Biomarkers as Tools to Enable Decision-Making in HD Drug Development

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• Definitions of the preclinical, prodromal and mild populations are operationalized for clinical trials
• Appropriate outcome measures will need to be established for each group of patients
• The clinical differences between patient groups will not be distinct for clinical trial populations, and will be even less distinct in clinical practice.

Alzheimer’s disease progression
Clinical Study Relationships

**Semagacestat**

- **FHD 10/2000**
  - SDSS LFAC → MDSS LFAD
  - 6-week AD Bridging LFAE
  - Single dose increase LFAI
  - Dose finding, tolerability LFAJ

**FRD 03/2008**
  - Leucine LFAM
  - Phase III Disease Progression

**Solanezumab**

- **FHD 6/2004**
  - SDSS LZAH
  - Dose finding, tolerability LZAJ

**FRD 05/2009**
  - Phase III Disease Progression
Change in plasma $A\beta_{1-40}$ following single and multiple doses of 60 – 140 mg of LY450139

**LFAI Means 60, 100 and 140 mg**

- Mean 60 mg
- Mean 100 mg
- Mean 140 mg
- Line at Zero

**Single dose data (Volunteers)**
Clin Neuropharmacol 2007;30:317-325

**Multiple dose data from AD patients**
(taken from last dose of 14 week treatment period)
Arch Neurol 2008;65:1031-1038
Single Oral Dose of Semagacestat (LY): Effect on Newly Synthesized CSF Aβ_{1-x}

12 hours after dosing

Statistically significant dose-dependent decrease (%) in CSF Aβ:
LY 100 mg (47%), LY 140 mg (52%), LY 280 mg (84%)

Results of Potential Disease Modifiers

Phase 3 Studies

Atorvastatin/Simvastatin, Dimebon, Flurbiprofen, Leuprolide, Rosiglitazone, Tramiprosate, Xaliproden, Semagacestat

Aβ based

Dimebon
Leuprolide
Rosiglitazone

Atorvastatin/Simvastatin
Flurbiprofen
Tramiprosate
Semagacestat

Bio-markers

No cognitive effect

Cognitive effect
Solanezumab Clinical Study Relationship Diagram

- **Phase 1**: FHD 6/2004
- **Phase 2**: POC 12/2007
- **Phase 3**: FRD 05/2009

**SDSS LZAH**
- Dose finding, tolerability LZAJ

**Phase 3**
- Disease Progression
- LZAM, LZAN

**LZAX EXPEDITION 3**
- LZAO – Phase 3 Open Label Extension

**AD AD**
- Phase 2
- Phase 3
- DIAN:TU

**Preclinical AD**
- Phase 2
- Phase 3
- A4
Change in Plasma Aβ_{1-40} after m266.2 or LY2062430 in PDAPP Mice or AD Patients


LY2062430 LZAH Final Study Report

Source Data: http://webtop.am.lilly.com:33602/genesis:/Pharmacokinetics/Compound_related/H8A_LY2062430/1.7_Clinical_LZAH/Post final %20datalock%20PKpd%20_20060912%20/Dataset_Creation%20/output/LZAH_conven_withI64I65_17OCT06.xls

S-PLUS Script: http://webtop.am.lilly.com:33602/genesis:/Pharmacokinetics/Compound_related/H8A_LY2062430/1.7_Clinical_LZAH/Post final %20datalock%20PKpd%20_20060912%20/working/final_lzah_abeta_analysis.ssc

1. Data on File, Eli Lilly and Company
2. Siemers E Clin Neuropharm 2010
Simulated Population Mean Free Aβ Concentrations with Dosing for 24 Weeks

Calculated plasma free Aβ concentrations are consistent with dosing Q4 weeks (or less frequently).
Solanezumab Binds to Aβ in CSF and Shifts Equilibria in AD Patients (Day 79)

**CSF Aβ_{1-40} (bound and unbound) increases**

![Graph showing CSF Aβ_{1-40} changes from baseline](chart1)

**CSF Aβ_{1-42} (bound and unbound) increases**

![Graph showing CSF Aβ_{1-42} changes from baseline](chart2)

**CSF Aβ_{1-40} (unbound only) decreases**

![Graph showing CSF unbound Aβ_{1-40} changes from baseline](chart3)

**CSF Aβ_{1-42} (unbound only) increases**

![Graph showing CSF unbound Aβ_{1-42} changes from baseline](chart4)
ADAS-Cog$_{14}$ in **Mild AD Population (EXP1 and EXP2)**

**EXP1** *(secondary endpoint)*

- Placebo
- SLZ

p=.006

**EXP2** *(primary endpoint)*

p=.120
# Solanezumab Efficacy Results Summary

<table>
<thead>
<tr>
<th></th>
<th>EXP1 overall</th>
<th>EXP1 mild</th>
<th>EXP2 overall</th>
<th>EXP2 mild</th>
<th>Pooled overall</th>
<th>Pooled mild</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADAScog$_{11}$</td>
<td>.312</td>
<td>.008</td>
<td>.060</td>
<td>.097</td>
<td>.042</td>
<td>.001</td>
</tr>
<tr>
<td>ADAScog$_{14}$</td>
<td>.155</td>
<td>.006</td>
<td>.075</td>
<td>.120</td>
<td>.025</td>
<td>.001</td>
</tr>
<tr>
<td>MMSE</td>
<td>.067</td>
<td>.002</td>
<td>.004</td>
<td>.099</td>
<td>.002</td>
<td>.001</td>
</tr>
<tr>
<td>Functional</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADCS-ADL</td>
<td>.931</td>
<td>.302</td>
<td>.062</td>
<td>.076</td>
<td>.217</td>
<td>.057</td>
</tr>
<tr>
<td>ADCS-iADL</td>
<td>.919</td>
<td>.319</td>
<td>.080</td>
<td>.029</td>
<td>.250</td>
<td>.045</td>
</tr>
</tbody>
</table>

*p values for solanezumab-placebo difference at 80 weeks*

**BOLD** = primary outcome(s)

**RED** = statistical significance
## Comparisons between EXPEDITION 1-2 and EXPEDITION3

<table>
<thead>
<tr>
<th></th>
<th>EXPEDITION1/2</th>
<th>EXPEDITION3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of patients</strong></td>
<td>500/arm</td>
<td>1050/arm</td>
</tr>
<tr>
<td><strong>Number of countries</strong></td>
<td>16</td>
<td>11</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>18 months double-blind (open label extension)</td>
<td>18 months double-blind (open label extension)</td>
</tr>
<tr>
<td><strong>Patient population</strong></td>
<td>Mild to moderate (MMSE 26-16)</td>
<td>Mild (MMSE 26-20)</td>
</tr>
<tr>
<td><strong>Requirement for amyloid pathology</strong></td>
<td>None</td>
<td>Amyloid positive by PET or CSF</td>
</tr>
</tbody>
</table>
Patients could continue stable standard of care for AD, including drug and non-drug treatments, throughout the study.

Abbreviations: AD=Alzheimer’s disease; ADAS-Cog$_{14}$=AD Assessment Scale-Cognitive 14-item Subscale; LS=least squares; n=number; SE=Standard Error.
EXP, EXP2, Pooled, EXP3: Solanezumab Initiated in Mild AD Dementia

Change in Cognition - ADAS-Cog₁₄

Patients could continue stable standard of care for AD, including drug and non-drug treatments, throughout the study.

Abbreviations: AD=Alzheimer’s disease; ADAS-Cog₁₄=AD Assessment Scale-Cognitive 14-item Subscale; LS=least squares; n=number; SE=Standard Error.

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EXPEDITION3: Solanezumab Initiated in Mild AD Dementia

Change in Total CSF $A\beta_{1-42}$
EXPEDITION3: Solanezumab Initiated in Mild AD Dementia Baseline Temporal Lobe Volume vs. ADAS-Cog_{14} Change

Temporal Atrophy, % Change from Baseline vs. ADAS-Cog_{14} Change from Baseline

- Placebo N=720
  - $y = -0.1037x - 3.936$
  - $R^2 = 0.25$

- Solanezumab N=741
  - $y = -0.1019x - 3.747$
  - $R^2 = 0.25$

Mean ADAS-Cog_{14} Change from Baseline

- 10.6% slowing of cognitive decline
- 6.5% slowing of atrophy

$p=0.013$
EXPEDITION Studies
Frequency of Baseline Florbetapir SUVr

<table>
<thead>
<tr>
<th></th>
<th>EXP3</th>
<th>EXP/2 Pooled Mild</th>
<th>EXP/2 Pooled Mild SUVR≥1.1</th>
<th>EXP/2 Pooled Moderate</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>1829</td>
<td>251</td>
<td>182</td>
<td>137</td>
</tr>
<tr>
<td>Mean SUVr (SD)</td>
<td>1.51 (0.19)</td>
<td>1.31 (0.28)</td>
<td>1.45 (0.20)</td>
<td>1.39 (0.25)</td>
</tr>
</tbody>
</table>
EXPEDITION Studies

Florbetapir PET Change vs Baseline Florbetapir SUVR

Subject Specific White Matter Correction Factor

EXPEDITION Studies

Florbetapir PET Change vs Baseline Florbetapir SUVR

Subject Specific White Matter Correction Factor
Back-ups
ADAScog\textsubscript{11} in Moderate* Population EXPEDITION1, EXPEDITION2, and Pooled

EXPEDITION1

EXPEDITION2

Pooled

p=.106

p=.536

p=.813

* Moderate defined as MMSE 16-19 at Visit 1
Small sample sizes make assessment of solanezumab effect in amyloid-positive versus amyloid-negative patients problematic.

**Mild Patients**

**All**

Placebo (n = 660)
Solanezumab (n = 654)

**Mild Patients**

Florbetapir or Aβ$_{1-42}$ Positive

Placebo (n = 156)
Solanezumab (n = 137)

**Mild Patients**

Florbetapir or Aβ$_{1-42}$ Negative

Placebo (n = 37)
Solanezumab (n = 38)

Abbreviation: ADAS-Cog=Alzheimer’s Disease Assessment Scale-Cognitive subscale; CSF=cerebrospinal fluid.
EXPEDITION3: Solanezumab Initiated in Mild AD Dementia Baseline Flortaucipir-PET MUBADA vs. ADAS-Cog$_{14}$ Change

Flortaucipir-PET MUBADA SUVR

Baseline Flortaucipir-PET MUBADA SUVR

ADAS-Cog$_{14}$ Change from Baseline

Placebo
n = 85
$r^2 = 0.2014$
p < 0.001

Solanezumab
n = 91
$r^2 = 0.2412$
p < 0.001
Solanezumab Clinical Study Relationship Diagram

Completed Studies
- SDSS LZAH
- LZAH

Ongoing Studies
- Phase 1
  - FHD 6/2004
- Phase 2
  - POC 12/2007
- Phase 3
  - FRD 05/2009

Planned Studies
- Phase 3
  - Disease Progression
    - LZAM, LZAN

Other Biopharm
- LZAX EXPEDITION 3
  - LZAO – Phase 3 Open Label Extension

MILD AD
- SDSS
  - Dose finding, tolerability
    - LZAJ

AD
- DIAN:TU
  - Phase 2
    - 2013
  - Phase 3
    - 2013

Preclinical AD
- A4
  - Phase 3