A Placebo-controlled, Double-blind Trial of the Selective Aβ-42 Lowering Agent, MPC-7869 (R-flurbiprofen) in Patients with Mild to Moderate Alzheimer’s Disease

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*Disclosure: In the past 2 years, GW has been a paid consultant for Eisai, Johnson & Johnson, Lundbeck, Marix Drug Development, Myriad Pharmaceuticals, Novartis, Pfizer, and Shire.
MPC-7869 Clinical Rationale

- Selective Aβ42-lowering agent *in vitro* & *in vivo*
  - Allosteric modulation of γ-secretase
- Reduces insoluble amyloid in mouse brain
- Improves spatial reference learning and memory performance in mice
- Effective concentrations achievable in humans at clinically safe doses
Effect of MPC-7869 in Subjects with Mild to Moderate AD

Phase 2 Study

- Multi-center, Randomized, Double-Blind, Placebo-Controlled
- 207 Subjects in 3 treatment groups (1:1:1)
  - 400 mg BID
  - 800 mg BID
  - Placebo BID
- 12 months treatment
- 31 sites in Canada and the United Kingdom
Effect of MPC-7869 in Subjects with Mild to Moderate AD

- Mild to moderate Alzheimer’s (MMSE 15-26)
- Stable cholinesterase inhibitor allowed
- Primary Efficacy outcomes (measured throughout)
  - Cognition
    - ADAS-cog
  - Activities of Daily Living
    - ADCS-ADL
  - Global Function
    - CDR Sum of Boxes
Prospective Statistical Analysis Plan

ITT Population

Primary Analysis Assumption:
No Treatment by Severity Interaction

Assumption Not Met (p = 0.03)
Planned Analysis of MMSE < and ≥ 20

Mild AD (MMSE ≥ 20)

Primary Outcomes:
ADAS-cog
ADCS-ADL
CDR-sb

Exploratory Analyses:
400 mg BID vs. Placebo,
Drug Concentration Effect

Moderate AD (MMSE < 20)

Primary Outcomes:
ADAS-cog
ADCS-ADL
CDR-sb

Exploratory Analyses:
400 mg BID vs. Placebo,
Drug Concentration Effect

800 mg BID vs. Placebo
# Demographics by Treatment Group

## Mild patients (MMSE ≥20)

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=46)</th>
<th>400 mg BID (n=36)</th>
<th>800 mg BID (n=48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of Total Patients</td>
<td>75%</td>
<td>58%</td>
<td>73%</td>
</tr>
<tr>
<td>Age</td>
<td>76</td>
<td>75</td>
<td>76</td>
</tr>
<tr>
<td>Gender (%M)</td>
<td>59%</td>
<td>58%</td>
<td>50%</td>
</tr>
<tr>
<td>% AChEI Use</td>
<td>100%</td>
<td>94%</td>
<td>94%</td>
</tr>
<tr>
<td>Education % College</td>
<td>43%</td>
<td>39%</td>
<td>29%</td>
</tr>
</tbody>
</table>
## Baseline Scales

### Mild patients (MMSE ≥20)

<table>
<thead>
<tr>
<th>Scale</th>
<th>Placebo (n=46)</th>
<th>400 mg BID (n=36)</th>
<th>800 mg BID (n=48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADAS-cog (*80 point)</td>
<td>27.5</td>
<td>28.6</td>
<td>28.3</td>
</tr>
<tr>
<td>ADAS-cog (70 point)</td>
<td>19.1</td>
<td>19.9</td>
<td>19.4</td>
</tr>
<tr>
<td>ADCS-ADL</td>
<td>58.7</td>
<td>61.4</td>
<td>59.8</td>
</tr>
<tr>
<td>CDR-sb</td>
<td>5.7</td>
<td>5.0</td>
<td>6.0</td>
</tr>
<tr>
<td>MMSE</td>
<td>22.9</td>
<td>23.1</td>
<td>22.8</td>
</tr>
</tbody>
</table>

*Includes delayed recall subscale*
Cognition—Mild Subjects*

Mean Change in ADAS-cog

-2 -1 0 1 2 3 4 5 6 7 8

0 0.215 0.201 0.036 0.305

Month

*MMSE ≥ 20 Score Patients Over Time, LOCF

34% Effect

800 mg BID (n=48)
400 mg BID (n=36)
Placebo (n=46)
Activities of Daily Living—Mild Subjects*

Mean Change in ADCS-ADL

*MMSE ≥ 20 Score Patients Over Time, LOCF

MPC-7869
Global Function—Mild Subjects

Mean Change in CDR-sb

-1.0
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0

Change

0 1 2 3 4 5 6 7 8 9 10 11 12
Month

0.545
0.211
0.291

36% Effect

800 mg BID (n=48)

Placebo (n=46)

400 mg BID (n=36)

*MMSE ≥ 20 Score Patients Over Time, LOCF
There was a significant concentration response relationship ($p = 0.038$).

High concentration was defined as plasma drug concentration above 75 µg/ml.

29 mild patients had high drug concentrations (60% of 800 mg BID group).
Cognition—Mild Patients*, High Drug Group

Mean Change in ADAS-cog

Plasma Concentration:

- High (n=29) 0.371
- None (n=46) 0.329

*MMSE ≥ 20 Score Patients Over Time, LOCF
Activities of Daily Living—Mild Patients*, High Drug Group

Mean Change in ADCS-ADL

*MMSE ≥ 20 Score Patients Over Time, LOCF
Global Function—Mild Patients*, High Drug Group

Mean Change in CDR-sb

*MMSE ≥ 20 Score Patients Over Time, LOCF
Discontinuations Over Time

Cumulative Discontinuations Over Time

Number of Subjects

- Placebo
- 400 mg BID
- 800 mg BID

- 3 months
- 6 months
- 9 months
- 12 months
Safety Summary

- Overall, MPC-7869 appeared very well tolerated
- Discontinuations over time were similar between treatment groups
- Observed transient dose-related eosinophilia
  - No apparent clinical significance
- No obvious safety differences between mild and moderate patients
- No obvious safety differences between 400 mg BID and 800 mg BID groups
Effect of MPC-7869 in Subjects with Mild to Moderate AD Over 12 Months

Phase 2 Summary:

- Mild and moderate AD subjects responded differently to treatment over 12 months
  - Mild subjects responded; moderate subjects did not

- Mild AD subjects on 800 mg twice daily showed positive trends in all 3 outcome measures

- Mild AD subjects with the highest blood levels of MPC-7869 showed statistically significant benefits in:
  - Activities of Daily Living
  - Global Function
  - and positive trends, (not statistically significant) in Cognition