Methods: This was a randomized, double-blind, placebo-controlled, multiple-dose study in stable schizophrenia subjects washed out of their current antipsychotic medications ($n = 47$) and healthy Japanese subjects ($n = 30$). Ten subjects per cohort were enrolled and randomized to either TAK-063 or placebo (8 active and 2 placebo). Schizophrenia subjects were dosed once daily (QD) 3, 10, 20, 30, and 100 mg, and healthy Japanese subjects were dosed 3, 10, and 20 mg TAK-063 or placebo QD in the fed state using tablets for 7 days. Safety assessments were recorded throughout; serial plasma and urine samples were collected on days 1 and 7, with predose plasma samples on days 4, 5, and 6.
Results: TAK-063 was safe and generally well tolerated in both groups. There were no serious adverse events (AEs). Most AEs were of mild or moderate intensity. Somnolence, the most frequent AE in both treatment groups, was especially prevalent in schizophrenia subjects following 100 mg QD. Extrapyramidal syndrome (EPS), mainly dystonia, was observed in 14 schizophrenia subjects and 1 healthy Japanese subject treated with TAK-063. EPS was also observed in 1 schizophrenia subject in the placebo group. No clinically significant changes in the physical examination, clinical laboratory tests, or ECGs were observed. Blood pressure and pulse rate parameters were consistent with treatment-emergent AEs of orthostatic tachycardia and orthostatic hypotension and were similar between placebo and treatment groups. In the two groups, PK was broadly similar; in addition to TAK-063, a metabolite (M-I) was also quantified and exhibited a similar profile to TAK-063. TAK-063 was absorbed with a median Tmax of 1.5 to 4 hours. Cmax and AUC24 values of TAK-063 and M-I increased in a dose-related manner up to 30 mg in schizophrenia subjects and up to 20 mg in Japanese subjects, with modest accumulation upon repeat dosing. At doses of 30 to 100 mg, the increase in exposure was less than dose proportional. Renal clearance was a minor elimination route ($< 0.1\%$ of dose).
Discussion: TAK-063 was safe and well tolerated in schizophrenia and healthy Japanese subjects at all doses tested; somnolence was the most commonly observed AE. At equivalent doses, reports of EPS were higher in subjects with schizophrenia than in healthy Japanese subjects, despite similar PK between groups. At doses of 30 to 100 mg, the increase in exposure was less than dose proportional, likely due to solubility-limited oral bioavailability.

M61. Stabilility in a 52-week schizophrenia extension study of treatment with long-acting injectable aripiprazole lauroxil

Arielle Stanford[1], Robert Risinger*[1], Yangchun Du[1], Jacqueline Zummo[1], Hassan Jamal[1], Chih-Chin Liu[1], Amy Claxton[1]
[1]*Alkermes, Inc.*

Background: Aripiprazole lauroxil (AL; ARISTADA™, Alkermes, Inc.), a long-acting injectable antipsychotic, is approved for the treatment of schizophrenia. Clinical stability is a highly desirable treatment outcome, as it can predict better long-term outcomes including reduced hospitalizations. We assessed symptom stability in schizophrenia patients treated with AL in an efficacy study as well as the long-term safety extension study.
Methods: In a double-blind placebo-controlled study of acutely ill patients diagnosed with schizophrenia, subjects ($N = 622$) were randomized to receive AL 441 mg, AL 882 mg, or placebo intramuscular injection (IM) once-monthly. Subjects received daily oral aripiprazole (15 mg) or matching placebo for the first 3 weeks after randomization, and continued with IM treatment for 12 weeks. Both new subjects with stable schizophrenia and those who completed the study were eligible to enroll into a 1 year active treatment extension study ($N = 478$). New subjects received monthly injections with AL 882 mg, and rollover subjects received monthly injections with either AL 441 mg or AL 882 mg, depending on the treatment in the preceding trial. Subjects from the placebo arm received 441 or 882 mg corresponding to low/high placebo volume treatment. Similar to the 12-week randomized study, all new and placebo rollover subjects also received oral aripiprazole (15 mg) for 3 weeks. The exploratory analysis of the 1-year extension study included subjects who met two stability criteria: Positive and Negative Syndrome total Score (PANSS) ≤ 80 and PANSS ≤ 4 on each of items P2, P3, P6, and G9 simultaneously for 12 continuous weeks. For subjects who were stabilized, remission and relapse rates were assessed using the Schizophrenia Working Group remission criteria (SWGRC). Remission was defined as a PANSS ≤ 3 for each of items P1, G9, P3, P2, G5, N1, N4, and N6 for ≥ 6 continuous months. Relapse criteria was defined as an increase of 10 points or more in PANSS total score from the end of the stabilization period.
Results: The full analysis set contained data from 462 subjects; 396 (86%) subjects reached stabilization within a median time of 85 days, while 66 subjects never met stability criteria. Among 396 stabilized subjects, 383 (97%) remained stable for the entire study, only 39 (10%) relapsed after achieving stabilization, and 233 (60%) achieved symptom remission. Among the 66 subjects who did not meet stability criteria, 30 subjects were not treated for a sufficient period as they discontinued before day 85. For the other 36 subjects, treatment emergent adverse events included schizophrenia (17%) and insomnia (11%). Overall, 318 subjects completed the entire long term safety extension study and 313 (98%) stayed stable after achieving stabilization.
Discussion: The majority of subjects with schizophrenia who were treated with AL achieved response and remained stable for ≥ 52 weeks. As most safety extension studies have the limitation of selecting for responders, about half the study subjects were treated de novo. Nonetheless, over half of the subjects achieved remission.

M62. Specificity and prognostic accuracy of the basel screening instrument for psychosis (BSIP) and the so far often neglected problem of false negatives

Martina Papmeyer*[1], Jacqueline Aston[2], Judith Everts-Graber[2], Ulrike Heitz[2], Erich Studerus[2], Stefan Borgwardt[2], Rolf-Dieter Stieglitz[2], Anita Riecher-Rössler[2]
[1]*University of Bern,* [2]*University of Basel*

Background: Previous research on the prospective clinical assessment of the prodromal period of schizophrenic psychoses has mainly focussed on transition rates of individuals considered being in an at-risk mental state for the disease. By contrast, relatively little attention has been paid to the clinical outcome of individuals who were referred to early detection centers, but initially not considered to be at increased risk of psychosis. Incorrect classification of individuals as being "not at-risk" may, however, have severe consequences such as a delay of adequate treatment. Therefore, we conducted a comprehensive 4-year follow-up clinical assessment of individuals initially not considered to be at increased risk of psychosis on the basis of the Basel Screening Instrument for Psychosis (BSIP) [1]. Moreover, we evaluated the specificity, sensitivity, and positive and negative predictive value of the BSIP.
Methods: 87 individuals were screened with the BSIP as part of the prospective 'Früherkennung von Psychosen' (FePsy; early detection of psychosis) study [2]. 64 of these were classified at baseline as being in an at-risk mental state for psychosis and followed up at regular time intervals for at least 2 and up to 5 years to determine whether transition to psychosis had occurred. 23 subjects were classified at baseline as not at-risk and re-assessed after 4 years. Clinical characteristics of these were analyzed descriptively. Moreover, sensitivity, specificity, and positive and negative predictive value of the BSIP were computed.
Results: During the follow-up period, none of the individuals initially classified as not being at increased risk of psychosis in fact did transition to psychosis. At follow-up, the majority of this study group was diagnosed with depressive or anxiety disorders. The average psychopathological symptom severity of these individuals corresponded to "mildly ill" and the average level of functioning to "some difficulty in social or occupational functioning". In contrast, of the individuals positively identified as being in an at-risk mental state at baseline, 21 had developed psychosis. The sensitivity of the BSIP was 1.0, the specificity 0.35.
Discussion: Misclassification of individuals as being not at increased risk of psychosis appears to be relatively rare. These individuals mainly suffer from depressive and anxiety disorders years after initial assessment and show varying degrees of symptom severity and