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

John M Kane[a,b,c], Suresh Durgam[d], Andrew Satlin[e], Kimberly E Vanover[e], Richard Chen[d], Robert Davis[d] and Sharon Mates[d]

Lumateperone, an antipsychotic that is US Food and Drug Administration-approved for the treatment of schizophrenia, has a novel mechanism of action that may confer beneficial effects with improved tolerability. This pooled analysis of three randomized, double-blind, placebo-controlled trials was conducted to evaluate the safety and tolerability of lumateperone 42 mg. The pooled population comprised 1073 patients with an acute exacerbation of schizophrenia randomized to placebo ($n=412$), lumateperone 42 mg ($n=406$) or risperidone 4 mg ($n=255$). Treatment-emergent adverse events (TEAEs) were predominantly mild and rates of discontinuation due to TEAEs with lumateperone 42 mg (0.5%) were similar to placebo (0.5%) and lower than risperidone (4.7%). The only TEAEs that occurred at a rate of ≥5% and twice placebo for lumateperone were somnolence/sedation and dry mouth. Mean change from baseline in metabolic parameters and prolactin were similar to or reduced in lumateperone 42 mg relative to placebo-treated patients and were smaller than risperidone. Mean change in weight and rates of extrapyramidal symptoms-related TEAEs were similar for lumateperone 42 mg and placebo-treated patients and less than for risperidone-treated patients. This pooled analysis demonstrates the safety and favorable tolerability profile of lumateperone 42 mg. *Int Clin Psychopharmacol* 36: 244–250 Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc.

Introduction

Currently available antipsychotic medications for the treatment of schizophrenia vary widely in safety and tolerability (Solmi *et al.*, 2017; Huhn *et al.*, 2019). Adverse events associated with many antipsychotics include weight gain, metabolic dysfunction, extrapyramidal symptoms (EPS), hyperprolactinemia and corrected QT interval (QTc) prolongation (Solmi *et al.*, 2017). These adverse effects compound the already increased morbidity and premature mortality associated with schizophrenia (Correll et al., 2015, 2017) and are a major driver of the high discontinuation rates of antipsychotic treatment (Lieberman *et al.*, 2005; Roussidis *et al.*, 2013). To improve adherence to antipsychotics and avoid the health risks associated with currently available treatments, it is imperative to identify effective antipsychotic options with more favorable safety profiles.

Lumateperone (lumateperone tosylate, ITI-007) is a mechanistically novel antipsychotic that is US Food and Drug Administration-approved for the treatment of schizophrenia, with a unique mechanism of action (MoA) that simultaneously modulates serotonin, dopamine and glutamate neurotransmission [Li *et al.*, 2014; Snyder *et al.*, 2015; Caplyta (lumateperone), 2019]. Specifically, lumateperone is a potent serotonin 5-HT_{2A} receptor antagonist, a dopamine D_2 receptor presynaptic partial agonist and postsynaptic antagonist, a D_1 receptor-dependent indirect modulator of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid and N-Methyl-D-aspartate currents, and a serotonin reuptake inhibitor (Snyder *et al.*, 2015). This novel MoA predicts beneficial effects across a wide range of symptoms associated with schizophrenia as well as improved tolerability compared with current antipsychotics.

The efficacy, safety and tolerability of lumateperone in adults with schizophrenia were investigated in three randomized, double-blind, placebo-controlled studies (study 005 [NCT01499563], study 301 [NCT02282761] and study 302 [NCT02469155]) (Lieberman *et al.*, 2016; Correll *et al.*, 2020). In two of these studies (005 and 301), lumateperone 42 mg met the primary endpoint, with

---

DOI: 10.1097/YIC.0000000000000371

significant reduction vs. placebo in Positive and Negative Syndrome Scale (PANSS) Total score (Lieberman *et al.*, 2016; Correll *et al.*, 2020). In study 302, the difference between lumateperone 42 mg vs. placebo did not reach significance; however, the magnitude of improvement from baseline in PANSS Total score was similar to that reported in the positive studies (005 and 301). This pooled analysis of the three placebo-controlled studies was conducted to further evaluate the safety and tolerability of lumateperone 42 mg in the treatment of schizophrenia.

Methods
Study designs and patient population
Data were pooled from three similarly designed, double-blind, placebo-controlled trials of lumateperone in patients with an acute exacerbation of schizophrenia (study 005, study 301 and study 302). Detailed study designs for studies 005 and 301 have been described previously (Lieberman *et al.*, 2016; Correll *et al.*, 2020), and a detailed study design for study 302 is included in Supplementary Material, Supplemental digital content 1, *http://links.lww.com/ICP/A87*. All studies included an inpatient treatment period with lumateperone 42 mg followed by 2 weeks of safety follow-up (Supplementary Table 1, Supplemental digital content 1, *http://links.lww.com/ICP/A87*). The studies were approved by Institutional Review Boards and all participating patients provided written informed consent. The study populations comprised patients, age 18−60 years (maximum age of 55 years for study 005), with a clinical diagnosis of schizophrenia according to Diagnostic Statistical Manual of Mental Disorders (DSM), fourth edition text revision (American Psychiatric Association, 2000) or fifth edition (American Psychiatric Association, 2013) criteria and confirmed by the Structured Clinical Interview for DSM Disorders-Clinical Trial Version (SCID-CT) (First *et al.*, 2007) or modified SCID (First *et al.*, 2014), experiencing an acute exacerbation of schizophrenia lasting ≤4 weeks. Acute exacerbation was defined at screening as a Clinical Global Impression − Severity (ECDEU, 1976) score of ≥4 and a Brief Psychiatric Rating Scale (Overall and Gorham, 1988) score of ≥40 with a score of ≥4 on at least two of four positive symptoms, including: suspiciousness, conceptual disorganization, hallucinatory behavior and unusual thought content. Patients were required to have a previous response to antipsychotic therapy and to discontinue previous antipsychotics prior to treatment with lumateperone.

Lumateperone 42 mg or placebo were administered to patients once daily in an inpatient setting. Studies 005 and 301 had 28-day lumateperone treatment periods whereas study 302 had a 42-day lumateperone treatment period. Additionally, studies 005 and 302 included an active control, risperidone 4 mg, for assay sensitivity. The 4-mg dose was chosen as it falls within the treatment guidelines and is a recommended dose of risperidone

[Williams, 2001; Kim and Kim, 2003; Risperdal (risperidone), 2021]. Patients were evaluated for safety at baseline, weekly on-treatment and at an end-of-study visit. Following study treatment, patients were stabilized on currently available antipsychotics prior to discharge.

Post hoc analyses
Safety and tolerability data for patients who received lumateperone 42 mg and placebo were pooled from all three studies, and risperidone 4-mg data were pooled from two studies (005 and 302). The safety analysis set included all patients who received ≥1 dose of study medication. Safety assessments were summarized using descriptive statistics and included evaluation of treatment-emergent adverse events (TEAEs), including severity and rates of discontinuation, physical examinations, changes in laboratory parameters, electrocardiogram and vital signs.

A TEAE was defined as an adverse event that started or worsened on or after the first day of study drug, with adverse events coded using the Medical Dictionary for Regulatory Activities (MedDRA) v17.1. The incidence rates of TEAEs during the studies were reported by system organ class and preferred terms. The incidence rates of EPS-related TEAEs during the studies were summarized by the standard MedDRA query for narrow categories. Motor symptoms were assessed using the Barnes Akathisia Rating Scale (BARS), Abnormal Involuntary Movement Scale (AIMS) and Simpson-Angus Scale (SAS) and were summarized with descriptive statistics for the baseline, actual and change from baseline at the last on-treatment values. Incidence rates of suicidal ideation and behavior during the studies were assessed using the Columbia−Suicide Severity Rating Scale (C-SSRS). To accommodate for patient dropout, the change from baseline to last on-treatment value for select assessments, including weight and clinical laboratory parameters, were summarized with descriptive statistics and analyzed using an analysis of covariance (ANCOVA) model with effects for baseline value and treatment. A standard α = 0.05 cutoff was applied to the nominal *P* values for treatment comparison.

Results
Patient disposition
The pooled safety population comprised 1073 patients (Fig. 1). Completion rates were high and similar between the lumateperone (77.6%) and placebo (74.8%) groups, with the risperidone group having a lower completion rate (65.9%). The most frequently reported reason for discontinuation from the studies in any group was the withdrawal of consent (placebo, 10.7%; lumateperone, 12.1% and risperidone, 17.6%). Additionally, discontinuations due to TEAEs in the lumateperone group were low (0.5%), similar to that of the placebo group (0.5%) and lower than the risperidone group (4.7%). Discontinuations due to lack of efficacy in the lumateperone 42-mg group were low (3.9%), similar to that of the risperidone group (4.3%) and lower than the placebo group (8.0%).

Fig. 1
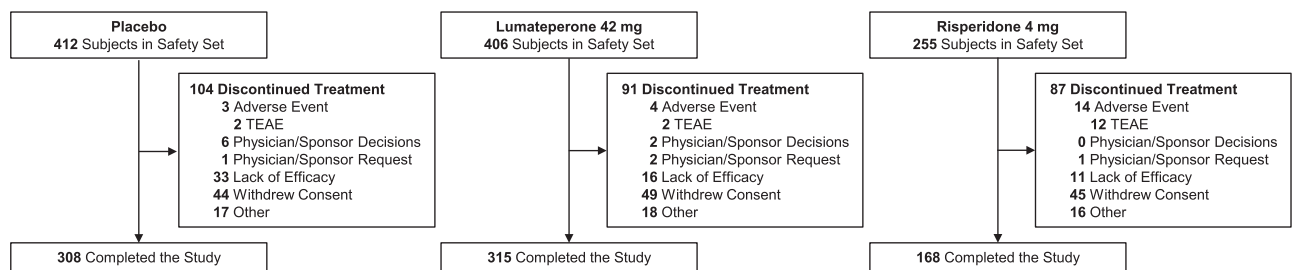
Patient disposition. TEAE, treatment-emergent adverse events.

Table 1   Baseline demographics and clinical characteristics

	Placebo n=412	Lumateperone 42 mg n=406	Risperidone 4 mg n=255
Age, mean (SD), years	42 (10.1)	41 (10.2)	42 (10.3)
Men, %	77.7	73.6	80.4
Race, %			
White	22.8	18.7	22.0
Black	71.4	78.3	73.3
Other	5.8	3.0	4.7
Body weight, mean (SD), kg	85.8 (16.9)	87.2 (17.5)	88.1 (18.2)
BMI, mean (SD), kg/m²	28.4 (5.3)	28.7 (5.3)	28.8 (5.4)
Years since first schizophrenia diagnosis, mean (SD)	17.3 (10.4)	16.5 (10.2)	17.3 (10.3)

Demographics and baseline characteristics were similar across treatment groups (Table 1). Most patients were men (73.6–80.4%), black (71.4–78.3%) with a mean age of 41–42 years. The mean treatment duration for lumateperone 42 mg was 29.9 days, which was similar to that of placebo (29.6 days) and risperidone (29.1 days), with a total exposure to lumateperone being 33.2 patient-years.

Treatment-emergent adverse events

TEAEs were reported in more patients treated with lumateperone 42 mg (65.8%) or risperidone (68.6%) compared with placebo (55.6%) (Table 2). The proportion of patients experiencing drug-related TEAEs in the lumateperone, risperidone and placebo groups were 52.2, 55.3 and 39.1%, respectively. The most common TEAEs that occurred at a rate ≥5% and twice that of placebo were somnolence/sedation and dry mouth with both lumateperone and risperidone treatments. The TEAE of weight increase was more common with risperidone (6.3%) than with lumateperone (2.0%) or placebo (2.7%). The majority of TEAEs were considered mild or moderate in severity (placebo, 99.8%; lumateperone 42 mg, 99.0% and risperidone 4 mg, 97.6%). Two patients discontinued lumateperone treatment due to severe drug-related TEAEs, one being orthostatic hypertension (0.2%) and the other dry mouth (0.2%). The only TEAE leading to discontinuation of >1% of any group was akathisia, which led to discontinuation of three patients (1.2%) treated with risperidone and no patients in the placebo or lumateperone groups.

Table 2   Treatment-emergent adverse events[a]

Event, n (%)	Placebo n=412	Lumateperone 42 mg n=406	Risperidone 4 mg n=255
TEAE Summary			
Patients with ≥1 TEAE	229 (55.6)	267 (65.8)	175 (68.6)
With drug-related TEAE	161 (39.1)	212 (52.2)	141 (55.3)
With treatment-emergent SAE	1 (0.2)	1 (0.2)	0
Discontinuations due to TEAE or SAE			
TEAE	2 (0.5)	2 (0.5)	12 (4.7)
Drug-related TEAE	2 (0.5)	2 (0.5)	12 (4.7)
Treatment-emergent SAE	0	0	0
TEAEs occurring in ≥2% of lumateperone 42 mg group and greater than placebo			
Somnolence/sedation	41 (10.0)	98 (24.1)	61 (23.9)
Headache	58 (14.1)	81 (20.0)	42 (16.5)
Nausea	20 (4.9)	38 (9.4)	19 (7.5)
Dry mouth	9 (2.2)	24 (5.9)	12 (4.7)
Constipation	23 (5.6)	24 (5.9)	9 (3.5)
Dizziness	11 (2.7)	20 (4.9)	10 (3.9)
Blood creatine phosphokinase increased	3 (0.7)	17 (4.2)	11 (4.3)
Diarrhea	11 (2.7)	14 (3.4)	3 (1.2)
Vomiting	7 (1.7)	11 (2.7)	8 (3.1)
Back pain	9 (2.2)	10 (2.5)	7 (2.7)
Fatigue	4 (1.0)	11 (2.7)	3 (1.2)
Abdominal pain	7 (1.7)	10 (2.5)	1 (0.4)
Upper respiratory tract infection	5 (1.2)	10 (2.5)	3 (1.2)
Pain in extremity	6 (1.5)	9 (2.2)	2 (0.8)
Decreased appetite	3 (0.7)	9 (2.2)	4 (1.6)
Urinary tract infection	5 (1.2)	8 (2.0)	3 (1.2)

AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event; TEAE, treatment-emergent adverse event.
[a]AEs were coded using MedDRA version 17.1.

There were two treatment-emergent serious adverse events (SAE) including one patient (0.2%) with asthma in the placebo group and one patient (0.2%) with agitation in the lumateperone group; neither SAE was drug-related according to the investigator. There were no deaths in the treatment period. In the post-treatment period, two patients died due to an unknown cause (placebo group) and suspected recreational drug use (risperidone group). Neither death was related to study medication according to the investigator. The proportion of patients with suicidal ideation as measured by the C-SSRS was low in all treatment groups (≤2.5%), and there were no reports of suicidal attempt or completed suicide in any treatment group.

Extrapyramidal symptoms and motor assessments

The rate of EPS-related TEAEs with lumateperone treatment (3.0%) was similar to that of placebo (3.2%) and lower than the rate with risperidone treatment (6.3%) (Supplementary Table 1, Supplemental digital content 1, *http://links.lww.com/ICP/A87*). The most common EPS-related TEAE was akathisia, which occurred at a higher rate with risperidone treatment (4.7%) than with placebo (2.9%) or lumateperone (2.0%) treatment. Benztropine treatment rates for EPS were similar in the lumateperone (2.5%) and placebo (2.2%) groups, but higher in the risperidone group (9.0%). There was no association of lumateperone treatment with the incidence of EPS as measured by mean change from baseline in the BARS total, AIMS and SAS scores (Supplementary Table 1, Supplemental digital content 1, *http://links.lww.com/ICP/A87*).

Body weight

Mean change from baseline (SD) in body weight to the last on-treatment value was similar in the lumateperone [+1.6 (2.85) kg] and placebo groups [+1.3 (3.16) kg], with larger weight gain observed in the risperidone group [+2.6 (4.73) kg] (Table 3). The difference between lumateperone 42 mg and risperidone was statistically significant in an ANCOVA analysis [least-squares mean difference (LSMD), –1.03 kg; 95% confidence interval (CI), –1.57 to –0.50; $P < 0.001$]. The increase in weight with risperidone was significantly greater than that with placebo (LSMD vs. placebo, 1.35; 95% CI, 0.81–1.88; $P < 0.0001$). Both placebo and lumateperone had a similar proportion of patients who experienced potentially clinically significant (PCS, ≥7% change from baseline) increases in weight (placebo, 9.2%; lumateperone 42 mg, 9.1%). Conversely, a higher proportion of risperidone patients experienced PCS increases in weight (22.0%); the difference between lumateperone 42 mg and risperidone 4 mg was statistically significant in a logistic regression analysis (odds ratio, 0.341; 95% CI, 0.213–0.546; $P < 0.001$). Rates of PCS weight decrease were similar between groups (placebo, 1.8%; lumateperone, 1.0% and risperidone, 2.5%).

Metabolic parameters

Lumateperone treatment was associated with similar mean changes from baseline as placebo, which were both lower than risperidone for cardiometabolic parameters of fasting glucose, total cholesterol and low-density lipoprotein (LDL) cholesterol (Table 3). In ANCOVA analyses comparing lumateperone with placebo, there were no significant differences ($P > 0.05$) between mean change from baseline in metabolic parameters. Triglycerides decreased with lumateperone treatment (–1.7 mg/dL) but increased with placebo (4.6 mg/dL) and risperidone (20.4 mg/dL) treatment. In ANCOVA analyses comparing lumateperone with risperidone treatment, lumateperone was associated with significantly greater reduction from baseline to last on-treatment value than risperidone for

Table 3 Safety parameters, change from baseline to last on-treatment value

	Placebo $n = 412$	Lumateperone 42 mg $n = 406$	Risperidone 4 mg $n = 255$
Body weight			
Mean change (SD), kg	1.3 (3.16)	1.6 (2.85)	2.6 (4.73)
≥7% increase from baseline, %	9.2	9.1	22.0
≥7% decrease from baseline, %	1.8	1.0	2.5
Vital signs, mean change (SD)			
SBP, supine, mmHg	0.1 (10.65)	−1.1 (11.4)	−1.1 (11.89)
DBP, supine, mmHg	−0.4 (8.24)	−0.3 (8.47)	−1.1 (8.35)
Pulse rate, supine, bpm	2.0 (11.70)	1.0 (10.06)	6.2 (11.10)
Respiration, breaths/min	0.0 (1.85)	0.0 (1.63)	0.5 (1.87)
Temperature, fahrenheit	0.0 (0.36)	0.0 (0.35)	−0.0 (0.38)
Metabolic parameters, mean change (SD)			
Total cholesterol, mg/dL	−1.6 (24.66)	−3.0 (24.69)	4.8 (26.14)
LDL cholesterol, mg/dL	1.0 (21.49)	1.2 (21.22)	3.5 (22.51)
HDL cholesterol, mg/dL	−4.2 (7.96)	−3.3 (9.32)	−2.4 (9.60)
Triglycerides, mg/dL	4.6 (51.57)	−1.7 (58.97)	20.4 (62.53)
Insulin, μIU/mL	0.9 (25.60)	2.4 (56.46)	7.7 (29.68)
Fasting glucose, mg/dL	2.1 (14.68)	0.7 (15.11)	7.7 (28.70)
Clinical laboratory parameters, mean change (SD)			
Prolactin, ng/mL	−0.2 (8.46)	−1.3 (8.86)	34.9 (39.38)
Bilirubin, mg/dL	0.02 (0.187)	0.02 (0.170)	−0.03 (0.140)
Alanine aminotransferase, U/L	−1.2 (16.90)	2.2 (29.84)	3.2 (27.98)
Alkaline phosphatase, U/L	−0.6 (9.46)	−2.3 (8.63)	−1.3 (10.01)
Aspartate aminotransferase, U/L	−0.7 (11.21)	−1.6 (37.05)	0.1 (15.37)

bpm, beats per minute; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

total cholesterol (LSMD –7.85 mg/dL; 95% CI, –11.80 to –3.90; $P < 0.001$), triglycerides (LSMD –22.45 mg/dL; 95% CI, –30.97 to –13.93; $P < 0.001$) and fasting glucose (LSMD –6.86 mg/dL; 95% CI, –9.69 to –4.04; $P < 0.001$) (Fig. 2).

Vital signs

There were minimal changes with lumateperone for SBP and DBP, and the changes were similar to placebo (Table 3). A slight increase in the mean (SD) pulse rate with lumateperone [1.0 (10.06) beats per minute (bpm)] was similar to that of placebo [2.0 (11.70) bpm] and smaller than the increase with risperidone [6.2 (11.10) bpm]. There were no mean changes in the mean respiratory rate or body temperature for any treatment group (Table 3).

ECG measures

No patients in the lumateperone or placebo group had a QTcF interval of >480 ms, whereas one patient (0.4%) in the risperidone group had a QTcF interval of >480 ms. There was one patient each in the lumateperone (0.2%) and risperidone (0.4%) groups and no placebo-treated patients with a QTcF increase of >60 ms. There were also slight changes from baseline in all groups for mean (SD) QTcF [placebo, 0.7 (12.67) ms; lumateperone, 3.2 (12.75) ms, risperidone 2.0 (12.63) ms].

Clinical laboratory parameters

No patients in the study met the criteria for Hy's law. Slight increases from baseline to the end of treatment in mean bilirubin, alanine aminotransferase and gamma

Fig. 2
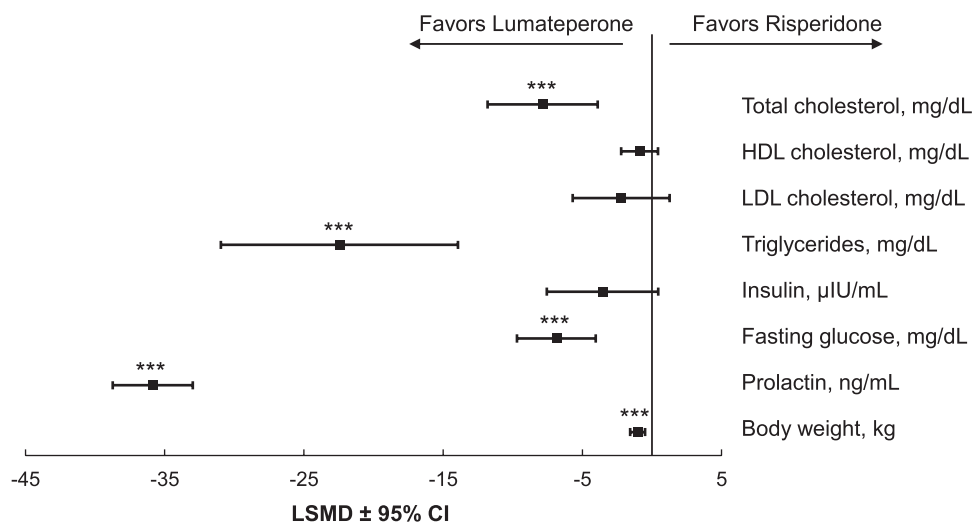
Least-squares mean difference of lumateperone vs. risperidone for mean change in key safety parameters. ***P< 0.001 LSMD for lumateperone vs. risperidone from an ANCOVA analysis of least-squares mean change from baseline to last on-treatment value. ANCOVA, analysis of covariance; CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LSMD, least-squares mean difference.

glutamyl transferase with lumateperone treatment were not clinically relevant (Table 3). There were minor decreases from baseline with lumateperone treatment for alkaline phosphatase and aspartate aminotransferase (Table 3). Risperidone treatment resulted in increased levels of prolactin (34.9 ng/mL) relative to placebo (−0.2 ng/mL) or lumateperone (−1.3 ng/mL) treatment. ANCOVA analyses showed that risperidone significantly increased prolactin compared with placebo (LSMD, 34.90; 95% CI, 32.10−37.70; $P<0.0001$) or lumateperone (LSMD 35.85 ng/mL; 95% CI, 32.98−38.73; $P<0.001$) (Fig. 2).

Discussion
In this pooled analysis of safety data from three short-term, randomized, placebo-controlled trials of lumateperone 42 mg in adult patients with an acute exacerbation of schizophrenia, lumateperone was generally safe and well-tolerated. The majority of patients completed the studies and discontinuation of lumateperone due to TEAEs was rare, occurring at a similar rate with lumateperone and placebo and at a lower rate than risperidone treatment. A lack of tolerability with other antipsychotics has led to poor adherence (Lieberman et al., 2005). The benign TEAEs profile and infrequent early discontinuations of lumateperone treatment predict improved adherence with lumateperone. Improved adherence is associated with better outcomes in people taking antipsychotics (Haddad et al., 2014).

The only TEAEs that occurred at a clinically meaningful rate (≥5% and twice placebo) for lumateperone were

somnolence/sedation and dry mouth. These TEAEs, as well as the TEAE of weight increase, were also observed at clinically meaningful rates with risperidone treatment. The rate of somnolence/sedation was similar with lumateperone and risperidone (24.1 and 23.9%, respectively) and none were severe in intensity. A 1-year open-label study assessing the effect of lumateperone treatment taken in the morning vs the evening found a lower incidence of somnolence/sedation (5.8%) with evening administration. This suggests that nightly administration may reduce somnolence and sedation (Vanover et al., 2019).

Antipsychotics are often associated with EPS, which are reported as highly bothersome side effects by both patients and psychiatrists in clinical practice, adversely impacting quality of life (Briggs et al., 2008; Llorca et al., 2017; Solmi et al., 2017). EPS-related TEAEs, including akathisia, with lumateperone were uncommon and similar to placebo, but occurred more frequently with risperidone, particularly akathisia. Additionally, there were no notable mean changes in EPS, including akathisia and dyskinesia, on the BARS total, AIMS and SAS clinician-rated scales. The limited EPS and motor adverse effects of lumateperone may arise from the low striatal D_2 receptor occupancy (D_2RO) of lumateperone at therapeutically relevant doses, with approximately 40% D_2RO at its recommended therapeutic dose of 42 mg in patients with schizophrenia (Vanover et al., 2019). This D_2RO is notably lower than most other antipsychotics which are associated with 65−80% D_2RO at therapeutically relevant doses, other than clozapine (48−61% occupancy) (Vanover et al., 2019). The MoA at the D_2 receptor as a presynaptic

partial agonist and postsynaptic antagonist may contribute to the action of lumateperone at lower D_2 occupancy than other atypical antipsychotics (Snyder *et al.*, 2015).

People with schizophrenia are at an elevated risk for metabolic syndrome, coronary heart disease, congestive heart failure and cerebrovascular disease (Vancampfort *et al.*, 2015; Correll *et al.*, 2017). This heightened risk is further elevated by the use of most currently available antipsychotics, which are associated with weight gain, diabetes and hypertension (Vancampfort *et al.*, 2015; Correll *et al.*, 2017; Solmi *et al.*, 2017). Patients in the lumateperone group had a similar profile as placebo for cardiometabolic parameters of fasting glucose, total cholesterol and LDL cholesterol. Lumateperone also had significantly greater reductions than risperidone for total cholesterol, triglycerides and fasting glucose. Anticipated weight gain is an important factor for patients considering the initiation of treatment with antipsychotic medication (Achtyes *et al.*, 2018). Unlike other antipsychotics, the mean change from baseline in body weight in patients treated with lumateperone was low and similar to placebo, with patients treated with lumateperone exhibiting a significant reduction in weight compared with risperidone-treated patients. Rates of PCS weight increase with lumateperone were similar to placebo and notably lower than with risperidone, and this distinct and favorable safety profile may support lumateperone as a treatment option when initiating antipsychotic therapy. There was no significant difference with lumateperone treatment compared with placebo for mean change in metabolic parameters or weight gain. However, as these pooled studies were of relatively short-term duration, additional monitoring is warranted to assess the long-term metabolic effects of lumateperone.

Lastly, there was no clinically significant increase in QT interval with lumateperone treatment, and treatment-emergent QTcF increases were rare, with no clinically relevant effects on cardiac repolarization. There was a minor reduction in mean prolactin from baseline with lumateperone treatment with notable increases with risperidone treatment. The change in prolactin with lumateperone treatment was not significantly different from placebo but was significantly different from risperidone. This may be clinically relevant as hyperprolactinemia, which is observed with many antipsychotics, may be associated with sexual and reproductive system dysfunction (Solmi *et al.*, 2017).

Conclusion
In this pooled analysis of short-term trials of lumateperone treatment for an acute exacerbation of schizophrenia, lumateperone 42 mg had a safety profile similar to placebo, and no new safety signals were identified compared with the findings in the individual clinical studies. TEAEs were predominantly mild and EPS were rare. There was no prolactin increase during short-term lumateperone treatment, and lumateperone 42 mg had a cardiometabolic profile more favorable than risperidone 4 mg and similar to placebo. This pooled analysis supports the safety and the distinct and favorable tolerability profile of once-daily lumateperone 42 mg.

References
(2019). *Caplyta (lumateperone) [package insert]*. New York, NY: Intra-Cellular Therapies, Inc.

(2021). *Risperdal (risperidone) [package insert]*. Titusville, NJ: Janssen Pharmaceuticals, Inc.

Achtyes E, Simmons A, Skabeev A, Levy N, Jiang Y, Marcy P, Weiden PJ (2018). Patient preferences concerning the efficacy and side-effect profile of schizophrenia medications: a survey of patients living with schizophrenia. *BMC Psychiatry* **18**:292.

American Psychiatric Association (2000). *Diagnostic and statistical manual of mental disorders*. Washington, DC: American Psychiatric Publishing.

American Psychiatric Association (2013). *Diagnostic and statistical manual of mental disorders*. Arlington, VA: American Psychiatric Publishing.

Briggs A, Wild D, Lees M, Reaney M, Dursun S, Parry D, Mukherjee J (2008). Impact of schizophrenia and schizophrenia treatment-related adverse events on quality of life: direct utility elicitation. *Health Qual Life Outcomes* **6**:105.

Correll CU, Davis RE, Weingart M, Saillard J, O'Gorman C, Kane JM, *et al.* (2020). Efficacy and safety of lumateperone for treatment of schizophrenia: a randomized clinical trial. *JAMA Psychiatry* **77**:349–358.

Correll CU, Detraux J, De Lepeleire J, De Hert M (2015). Effects of antipsychotics, antidepressants and mood stabilizers on risk for physical diseases in people with schizophrenia, depression and bipolar disorder. *World Psychiatry* **14**:119–136.

Correll CU, Solmi M, Veronese N, Bortolato B, Rosson S, Santonastaso P, *et al.* (2017). Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness: a large-scale meta-analysis of 3,211,768 patients and 113,383,368 controls. *World Psychiatry* **16**:163–180.

ECDEU (1976). *Assessment manual for psychopharmacology*. MD: U.S. Department of Health Education, and Welfare.

First MB, Williams JB, Karg RS, Spitzer RL (2014). *Structured clinical interview for DSM-5 disorders - clinical trials version (SCID-5-CT, modified for ITI-007-301)*. Arlington, VA: American Psychiatric Association.

First MB, Williams JBW, Spitzer RL, Gibbon M (2007). *Structured clinical interview for DSM-IV-TR Axis I disorders, clinical trials version (SCID-CT)*. New York: Biometrics Research, New York State Psychiatric Institute.

Haddad PM, Brain C, Scott J (2014). Nonadherence with antipsychotic medication in schizophrenia: challenges and management strategies. *Patient Relat Outcome Meas* **5**:43–62.

Huhn M, Nikolakopoulou A, Schneider-Thoma J, Krause M, Samara M, Peter N, *et al.* (2019). Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. *Lancet* **394**:939–951.

Kim C-H, Kim C-Y (2003). Optimal dosing and long-term effects of risperidone. *Clin Psychopharmacol Neurosci* **1**:135–146.

Li P, Zhang Q, Robichaud AJ, Lee T, Tomesch J, Yao W, *et al.* (2014). Discovery of a tetracyclic quinoxaline derivative as a potent and orally active multifunctional drug candidate for the treatment of neuropsychiatric and neurological disorders. *J Med Chem* **57**:2670–2682.

Lieberman JA, Davis RE, Correll CU, Goff DC, Kane JM, Tamminga CA, *et al.* (2016). ITI-007 for the treatment of schizophrenia: a 4-week randomized, double-blind, controlled trial. *Biol Psychiatry* **79**:952–961.

Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, *et al.*; Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators (2005). Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med* **353**:1209–1223.

Llorca PM, Lançon C, Hartry A, Brown TM, DiBenedetti DB, Kamat SA, François C (2017). Assessing the burden of treatment-emergent adverse events associated with atypical antipsychotic medications. *BMC Psychiatry* **17**:67.

Overall JE, Gorham DR (1988). The Brief Psychiatric Rating Scale (BPRS): recent developments in ascertainment and scaling. *Psychopharmacol Bull* **24**:97–98, 99.

Roussidis A, Kalkavoura C, Dimelis D, Theodorou A, Ioannidou I, Mellos E, *et al.* (2013). Reasons and clinical outcomes of antipsychotic treatment switch in outpatients with schizophrenia in real-life clinical settings: the ETOS observational study. *Ann Gen Psychiatry* **12**:42.

Snyder GL, Vanover KE, Zhu H, Miller DB, O'Callaghan JP, Tomesch J, *et al.* (2015). Functional profile of a novel modulator of serotonin, dopamine, and glutamate neurotransmission. *Psychopharmacology (Berl)* **232**:605–621.

Solmi M, Murru A, Pacchiarotti I, Undurraga J, Veronese N, Fornaro M, *et al.* (2017). Safety, tolerability, and risks associated with first- and second-generation antipsychotics: a state-of-the-art clinical review. *Ther Clin Risk Manag* **13**:757–777.

Vancampfort D, Stubbs B, Mitchell AJ, De Hert M, Wampers M, Ward PB, *et al.* (2015). Risk of metabolic syndrome and its components in people with schizophrenia and related psychotic disorders, bipolar disorder and major depressive disorder: a systematic review and meta-analysis. *World Psychiatry* **14**:339–347.

Vanover K, Satlin A, Durgam S, Weingart M, Saillard J, Sanchez J, *et al.* (2019). S117. Favorable long-term safety profile of lumateperone (ITI-007): results from a 12-month open-label safety study in patients with stable symptoms of schizophrenia. *Schizophr Bull* **45**:S351.

Williams R (2001). Optimal dosing with risperidone: updated recommendations. *J Clin Psychiatry* **62**:282–289.