Addex and Merck & Co., Inc.

the mGluR5 PAM deal
Agreement

- Merck received an exclusive license to develop Addex’ ADX63365 and associated backup compounds
- ADX63365 is a metabotropic glutamate receptor 5 (mGluR5) positive allosteric modulator (PAM)
- ADX63365 is a drug candidate for schizophrenia and other conditions
- Merck is responsible for clinical development
- Addex will participate on a joint oversight committee
- Schizophrenia is the first indication, additional indications are undisclosed
- Addex has received an option to co-promote in certain EU countries
Financial Terms

• Addex receives $22 million upfront

• Addex is eligible to receive $455 million in research, development, regulatory and sales milestones for the first product in two indications

• Addex is eligible for an additional $225 million in development, regulatory and sales milestones for a second product in two indications

• Addex is eligible for undisclosed royalties
Financial Guidance

- Full year unaudited cash burn for 2007 is CHF37.7m
  - Operating cash burn is CHF35.0m
  - Capex cash burn is CHF2.7m

- Full year cash burn guidance for 2008 is CHF25 to 30 million
  - Operating cash burn of CHF20 to 23m
  - Capex cash burn of CHF5 to 7m
Schizophrenia
Schizophrenia is a chronic, severe, and disabling brain disease

Epidemiology
• Affects ~ about 1.1% of the U.S. population over 18, according to NIMH
• Appears in the late teens to early thirties (earlier in males)
• Estimates suggest that no more than one in five individuals recovers completely

Symptoms
• Positive symptoms include: delusions, hallucination, neurosis
• Negative symptoms include: depression and anti-social behavior
• Cognitive dysfunction: excludes young patients from higher education or jobs

Marketed drugs (D2 blockers) offer value but do not reverse cognitive dysfunction
• Eli Lilly 2007 olanzapine sales are expected to be ~$4.5 billion
• J&J 2007 risperidone sales are expected to be ~$4.5 billion
• Side effects with D2 blockers: weight gain, extrapyramidal symptoms & hyperprolactinemia
mGluR5 PAM in Schizophrenia
mGluR5 in Schizophrenia

• In preclinical testing, mGluR5 activation has shown anti-psychotic effects similar to marketed drugs

• Anti-psychotic effect allows pursuit of first-line monotherapy label
  – Novel mechanism suggests the possibility of avoiding side effects associated with poor compliance with currently marketed drugs:
    • weight gain
    • extrapyramidal symptoms (EPS)
    • hyperprolactinemia
  – Combination with marketed products possible

• mGluR5 activation reverses cognitive dysfunction in preclinical models
  – Preclinical data have been published by Merck & others
  – Marketed products do not reverse cognitive decline

• Additional efficacy on negative symptoms to be evaluated
mGluR5 PAM & mGluR2 PAM

different approaches to treating Schizophrenia
mGluR2 & mGluR5 PAM

• mGluR2/3 activation is clinically validated in schizophrenia (and anxiety)
  — mGluR2/3 agonist efficacious on positive and negative symptoms of schizophrenia
  — mGluR2/3 agonist efficacy similar to olanzapine BUT:
    • *no* weight gain
    • *no* EPS
    • *no* hyperprolactinemia

• mGluR5 rationale is very strong
  — mGluR5 is linked to NMDA receptor function
  — NMDA shown in humans to induce schizophrenia symptoms
  — mGluR5 PAM has demonstrated effects in animal models of schizophrenia
    • for positive symptoms
    • for cognition
Allosteric Modulators

Addex’ goal is to become a world class pharmaceutical company
Allosteric Modulation

~a non-competitive approach~

Negative Allosteric Modulator

Positive Allosteric Modulator

Endogenous ligand

Orthosteric agonists and antagonists compete for the same « active site » targeted by the natural activators (i.e. endogenous ligands).

Allosteric modulators bind at different sites (generally on the part of the GPCR found in the cell membrane) and therefore work via a non-competitive mechanism.

GPCR

cell membrane

inside cell

outside of cell

NAM reduces signal

PAM increases signal
Orthosteric ≠ Allosteric

Orthosteric are steady state

Allostery preserves natural rhythm

- PAMs & NAMs do not activate/deactivate receptors – the natural ligand does
- Natural physiological rhythm may mean fewer side effects and/or better efficacy
- Addex chemists can fine tune how much a PAM/NAM turns the signal up/down
- “Dimmer switch” approach offers more sophisticated therapeutic strategies
Addex can target all GPCR Families

<table>
<thead>
<tr>
<th>Family 1</th>
<th>Family 2</th>
<th>Family 3</th>
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<tbody>
<tr>
<td>Muscarinic receptors</td>
<td>Calcitonin</td>
<td>mGluR1-8</td>
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<td>Odorants</td>
<td>PTH</td>
<td>Ca++</td>
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<td>Catecholamines</td>
<td>VIP</td>
<td>GABA</td>
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<td>Adenosine</td>
<td>PACAP</td>
<td>Pheromones (VR, GoVN)</td>
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<td>Opioid receptors</td>
<td>GnRH</td>
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<td>Anandamide</td>
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<td>GLP-1</td>
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<td>Glucagon</td>
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Peptides
- Cytokines
- Il8

Formyl Met-Leu-Phe (fMLP-peptide)
- PAF-acether
- Thrombin

Glycoproteins
- Hormones (LH, TSH, FSH)
Addex Pipeline
## Allosteric Modulator Pipeline

<table>
<thead>
<tr>
<th>Discovery</th>
<th>Preclinical</th>
<th>Phase I</th>
<th>Phase IIa</th>
<th>Milestones</th>
<th>Partner</th>
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<tbody>
<tr>
<td>ADX10059 (metabotropic glutamate receptor 5 NAM)</td>
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<td>Ph Ia endpoint met Ph IIb start: mid 2008</td>
<td>To be partnered after Ph IIb</td>
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<td>Gastroesophageal Reflux Disease (GERD)</td>
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<td>ADX63365 (mGluR5 PAM)</td>
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**NAM** = negative allosteric modulator  
**PAM** = positive allosteric modulator
Deals Bring More Validation for Addex
1) Finding drug-like mGluR5 PAMs has been challenging for pharma. This deal provides Merck exclusive rights to Addex’ ADX63365, a selective mGluR5 PAM, as well as multiple backup compounds.

2) Finding drug-like mGluR4 PAMs has been challenging for pharma. Merck and Addex signed a separate deal in early December to discover and develop selective mGluR4 PAMs for Parkinson’s disease.

3) Finding drug-like mGluR2 PAMs has been challenging for pharma. Addex signed in 2004 a deal with Johnson & Johnson to discover and develop selective mGluR2 PAMs for schizophrenia and anxiety.

4) ADX10059, an mGluR5 negative allosteric modulator (NAM), has met primary endpoints, achieving clinical proof of concept, in both migraine and gastroesophageal reflux disease (GERD).
allosteric modulators for human health

Q&A

www.addexpharma.com