1. Brief Description/Background

- Unique mechanism of action due to tripartite modulation
  - 5-HT2A antagonist and SERT inhibitor
  - Pre-synaptic D2 partial agonist & postsynaptic D2 antagonist
  - Indirect D1 receptor-dependent modulation of glutamate (NMDA & AMPA)

- At low dose: ↑ sleep, ↓ agitation and aggression
- At higher dose: antipsychotic and antidepressant efficacy

Correll, 2020. JAMA Psychiatry
1. Brief Description/Background

- 6-week, randomized, double-blind, placebo-controlled (n=150) lumateperone 42 mg (n=150) and 28 mg (n=150) vs placebo.
- Significant improvement in PANSS score.
- No difference in weight, metabolism, EPS, akathisia.
- Two placebo-controlled studies for bipolar depression.
- No significant difference in depressive symptoms, akathisia, weight.
- Rates of akathisia and EPS were similar to placebo.

2. Indication(s)

- Intra-Cellular Therapies - Atypical antipsychotic FDA-approved (2019) for schizophrenia.
- Submitted in 2021 for FDA approval for the treatment of depressive episodes associated with bipolar I or II disorder both as monotherapy and as an adjunctive therapy in adults.
- Rapidly absorbed, once-daily 42 mg administered orally with food.
- Low risk for EPS and cardiometabolic side effects.

3. Considerations

- Black box: ↑ risk of death for elderly patients with dementia-related psychosis.
- Adverse effects: headache, somnolence, dizziness, sedation, fatigue, and constipation.
- Cautions when administered with inducers/inhibitors of CYP3A4.
- Cost (~ $1600/month).