unmedicated patients with psychosis. Future clinical trials would benefit from frameworks built into clinical services, to signpost patients not responding to medication and those discontinuing medication to clinical trials of alternatives.

T41. SAFETY PROFILE OF ADJUNCTIVE PIMAVANSERIN IN THE ENHANCE STUDY, A PHASE 3 TRIAL FOR THE POTENTIAL TREATMENT OF SCHIZOPHRENIA IN PATIENTS WITH AN INADEQUATE RESPONSE TO ANTIPSYCHOTIC TREATMENT

Dragana Bugarski-Kirola*[1], Rene Nunez[1], Ramzey Odetalla[1], Mohammed A. Bari[2], Istvan Bitter[3], Peter D. Feldman[1], I-Yuan (Cathy) Liu[1], Srdjan Stankovic[1]
[1]ACADIA Pharmaceuticals, Inc.; [2]Synergy Clinical Research Centers; [3]Semmelweis University

Background: Many patients with schizophrenia (SCZ) do not fully respond to antipsychotic (AP) treatment despite adherence and require augmentation, often with an AP with similar mode of action. Evidence supporting polypharmacy is limited and adding another AP increases associated risks of adverse effects, including extrapyramidal symptoms and cardiometabolic disturbances. Pimavanserin (PIM) is a highly selective serotonin 5-HT2A inverse agonist/antagonist approved for the treatment of Parkinson's disease psychosis. The phase 3 ENHANCE study evaluated adjunctive PIM in patients with SCZ and inadequate response to their current AP. As previously reported (ACNP 2019), the primary efficacy endpoint of ENHANCE (change in Positive and Negative Syndrome Scale [PANSS] total score) did not achieve statistical significance. Other prespecified analyses did yield nominal statistical separation from placebo, including changes in PANSS Negative Symptoms subscale, and in PANSS total score for the subgroup of European patients. Here we describe key safety results.
Methods: ENHANCE was a 6-week, randomized, double-blind, placebo (PBO)-controlled study of adjunctive PIM in patients with SCZ and inadequate response to their prescribed AP (aripiprazole, olanzapine, risperidone, and others). Patients included were age 18–55 years with PANSS total score of ≥65 and ≤110, and scores of ≥4 on ≥2 items including delusions, hallucinatory behavior, and/or suspiciousness/persecution; Clinical Global Impression-Severity scale score ≥4 was also required. The starting dose of PIM or PBO was 20 mg daily and could be adjusted up to 34 mg or down to 10 mg daily after 1 week based on investigator discretion. Safety was evaluated in all randomized patients who received ≥1 dose of study drug.
Results: All 396 randomized patients (PIM, n=198; PBO, n=198) were included in the safety analysis set. Treatment-emergent adverse events (TEAEs) were reported in 39.9% and 36.4% of patients in the PIM and PBO groups, respectively; most frequent TEAEs were headache (PIM 6.6%, PBO 9.1%), somnolence (PIM 6.6%, PBO 3.5%), and insomnia (PIM 5.1%, PBO 3.5%). Changes from baseline in Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Scale global clinical assessment of akathisia (GCAA), and Simpson–Angus Scale (SAS) scores were similar in the PIM and PBO groups. No patient developed dyskinesia (defined as a score ≥3 on any, or ≥2 on 2 of the first 7 AIMS items). Akathisia (GCAA score ≥2) in patients without baseline akathisia occurred in 4/186 (2.2%) patients receiving PIM and 1/189 (0.5%) receiving PBO. Parkinsonism (SAS total score >3) in patients without Parkinsonism at baseline occurred in 3/181 (1.7%) patients receiving PIM and 4/182 (2.2%) receiving PBO. No patient in either treatment arm had QTcF prolongation >500 msec or Torsades de Pointes during the study period; 2 (1.1%) patients in the PIM arm and 0 in the PBO arm had post-baseline QTcF prolongation >60 msec. Hypotension was reported in 1 patient in each treatment group; no patient had clinically important changes from baseline in blood pressure during treatment. Weight increase ≥7% from baseline was reported in 5/189 (2.6%) patients in the PIM group and 3/191 (1.6%) in the PBO group. Mean changes from baseline in PIM and PBO groups for fasting glucose were 0.07 mmol/L and 0.01 mmol/L; for triglycerides were -0.007 mmol/L and -0.136 mmoL/L, and for cholesterol were -0.10 mmol/L and -0.03 mmol/L, respectively.
Discussion: Results of ENHANCE provide evidence that the addition of PIM to frequently used APs is well tolerated in patients with SCZ.

T42. HIGH ADHERENCE TO CURRENT ANTIPSYCHOTIC AND ADJUNCTIVE PIMAVANSERIN IN THE ENHANCE STUDY, A PHASE 3 TRIAL TO EVALUATE THE TREATMENT OF SCHIZOPHRENIA IN PATIENTS WITH AN INADEQUATE RESPONSE TO ANTIPSYCHOTIC TREATMENT

Brandon Abbs*[1], Dragana Bugarski-Kirola[1], I-Yuan (Cathy) Liu[1], Mona Darwish[1], Srdjan Stankovic[1]
[1]ACADIA Pharmaceuticals Inc.

Background: Individuals with schizophrenia experience an inadequate response to antipsychotic (AP) treatment at a high rate, up to 70% in some cases (McEvoy et al. 2006). Possible reasons for this include subtherapeutic AP blood levels and medication ineffectiveness. Although patient self-report and clinician opinion are commonly used to identify non-adherence, they are unreliable. AP polypharmacy for inadequate response remains widespread despite a lack of supportive evidence. Few completed trials offer guidance on the optimal trial design and procedures to establish inadequate response at screening/baseline.
Adequate treatment is defined as an AP taken at a therapeutic dose for a sufficient duration (Taylor et al. 2012). Confirming treatment stability and adherence, both prior to enrollment and during the trial, is necessary to ensure sufficient exposure to an AP prior to deeming a response inadequate and justifying augmentation. Measuring adherence during the trial is necessary to ensure correct interpretation of trial results.
We present the trial design and adherence data from a recently completed Phase 3 clinical trial of an adjunctive therapy in inadequately responding patients with schizophrenia. The trial did not meet the primary endpoint (Bugarski-Kirola, et al. 2019).
Methods: ENHANCE was a 6-week, randomized, double-blind study of adjunctive pimavanserin (PIM; a 5-HT2A inverse agonist) versus placebo to evaluate the treatment of schizophrenia in patients with an inadequate response to their prescribed AP (aripiprazole, olanzapine, risperidone, and others). During screening, patients provided documentation showing treatment stability for at least 8 weeks prior to screening, a blood sample was tested for adherence, and a telemedicine interview was completed with an independent clinician. After randomization, blood sampling occurred at Baseline, Week 1, Week 3, and Week 6 for pharmacokinetic (PK) assessments of the AP and adjunctive PIM.
Results: ENHANCE screened 633 patients with 35 rescreens for a total of 668 screenings. Adherence to background AP was high for all patients screened as background AP levels were detected in 90.6% of patients. However, the most common reason for screen failure was still a failure to detect background AP (16.9% of all screen failures). Other common reasons for screen failure included lack of prescription stability/appropriate dosing, investigators determining the patient was inappropriate for the study, and withdrawal of consent, the latter of which often reflected the rigorous screening process required for the study. Proactively screen failing non-adherent patients led to higher levels of adherence at Baseline compared to screening with 94.9% of patients demonstrating adherence at Baseline. Moreover, this is a substantial improvement over the theoretical adherence rate of 84.5% had non-adherent patients been randomized. The high rate of adherence at Baseline for background AP was maintained at Weeks 1, 3 and 6. High adherence was also found for adjunctive PIM. 198 patients were randomized to the PIM treatment arm, 190 had a blood sample at Week 1 with 187 (98.4%) showing measurable levels of PIM, and 182 had a blood sample at Week 3 with 180 (98.9%) showing measurable

levels of PIM. Patients leaving the study (either at Week 6 of treatment or as a result of early termination) showed a 96.8% adherence rate.
Discussion: By employing rigorous screening procedures, including testing for AP treatment adherence, the ENHANCE study enrolled a representative sample of patients with a confirmed inadequate response to their current AP and achieved a high level of treatment adherence (both to patient's AP treatment and study drug).

T43. PREDNISOLONE VERSUS PLACEBO AS AUGMENTATION THERAPY IN PSYCHOTIC DISORDERS

Nasib Lyliana[1], Inge Winter*[1], Rene Kahn[1], Iris Sommer[2]
[1]University Medical Center Utrecht; [2]UMC Groningen

Background: An increasing body of evidence suggests that immune dysregulation is involved in the pathophysiology of psychotic disorders. Some, but not all, anti-inflammatory drugs have shown positive effects on symptom severity. Given the need for new treatment options in psychosis, anti-inflammatory medication should be explored as a potential treatment to improve outcome. Being a potent glucocorticosteroid that adequately passes through the blood-brain barrier, prednisolone qualifies as a potential candidate. This proof-of-concept study aims to explore the effect of prednisolone, compared to placebo, on symptom severity in patients with a psychotic disorder who are on a stable dose of antipsychotic medication.
Methods: The study was conducted from July 2015 until April 2019 in four centers in the Netherlands and Belgium. Patients with a psychotic disorder were randomized, double blind, 1:1 to prednisolone or placebo in addition to their antipsychotic treatment. Patients randomized to prednisolone started with 40 mg/day, tapered down to zero in six weeks. Several procedures were implemented to ensure patient safety during prednisolone exposure (e.g. regular safety labs). The primary objective was to compare change in symptom severity, measured through the Positive and Negative Syndrome Scale (PANSS), in patients treated with prednisolone versus placebo, in additional to a stable antipsychotic regimen. To this end, a mixed model repeated measures ANOVA was applied.
Results: 42 participants were randomized, equally divided across the treatment arms. The six week treatment period was completed by 20 patients randomized to placebo and 19 patients randomized to prednisolone. There were no baseline differences in demographics, symptom severity, depression or global functioning between the treatment groups. There was no difference in symptom improvement between patients treated with prednisolone compared to placebo at the end of the six week treatment period (p=.304). Global functioning and depression were not significantly different between treatment arms end of treatment. No Serious Adverse Events (SAEs) occurred during the treatment phase.
Discussion: The results of this proof-of-concept study do not support the immune hypothesis of psychosis: there was no difference in symptom improvement after a six week treatment with prednisolone compared to placebo, in addition to a stable regimen of antipsychotics. The small sample size is the main limitation of this trial. Even though prednisolone did not show to be a potential candidate for augmentation therapy in psychosis, it is of interest to note that patients did not deteriorate when using prednisolone nor were there more SAE's in the active treatment arm. This argues against the general safety concerns for prescribing prednisolone in patients with psychosis for the treatment of immune disorder, although additional research is needed.

T44. 12-MONTH FOLLOW UP OF METABOLIC MEASURES FOLLOWING A RANDOMISED CONTROLLED TRIAL OF TREATMENT OF CLOZAPINE ASSOCIATED OBESITY AND DIABETES WITH EXENATIDE (CODEX)

Dan Siskind*[1], Anthony Russell[2], Steve Kisely[3]
[1]Metro South Addiction and Mental Health Service; [2]University of Queensland; [3]University of Queensland and MSAMHS

Background: Clozapine is associated with high rates of obesity and type 2 diabetes (T2DM). Exenatide, a glucagon-like peptide-1 (GLP-1) receptor agonist, can counter clozapine-associated GLP-1 dysregulation. Our randomized, controlled (RCT), open-label, pilot trial of once-weekly extended-release subcutaneous exenatide or treatment as usual (TAU) for 24 weeks (n=28), found 6/14 people on exenatide achieved >5% weight loss vs 1/14 receiving usual care (P = .029). Compared with TAU, participants on exenatide had greater mean weight loss body mass index (BMI) reduction, and reduced fasting glucose and glycated haemoglobin (HbA1c) levels.
Methods: We followed up CODEX trial participants at 12 months following the end of the trial. We collected information on weight, BMI, waist circumference, blood pressure, fasting glucose, HbA1c, and use of metformin. The primary outcome of interest was change in weight. Change in these parameters from trial baseline to 12 months post endpoint and trial endpoint to 12 months post endpoint was compared between those formerly in the exenatide and TAU arms.
Results: There were no significant differences between baseline and 12-months post endpoint for any of the variables. Data from endpoint to 12-month follow up point showed significantly greater increases among the former exenatide group compared to the former TAU group for weight, BMI, and proportion with >5% weight gain. Stratifying the dataset by whether participants were on metformin six months after the end of the trial did not alter the overall results.
Discussion: There were significant increases in weight and BMI in the 12 months post endpoint for the former exenatide group, however there were no significant differences in weight and BMI between baseline and 12-month post endpoint. This is in keeping with other GLP-1RA studies. This information suggests the need for continued use of exenatide among people on clozapine who have achieved weight loss.

T45. THE EFFICACY AND HETEROGENEITY OF ANTIPSYCHOTIC RESPONSE IN SCHIZOPHRENIA: A META-ANALYSIS

Rob McCutcheon*[1], Toby Pillinger[1], Yuya Mizuno[1], Adam Montgomery[2], Haridha Pandian[2], Luke Vano[1], Tiago Reis Marques[1], Oliver Howes[1]
[1]King's College London, Institute of Psychiatry; [2]South London and Maudsley NHS Foundation Trust

Background: Antipsychotics are more effective than placebo in reducing symptoms in schizophrenia. However, response to treatment appears to vary, and as such it has been proposed that different subtypes of schizophrenia exist, defined by treatment-response. This has not been formally examined using meta-analysis.
Methods: Randomised controlled trials comparing placebo and antipsychotics for the acute treatment of schizophrenia published between January 1 1950 and November 30, 2018 were examined. Mean change and variance of change in symptoms were extracted from each study, alongside publication year, participant age and gender, baseline symptom severity, antipsychotic dose, and use of placebo lead-in. Relative variability of symptomatic improvement in antipsychotic-treated individuals compared to placebo-treated individuals was quantified using coefficient of variation ratio (CVR). Mean difference in symptom change was quantified using Hedges' g. The significance of potential moderating factors was assessed using meta-regression and sensitivity analyses. In addition, individual patient data from two clinical trials (N=522) was examined in terms of both the distribution of total symptom change, and the variability of individual symptoms and symptom factors.
Results: 11,006 articles were identified. 66 met inclusion criteria, reporting on 17,202 participants. Compared with placebo, antipsychotic-treated