I will discuss investigational use in my presentation.

I have financial relationships to disclose:

Employee of: Eli Lilly and Company
Stockholder in: Eli Lilly and Company
Lessons from the mGluR2/3 Agonist (pomaglumetad methionil) Schizophrenia Treatment Development Program

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R&D Model Yielding Costs to Successfully Discover a Single New Molecular Entity

<table>
<thead>
<tr>
<th>Step</th>
<th>Discovery</th>
<th>Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>p(TS)</td>
<td>80%</td>
<td>75%</td>
</tr>
<tr>
<td>WIP needed for 1 launch</td>
<td>24.3</td>
<td>19.4</td>
</tr>
<tr>
<td>Cost per WIP per Phase</td>
<td>$1</td>
<td>$2.5</td>
</tr>
<tr>
<td>Cycle time (years)</td>
<td>1.0</td>
<td>1.5</td>
</tr>
<tr>
<td>Cost per launch (out of pocket)</td>
<td>$24</td>
<td>$49</td>
</tr>
<tr>
<td>% Total cost per NME</td>
<td>3%</td>
<td>6%</td>
</tr>
<tr>
<td>Cost of capital</td>
<td>11%</td>
<td></td>
</tr>
<tr>
<td>Cost per launch (capitalized)</td>
<td>$94</td>
<td>$166</td>
</tr>
</tbody>
</table>

| Phase I               | 54%       | 8.6         |
| Phase II              | 34%       | 4.6         |
| Phase III             | 70%       | 1.6         |

| Submission to launch  | 91%       | 1.1         |
| Launch                |           | 1           |

Costs in millions of dollars.
The Quick Win, Fast Fail Drug Development Paradigm

- **Traditional**
  - Scarcity of drug discovery
  - Preclinical development → Phase I → Phase II → Phase III
  - CS → FHD → FED → PD → Launch
  - Increase critical information content early to shift attrition to cheaper phase
  - Use savings from shifted attrition to re-invest in the R&D ‘sweet spot’

- **Quick win, fast fail**
  - Abundance of drug discovery
  - Preclinical development → POC → Confirmation, dose finding → R&D ‘sweet spot’ → FHD → PD → Launch

Identification of the mGlu2/3 receptor as a valid target for the treatment of schizophrenia
Existing Antipsychotics Act Predominantly Via Biogenic Amine Mechanisms

Olanzapine | Clozapine | Quetiapine | Risperidone
---|---|---|---
Ziprasidone | Haloperidol | Aripiprazole

5-HT = serotonergic; Musc = muscarinic; D₁, D₄, D₂ = dopaminergic; H₁ = histaminergic; mGlu2/3 = metabotropic glutamate receptors 2 and 3 (group II)
Dose-Dependent Reversal of Ketamine-Evoked LCGU by the mGlu2/3 Agonist LY404039 in Rat

**Graphical Representation**

- **Metabolic Rate** (μ mol/100g*min)
- **Cingulate Cortex**
- **Prefrontal Cortex**
- **Thalamus**

- **Ketamine Alone**
- **3 mg/kg LY + Ket**
- **10 mg/kg LY + Ket**
- **30 mg/kg LY + Ket**

* * p < 0.05 versus Vehicle (comparison corrected)

**Legend**

DG = Deoxy-D-Glucose; IP = intraperitoneal; IV = intravenous; Ket = Ketamine; LCGU = local cerebral glucose utilization.

Lilly Data on File; B.Kinon presented at 7th International Meeting on Metabotropic Glutamate Receptors, Taormina, 2-7 October 2011.
Reversal of PCP-Induced Hyperlocomotion in D2 and mGlu2/3 Receptor KO Mice

D$_2$ = dopamine 2; KO = knockout; mGlu2/3 = metabotropic glutamate receptors 2 and 3; PCP = phencyclidine; Veh = Vehicle

mGlu2/3 Receptor Agonism Potentiates Risperidone AP-Like Behavioral/Neurochemical Effects in Rat

Conditioned Avoidance Responding

<table>
<thead>
<tr>
<th>Dose</th>
<th>% Avoidance Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>-</td>
</tr>
<tr>
<td>0.3 mg/kg Risp</td>
<td>*</td>
</tr>
<tr>
<td>5 mg/kg LY</td>
<td>*</td>
</tr>
<tr>
<td>Risp + 5 LY</td>
<td>*</td>
</tr>
<tr>
<td>0.3 mg/kg Risp</td>
<td>*</td>
</tr>
<tr>
<td>20 mg/kg LY</td>
<td>#</td>
</tr>
<tr>
<td>Risp + 20 LY</td>
<td>#</td>
</tr>
</tbody>
</table>

* p < 0.05 vs Vehicle
# p < 0.05 vs 0.3 Risperidone

Dopamine Efflux in Prefrontal Cortex

Studies conducted with LY404039 (active compound of LY2140023 prodrug)

AP = antipsychotic; DA = dopamine; mGlu2/3 = metabotropic glutamate receptors 2 and 3; Risp = risperidone

Lilly Data on File; McKinzie et al. Schizophr Bull 2011;37(suppl 1):110.
Lesson 1

- Pomaglumetad methionil (LY2140023 monohydrate; pomaglumetad) as monotherapy should improve the acute symptoms of schizophrenia in the clinic
- Pomaglumetad add-on to SoC APD treatment may confer additional efficacy
- Pomaglumetad 40mg BID should provide exposure in humans (CSF) equivalent to exposure in rat (brain) that blocked PCP response
Lesson 1

♦ Proof of Concept Study (HBBD) was designed and implemented

♦ Monotherapy for symptomatic patients suffering from schizophrenia
Effects of Pomaglumetad (40mg BID) on PANSS Total in Patients with Schizophrenia

Lesson 2

- HBBD was a positive study
- Pomaglumetad may be an effective APD in acutely ill patients
- Pomaglumetad 40mg BID appears to be a safe and efficacious dose
- HBBD clinical trial design seems appropriate
- Further exploration of dose-response is needed
Lesson 2

- Phase 2b Dose-ranging Study (HBBI) was designed and implemented
- 4 doses of pomaglumetad: 5, 20, 40, 80mg BID
- PBO control; OLZ active control
- N=669 randomized; Sites=55; Countries=9
Reduction in the PANSS Total Score from Baseline to Endpoint in the HBBI and HBBD Studies

**HBBI Study (ITT)**

- Placebo (n=122)
- LY 05 mg (n=121)
- LY 20 mg (n=122)
- LY 40 mg (n=120)
- LY 80 mg (n=122)
- Olanzapine (n=62)

**HBBD Study (ITT)**

- LY2140023 (n=97)
- Olanzapine (n=34)
- Placebo (n=62)

**p<.01  ***p<.001


ITT = intent-to-treat population; PANSS = Positive and Negative Syndrome Scale; LS = least square
High Placebo Response Sites: PANSS Total Sites with a Mean Placebo Reduction from Baseline on PANSS: Total >20 Points LOCF

Mean Change in PANSS Total

Excluding 17 HPS

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean Change (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>-9.5 (85)</td>
</tr>
<tr>
<td>LY 5 mg</td>
<td>-10.3 (90)</td>
</tr>
<tr>
<td>LY 20 mg</td>
<td>-11.7 (90)</td>
</tr>
<tr>
<td>LY 40 mg</td>
<td>-13.1 (88)</td>
</tr>
<tr>
<td>LY 80 mg</td>
<td>-14.2 (91)</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>-16.5 (46)</td>
</tr>
</tbody>
</table>

* p<.05 placebo vs olanzapine
** p<.01 placebo vs olanzapine

Only 17 HPS

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean Change (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>-12.0 (33)</td>
</tr>
<tr>
<td>LY 5 mg</td>
<td>-12.4 (31)</td>
</tr>
<tr>
<td>LY 20 mg</td>
<td>-13.6 (28)</td>
</tr>
<tr>
<td>LY 40 mg</td>
<td>-14.6 (27)</td>
</tr>
<tr>
<td>LY 80 mg</td>
<td>-15.3 (27)</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>-18.0 (15)</td>
</tr>
</tbody>
</table>

* p<.05 placebo vs most Tx arms (14/20 comparisons made)

HPS = high placebo sites; LOCF = last-observation-carried-forward; PANSS = Positive and Negative Syndrome Scale; Tx = treatment

Lesson 3

- HBBI was a failed study
- An anomalous high PBO response evident in a minority of sites may have contributed to the failed/inconclusive outcome
- Expectation of therapeutic benefit may have overwhelmed true efficacy signal of pomaglumetad
- Little understanding of dose-response was gained
- Association of seizures with pomaglumetad was identified
A long-term safety study (HBBR) was designed and implemented to help understand safety and tolerability of pomaglumetad beyond 4 weeks of treatment.
Primary Objective: No Between-Group Difference Was Observed for Kaplan-Meier Time to Discontinuation Due to Adverse Events

Primary Objective: No Between-Group Difference Was Observed for Kaplan-Meier Time to Discontinuation Due to Adverse Events

LOGRANK test: $p = .184$

LY = Lilly2140023; SOC = standard of care

Extensive repeat electroencephalogram assessments of all study patients did not demonstrate any abnormal seizure-like changes that were frequent nor remarkably different between treatment arms (pomaglumetad, 0%; SOC, 3.4%).

SOC = standard of care

Differential Rate of Discontinuation for Lack of Efficacy May Reflect Greater Heterogeneity of Response to Pomaglumetad Versus Standard of Care Treatment

LY = Pomaglumetad; SOC = standard of care
B Kinon. Presented at 7th International Meeting on Metabotropic Glutamate Receptors, Taormina, 2-7 October 2011.

LOGRANK test: $p$-value=.007
Effect of HTR2A SNP rs7330461 and NRG1 SNP rs10954863 on Change in PANSS Total in Study HBBD

LS = least-squares; PANSS = Positive and Negative Syndrome Scale; SNP = single nucleotide polymorphism; SOC = standard of care

HTR2A SNP rs7330461 is Associated with Differential Response to Pomaglumetad and Standard of Care in Caucasian Patients in Study HBBR

**Pomaglumetad**

<table>
<thead>
<tr>
<th></th>
<th>LY A/A (n=25)</th>
<th>LY A/T (n=20)</th>
<th>LY T/T (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 0</td>
<td></td>
<td>-10</td>
<td>-20</td>
</tr>
<tr>
<td>Week 1</td>
<td>-20</td>
<td>-15</td>
<td>-10</td>
</tr>
<tr>
<td>Week 2</td>
<td>-20</td>
<td>-15</td>
<td>-10</td>
</tr>
<tr>
<td>Week 3</td>
<td>-20</td>
<td>-15</td>
<td>-10</td>
</tr>
<tr>
<td>Week 4</td>
<td>-20</td>
<td>-15</td>
<td>-10</td>
</tr>
</tbody>
</table>

P<0.05 (one-sided) at Weeks 3 and 4 based on the association test

T/T and A/T - Better Response to LY2140023
A/A - Reduced Response to LY2140023

**SOC**

<table>
<thead>
<tr>
<th></th>
<th>SOC A/A (n=25)</th>
<th>SOC A/T (n=27)</th>
<th>SOC T/T (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 0</td>
<td></td>
<td>-5</td>
<td>-10</td>
</tr>
<tr>
<td>Week 1</td>
<td>0</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Week 2</td>
<td>5</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>Week 3</td>
<td>10</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td>Week 4</td>
<td>15</td>
<td>20</td>
<td>25</td>
</tr>
</tbody>
</table>

P<0.05 (one-sided) at Weeks 16 and 20 based on the association test

A/A and A/T - Better Response to SOC
T/T - Reduced Response to SOC

LY = Pomaglumetad; PANSS = Positive and Negative Syndrome Scale; SOC = standard of care

Lesson 4

- HBBR helped discharge safety signal associated with seizures
- Open-label design confounded the identification of any definitive efficacy signal of pomaglumetad treatment
- Replication of PGx findings encouraged a tailored therapy strategy for pomaglumetad
Lesson 4

- A Phase 3 strategy was developed and implemented
- Monotherapy pivotal trials were designed to minimize anomalous PBO response and to utilize tailored therapy in a fall-back design
- Pomaglumetad 40mg BID was considered most probable efficacy dose
- A POC trial (HBCO) of pomaglumetad add-on to SOC for treatment of negative sx was designed and implemented as a parallel track to registration
HBBM Population Description

1. All efficacy-evaluable patients*

2. Predefined Subpopulation Composition

Genotype All Patients

rs7330461
Self-reported Ethnicity/Race

Non-Hispanic White
All Others

A/A
T Carriers
All Genotypes

Predefined Subpopulation

*An efficacy-evaluable patient is defined as an intent-to-treat patient (ITT, i.e., randomized and received at least one dose) who is NOT a placebo responder during the lead-in phase.
HBBM Primary Objective: Pomaglumetad Fails to Separate from PBO on the PANSS Total in the Overall Population

Change in PANSS Total Score (LS Mean +/- SE)

Week

LY = Pomaglumetad; PBO = placebo, RIS = risperidone

ITT = intent-to-treat; LS = least-square; PANSS = Positive and Negative Syndrome Scale; SE = standard error

HBBM Primary Objective: Pomaglumetad Fails to Separate from PBO on the PANSS Total in the Predefined Subpopulation

Efficacy-Evaluable ITT in Predefined Subpopulation

LY = Pomaglumetad; PBO = placebo, RIS = risperidone

ITT = intent-to-treat; LS = least-square; PANSS = Positive and Negative Syndrome Scale; SE = standard error

HBCO Results: NSA-16 – Primary Analysis Pomaglumetad Add-on Fails to Separate from PBO Add-on

Plot of Least Square Means in NSA-16 Total Score Change from Baseline by Visit (ITT)

LY = Pomaglumetad; PBO = placebo, SOC = standard of care (olanzapine, risperidone, aripiprazole, or quetiapine)

ITT = intent-to-treat; LS = least square; NSA-16 = 16-item Negative Assessment scale; SE = standard error

Seizure Incidence Associated with Pomaglumetad and with Atypical Antipsychotic Drugs

<table>
<thead>
<tr>
<th>Study Details</th>
<th>Crude Incidence</th>
<th>Exposure adjusted incidence (per patient year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pomaglumetad at end of HBBI (LY exposure: 582)</td>
<td>0.69 %</td>
<td>0.115</td>
</tr>
<tr>
<td>Pomaglumetad* as of 26Jun2012 (monotherapy) (LY exposure: 2275)</td>
<td>0.264%</td>
<td>0.011</td>
</tr>
<tr>
<td>Atypical antipsychotics submitted to FDA (Alper et al 2007)</td>
<td>0.8%</td>
<td>0.012</td>
</tr>
</tbody>
</table>

*These rates include all completed and ongoing trials of LY monotherapy in schizophrenia. Some ongoing trials are still blinded. Cases of seizures under blinded medication are assumed to be on LY. In addition, the number of LY exposures from blinded trials are also an estimation. Definite numbers will be calculated once trials are completed and unblinded.
Lesson 5

- HBBM was a conclusive though negative trial for all-comers and for the racially defined subpopulation.
- Add-on study HBCO was negative for pomaglumetad-treatment of negative symptoms.
- Exposure adjusted incidence of seizure was determined to be comparable to currently available schizophrenia treatments.
- An effective dose-range for poma could not be determined.
Potential Reasons for These Negative Trials

- Selection of a pomaglumetad non-responsive population may have inadvertently occurred as we specifically sought to recruit neuroleptic-responsive patients
  - Neuroleptic responsive patients may have a dopamine-mediated disease.\textsuperscript{1,2}
  - Neuroleptic responsive patients may not necessarily have a glutamate-mediated disease
- Pomaglumetad may require a hyperglutamatergic patient in order to effect an antipsychotic response
  - Hyperglutamatergic state associated with acutely ill early-in-disease patient as opposed to the chronic patient.\textsuperscript{1,3}


Continued…
Potential Reasons for These Negative Trials

♦ Downregulation of mGluR2 due to previous antipsychotic drug treatment may have occurred thus diminishing the effectiveness of pomaglumetad at its presumed target

♦ Minor allele (T) at 5HT2a snp may be requisite for response to pomaglumetad

Early-in-Disease Patients May Respond to Pomeglumetad: A Post-hoc Analysis

Study HBBM

Early-in-Disease Patients
Duration of Illness ≤3 yrs
LSMean, Change from Baseline
- Placebo (n=34)
- LY40 (n=37)
- LY80 (n=22)
- RIS (n=9)

Late-in-Disease Patients
Duration of Illness ≥10 yrs
LSMean, Change from Baseline
- Placebo (n=159)
- LY40 (n=158)
- LY80 (n=158)
- RIS (n=83)

* p-value ≤ 0.05 vs. Placebo
SE range: 2.12-6.08

* p-value ≤ 0.05 vs. Placebo
SE range: 1.06-1.86

Patients Exposed ONLY** to Dopamine-D2-Predominant Antipsychotics May Respond to Pomaglumetad

**No substantial exposure to 5HT2a antagonists in past 2 years: A post-hoc analysis

Change in PANSS Total Score in NHW T/T Homozygotes at rs7330461: Pomaglumetad 40 mg Showed Significantly Greater Improvement than Placebo

Concluding Lessons

- Animal models of psychosis may identify valid targets but not necessarily suggest the appropriate clinical population to "target".
- Early Phase 2 exploratory trials should be designed to better understand phenotypic and genotypic distinction between responders and non-responders.
- Late Phase 2 trials should be designed to conclude on best targeted approach and optimal dose.
- Phase 3 trials should be designed to be confirmatory of prior best assumptions.
- Negative Phase 3 programs may provide a useful platform for new hypothesis generating/testing.