Lurasidone Meeting

June 12, 2009

Dainippon Sumitomo Pharma Co., Ltd.
Lurasidone: Clinical Studies
Summary

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Vice President, Clinical Development
Dainippon Sumitomo Pharma America
Lurasidone Development Timeline

1990-1995

- Lurasidone Discovery (Japan)

2000

- First in Man (Japan)

2002

- US Schizophrenia IND

2004

- Schizophrenia Phase 2

2005

- Merck Outlicensed

2006

- Schizophrenia Phase 3

2007

- EOP 2 FDA Meeting

2008

- Schizophrenia Pre-NDA Meeting

2009

- US Schizophrenia NDA

2010

- US Bipolar Depression sNDA

2011

- Bipolar Depression Phase 3
Problems with Current Antipsychotic Agents

- Lack of efficacy
- EPS/akathisia
- Prolactin increase
- Metabolic syndrome
  - Weight gain
  - Lipid increase
  - Diabetes
- QTc prolongation
- Sedation
- Poor functioning
- Reduced adherence to treatment
### ADA/APA Consensus Statement on Antipsychotic Drugs and Obesity and Diabetes

<table>
<thead>
<tr>
<th>Drug</th>
<th>Weight Gain</th>
<th>Diabetes Risk</th>
<th>Dyslipidemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>clozapine</td>
<td>+ + +</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>olanzapine</td>
<td>+ + +</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>risperidone</td>
<td>+ +</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>quetiapine</td>
<td>+ +</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>aripiprazole*</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ziprasidone*</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

+ = increased effect; - = no effect; D = discrepant results.

*Newer drugs with limited long-term data. Diabetes Care/J Clin Psych, 2004 and others
CATIE Schizophrenia Study: Time to Discontinuation for Any Cause

### Psychiatrists Perceive the Greatest Unmet Needs in the Treatment of Schizophrenia and Bipolar Disorder to Involve Better/More Consistent Efficacy Balanced with Tolerable Side Effects

<table>
<thead>
<tr>
<th>Unmet Needs</th>
<th>Schizophrenia</th>
<th>Bipolar Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Better Efficacy</strong></td>
<td>◆ Uniform effectiveness (balanced with side effect burden)</td>
<td>◆ More uniformly effective for depressed phase</td>
</tr>
<tr>
<td></td>
<td>◆ Treatment of positive symptoms - violence, loss of self-control</td>
<td>◆ Drugs that work alone to treat all stages</td>
</tr>
<tr>
<td></td>
<td>◆ Something to enhance cognitive functioning of patients, improve intellectual capacity</td>
<td>◆ Control of agitation</td>
</tr>
<tr>
<td></td>
<td>◆ New alternatives – “There are still a number of patients who are quite sick with available medications. We need new mechanisms, an increased arsenal.”</td>
<td></td>
</tr>
<tr>
<td><strong>Fewer Side Effects</strong></td>
<td>◆ Better performance in terms of metabolic effects and weight gain (effects impact compliance)</td>
<td>◆ Fewer metabolic effects</td>
</tr>
<tr>
<td></td>
<td>◆ Limited side effects</td>
<td></td>
</tr>
<tr>
<td><strong>Lower Cost</strong></td>
<td>◆ Less expensive medications (issue for 30% of patients)</td>
<td>◆ Less expensive medications (issue for 10-20% of patients)</td>
</tr>
<tr>
<td><strong>Simpler Administration</strong></td>
<td>◆ Simple regimen, maybe a combination of meds patients typically take in a single capsule</td>
<td>◆ QD medications</td>
</tr>
</tbody>
</table>

DSP, data on file, 2009
## Receptor Binding Profiles: Lurasidone and Other Agents

<table>
<thead>
<tr>
<th>Binding Affinities (Ki; nM)</th>
<th>Lurasidone</th>
<th>Risp</th>
<th>Olanz</th>
<th>Quet</th>
<th>Zip</th>
<th>Aripip</th>
<th>Cloz</th>
</tr>
</thead>
<tbody>
<tr>
<td>$D_2$ Antipsychotic</td>
<td>1.7</td>
<td>2.9</td>
<td>14</td>
<td>200</td>
<td>3</td>
<td>3.3</td>
<td>110</td>
</tr>
<tr>
<td>$5-HT_{2A}$ Antipsychotic/Attenuate EPS</td>
<td>2.0</td>
<td>0.2</td>
<td>5.8</td>
<td>340</td>
<td>0.3</td>
<td>34</td>
<td>9.2</td>
</tr>
<tr>
<td>$5-HT_{1A}$ Mood/Cognition</td>
<td>6.8</td>
<td>260</td>
<td>2700</td>
<td>320</td>
<td>8.5</td>
<td>2.1</td>
<td>120</td>
</tr>
<tr>
<td>$5-HT_7$ Mood/Cognition</td>
<td>0.50</td>
<td>6.6</td>
<td>110</td>
<td>310</td>
<td>6.0</td>
<td>10</td>
<td>18</td>
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<tr>
<td>$\alpha_{2c}$ Cognition</td>
<td>11</td>
<td>11</td>
<td>210</td>
<td>350</td>
<td>400</td>
<td>38</td>
<td>16</td>
</tr>
<tr>
<td>Histamine H1 Impair cognition, sedation, weight gain</td>
<td>&gt;1000</td>
<td>3.5</td>
<td>3.8</td>
<td>9.0</td>
<td>510</td>
<td>67</td>
<td>2.0</td>
</tr>
<tr>
<td>$ACh M1$ Impair cognition</td>
<td>&gt;1000</td>
<td>&gt;1000</td>
<td>7.6</td>
<td>210</td>
<td>&gt;1000</td>
<td>&gt;1000</td>
<td>4.9</td>
</tr>
<tr>
<td>$\alpha_1$ Orthostatic hypotension, sedation</td>
<td>48</td>
<td>2</td>
<td>19</td>
<td>7</td>
<td>2</td>
<td>26</td>
<td>7</td>
</tr>
</tbody>
</table>

Lurasidone data on file, 2008  
Bymaster, et al. Neuropsychopharmacology, 1996; 14:87-96 and others
Lurasidone Dose-Dependently Competes with [3H]SB-269970 Binding in Rat

Am-Amygdala
Hy-Hypothalamus
Hi-Hippocampus

Lurasidone 1 nM
Lurasidone 10 nM
Lurasidone 100 nM
Lurasidone 1000 nM
Lurasidone (SM-13496), a novel atypical antipsychotic drug, reverses MK-801-induced impairment of learning and memory in the rat passive-avoidance test

Takeo Ishiyama *, Kumiko Tokuda, Tadashi Ishibashi, Akira Ito, Satoko Toma, Yukihiro Ohno

Pharmacology Research Laboratories, Dainippon Sumitomo Pharma Co. Ltd., Enoki 33-94, Suita, Osaka, 564-0053, Japan

Received 25 January 2007; received in revised form 8 June 2007; accepted 12 June 2007
Available online 10 July 2007

Abstract

Lurasidone (SM-13496) is a novel atypical antipsychotic with high affinities to dopamine D₂, serotonin 5-HTS, 5-HT₂A, 5-HT₁A receptors and α₂C adrenoreceptor. In this study, the effects of lurasidone on the rat passive-avoidance response and its impairment by the N-methyl-D-aspartate (NMDA) receptor antagonist MK-801 (dizocilpine) were evaluated and compared with those of other antipsychotics. The passive-avoidance response was examined by measuring the step-through latency, 1 day after the animals received foot-shock training. When given before the training session, lurasidone did not affect the passive-avoidance response at any dose tested (1–30 mg/kg, p.o.). All the other atypical antipsychotics examined (i.e., risperidone, olanzapine, quetiapine, clozapine and aripiprazole), however, significantly reduced the step-through latency at relatively high doses. A pre-training administration of lurasidone significantly and dose-dependently reversed the MK-801-induced impairment of the passive-avoidance response. At doses lower than those that affected the passive-avoidance response, risperidone, quetiapine, and clozapine partially reduced the MK-801-induced impairment, whereas haloperidol, olanzapine, and aripiprazole were inactive. In addition, the post-training administration of lurasidone was as effective in countering the MK-801 effect as the pre-training administration, suggesting that lurasidone worked, at least in part, by restoring the memory consolidation process disrupted by MK-801. These results suggest that lurasidone is superior to other antipsychotics in improving the MK-801-induced memory impairment and may be clinically useful for treating cognitive impairments in schizophrenia.

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Keywords: Learning; Memory; NMDA receptor antagonist; Serotonin-dopamine antagonist; Schizophrenia; Passive avoidance
Lurasidone Reverses MK-801 Induced Learning & Memory Impairment

**Training**
- **naive rats**

**Test**
- 1 day later
  - do not enter the dark room

MK801

MK801 + Lurasidone
Lurasidone Phase 2 Studies

- DSM-IV schizophrenia, requiring hospitalization
- 6-week, randomized, double-blind, placebo-controlled
- All studies involved US sites only
- Primary end point: BPRS derived from PANSS (BPRSD)
- Hospitalization required for 2-4 weeks
Study 006: PANSS Total Score (ITT-LOCF)

Mean Change from Baseline

- Placebo (n=49)
- Lurasidone 40 mg (n=49)
- Lurasidone 120 mg (n=47)

†p=0.06
*p≤0.05; **p=0.01
Ogasa et al. ICOSR 2003
Study 196: PANSS Total Score (ITT-LOCF)

Weeks

Mean Change from Baseline

Placebo (n=90)  
Lurasidone 80 mg (n=90)

*p≤0.01

Lurasidone in the Treatment of Acute Schizophrenia: A Double-Blind, Placebo-Controlled Trial

Mitsutaka Nakamura, Ph.D.; Masaaki Ogasa, M.S.; John Guarino, Ph.D.; Debra Phillips, A.S.; Joseph Severs, M.S.; Josephine Cucchiara, Ph.D.; and Anthony Loebel, M.D.

Objective: Lurasidone is a novel psychotropic agent with high affinity for D2 and 5-HT2A receptors, as well as for receptors implicated in the enhancement of cognition and mood and the reduction of negative symptoms (5-HT1A, 5-HT2A, and D3). The objective of the study was to evaluate the safety and efficacy of lurasidone in patients hospitalized for an acute exacerbation of DSM-IV-defined schizophrenia.

Method: Patients were randomly assigned to 6 weeks of double-blind treatment with a fixed dose of lurasidone 80 mg (N = 90), 75.6% male, mean age = 39.7 years, mean baseline score on the Brief Psychiatric Rating Scale derived from the Positive and Negative Symptom Scale (BPRS) = 55.1) or placebo (N = 90, 77.8% male, mean age = 41.5 years, mean BPRS score = 56.1). The primary efficacy measure was the BPRS. The study was conducted from May to December 2004.

Results: At day 42, last-observation-carried-forward endpoint, treatment with lurasidone was associated with significant improvement compared to placebo on the BPRS (mean square change ± SE = -8.2 ± 1.3 vs. -4.2 ± 1.4; p = .012), as well as on all secondary efficacy measures, including the PANSS total score (14.1 ± 2.1 vs. 5.5 ± 2.2; p = .004) and the PANSS positive (-4.3 ± 0.7 vs. -1.7 ± 0.7; p = .009), negative (-2.9 ± 0.5 vs. -1.3 ± 0.4; p = .025), and general psychopathology (-7.0 ± 1.1 vs. -2.7 ± 1.2; p = .006) subscales. Significant improvement was seen as early as day 5, based on BPRS, PANSS, and Clinical Global Impression-Severity of Illness assessments. Treatment with lurasidone was generally well tolerated and was not associated with adverse changes in metabolic or electrocardiogram parameters. There were no clinically significant differences between lurasidone and placebo in objective measures of extrapyramidal symptoms. The primary objective of the current study was to evaluate the efficacy of lurasidone in the treatment of patients suffering from an acute exacerbation of schizophrenia. The secondary objectives were to assess the safety and...
Depressive Symptom Change: Phase 2 Data

Studies 006, 196

**PANSS**

Anxiety/Depression

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Lurasidone 80mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Depression</td>
<td>*</td>
<td>*</td>
</tr>
</tbody>
</table>

Studies 196

**MADRS**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Lurasidone 80mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=83</td>
<td>n=86</td>
</tr>
</tbody>
</table>

Baseline: Placebo 14.5, Lurasidone 14.2
LOCF at end point
*p<0.05 using ANCOVA
PANSS Cognitive Subscale

Study 196

Mean Change

$\begin{array}{c}
\text{Placebo} \\
\text{Lurasidone}
\end{array}
$

$p = 0.0015$

Simpson Angus Scale (SAS): Pooled Phase 2 Studies*

*Studies 006, 049, 196
SAS scored 0-5 on 10 items for max possible score of 50
Barnes Akathisia Rating Scale (BARS): Pooled Phase 2 Studies*

*Studies 006, 049, 196
BAS scored 0-5 on Global Clinical Assessment of akathisia; maximum score = 5
Serum Prolactin: Pooled Phase 2 Studies*

*Studies 006, 049, 196
CATIE Schizophrenia Study: Prolactin

Mean change from Baseline (ng/dL)

- Ziprasidone (n=143): -4.5 ng/dL
- Risperidone (n=262): 15.4 ng/dL
- Quetiapine (n=268): -9.3 ng/dL
- Olanzapine (n=286): -6.1 ng/dL
- Perphenazine (n=212): 0.4 ng/dL

Mean Modal Dose

- Ziprasidone: 112.8 mg/d
- Risperidone: 112.8 mg/d
- Quetiapine: 543.4 mg/d
- Olanzapine: 20.1 mg/d
- Perphenazine: 20.8 mg/d

Weight Gain: Pooled Phase 2 Studies*

Mean Change (kg)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean Change</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0.16</td>
<td>208</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>0.46</td>
<td>387</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>0.10</td>
<td>71</td>
</tr>
</tbody>
</table>

*Studies 006, 049, 196
Estimated Mean Weight Gain at 10 Weeks with Antipsychotics

Mean Change in Body Weight (kg)

-3 -2 -1 0 1 2 3 4 5 6

Placebo  Molindone  Ziprasidone  Fluphenazine  Haloperidol  Risperidone  Chlorpromazine  Sertindole  Thioridazine  Olanzapine  Clozapine

- Conventional Antipsychotics
- Second-generation Antipsychotics

Lipid Profile: Pooled Phase 2 Studies#

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Lurasidone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol</td>
<td>-30</td>
<td>-25</td>
</tr>
<tr>
<td>HDL*</td>
<td>-10</td>
<td>-5</td>
</tr>
<tr>
<td>LDL*</td>
<td>-22</td>
<td>-15</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>-30</td>
<td>-25</td>
</tr>
</tbody>
</table>

Studies 006, 049 and 196
*Not measured in study 049
Fasting measures obtained per protocol
CATIE Schizophrenia Study: Triglycerides

Mean Change from Baseline (mg/dL)

-18.1 19.2 42.9 8.3

n=143 n=268 n=286 n=212

Ziprasidone  Risperidone  Quetiapine  Olanzapine  Perphenazine

Mean Modal Dose

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mean Modal Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ziprasidone</td>
<td>112.8 mg/d</td>
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<td>20.1 mg/d</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>20.8 mg/d</td>
</tr>
</tbody>
</table>

A Randomized, Double-Blind Study Comparing 3 Fixed Doses of Lurasidone to Placebo in Patients With Acute Schizophrenia: A Phase 3 Trial

Study D1050229 (PEARL 1)
PEARL 1: Study Design

**Double-Blind Phase**
- Lurasidone 40 mg/d, n=120
- Lurasidone 80 mg/d, n=120
- Lurasidone 120 mg/d, n=120
- Placebo, n=120

**Open-Label Extension Phase**
- Lurasidone 40-120 mg/d

**Timeline**
- Screening
- Baseline
- 6 weeks
- 22 months

Participants are randomized to one of four groups: Lurasidone 40 mg/d, Lurasidone 80 mg/d, Lurasidone 120 mg/d, or Placebo.
Key Entry Criteria

◆ DSM-IV schizophrenia
  • Acute exacerbation ≤2 months
  • ≤2 weeks hospitalization prior to screening
  • No significant improvement between screening and baseline

◆ Age 18-75 yrs

◆ Baseline Assessments
  • PANSS score ≥80; ≥4 (moderate) on at least 2 positive psychotic items
  • CGI-S ≥4

◆ Medically stable

◆ Not treatment resistant
  • Based on failure to respond to ≥2 prior antipsychotic trials
Efficacy Endpoints

◆ Primary endpoint
  • Baseline to 6-week/endpoint change in PANSS Total Score, using mixed model repeated measures (MMRM) analysis adjusted by Hommel procedure for multiple comparisons (dose/endpoints)
    • ANCOVA LOCF used for sensitivity analysis

◆ Key secondary endpoint
  • CGI-S change
**PANSS Total (MMRM)**

- Baseline Day 4 Wk 1 Wk 2 Wk 3 Wk 4 Wk 5 Wk 6
- Placebo (n=124)
- 40 mg Lurasidone (n=118)
- 80 mg Lurasidone (n=123)
- 120 mg Lurasidone (n=121)

<table>
<thead>
<tr>
<th>Week</th>
<th>Placebo</th>
<th>40 mg</th>
<th>80 mg</th>
<th>120 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>0.011</td>
<td>0.010</td>
<td>0.017</td>
<td>0.018</td>
</tr>
<tr>
<td>Day 4</td>
<td>0.031</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Wk 1</td>
<td></td>
<td>0.017</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wk 2</td>
<td></td>
<td></td>
<td>0.018</td>
<td></td>
</tr>
<tr>
<td>Wk 3</td>
<td></td>
<td></td>
<td></td>
<td>0.017</td>
</tr>
<tr>
<td>Wk 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wk 5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endpoint</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
PEARL 1: PANSS Total ≥30% Responder Analysis

- Lur 40 mg/d: 46% (n=122)
- Lur 80 mg/d: 52% (n=119) * P=0.028
- Lur 120 mg/d: 50% (n=124) † p=0.058
- Placebo: 38% (n=124)

Note: * indicates statistical significance at P=0.028, † indicates statistical trend at P=0.058.
PANSS Total: Per Protocol Population

Lur 40 mg  Lur 80 mg  Lur 120 mg  Placebo

n=100  n=89  n=94  n=102

LS Mean Change (LOCF)

*  *  *

p=0.004  p=0.032
PANSS Positive Subscale (MMRM)

Baseline Day 4 Wk 1 Wk 2 Wk 3 Wk 4 Wk 5 Wk 6 Endpoint

Placebo (n=124)
40 mg Lurasidone (n=118)
80 mg Lurasidone (n=123)
120 mg Lurasidone (n=121)

*p<0.05
**p<0.01
***p<0.001
CGI-S (MMRM)

Baseline Day 4 Wk 1 Wk 2 Wk 3 Wk 4 Wk 5 Wk 6 Endpoint

Placebo (n=124) 40 mg Lurasidone (n=122) 80 mg Lurasidone (n=119) 120 mg Lurasidone (n=124)

* 0.025 0.029 0.009 0.006 0.005
* 0.048 0.029 0.029
* 0.009

PEARL 1: Weight Change (LOCF)

Median Change from Baseline (kg)

- Lurasidone: 0.3 (n=364)
- Placebo (N=124): 0.0
PEARL 1:
Simpson Angus Scale (SAS)

SAS scored 0-5 on 9 items for max possible score of 45
PEARL 1: Barnes Akathisia Rating Scale (BAS)

Global Clinical Assessment

BAS scored 0-5 on Global Clinical Assessment of akathisia for a maximum possible score of 5
PEARL 1: Serum Prolactin

Median Change (ng/mL)

Lurasidone: 0.70 (n=361)
Placebo: 0.35 (n=122)
PEARL 1: Lipid Profile

LOCF endpoint values; fasting per protocol; includes all subjects
PEARL 1:
QTcF Interval Change (LOCF)

- Lur 40 mg/d: 1.9 (n=120)
- Lur 80 mg/d: 1.2 (n=117)
- Lur 120 mg/d: 1.8 (n=122)
- Placebo: 2.1 (n=120)
Treatment-Emergent Adverse Event Rates (Incidence ≥10%)

Phase 2 and 3 Data
Studies 006/049/196/PEARL 1

Placebo (n=339)
- Sedation: 6.2%
- Nausea: 6.5%
- Somnolence: 4.7%
- Akathisia: 4.1%

Lurasidone 40 mg (n=241)
- Sedation: 11.2%
- Nausea: 10.8%
- Somnolence: 8.7%
- Akathisia: 11.2%

Lurasidone 80 mg (n=282)
- Sedation: 11.6%
- Nausea: 6.5%
- Somnolence: 10.6%
- Akathisia: 14.9%

Lurasidone 120 mg (n=173)
- Sedation: 12.8%
- Nausea: 12.8%
- Somnolence: 13.3%
- Akathisia: 21.4%

Lurasidone Efficacy: Summary

**Consistent efficacy**

- 40, 80 and 120 mg/d shown effective across 3 placebo-controlled trials
- Rapid onset (day 3 or 4) with subsequent sustained improvement noted in placebo-controlled trials
- Potential for improvement of cognitive deficits, based on preclinical and clinical data
Lurasidone Safety: Summary

*Lurasidone is well tolerated*

- Low rates of EPS and akathisia
- Minimal prolactin change
- Neutral effects on weight, lipids and glucose
- Modest change in QTc interval
- Self-reported AEs are generally mild and transient

*Potential for Ongoing Adherence to Treatment*
Lurasidone Development Program
PEARL 1 and 2 Trials: Lurasidone in Acute Schizophrenia

Study 229  PEARL #1
- Lurasidone 40 mg
- Lurasidone 80 mg
- Lurasidone 120 mg
- Placebo

Double-blind, 6 weeks

Lurasidone 40-120 mg
Open-label, 2 years

Study 231  PEARL #2
- Lurasidone 40 mg
- Lurasidone 120 mg
- Olanzapine 15 mg
- Placebo

Double-blind, 6 weeks

Lurasidone 40-120 mg
Open-label, 6 months

N=480/study
Lurasidone: QD dosing schedule
PEARL 3: Lurasidone in Acute Schizophrenia

Studies 233/234
PEARL #3

- Lurasidone 80 mg
- Lurasidone 160 mg
- Quetiapine XR 600 mg
- Placebo

Lurasidone 40-160 mg
Quetiapine XR 200-800 mg

Double-blind, flexible dose, 1 year

Double-blind, 6 weeks

N=480/study
Lurasidone: QD dosing schedule
Long-Term Safety Study With Cognitive Sub-Study

Double-Blind Phase

- Lurasidone 40-120mg/d
  - N=400 (200 for sub-study)
- Risperidone 2-6mg/d
  - N=200 (100 for sub-study)

Cognition Sub-Study

- MCCB: MATRICS Consensus Cognitive Battery
- UPSA-B: UCSD Performance-Based Skills Assessment - Brief Version

Open-Label Continuation Phase

- Lurasidone 40-120mg/d
  - 12 months
  - 6 Months
    - MCCB
    - UPSA-B

6 months
Atypical Use Has and Will Continue to Expand

- Schizophrenia
  - Acute Mania
  - Treatment-Resistant Depression
- Bipolar
  - Maintenance
  - Bipolar Depression
  - Depression/Anxiety
- Depression
  - Depression/Schizophrenia

Atypicals

Mood Stabilizers

Antidepressants
PREVAIL: Lurasidone in Bipolar Depression

Program to Evaluate the Antidepressant Impact of Lurasidone
PREVAIL Add-On Design (Study 235)
PREVAIL Monotherapy Design (Study 236)

Double-Blind Phase

(Study 235)

Screening 3-28 days

Baseline Day 0

Lurasidone 20-120 mg/d + Lithium or Valproate

Placebo + Lithium or Valproate

PREVAIL Extension Study

Total n=340 (n=170/arm).

(Study 236)

Screening 3-28 days

Baseline Day 0

Lurasidone 20-60 mg/d

Lurasidone 80-120 mg/d

Placebo

PREVAIL Extension Study

Total n=504 (n=168/arm).

6 weeks
Enrollment Initiated 2Q ’09
Lurasidone Commercial Overview

Joseph Yen Lin
Vice President, Marketing
Dainippon Sumitomo Pharma America
Agenda

I. Market and Disease State Overview

II. Competitive Landscape
Market Overview

Overall Growth

*The atypical antipsychotic market is large and continues to grow at a robust rate*

<table>
<thead>
<tr>
<th>Year</th>
<th>Sales ($Billions)</th>
<th>Growth Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>$9.3B</td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>$10.1B</td>
<td>+8.6%</td>
</tr>
<tr>
<td>2006</td>
<td>$11.3B</td>
<td>+11.9%</td>
</tr>
<tr>
<td>2007</td>
<td>$12.7B</td>
<td>+12.4%</td>
</tr>
<tr>
<td>2008</td>
<td>$14.1B</td>
<td>+11.0%</td>
</tr>
</tbody>
</table>

Source: IMS NSP Data, 2004-2008
Market Overview
Growth by Diagnosis

Growth in the atypical antipsychotic category is being driven by use in bipolar disorder and schizophrenia.

Source: Estimated from IMS NSP Data, 2004-2008 and NDTI 2004 to 2008
Schizophrenia Disease State Overview
Patient Flow

- U.S. lifetime prevalence of schizophrenia is 1%; approximately 2.5 million affected

- High rates of diagnosis (80%) and treatment (85%)

- Atypical antipsychotics considered the gold standard for schizophrenia

- High rates of patient discontinuation and switching
  - Lack of efficacy
  - Side effects
  - Need for new treatment options
Effectiveness of Antipsychotic Drugs in Patients with Chronic Schizophrenia

Jeffrey A. Lieberman, M.D., T. Scott Stroup, M.D., M.P.H., Joseph P. McEvoy, M.D., Marvin S. Swartz, M.D., Robert A. Rosenheck, M.D., Diana O. Perkins, M.D., M.P.H., Richard S.E. Keefe, Ph.D., Sonia M. Davis, Dr.P.H., Clarence E. Davis, Ph.D., Barry D. Lebowitz, Ph.D., Joanne Severe, M.S., John K. Hsiao, M.D., for the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators

“…patients with chronic schizophrenia in this study discontinued their antipsychotic study medications at a high rate, indicating substantial limitations in the effectiveness of the drugs.”
Bipolar Disease State Overview
Patient Flow

- U.S. lifetime prevalence of bipolar disorder is 2.6%; over 6 million affected
- Relatively lower rates of diagnosis (45%) and treatment (80%) as compared to schizophrenia
- Multiple agents currently used in treatment – lithium, antiepileptic agents
- Atypicals increasingly used to treat bipolar depression
- Only 1 atypical currently approved for bipolar depression (Seroquel)
Key Takeaways

<table>
<thead>
<tr>
<th>Opportunities</th>
<th>Challenges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large, growing market for atypical antipsychotics</td>
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<td>High rate of dissatisfaction and switch; need for new treatment options</td>
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<td>Increasing use for the treatment of bipolar disorder is a significant driver of atypical antipsychotic market growth</td>
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</tr>
</tbody>
</table>
Agenda

I. Market and Disease State Overview

II. Competitive Landscape
Atypical Antipsychotic Market
Current Competitive Environment

Seroquel is the clear market leader; impact of generic risperidone not yet evident

Source: IMS DataView
Atypical Antipsychotic Market
Perceptual Mapping in Schizophrenia

Better-Tolerated Medications (i.e. limited weight gain, metabolic issues); Less Efficacious

More Efficacious Medications; Less Well-tolerated (i.e. weight gain, metabolic issues, EPS)

New product opportunity

Cognitive Functioning

Safety/Tolerability

Efficacy
APS Market Evolution: New Competitors, Generic Entries

Up to 3 new competitors within the next 12 months

Large brands turning generic 2011-2013
Antipsychotic Payer Mix

Public and private payers likely to increase control over utilization of branded products when more generics become available

- Medicare Part D: 17%
- Medicaid: 23%
- Commercial Managed Care: 39%
- Dual Eligibles: 7%
- Other: 14%

Source: IMS

Manage access through tiered co-payments (higher co-pay for more restricted medications)

Manage access through preferred drug lists (PDLs); manufacturers provide supplemental rebates to gain access to PDL
## Key Takeaways

### Opportunities

- Large, growing market for atypical antipsychotics
- High rate of dissatisfaction and switch; need for new treatment options
- Increasing use for the treatment of bipolar disorder is a significant driver of atypical antipsychotic market growth
- Market opportunity for more efficacious, better tolerated medications

### Challenges

- Highly competitive market with large brands
- New competitor launches pending
- Genericization of market beginning in 2011 will change market dynamics → payers more likely to control utilization of branded products
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