Lumateperone (ITI-007): A Novel Investigational Agent With Broad Therapeutic Potential Across Multiple Neuropsychiatric Disorders

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ABSTRACT

Introduction: Lumateperone (ITI-007), a first-in-class investigational agent which simultaneously modulates serotonin, dopamine, and glutamate, is currently in phase 3 clinical development for schizophrenia, bipolar depression and agitation associated with dementia, including Alzheimer's disease. Acting synergistically via serotonergic, dopaminergic and glutamatergic systems, it represents a new therapeutic approach for neuropsychiatric disorders. At lower doses lumateperone is a potent 5-HT2A receptor antagonist. As the dose is increased lumateperone also acts as a mesolimbic/mesocortical dopamine phosphoprotein modulator (DPPM) with activity as a pre-synaptic partial agonist and post-synaptic antagonist at D2 receptors, a SERT inhibitor and an indirect glutamate (NMDA and AMPA) enhancer downstream from dopamine D1 receptor activation. Together, these unique pharmacological features predict enhancement of sleep and reduction of agitation and aggression at lower doses, and antipsychotic and antidepressant efficacy at higher doses. Additionally, efficient dopaminergic modulation with relatively low striatal D2 receptor occupancy as well as a lack of affinity for off-target muscarinic and histaminergic receptors predict a favorable side effect profile.

Methods: Lumateperone has been evaluated in randomized, double-blind, placebo-controlled clinical trials across a wide range of doses. Low doses of lumateperone were evaluated in patients with primary insomnia, healthy geriatric volunteers and elderly patients with dementia and are currently in Phase 3 development for the treatment of agitation associated with dementia including Alzheimer's disease. Higher doses of lumateperone have been evaluated for efficacy in three large, randomized, placebo-controlled trials in patients with schizophrenia. These doses are also being evaluated in two placebo-controlled trials in patients with depressive episodes associated with bipolar disorder.

Results: In a Phase 2 trial in patients with primary insomnia, ITI-007 (1 – 10 mg) demonstrated a dose-related increase in deep slow wave sleep, decrease in wake after sleep onset, and increase in total sleep time with no next-day hang-over effects. In patients with dementia, ITI-007 9 mg was safe, well-tolerated, and improved measures of cognition.

In two late-stage schizophrenia studies ITI-007 60 mg met the primary endpoint and demonstrated efficacy with statistically significant superiority over placebo at Day 28 as measured by the PANSS total score. Across all schizophrenia studies to date, lumateperone has been well-tolerated with a safety profile similar to placebo. In two studies that included risperidone as an active control, lumateperone demonstrated statistically significant advantages over risperidone on key safety and tolerability parameters including glucose, lipids and weight gain. Doses of 40 and 60 mg ITI-007 were selected for evaluation in two double-blind, placebo-controlled clinical trials (one as monotherapy and one as adjunctive therapy) in patients with Bipolar I or II disorder with a current episode of depression.

Conclusion: Lumateperone represents a new approach to the treatment of several neuropsychiatric conditions with unique pharmacologic properties and a differentiating clinical profile. Given the potent SERT activity and modulation of glutamate through AMPA and NMDA, the clinical development of this novel agent is expected to continue into other depressive disorders in the future.

RESULTS

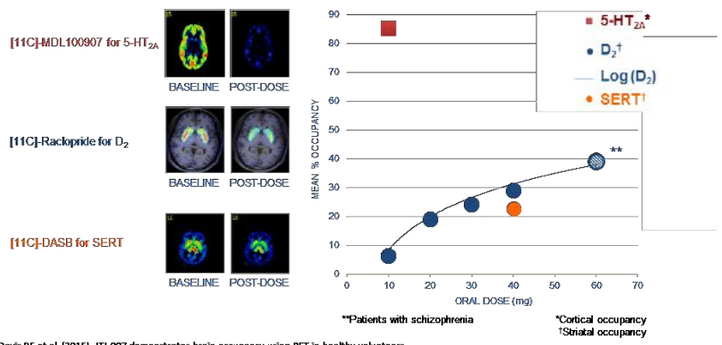
BACKGROUND – Functional Properties of Lumateperone (ITI-007)

Target/Ki (nM)	5-HT2A	D_2	D_1	SERT
Lumateperone	0.54	32	52	62

Lumateperone is a:

- 5-HT2A receptor antagonist
- Dopamine D2 phosphoprotein modulator (DPPM)
  - Pre-synaptic partial agonist/Post-synaptic antagonist
- Glutamatergic phosphoprotein modulator (D1 receptor)
- Serotonin reuptake inhibitor

The Unique Pharmacology of Lumateperone: Receptor Activation as Seen in PET Studies

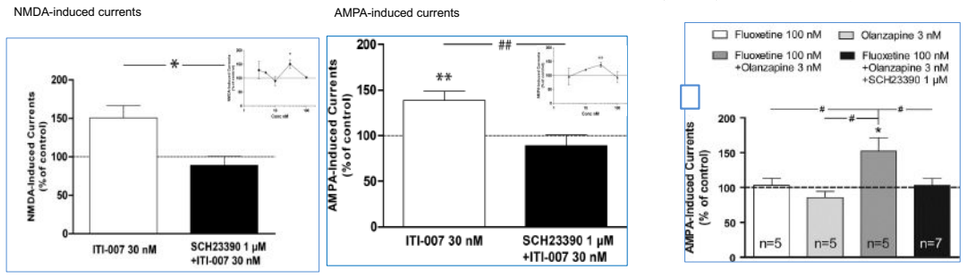


Davis RE et al. (2015). ITI-007 demonstrates brain occupancy using PET in healthy volunteers. Psychopharmacology (Berl). 232(15):2863-72.

Lumateperone, Given Alone, Uniquely Enhances both NMDA and AMPA Receptor Currents in mPFC Neurons Via Activation of D1 Receptors

Lumateperone: Alone enhances NMDA- and AMPA-induced currents

Olanzapine enhances AMPA-induced currents only in the presence of the SSRI, Fluoxetine



Left (above): Lumateperone (ITI-007), alone, bath applied to rat mPFC slices (3-100nM) enhanced NMDA and AMPA currents 5 min later measured using intracellular whole-cell patch clamp techniques (Björkholm et al., 2015). The effect of lumateperone (30nM) (*p<0.05; **p<.01, t-test) was fully blocked in the presence of the D1 receptor antagonist, SCH-23390 (1µM) (*p<0.05; **p<.01; ##, p<.01, t-test) (inset graphs). **Right (above)**: Combined administration of the antipsychotic, olanzapine, and the SSRI, fluoxetine, induces rapid antidepressant activity in humans and animals (Tohen et al., 2010); likewise, combined application of olanzapine + fluoxetine is required to induce AMPA receptor currents in vitro.

ITI-007-004 Trial

Phase 2 Trial in Patients with Primary Insomnia

Low doses of ITI-007 (1, 5, and 10 mg) significantly improved slow-wave sleep (SWS) and wake after sleep onset (WASO) in a randomized, double-blind cross-over design in patients with primary insomnia.

Outcome Measure (n=18)	Mean Change from Baseline (min)				p-value
			ITI-007		
	Placebo	1 mg	5 mg	10 mg	
SWS	-3.75	0.47	5.53	8.94	p = 0.002
WASO	-1.86	-12.69	-14.31	-33.22	p = 0.001

RESULTS (cont'd)

ITI-007-200 Trial

Safety trial in healthy geriatric subjects and patients with dementia, including Alzheimer's Disease

	Part 1: Healthy Geriatric			Part 2: Dementia Patients
	Cohort 1	Cohort 2	Cohort 3	Cohort 1
ITI-007 dose	7.5mg QAM	15mg QAM	30mg QAM	9mg QPM
N (ITI-007/placebo)	8:2	7:1	7:2	5:3

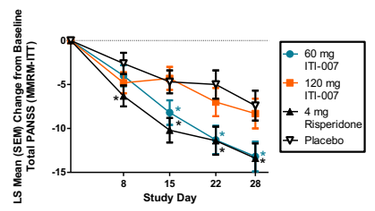
Entry criteria: healthy volunteers: ≥65 yrs old, MMSE ≥26; dementia patients: clinical diagnosis of dementia, ≥65 yrs old, MMSE ≤26

- ITI-007 was safe and well tolerated up to and including a dose of 30 mg, the highest dose tested in this study.
- There were no clinically significant changes in ECGs (including no QTc interval prolongation), vital signs, or clinical laboratory values.
- Pharmacokinetic results indicate that dosing of ITI-007 has a linear and dose-related increase in blood drug levels.
- ITI-007 improved verbal learning and memory in healthy geriatric patients and enhanced recognition memory in elderly patients with dementia.

ITI-007-005 Trial in Schizophrenia (N=335)

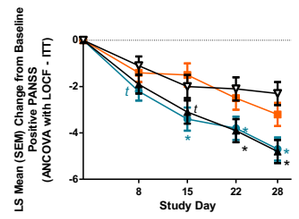
Positive Clinical Trial, Met Primary Endpoint 60 mg ITI-007 Demonstrated Antipsychotic Efficacy

POSITIVE AND NEGATIVE SYNDROME SCALE (PANSS) TOTAL SCORE AT DAY 28



MMRM: ITT**

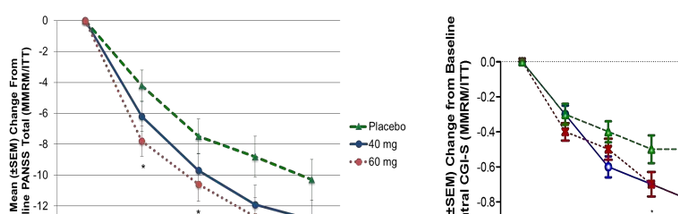
PANSS POSITIVE SUBSCALE AT DAY 28



LOCF: ITT

**On the pre-specified primary analysis (MMRM/ITT), 60 mg ITI-007 separated from placebo on Day 28, p = 0.017, ES = 0.4
On the pre-specified sensitivity analysis (ANCOVA/ITT with LOCF), 60 mg ITI-007 again separated from placebo, p = 0.011, ES = 0.4

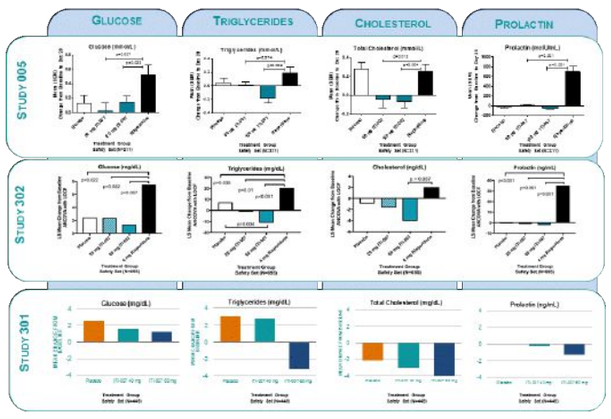
ITI-007-301 Trial in Schizophrenia (N=450)



60 mg ITI-007 separated from placebo as early as week 1, and maintained efficacy at every time point to study endpoint on the PANSS total score.

Both 40 mg and 60 mg were statistically significantly superior to placebo on CGI-S at study day 22 and 28.

Consistent Placebo-Like Safety for Lumateperone And Superiority Over Risperidone on Key Parameters

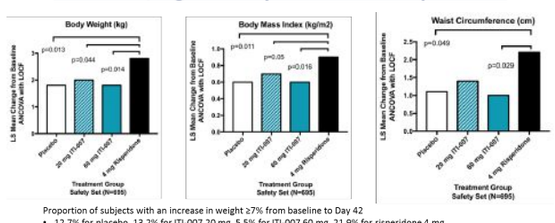


Most frequent adverse events with once daily oral administration in the morning were predominantly mild somnolence and sedation

Discontinuation rates due to AEs were low for lumateperone and similar to placebo

Lumateperone demonstrated a superior safety profile to risperidone

Study 302: Patients treated with Lumateperone Showed Placebo-Like Weight Change Measures, Significantly Better than Risperidone



Proportion of subjects with an increase in weight ≥7% from baseline to Day 42
- 12.7% for placebo, 13.2% for ITI-007 20 mg, 5.5% for ITI-007 60 mg, 21.9% for risperidone 4 mg
- Placebo-adjusted: 0.5% for ITI-007 20 mg, -7.2% for ITI-007 60 mg, 9.2% for risperidone 4 mg

CONCLUSIONS

- Lumateperone (ITI-007) is an investigational new drug acting via serotonin, dopamine and glutamate.
- Lumateperone enhanced both NMDA and AMPA-induced currents in mPFC pyramidal neurons via activation of D1 receptors. These changes have been implicated in the mechanism of action of rapid-acting antidepressants.
- Lumateperone represents a potential new approach to the treatment of a broad array of psychiatric and neurological symptoms.
- Lumateperone demonstrated antipsychotic efficacy in 2 large, late-stage, randomized, double-blind clinical trials in schizophrenia to date.
- Pharmacological, pharmacodynamic and efficacy/safety profiles support development of lumateperone in the low dose range for the treatment of behavioral disturbances in dementia and in the higher dose range for the treatment of schizophrenia and bipolar depression.
- Lumateperone is well-tolerated with a safety profile similar to placebo in over 1500 individuals exposed in clinical trials to date.
- Lumateperone is currently being evaluated in Phase 3 clinical trials for the treatment of schizophrenia, bipolar depression and agitation associated with dementia, including Alzheimer's disease.

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COG, RED, SM, and KEV are full time employees of Intra-Cellular Therapies. Contact: cogorman@intracellulartherapies.com