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DRUG EVALUATION



# An evaluation of lumateperone tosylate for the treatment of schizophrenia

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**ABSTRACT**

**Introduction**: Schizophrenia, a devastating disorder with onset in adolescence or young adulthood, afflicts 1% of the population leading to severe social, educational, and occupational impairments. Lumateperone is a first-in-class investigational drug under development for the treatment of multiple neuropsychiatric and neurodegenerative disorders including schizophrenia. Its unique receptor affinity profile together with synergistic modulation of serotonergic, glutamatergic, and dopaminergic pathways imparts efficacy over a broad-spectrum of symptoms associated with schizophrenia.

**Areas covered**: This narrative drug evaluation includes a review of lumateperone tosylate (lumateperone, ITI-007, ITI-722, Intra-Cellular Therapies, Inc.) for patients with schizophrenia. This review describes the receptor affinity profile, pharmacodynamics, pharmacokinetics, distribution, metabolism, and clinical trials that address how lumateperone could potentially emerge as an important therapeutic option for schizophrenia patients.

**Expert opinion**: The unique pharmacological properties of lumateperone may provide the key to dramatically ameliorate the symptoms of schizophrenia as indicated by some clinical trials. Future clinical trials may be enhanced by the administration of more comprehensive long-term behavioral measures and utilization of molecular imaging to confirm the target engagement of the many possible sites of action. The results of ongoing and future studies will provide the evidence to determine if lumateperone will revolutionize the therapy of schizophrenia.

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**KEYWORDS**
Bioavailability; clinical trial; distribution; dopamine D1 receptor; dopamine D2 receptor; efficacy; excretion; metabolism; schizophrenia; serotonin 5-HT2A receptor; serotonin transporter

## 1. Introduction

Schizophrenia, a devastating illness afflicting 1% of the population around the world, has both genetic and environmental causes [1]. Delayed cortical migration in the prenatal period characterizes those individuals who are likely to develop schizophrenia [2]. It is characterized by the development in adolescence or young adulthood of positive symptoms, including (1) hallucinations (perceptions of sensory stimuli absent from the environment) (2) delusions (fixed false beliefs), (3) disorganized speech and (4) grossly disorganized or catatonic behavior [3] and negative symptoms, including affective blunting, alogia (impoverished cognition), avolition, apathy, anhedonia, asociality, and inattention [4]. Despite current treatments, many individuals with schizophrenia remain incapable of taking care of themselves [5].

The dopamine hypothesis of schizophrenia proposed that positive symptoms of schizophrenia result from dysfunction of dopaminergic neurotransmission [6]. In the resting tonic state, people with schizophrenia may exhibit lower extracellular dopamine than healthy individuals; in the excited phasic state, people with schizophrenia may experience higher intrasynaptic dopamine levels than healthy individuals [7]. The excessive intrasynaptic dopamine may be associated with the positive symptoms of schizophrenia.

While the first and second-generation antipsychotics provide some symptomatic improvement, their inability to manage both positive and negative symptoms and a wide array of neurological and metabolic side effects demand more research into compounds that will help decide better treatment choices for individuals with schizophrenia.

The purpose of the present article is to present and analyze the current knowledge about the pharmacotherapy of lumateperone tosylate (lumateperone, ITI-007, ITI-722, Intra-Cellular Therapies, Inc.), an orally administered antipsychotic drug, being developed for the potential treatment of schizophrenia [8–15], bipolar depression, and agitation associated with Alzheimer's disease [16]. A search of items for 'lumateperone' and 'ITI-007' was made on PubMed, ScienceDirect, Web of Science, Google Scholar, and https://clinicaltrials.gov. Additionally, press releases were reviewed from google.com.

## 2. Overview of the market

First-generation antipsychotics (i.e., haloperidol, chlorpromazine) are agents that block the dopamine $D_2$ receptor and act on different regions such as mesolimbic, mesocortical, nigrostriatal and tuberoinfundibular pathways. They are mainly

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**Article highlights**

- Lumateperone is a first-in-class investigational drug under development for the treatment of multiple neuropsychiatric and neurodegenerative disorders including schizophrenia.
- The unique pharmacologic profile of lumateperone allows synergistic modulation of serotonergic, dopaminergic, and glutamatergic neurotransmission.
- Phase I studies established the safety of lumateperone in healthy male volunteers without serious adverse events.
- Phase II and III studies established that lumateperone did not cause significant cardiometabolic adverse effects.
- Ongoing and future studies will determine if lumateperone will be approved by FDA as a long-term therapeutic agent of schizophrenia.

protein-bound and highly lipophilic. These antipsychotics are primarily metabolized by the cytochrome P450 2D6 and P450 3A4 systems in the liver and excreted in urine and feces [8]. While $D_2$ receptor blockade is responsible for their antipsychotic efficacy, they have effects on other receptors, such as muscarinic, adrenergic alpha 1 and histamine H1. Blockade of these receptors is related to their side effects profile including a higher risk of neurological side effects like parkinsonism, dyskinesia, and extrapyramidal symptoms like dystonia. Thus, while the first generation antipsychotics are effective against positive symptoms of schizophrenia, they are not effective against the negative symptoms like alogia, avolition, asociality, blunted facial expressions and anhedonia [9,17].

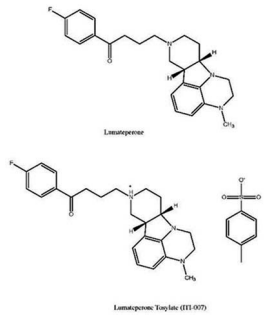
The 'atypical' or second-generation antipsychotics (i.e., aripiprazole, iloperidone, lurasidone, pimavanserin, and risperidone) differ from the first generation antipsychotics in their mode of action, where their binding affinity for serotonin 5-$HT_{2A}$ receptor (and off-target receptors such as muscarinic, histamine H1, adrenergic α1A receptors) is greater than that for the dopamine $D_2$ receptor. This has been suggested to reduce the neuromotor side effects but they cause other side effects, including dyslipidemia, hypotension, weight gain, sexual dysfunction, and metabolic side effects including elevated lipids and diabetes mellitus [10,18].

While current medications for schizophrenia with efficacy against positive and negative symptoms do exist, there is an unmet need for a drug with a benign adverse effect profile [9,10].

## 3. Introduction to the compound

Several compounds are currently being evaluated in clinical trials for the treatment of schizophrenia [11]. Unlike other second-generation antipsychotics, that are $D_2$ receptor antagonists or partial agonists with high affinity and low intrinsic efficacy for both presynaptic and postsynaptic $D_2$ receptors, lumateperone has a novel mechanism of action where it is a partial agonist at presynaptic $D_2$ receptors and an antagonist at postsynaptic $D_2$ receptors [13]. It also works simultaneously on dopaminergic, serotonergic, and glutamatergic neurotransmission for the relief of symptoms of schizophrenia and multiple other neuropsychiatric disorders [9,13] with minimal off-target receptor activity [11].

**Box 1.** Drug summary box.

| | |
|---|---|
| Drug name | Lumateperone tosylate (lumateperone) |
| Phase | Under FDA review, currently recruiting for additional Phase 2 study |
| Indication | Schizophrenia |
| Pharmacology description | • 5 Hydroxytryptamine 2A receptor antagonist<br>• 5 Hydroxytryptamine uptake inhibitor<br>• Dopamine D2 receptor agonist<br>• Dopamine receptor antagonist |
| Route of administration | Oral, once daily |
| Chemical structure |  |
| Pivotal trial(s) | [9,10,15,24] |

## 4. Chemistry

Lumateperone, also known as ITI-007 or ITI-722 [4-((6bR,10aS)-3-methyl-2,3,6b,9,10,10a-hexahydro-1H,7Hpyrido[3′,4′:4,5]pyrrolo[1,2,3-de]-quinoxalin-8-yl)-1-(4-fluoro-phenyl)-butan-1-one 4-methylbenzenesulfonate], exists as the tosylate salt [8,10,11] (See Box 1). The structure of ITI-007 was based on combining a tetracyclic core with a butyrophenone side chain [10,19]. (See Box 1).

## 5. Pharmacodynamics

The unique pharmacologic profile of lumateperone allows it to synergistically modulate serotonergic, dopaminergic, and glutamatergic neurotransmission.

### *5.1. Serotonin 5-$HT_{2A}$ receptor and serotonin transporter (SERT)*

Receptor occupancy studies have shown that lumateperone acts as an antagonist for serotonin 5-$HT_{2A}$ receptor with a $K_i = 0.54$ nM, which is 60-fold higher than its affinity for $D_2$ receptors ($K_i = 32$nM) and serotonin transporter (SERT) ($K_i = 62$ nM) [13]. This allows for lumateperone to be used in different doses as required, for specific *in vivo* receptor engagement and target effect. At low dose, lumateperone acts selectively as a 5-$HT_{2A}$ receptor antagonist, promoting sleep and reducing hostility and aggression, while at higher doses, it exhibits a reduction in depressive and psychotic symptoms [13,20]. This difference in receptor affinities might also explain the minimal cataleptic side effects in mice studies [21]. It is important to note that the 5-$HT_{2A}$ receptor antagonism

synergizes with SERT inhibition for greater antidepressant efficacy than SERT inhibition alone [9].

### 5.2. Dopamine $D_2$ receptor

Lumateperone also acts as a postsynaptic antagonist and a presynaptic partial agonist at dopamine $D_2$ receptors in the striatum of mice, with functional mesolimbic/mesocortical selectivity. Due to its postsynaptic $D_2$ receptor antagonism, lumateperone increases the phosphorylation of the glycogen synthase kinase 3 (GSK3), a signaling molecule in dopamine $D_2$ receptor containing neurons in the prefrontal cortex and nucleus accumbens. This allows for functional blockade of dopamine without increasing dopamine turnover and contributes to antipsychotic efficacy without motor side effects or prolactin increase observed with dopamine receptor blockers that target mesolimbic/mesocortical and nigrostriatal systems [22].

### 5.3. Dopamine $D_1$ receptor and glutamate GluN2B receptor

Lumateperone acts upon dopamine $D_1$ receptors with dose-dependent high affinity ($K_i$ = 52 nM) that results in phosphorylation of the GluN2B (NR2B) subunit of the *N*-methyl-D-aspartate receptor (NMDAR), thereby increasing glutamatergic neurotransmission through both AMPA and NMDA channels in the prefrontal cortex [10]. Glutamate neurotransmission, mediated through NMDA-type receptors, is deficient in schizophrenic patients [23].

## 6. Pharmacokinetics and metabolism

### 6.1. Time course of absorption

After the oral administration of lumateperone to humans, $T_{max}$ occurred at 3 to 4 h [10] and plasma concentrations of 0.05 to 50 ng/mL of lumateperone and 0.2 to 100 ng/mL of the metabolites were detected up to 8 h [9].

### 6.2. Bioavailability

Lumateperone exhibited a human plasma protein binding percentage of 97.4%, demonstrated considerable cytochrome P450 3A4 (CYP3A4) binding in the small intestine (ileum) because it was highly lipophilic at pH 7.4 (Log D at pH 7.4 = 3.38), and is markedly permeable across both the intestine and the blood-brain barrier due to its marked multidrug resistance protein 1 (MDR1) permeability (Papp A-B (x10-6) 15.8) [12].

### 6.3. Distribution

Lumateperone specifically acts on mesocortical and mesolimbic regions of the brain. In the medial prefrontal cortex, lumateperone produces dopamine release without dopamine release in the nigrostriatal pathways and activation of the motor system [9,10]. Thirty to 60 min after the administration of oral doses of 10, 20, 30, and 40 mg lumateperone, the drug occupies striatal dopamine $D_2$ receptors proportionally to the administered dose [9,24].

Lumateperone also produces marked occupancy of cortical serotonin 5-$HT_{2A}$ receptors at low doses (10 mg) with an average of 88% occupancy in the prefrontal cortex. At higher dose (40 mg) it produced maximal striatal SERT occupancy of 31%.

In nucleus accumbens, lumateperone modulates glutamate neurotransmission through a dopamine $D_1$ pathway after an increase in phosphorylation of GluN2B subunits of *N*-methyl-D-aspartate receptors (NMDARs) [13].

In the prefrontal cortex and the nucleus accumbens, lumateperone produces phosphorylation of glycogen synthase kinase 3 (GSK3) [13].

### 6.4. Metabolism

Ketone reductase reduces the carbonyl sidechain of lumateperone (See Drug Summary Box) to an alcohol (ICI200131), which is the major metabolite. In the liver, the isoenzyme cytochrome P450 3A4 (CYP3A4) dealkylates lumateperone to an *N*-desmethylated carbonyl metabolite (IC200161) or an *N*-desmethylated alcohol metabolite (IC200565) [12,25].

### 6.5. Excretion

At pH 7.4 lumateperone is insoluble in 0.33 mL phosphate-buffered saline (PBS). Since the molecular weight (565.740 g/mol) of lumateperone exceeds 300 g/mol, it is excreted in feces, instead of clearing the kidneys to be excreted in the urine. Since the metabolites of lumateperone are water-soluble, they are completely excreted in humans [12,26].

The half-life of lumateperone is 13 h. The half-lives of its metabolites are 20 h for ICI200161 and 21 h for ICI200131 [9,10].

## 7. Clinical efficacy

### 7.1. Phase I studies

Phase I studies established the safety of lumateperone at a single dose in healthy male volunteers that received ITI-007; no serious adverse events (SAE) were observed in this study. This was followed by daily doses of ITI-007 for 5 days in healthy volunteers and patients with stable schizophrenia, which was well tolerated and no clinically relevant side effects were observed by routine vital examinations [10,26].

### 7.2. Phase II studies

Phase II studies established the safety [10,24] and efficacy [8,10,24,25] of multiple doses of lumateperone in healthy volunteers and stable patients with schizophrenia [27].

In phase II clinical trial NCT01499563 (ITI-007-005), 335 acutely psychotic patients of schizophrenia were randomized to receive ITI-007 60 mg or 120 mg, risperidone 4 mg (active control) or placebo for 4 weeks. It was found that 60 mg lumateperone was safe and well-tolerated and both risperidone and lumateperone significantly improved symptoms of schizophrenia as assessed by

Table 1. Summary of completed and ongoing clinical studies with ITI-007 (AM- dose administered in the morning, PM- dose administered in the evening).

| Clinical trial Phase II | No. of patients with schizophrenia | Treatment groups/Duration of study | Outcome |
|---|---|---|---|
| NCT01499563, ITI-007-005 | 335 [15] | Placebo (inactive placebo for 28 days, AM) | Least squares (LS) mean change from baseline −7.4 points |
| Clinical trial Site: Long Beach, California, United States | | Risperidone 4 mg (once daily for 28 days, AM) | Improved PANSS score over placebo (LS mean change from baseline −13.4 points, $p = 0.013$) |
| | | Lumateperone 60 mg (once daily for 28 days, AM) | Improved PANSS score over placebo (LS mean change from baseline −13.2 points, $p = 0.017$) |
| | | Lumateperone120 mg (once daily for 28 days, AM) | Did not show significant improvement in efficacy over placebo (LS mean change −8.3 points, $p = .708$) |
| NCT02288845 | 10 [24] | Lumateperone 60 mg (once daily for 14 days, AM) | D2 receptor occupancy ($D_2RO$) was studied. |
| Clinical trial site: Johns Hopkins Medical Institute, Baltimore, USA. | | | |
| **Clinical trial Phase III** | **No. of patients with schizophrenia** | **Treatment groups/Duration of study** | **Outcome** |
| NCT02282761, ITI-007-301 | 450 [11,29] | Placebo (once daily for 28 days, AM) | Least squares (LS) mean change from baseline −10.3 points |
| Clinical trial site: Long Beach, California, United States | | Lumateperone 40 mg (once daily for 28 days, AM) | Did not show significant improvement in efficacy over placebo |
| | | Lumateperone 60 mg (once daily for 28 days, AM) | Improved PANSS score over placebo (LS mean change from baseline −14.5 points, effect size = −0.30, $p = 0.022$) |
| NCT02469155, ITI-007-302 | 696 [11,29] | Placebo (once daily for 6 weeks, AM) | High placebo response was seen. (LS mean change from baseline −15.1 points) |
| Clinical trial site: Long Beach, California, United States | | Risperidone 4 mg (once daily for 6 weeks, AM) | Improved PANSS score over placebo (LS mean change from baseline −20.5 points) |
| | | Lumateperone 20 mg (once daily for 6 weeks, AM) | PANSS score not significant over placebo (LS mean change from baseline −15.0 points) |
| | | Lumateperone 60 mg (once daily for 6 weeks, AM) | PANSS score (LS mean change from baseline −14.5 points) |
| ITI-007-303 (part 1) | 302 [30] | Standard of care (SOC) | Statistically significant improvements from SOC were observed in body weight, cardiometabolic and endocrine parameters, that got worse again when patients were switched back to SOC antipsychotic medication. |
| Clinical Site: Long Beach, California, United States | | Lumateperone 60 mg (once daily for 6 weeks, PM) | |
| | | Switched back to SOC and analyzed after 2 weeks | |
| ITI-007-303 (part 2) | 603 [33] (as of Sept 2019). Final number will vary depending on the number of completed studies. | 40–60 mg Lumateperone once daily (PM), along with patient's current medication. Patients will be weaned off their current medication within the first 7 days of starting Lumateperone treatment. | Currently recruiting |
| NCT03817528 | | | Estimated completion date: 1 March 2021 |
| Clinical trial site: New York State Psychiatric Institute | | Change from baseline in Total PANSS score will be followed for the duration of the year of treatment. | |

Positive and Negative Syndrome Scale (PANSS) between baseline and last day of study as compared to placebo [28] (Table1) (least squares [LS] mean change −13.2 points vs. −7.4 points [placebo]; P = 0.017 for lumateperone 60 mg and LS mean change −13.4 points vs. −7.4 points [placebo]; P = 0.013 for risperidone 4 mg). No significant change in PANSS score was observed for 120 mg lumateperone. At 60 mg, lumateperone also reduced PANSS positive symptom score of schizophrenia as compared to placebo (LS mean change −5.1 points vs. −2.7 points [placebo]; P = 0.002 for lumateperone 60 mg and LS mean change −5.2 points vs. −2.7 points [placebo]; P = 0.001 for risperidone 4 mg). In a subgroup of patients that displayed elevated negative symptoms, 60 mg lumateperone reduced PANSS negative symptoms subscale scores compared to placebo (LS mean change −3.0 points vs. −1.3 points [placebo], effect size = −0.34, nonsignificant difference), while risperidone, slightly increased negative symptoms relative to placebo (LS mean change +1.2 points vs. −1.3 points [placebo], effect size = +0.02). Secondary analyses on 45 patients indicated improved negative symptoms and symptoms of depression as measured by the CDSS (Calgary Depression Scale for Schizophrenia) [15,24].

In Study NCT02288845, 10 patients aged 18–60 years with stable schizophrenia received 60 mg lumateperone once daily for 2 weeks and $D_2$ receptor occupancy ($D_2RO$) was studied using positron emission tomography with $^{11}$C-raclopride as the radiotracer. The peak $D_2RO$ for 60 mg lumateperone was 39%, which is lower than other second-generation antipsychotics at their effective doses and probably contributes to the favorable safety and tolerability profile of lumateperone, with no clinically significant changes in vital signs, cardiometabolic measurements and a reduced risk for movement disorders and hyperprolactinemia [24].

### 7.3. Phase III studies

In a three-arm, placebo-controlled phase III clinical trial NCT02282761 (ITI-007-301), 450 patients were randomized to

receive ITI-007 (60 mg or 40 mg) or placebo for 4 weeks [27]. Lumateperone (60 mg) demonstrated a greater antipsychotic efficacy over placebo as assessed by the PANSS score (LS mean change from baseline −14.5 points, effect size = −0.30, P = 0.022 vs. −10.3 points in placebo). At 40 mg, lumateperone did not show statistically significant score reductions compared to placebo at the study end point. However, both 60 mg and 40 mg dose demonstrated improvement in the Clinical Global Impression Scale for Severity of Illness, reduction in PANSS positive subscale scores compared to placebo and improvement in PANSS Prosocial Symptom Factor.

In another phase III clinical trial NCT02469155 (ITI-007-302), 696 patients were randomized to receive ITI-007 60 mg or 20 mg, risperidone 4 mg (active control) or placebo for 6 weeks. In this study, PANSS score for active control, risperidone demonstrated change from baseline on the PANSS total score of −20.5 points, 60 mg, and 20 mg lumateperone demonstrated −14.6 points and −15.0 points, respectively, but a high placebo response was observed in this study (−15.1 score above baseline on PANSS total score in contrast to −7.4 points in NCT01499563 and −10.3 points in NCT02282761) [30] at the primary end point [31]. It is important to note that even though a high placebo response was observed in this study, risperidone arm separated from placebo while lumateperone did not, which needs to be addressed in further studies to conclude the efficacy of the drug as a long-term therapeutic agent.

An open-label safety switching trial (ITI-007-303) was conducted with 302 patients with stable symptoms of schizophrenia and currently on a standard of care medication, where they were switched from standard of care medication to 60 mg lumateperone once daily for 6 weeks, then switched back to standard of care and analyzed at a 2-week time point. When switched to lumateperone, the patients did not have cardiovascular or motor impairments as observed with current antipsychotic medications and showed statistically significant improvement in endocrine, weight gain, and cardiometabolic parameters. These improvements were reversed when patients were switched back to their current medication [30].

Another clinical trial NCT03817528, which is part 2 of the open-label study ITI-007-303 is currently evaluating long-term exposure (up to 1-year treatment duration) of lumateperone 60 mg in patients with schizophrenia and stable symptoms [32]. Besides showing a clinically significant decrease from standard of care baseline in weight gain, total cholesterol, low-density lipoprotein (LDL) cholesterol, prolactin and comorbid depression (assessed by CDSS score), lumateperone 60 mg treatment showed a reduction in PANSS Total score with continuing PANSS improvement throughout the study. Of the 693 patients that were included in this data, 107 patients had completed 1 year of treatment, so a larger sample size needs to be evaluated to assess the effect on PANSS score relative to the 6 week study NCT02469155 [32]. The primary focus of the ongoing long-term study is safety. The common treatment-emergent adverse events during 1 year of therapy were dry mouth (7.6%), headache (5.1%), and diarrhea (7.0%). Only 5.3% of the patients developed extrapyramidal symptoms combined including akathisia. The incidence of somnolence, which was seen in 20% of the treatment group dropped to placebo level when dosing was switched from morning to evening in the open-label program [33].

The results from these studies have been summarized in Table 1.

## 8. Post-marketing surveillance

Since lumateperone is not yet commercially available, post-marketing surveillance has not been accomplished.

## 9. Safety and tolerability

Lumateperone demonstrated a good cardiometabolic and motor safety and tolerability profile, that was similar to placebo between doses of 1–140 mg in healthy controls and Schizophrenia patients [10,14,30]. Across all trials, the common adverse effects observed were headache, dizziness, diarrhea, and sedation. At the doses, lumateperone was tested in phase II and phase III (40, 60,120 mg), it did not cause significant adverse effects like tachycardia or motor disturbances like akathisia, which are common side effects of risperidone (4 mg/day). Also, placebo-level changes were observed in weight gain, prolactin, fasting glucose, total cholesterol, and triglycerides levels, and can be attributed to low affinity of lumateperone to 5-$HT_{2B}$ and 5-$HT_{2C}$ subclass of serotonin receptors that are engaged by current antipsychotic medications [13].

## 10. Regulatory affairs

Lumateperone was under FDA review with a Prescription Drug User Fee Act (PDUFA) action date of December 2019. The drug was granted a fast track status owing to its positive safety profile in the initial Phase II and III clinical trials but at the time of publishing this article, the advisory meeting for review of the drug had been cancelled due to FDA needing an additional review of pre-clinical data [34]. It is yet to be determined whether the New Drug Application for lumateperone for the treatment of schizophrenia will be approved by the FDA or more data will be required for approval.

## 11. Conclusion

Lumateperone is a small-molecule neurotransmitter modulator of serotonin, dopamine, and glutamate signaling and is currently under FDA review for the treatment of schizophrenia. The combination of the unique pharmacodynamic, pharmacokinetic, and initial safety profile of lumateperone indicates that lumateperone could be a promising drug for the treatment of schizophrenia.

Lumateperone is a fast-absorbing drug, crosses the blood-brain barrier, is well metabolized and eliminated by the body and has shown significant efficacy against both positive and negative symptoms of schizophrenia [10,15]. It has a high affinity for serotonin 5-$HT_{2A}$ receptors, which are saturated at low doses. Other receptors like SERT, $D_2$, $D_1$/GluN2B (glutamate) are recruited at higher doses, which allows for its use in different neuropsychiatric and neurodegenerative diseases at

different doses while contributing to enhanced efficacy and minimum side effects.

Furthermore, lumateperone is regioselective at mesolimbic and mesocortical regions for dopamine $D_2$ receptor occupancy and has minimal to no affinity for off-target receptors reducing or eliminating cardiovascular, metabolic, and motor adverse effects present in currently available antipsychotic medications [9]. Further development of lumateperone could fill the unmet needs in producing a safer and more effective antipsychotic drug. While lumateperone offers promise to relieve the symptoms of schizophrenia with minimal adverse effects, a comprehensive evaluation of efficacy in long-term human studies will be required for establishing it as a better alternative to the current standard of care antipsychotics.

## 12. Expert opinion

The pharmacological profile of lumateperone offers several improvements over current schizophrenia medications. A prominent issue with currently available antipsychotic drugs is the potential for various adverse effects caused primarily by an affinity for numerous off-target receptors. Lumateperone improves upon this issue with regioselective $D_2$ receptor occupancy as well as little to no affinity for off-target receptors. The synergy of the drug's high affinity for 5-$HT_{2A}$ receptor antagonism at low doses, dose-dependent presynaptic dopamine $D_2$ partial agonism, and postsynaptic dopamine $D_2$ antagonism selective to mesolimbic and mesocortical areas, alongside SERT inhibition makes lumateperone an attractive medication for efficacy against a wide range of symptoms associated with schizophrenia as well as other disorders. Different doses of lumateperone could potentially target symptoms that previously required combinations of multiple medications. For instance, at low doses, lumateperone acts primarily as a 5-$HT_{2A}$ receptor antagonist that could be used to reduce insomnia, mood disorders [35], anxiety, aggression, and agitation alongside potentially reducing negative symptoms of schizophrenia. Additionally, human studies have not identified the serious adverse effects that characterize other efficacious antipsychotic agents.

With its favorable safety and tolerability profile and minimal effects on cardiometabolic parameters including fasting blood glucose, insulin, triglycerides, and HDL cholesterol, weight gain, and prolactin levels, lumateperone offers clear advantages over other therapies for schizophrenia.

However, additional data is needed before a conclusive assessment can be made about the efficacy of lumateperone for long-term treatment of schizophrenia. Lumateperone at 60 mg improved symptoms of schizophrenia with the same magnitude of change from baseline on the PANSS total score across three studies (spanning 4–6 weeks), which was similar to the active control risperidone. However, the high placebo response at certain sites in the 6-week study ITI-007-302 cannot solely account for lumateperone not showing an advantage over placebo since risperidone in the same study showed a marked change in PANSS scores.

The high placebo response may be explained by acknowledging the complexities of designing, conducting, analyzing, and interpreting multi-center clinical trials. The development of lumateperone for schizophrenia may benefit from the recommendations by the leading investigators of fragile X syndrome when multiple clinical trials were not successful [36,37]. Recommendations for improving clinical trials included innovations to insure rigorous and reproducible research with stakeholder involvement [38]. The utilization of more objective measures for observation, direct testing, and biological markers are recommended means to conduct optimal clinical trials. Therefore, future clinical trials of lumateperone may be enhanced by long-tern efficacy studies, utilization of more precise behavioral measures including the Scale for the assessment of Negative Symptoms [4], the Scale for the assessment of Positive Symptoms [3] and the utilization of molecular imaging to ascertain target engagement for the dopamine $D_1$ and $D_2$, serotonin 5-$HT_{2A}$, and glutamate GluN2B receptors and serotonin transporters [24].

Improved clinical trials may provide the evidence to determine if lumateperone will become the leading treatment for schizophrenia in 5 years. If Intra-Cellular Therapeutics is able to carry out a long-term efficacy trial or is able to analyze the collective data from clinical trials for other neurochemical imbalance disorders, lumateperone could be a successful first commercial drug by Intra-Cellular Therapeutics.

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