAS: A BRIEF HISTORY AND CONSIDERATIONS FOR THE FUTURE

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Background: Cognitive impairment is common in people with schizophrenia and is among the strongest predictors of functional decline in this patient group. Despite considerable efforts, there are however no pharmacological treatments for cognitive impairment associated with schizophrenia (CIAS) that have successfully reached efficacy criterion in phase III trials to receive regulatory market approval. The high rate of phase III failures calls into question the reasons why compounds keep failing, despite promising clinical evidence for cognitive improvement in phase II trials. This presentation will provide a brief history on these trials before moving on to discuss the extent to which objective cognitive performance has been used as an eligibility and/or stratification criterion in CIAS intervention trials. The potential implication of these findings for future CIAS research and development will be discussed.

Methods: A systematic search was carried out using ClinicalTrials.gov for all protocols associated with schizophrenia listed between January 2000 and October 2018. Eligible studies were
randomized, double-blind, placebo-controlled pharmacotherapy trials conducted in patients with a diagnosis of schizophrenia, in which a cognitive endpoint was the primary outcome measure. For all eligible trials, information was collated (where provided) on: (1) study characteristics (sponsor, year of publication, phase, country where the work was performed); (2) inclusion criteria; (3) any objective cognitive tasks used to assess patient eligibility; (4) randomization procedures; (5) primary and secondary study objectives; (6) pharmacological agent under study.

Results: Of the trials that used cognition as an endpoint, only a small minority employed inclusion criteria requiring the presence of an objectively measured cognitive deficit at baseline. In contrast, a much larger number of trials included exclusion criteria to eliminate subjects who had severe cognitive deficits or dementia. The only consistent inclusion criteria across clinical trials were confirmation of a diagnosis of schizophrenia, as determined using the Diagnostic and Statistical
Manual of Mental Disorders and/or the Positive and Negative Syndrome Scale.

Conclusions: Even when cognition is the primary outcome and an intervention is intended to ameliorate cognitive dysfunction, the majority of studies did not include formal eligibility criteria to ensure study participants had a cognitive deficit on entry into the trial. While this is consistent with consensus guidelines that have previously recommended such an approach, the increase in CIAS trial failures call this view into question, particularly as neither existing diagnostic criteria nor psychotic symptom severity is indicative of cognitive ability. An evidence-base is building which suggests that not all patients with schizophrenia may benefit from a pro-cognitive agent if they have relatively intact cognition at baseline, relative to normative performance thresholds. Exclusion of these individuals, or at least ensuring equal stratification of these 'normal' cognitive performers across trial arms during randomization, may provide additional power to observe pro-cognitive treatment effects in CIAS trials.

32.2 TWO GLOBAL PHASE III TRIALS OF ENCENICLINE FOR COGNITIVE IMPAIRMENT IN CHRONIC SCHIZOPHRENIA PATIENTS: RED FLAGS AND LESSONS LEARNED

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Background: Multiple lines of evidence indicate that alterations of the α7 nicotinic acetylcholine receptor (nAChR) may play a role in the pathophysiology of several neuropsychiatric disorders that manifest with cognitive impairment, including schizophrenia. Encenicline (EVP-6124), a selective α7 nAChR showed promising biomarker and clinical evidence for cognitive improvement as well as functional co-primaries in Phase II trials. Positive results led to the launch of two global Phase III trials (EVP-6124-015/016) aimed at assessing the efficacy and safety of once-daily encenicline tablets as a pro-cognitive treatment in stable patients with schizophrenia. Our primary hypothesis was that encenicline would demonstrate efficacy for the