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