9TH ANNUAL CHAIR SUMMIT
Master Class for Neuroscience Professional Development

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#CHAIR2016
Schizophrenia and Cognition

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Disclosures

- **Research/Grants***: Alkermes; Novartis Corporation/Vanda Pharmaceuticals*

- **Advisory Board***: Clinatara; Intracellular Therapies, Inc.*; Pierre Fabre*

- **Other Financial or Material Support**: Repligen Corporation

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Symptoms

Positive Symptoms:
- Suspiciousness/paranoia
- Gradiois/Delusions
- Unusual thought content

Negative Symptoms
- Blunted affect
- Emotional withdrawal
- Active social avoidance
- Lack of spontaneity
- Poor rapport

Cognitive Symptoms
- Poor attention
- Conceptual disorganization
- Difficulty in abstract thinking
- Disorientation

Cognitive dysfunction ("Dementia praecox")

Challenge: Single etiological mechanism to account for different classes of symptoms & cognitive deficits
Neuroanatomy of CIAS

Basal ganglia: Impaired GABA release, dopamine regulation

Frontal cortex: Impaired reversal learning (delusions), response inhibition (impulsivity)

Auditory cortex: Impaired tone matching, "echoic" memory

Hippocampus: Impaired memory formation/object recognition

Limbic system: Impaired fear extinction (paranoia)

Magnocellular visual system: Impaired stimulus encoding, attentional capture, motion detection face emotion recognition

Parietal cortex: Impaired attentional allocation, P300 generation
Schizophrenia Treatment Update

- Conventional Mechanism Treatments
- New Targets and Novel Treatments
- Neuromodulation
- Genetically Targeted Treatments
- Early Detection and Intervention Models
FDA Approved Antipsychotics

- Chlorpromazine - 1957
- Perphenazine - 1957
- Trifluoperazine - 1959
- Fluphenazine* - 1960
- Thioridazine - 1962
- Haloperidol* - 1967
- Thiothixene - 1967
- Molindone - 1974
- Loxapine - 1975
- Pimozide - 1984
- Clozapine - 1989
- Risperidone* - 1993
- Olanzapine* - 1996
- Quetiapine - 1997
- Ziprasidone - 2001
- Aripiprazole* - 2002
- Paliperidone* - 2006
- Iloperidone - 2009
- Asenapine - 2009
- Lurasidone - 2010
- Brexpiprazole - 2015
- Cariprazine - 2015
- Pimavanserin - 2016
  - ITI-007 - 2017?
  - F17464 - 2018?

* Long Acting Injectable Formulation
### Metabolic Adverse Effects of FDA Approved Antipsychotic Agents

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>Weight Gain</th>
<th>Diabetes Risk</th>
<th>Dyslipidemia</th>
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<tr>
<td>Aripiprazole*</td>
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<td>Asenapine</td>
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<td>Brexpiprazole</td>
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<td>Clozapine</td>
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<tr>
<td>Iloperidone</td>
<td>Moderate</td>
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*Includes all formulations

Lurasidone: Long-term Maintenance in Schizophrenia

- Double-blind, placebo-controlled, randomized withdrawal study enrolled adults (N = 676) aged 18 to 75 years with diagnosis of schizophrenia currently experiencing an acute exacerbation
  - PANSS total score ≥ 80 and at least 1 positive subscale item score ≥ 4
  - CGI-S scale score ≥ 4
- Patients received 12–24 weeks of open-label treatment with lurasidone (40–80 mg/d, flexibly dosed).
- Those reaching stabilization criteria were randomized to lurasidone (N = 144) or placebo (N = 141).

Lurasidone: Long-term Maintenance in Schizophrenia (cont’d)

- The efficacy of lurasidone for the maintenance treatment of patients with schizophrenia was demonstrated.
- In the double-blind phase, lurasidone significantly delayed time to relapse compared with placebo reflecting a 33.7% reduction in risk of relapse.
- Probability of relapse at the double-blind week 28 endpoint was 42.2% in the lurasidone group and 51.2% in the placebo group.
- Minimal changes in weight, lipid, glucose, and prolactin were observed throughout the study.

Brexpiprazole: Long-term Maintenance in Schizophrenia

- FDA has approved labeling update for maintenance treatment of schizophrenia (September 24, 2016)
  - Adults (N = 202) with schizophrenia aged 18 to 65 years in a long-term randomized withdrawal trial
  - Cross-titration from a prior antipsychotic to brexpiprazole and a 12 to 36-week, single-blind brexpiprazole stabilization phase.
  - After symptomatically stable on brexpiprazole for 12 consecutive weeks in the stabilization phase, patients randomized in a double-blind treatment phase to either brexpiprazole (N = 97) or placebo (N = 105).

The primary efficacy endpoint was the time from randomization to impending relapse. Safety and tolerability were also assessed.

Relapse determined by worsening symptoms defined by changes in PANSS or CGI-I scores; hospitalization for worsening psychotic symptoms; suicidal behavior or; violent/aggressive behavior.

The final analysis demonstrated a statistically significant longer time to relapse (13.5% brexpiprazole vs 38.5% placebo) (hazard ratio: 0.292, $p < .0001$) in patients randomized to brexpiprazole (1 mg/day to 4 mg/day) compared to placebo.

Negative Symptoms: An Unmet Therapeutic Need

- Current antipsychotic drugs (APDs) have therapeutic effects in patients with schizophrenia predominantly against positive symptoms, such as hallucinations and delusions.
- Most APDs show only modest effectiveness, if any, in treating the nonpsychotic symptoms of schizophrenia that are believed to be responsible for the poor social and academic/vocational functioning characteristics of the illness, including social withdrawal, flattened affect, depression, and cognitive impairment.
- Negative and cognitive symptoms contribute more to poor functional outcomes and quality of life for individuals with schizophrenia than do positive symptoms.
- Caregivers report high levels of burden secondary to negative symptoms.

Targets for Novel Drug Development

- Alpha-7 nicotinic receptor: partial agonists
- D1 receptor: partial agonists (DAR-100A, PF4958242)
- Glutamate
  - NMDA receptor allosteric modulators (glycine, serine, D-cycloserine)
  - Glycine transport inhibitors (bitopertin, sarcosine, BI425809)
  - AMPA receptor agonists
  - Metabotropic receptor partial agonists (pomaglumetad)
- M1 muscarinic receptor agonists
- GABA-A R subtype selective agonists
- Nona Peptides (Oxytocin)
- Cannabinoid receptors (CB-1) (Cannabadiol)
- Immunologic – Anti-inflammatory drugs
- Phosphodiesterase Inhibitors (1, 4, 9, 10)
Encenicline Cognitive Impairment in Patients with Schizophrenia
Investigational α7 nicotinic acetylcholine receptor partial agonist

This agent is not approved by the US FDA for schizophrenia
Phase IIb Schizophrenia Study

Study Design

- 12-week, randomized, double-blind, placebo-controlled study in patients with schizophrenia receiving stable atypical antipsychotic treatment

Note: MCCB administered in United States only due to unavailability of validated translated test battery

The dose represented is the free base form. Encenicline HCl 0.27 mg is equivalent to 0.3 mg and encenicline HCl 0.9 mg is equivalent to 1.0 mg

Phase IIb Schizophrenia Study
MATRICS consensus cognitive battery (MCCB)*

*The MCCB was performed only in the United States

\( p \) values vs. placebo. All data presented as mean ± SEM. ES = Cohen’s d effect Size

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WALTHAM, Mass. – March 24, 2016 - FORUM Pharmaceuticals Inc. today announced topline results from two Phase 3 clinical trials in patients with cognitive impairment in schizophrenia (CIS). While encenicline (FRM-6124) demonstrated a favorable safety and tolerability profile in both studies, neither study met its co-primary endpoints based on effect on cognitive function and patient function.

“These results are not what we might have hoped for on behalf of patients. We wish to thank over 1,500 patients who participated as well as the investigators at more than 200 clinical sites,” said Deborah Dunsire, MD, President and CEO of FORUM.

An unexpectedly high placebo response was observed in both trials. Activity was observed across certain sub-groups and secondary endpoints, and these results are being further analyzed.
Action Item

● There remains an unmet need for treatment options for cognition and negative symptoms in patients with schizophrenia.

● When choosing treatments, assess weight gain liability, efficacy in negative symptoms and patients’ ability to remain adherent to treatment.
Questions & Answers