Supplemental information for:

Safety and tolerability of lumateperone for the treatment of schizophrenia: a pooled analysis of late-phase placebo- and active-controlled clinical trials

AUTHORS:

John M Kane, MD[1-3]; Suresh Durgam, MD[4]; Andrew Satlin, MD[5]; Kimberly E Vanover, PhD[5]; Richard Chen PhD[4]; Robert Davis, PhD[4]; Sharon Mates, PhD[4]

[1]Center for Psychiatric Neuroscience, Feinstein Institute for Medical Research, Manhasset, NY, USA

[2]Division of Psychiatry Research, The Zucker Hillside Hospital, Northwell Health, New York, NY, USA

[3]Department of Psychiatry and Molecular Medicine, Donald and Barbara Zucker School of Medicine at Northwell/Hofstra, Hempstead, NY, USA

[4]Intra-Cellular Therapies, Inc., New York, NY, USA

[5]Formerly Intra-Cellular Therapies, Inc., New York, NY, USA

Corresponding Author: Suresh Durgam, MD

Contents

Supplemental Methods

The Study 302 randomized clinical trial (NCT02469155) was conducted from June 16, 2015, to August 22, 2016. Patients were recruited at 13 US clinical sites and admitted to an inpatient research unit for a screening period of 2 to 7 days before randomization. Eligible participants were aged 18 to 60 years and had a clinical diagnosis of schizophrenia according to the DSM-5, confirmed by the modified Structured Clinical Interview for DSM-IV-TR Axis I disorders, clinical trials version (SCID-CT). Patients were included if they were experiencing an acute exacerbation of psychosis, defined as a total score on the Brief Psychiatric Rating Scale (BPRS) ≥40, with a score ≥4 on ≥2 positive symptoms, and onset of the acute episode within 4 weeks of screening. Patients were required to have a score ≥4, indicating moderate to severe disease severity, on the Clinical Global Impression–Severity of Illness (CGI-S) at screening and baseline. Severity of illness was confirmed at baseline by a Positive and Negative Syndrome Scale (PANSS) total score ≥70, indicating moderate to extreme symptoms of schizophrenia. Patients had to have a previous response to antipsychotic therapy. Exclusion criteria included any patient who: was pregnant or breast-feeding; had previously participated in a lumateperone clinical trial; had moderate-to-severe substance use disorder ≤6 months of screening (DSM-5 criteria) or a positive qualitative urine drug or alcohol test at screening; was an imminent danger to themselves or others or reported suicidal ideation (Type 4 of 5 on C-SSRS) ≤6 months of screening or any suicidal behavior ≤2 years prior to screening; had abnormal laboratory values or clinical findings deemed clinically significant; had a history of human immunodeficiency virus; had a history of hepatitis B or C infection and evidence of active disease; or had presence or history of significant or uncontrolled hematological, renal, hepatic, endocrinological, neurological, or cardiovascular disease.

In this randomized, 6-week, double-blind, placebo-controlled, inpatient trial, patients were randomized centrally across sites in a 1:1:1 ratio to 1 of 3 treatments administered orally once daily in the morning: 42 mg of lumateperone, 4 mg of risperidone, or placebo in capsule form. Risperidone included a dose titration, administered at 2 mg on Day 1 and 4 mg thereafter. Central randomization occurred via an automated telephone or web-based system. Immediately after the 6-week study treatment period or at early discontinuation, patients were stabilized with standard-of-care treatment for up to 5 days. A follow-up safety assessment was performed approximately 1 week after the end of the stabilization period.

Safety was assessed by treatment-emergent adverse events (TEAEs) coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary Version 17.1, modified physical examinations, 12-lead electrocardiograms (ECGs), vital signs, and clinical laboratory tests. Motor tolerability and safety

were assessed by the Simpson-Angus Scale, Barnes Akathisia Rating Scale, and Abnormal Involuntary Movement Scale. Suicidality was evaluated by the Columbia Suicide Severity Rating Scale. Safety results were summarized descriptively by treatment group and visit (when applicable) for the safety analysis population, defined as all patients receiving ≥1 dose of study medication. The incidences of clinical laboratory tests, vital signs, and ECG results that met predefined markedly abnormal criteria were summarized. Selected safety end points (fasting total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, glucose, insulin, triglycerides, and prolactin levels) for treatment groups were compared with placebo. SAS statistical software, version 9.4 or later (SAS Institute Inc) was used for the statistical analyses.

The trial was conducted in compliance with the principles of the Good Clinical Practice guideline and was approved by the institutional review board. All participating patients provided written informed consent, and data were deidentified.

Supplement Table 1. Extrapyramidal Symptoms

	Placebo **n = 412**	**Lumateperone 42 mg** **n = 406**	**Risperidone 4 mg** **n = 255**
≥ 1 EPS-related TEAE, n (%)[a]	13 (3.2)	12 (3.0)	16 (6.3)
Akathisia	12 (2.9)	8 (2.0)	12 (4.7)
Dyskinesia	1 (0.2)	0	0
Dystonia	1 (0.2)	2 (0.5)	5 (2.0)
Tardive dyskinesia	0	2 (0.5)[b]	0
BARS Total score, Mean Change from Baseline (SD)[c]	0 (0.4)	–0.1 (0.8)	0.1 (1.1)
AIMS score, Mean Change from Baseline (SD)[c]	0 (0.7)	0.1 (0.8)	0.1 (0.5)
SAS score, Mean Change from Baseline (SD)[c]	0 (0.5)	0.1 (0.8)	0.1 (0.9)

[a] TEAEs related to EPS according to standard MedDRA query narrow criteria by preferred term. [b] Both cases of reported tardive dyskinesia started within 2 weeks of initiation of treatment and resolved during treatment and, therefore, are unlikely to be tardive dyskinesia. [c]Data shown are change from baseline to last on-treatment value.

AIMS, Abnormal Involuntary Movement Scale; BARS, Barnes Akathisia Rating Scale; SAS, Simpson-Angus Scale EPS, extrapyramidal symptom; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.