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ABSTRACT: Introduction: Neurological conditions can be influenced by meteorological parameters. Some may predict weather changes, such as migraines [Marrelli 1988], burning mouth syndrome [Hirsch 2017], phantasmia [Hirsch 2013], and Bell's Palsy [Danielides 2001]. However, climatic conditions inducing headaches in those with ventriculoperitoneal shunt (VPS) placements have not heretofore been described.

METHODS: A 46-year-old female presented with epochs of headaches coinciding with climatic changes. She had hydrocephalus secondary to infantile meningitis that was treated with a Medtronic Strata II adjustable VPS. After multiple revisions, she noticed a headache occurring only before thunderstorms or snowstorms. These headaches were constant, bilateral, "halo-like" downward pressure located only around her parietal regions. It persists all day and does not dissipate after onset, regardless of the storm passing. She rates it 8/10 on the pain scale, and is exacerbated by jarring, sneezing, and bending forward. It is only alleviated with acetazolamide, diminishing to 0/10. She denies any pain relief when supine, pain radiation, rhinorrhea, auras, or correlating psychological distress.

RESULTS: Abnormalities in physical examination: General: hammer toes. Neurological Examination: Cranial Nerve (CN) Examination: CN III, IV, VI: saccadization on horizontal eye movement and bilateral ptosis (left > right). CN IX, X: right uvula deviation. Motor Examination: left upward-outward drift with a positive left abductor digiti minimi sign. Reflexes: 3+ bilateral biceps, brachioradialis, and patellar; 3+ right tricep and 4+ left tricep. Hoffman's Reflex: positive bilaterally (left > right). Neuropsychological Tests: Mental Status Examination: Recent Recall: 1/4 objects in three minutes without improvement with reinforcement. Go-No-Go Test: 6/6. Animal Fluency Test: 21 (normal). Center for Neurologic Study-Lability Scale: 23 (pseudobulbar affect).

CONCLUSION: How climatic changes induce VPS headaches remains unclear. Barometric changes have been reported to cause sinus engorgement [Kaliner 2009], somatic pain [Silove 2006] and can worsen anxiety and

depression [Delyukov 1999]. Meteorological parameters may have induced or exacerbated her depression and anxiety, amplifying pain perception. Alternatively, barometric pressure can cause an increase in other somatic pains and stresses, which can augment awareness of additional, unrecognized somatic pains. It is also possible for barometric pressure to cause pain via nasal sinus or mucosal engorgement; thus, mimicking her VPS headache. Lastly, however unlikely, her pain may be a result of a transient VPS malfunction. The mechanism for such can be attributed to transient pressure changes caused by fluctuating blood pressure, inducing brief intrinsic intraperitoneal pressure changes. Nevertheless, querying patients suffering from VPS headaches whether climatic changes play a role in their symptoms is warranted.

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A Phase 3 Study to Determine the Antipsychotic Efficacy and Safety of ALKS 3831 in Adult Patients with Acute Exacerbation of Schizophrenia

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ABSTRACT: Background: ALKS 3831, currently under development for the treatment of schizophrenia, is composed of olanzapine (OLZ) and a fixed dose of 10 mg of samidorphan. In a Phase 2 study in stable patients with schizophrenia, ALKS 3831 mitigated OLZ-associated weight gain while maintaining an antipsychotic efficacy profile similar to OLZ.

STUDY OBJECTIVE: To assess the efficacy and safety of ALKS 3831 in patients with acute exacerbation of schizophrenia.

METHODS: This was a Phase 3, 4-week, randomized, double-blind, active and placebo (PBO)-controlled study of ALKS 3831 in patients with acute exacerbation of schizophrenia (ClinicalTrials.gov: NCT02634346). Eligible patients (N=403) were randomized 1:1:1 to receive ALKS 3831, OLZ, or PBO. Patients were treated in an inpatient setting for the first 2 weeks of the study and could be treated as inpatients or outpatients for the remaining 2 weeks. Patients were excluded if they received OLZ within 6 months prior to screening. Antipsychotic efficacy was assessed using the Positive and Negative Syndrome Scale (PANSS), and Clinical Global Impression–Severity (CGI-S) and CGI–Improvement (CGI-I) scales. Safety and tolerability were assessed as adverse events (AEs).

RESULTS: Of 401 randomized patients who received ALKS 3831, OLZ, or PBO, 91%, 89%, and 83% of patients, respectively, completed treatment. The most common reason for discontinuation was withdrawal by patient (6% in both the ALKS 3831 and PBO groups, and 7% in the OLZ group). Baseline characteristics were generally similar between groups; however, baseline mean body mass index was higher in the OLZ group than in the ALKS 3831 group. Baseline mean \pm standard deviation scores were 101.7 ± 11.9 for PANSS total score and 5.1 ± 0.7 for CGI-S scale score. The mean OLZ dose was 18.4 mg/day in both active treatment arms. Least squares (LS) mean difference \pm standard error (SE) vs PBO from baseline to Week 4 in PANSS total score was -6.4 ± 1.8 ($P < .001$) for the ALKS 3831 group and -5.3 ± 1.8 ($P = .004$) for the OLZ group. LS mean difference \pm SE vs PBO from baseline to Week 4 in CGI-S scale score was -0.4 ± 0.1 ($P = .002$) for the ALKS 3831 group and -0.4 ± 0.1 ($P < .001$) for the OLZ group. The percentage of patients with improvement in PANSS response ($\geq 30\%$ from baseline) at Week 4 was 60%, 54%, and 38% in the ALKS 3831, OLZ, and PBO groups, respectively. The percentage of patients with an improvement in CGI-I scale response (score of ≤ 2) at Week 4 was 58%, 51%, and 33% in the ALKS 3831, OLZ, and PBO groups, respectively. Discontinuation due to AEs was low in all groups. Common AEs ($\geq 5\%$ in any group) included weight gain, somnolence, dry mouth, anxiety, headache, and schizophrenia.

DISCUSSION: Treatment with ALKS 3831 was more effective than PBO, as measured by the PANSS and CGI-S scale, and its antipsychotic efficacy was similar to the active control OLZ. The safety profile of ALKS 3831 was similar to OLZ.

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A New Method for Initiating Treatment with the Long-acting Antipsychotic Aripiprazole Lauroxil

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ABSTRACT: STUDY OBJECTIVE: Slow release is a fundamental feature of long-acting injectable (LAI) antipsychotics. This property allows continuous drug exposure between dosing intervals. However, there can be a significant delay between giving the first LAI dose and achievement of efficacious plasma concentrations. This time period requires additional pharmacologic intervention. Until now, this delay was addressed with one of two strategies: 1) continuing with supplemental oral antipsychotic, or 2) giving more LAI up front (e.g. loading dose). A third strategy has now been developed to reduce the time needed for oral supplementation when starting the LAI aripiprazole lauroxil (AL) from 21 days to 1 day. A nano-crystalline milled dispersion of AL (ALNCD; brand name ARISTADA INITIO™) was formulated by reducing the AL particle diameter from micron-size particles to nanometer-sized particles. ALNCD has faster dissolution and a shorter half-life than AL and is designed to be used as a single injection along with a single oral aripiprazole dose of 30 mg as a 1-day alternative to the 21 days of oral aripiprazole supplementation. Here we provide an overview of the new 1-day initiation regimen for starting AL treatment, and demonstrate the relative contributions of each of its components.

METHODS: A blinded, randomized, phase 1, pharmacokinetic (PK), and safety study compared the 1-day initiation regimen with the 21-day oral aripiprazole regimen. A combination of observed data, and population pharmacokinetic model-based simulations were used to plot plasma aripiprazole concentrations of single doses of ALNCD, 30 mg oral aripiprazole, and AL, individually, and all three combined.