Safety and Efficacy of Tarenflurbil in Subjects With Mild Alzheimer’s Disease: Results From an 18-month Multicenter Phase 3 Trial

Robert C. Green, MD, MPH
Lon S. Schneider, MD
Kenton H. Zavitz, PhD
David A. Amato, PhD
Andrew P. Beelen, MD
Edward A. Swabb, MD, PhD

& the Tarenflurbil Phase 3 Study Group
Tarenflurbil Clinical Rationale

Tarenflurbil (Flurizan™, formerly R-flurbiprofen)

- Selective Aβ42-lowering agent *in vitro* & *in vivo*\(^1,2\)
  - \(\gamma\)-secretase modulator (GSM) via substrate targeting of APP, resulting in a less amyloidogenic Aβ profile
  - No effect on other substrates (eg, Notch)

- Improves spatial reference learning and memory performance in mice\(^3\)

- Phase 2 study provided evidence for dose-related effects on ADLs and global function in patients with mild AD\(^4\)

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US Phase 3 Protocol Overview

- Mild Alzheimer’s disease (MMSE 20-26)
- Stratified at randomization
  - Stable (≥6 months) cholinesterase inhibitor use/nonuse
  - Stable (≥3 months) memantine use/nonuse
- Two-arm study: 800 BID vs. placebo BID
- 18 months treatment, 30-day off-drug follow-up
- Efficacy endpoints (measured throughout)
  - **Primary**
    - ADAS-cog and ADCS-ADL
  - **Key Secondary**
    - CDR Sum of Boxes (sb)
  - **Other Secondary**
    - MMSE
    - NPI
    - QOL-AD
133 Trial Sites* in the US

*Having enrolled ≥ 1 subject
Trial Profile

Assessed
n=2408

Excluded
n=724

Randomized
n=1684

Assigned to placebo
n=822

Excluded Moderate
n=12

Discontinued
n=269 (33%)
  - Withdrew due to AE 77
  - Withdrew consent 116
  - Other 76

ITT Population Placebo
n=809

Completed Treatment Placebo
n=540

Per Protocol Population Placebo
n=502

Assigned to tarenflurbil
800 mg BID
n=862

Excluded Moderate
n=20

Discontinued
n=334 (39%)
  - Withdrew due to AE 141
  - Withdrew consent 134
  - Other 58

ITT Population 800 mg BID
n=840

Completed Treatment 800 mg BID
n=506

Per Protocol Population 800 mg BID
n=467

Assigned to tarenflurbil
400 mg BID
n=42

Preclinical analysis
Pre-specified Analysis Plan

- Change from baseline (CFB) at 18 months
  - z-score, LOCF

- Slopes analysis (SA)
  - repeated measures linear mixed model

- ‘Gatekeeper’ approach to control for multiple comparisons
  1. ADAS-cog and ADCS-ADL, CFB $p \leq 0.05$
  2. ADAS-cog SA, $p \leq 0.05$
  3. ADCS-ADL SA, $p \leq 0.05$
  4. CDR-sb, CFB, $p \leq 0.05$
  5. CDR-sb SA
Imputation Method: Z-score LOCF

A missing value at a given time point will be replaced with a value that is the same number of standard deviations from the treatment group mean at that time point as that subject’s last observed value.

$$z\text{-score} = \frac{(\text{observed value} - \text{treatment group mean})}{\text{treatment group standard deviation}}$$
Baseline Characteristics (ITT)

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=809)</th>
<th>800 mg BID (n=840)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr mean (SD)</td>
<td>74.7 (8.4)</td>
<td>74.6 (8.5)</td>
</tr>
<tr>
<td>range</td>
<td>53 – 100</td>
<td>53 – 100</td>
</tr>
<tr>
<td>% Female</td>
<td>52.5%</td>
<td>49.4%</td>
</tr>
<tr>
<td>Ethnicity (% white)</td>
<td>94.1%</td>
<td>94.9%</td>
</tr>
<tr>
<td>Weight, kg (mean BMI)</td>
<td>72.5 (26.3)</td>
<td>72.7 (26.1)</td>
</tr>
<tr>
<td>Time since diagnosis (months)</td>
<td>20.5</td>
<td>20.4</td>
</tr>
<tr>
<td>Education (% ≥ any college)</td>
<td>61.7%</td>
<td>63.0%</td>
</tr>
<tr>
<td>MMSE (SD)</td>
<td>23.3 (1.99)</td>
<td>23.3 (1.98)</td>
</tr>
</tbody>
</table>
# Mean Baseline Characteristics (ITT)

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=809)</th>
<th>800 mg BID (n=840)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ADAS-cog</strong> (<em>80 point</em>)</td>
<td>25.7 (8.9)</td>
<td>26.1 (8.5)</td>
</tr>
<tr>
<td><strong>ADAS-cog</strong> (70 point)</td>
<td>17.8 (7.7)</td>
<td>18.2 (7.4)</td>
</tr>
<tr>
<td><strong>ADCS-ADL</strong></td>
<td>63.6 (11.1)</td>
<td>63.6 (11.5)</td>
</tr>
<tr>
<td><strong>CDR-sb</strong></td>
<td>5.0 (2.4)</td>
<td>4.9 (2.3)</td>
</tr>
</tbody>
</table>

*Includes delayed recall subscale

Mean (SD)
Concomitant AD Therapy

Patients on Stable Therapy at Enrollment

- No Drug 19% (placebo, tarenflurbil)
  - (18.0, 19.2)
- AChEI alone 33% (tarenflurbil)
  - (33.1, 33.3)
- Memantine alone 6% (placebo, tarenflurbil)
  - (5.9, 6.5)
- Combination 41% (placebo, tarenflurbil)
  - (42.9, 40.8)

Preliminary analysis
Cognition — Change in ADAS-cog

ITT Analysis

Change from Baseline
ADAS-cog
(Mean±SE)

Month

Tarenflurbil
Placebo

p=0.860

Preliminary analysis
Cognition — Change in ADAS-cog

Per Protocol Analysis

Change from Baseline
ADAS-cog
(Mean±SE)

Month

Tarenflurbil

Placebo

p=0.865

Preliminary analysis
Activities of Daily Living — ADCS-ADL

ITT Analysis

Change from Baseline
ADCS-ADL
(Mean±SE)

Month
0 3 6 9 12 15 18

Tarenflurbil
Placebo

P=0.479

Preliminary analysis
Global Function — CDR-sb
ITT Analysis

Change from Baseline
CDR-sb
(Mean±SE)

Month
Tarenflurbil
Placebo
p=0.0036

Preliminary analysis
### Additional Analyses

- **Pre-specified in SAP**
  - Baseline scale severity
  - Baseline MMSE
  - ‘Improver’ analysis
  - ‘Progresser’ analysis
  - Concomitant AD med use
  - PK (full analysis pending)

- **Post-hoc**
  - Gender
  - BMI
  - CYP2C9 genotype (full analysis pending)
  - APOE genotype
APOE4 Carriers vs Non-carriers
ADAS-cog ITT Analysis

Change from Baseline
ADAS-cog
(Mean ±SE)

APOE e4 Carriers

<table>
<thead>
<tr>
<th>Month</th>
<th>Tarenflurbil (n = 363)</th>
<th>Placebo (n = 345)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
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<td>9</td>
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<td>12</td>
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<tr>
<td>15</td>
<td></td>
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<tr>
<td>18</td>
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</tbody>
</table>

58.5% e4 Carriers

APOE e4 Non-carriers

<table>
<thead>
<tr>
<th>Month</th>
<th>Tarenflurbil (n = 259)</th>
<th>Placebo (n = 244)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
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<tr>
<td>6</td>
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<td>9</td>
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<td>12</td>
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<tr>
<td>15</td>
<td></td>
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</tr>
<tr>
<td>18</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

41.5% e4 Non-carriers

Preliminary unadjusted analysis
APOE4 Carriers vs Non-carriers
ADCS-ADL ITT Analysis

Preliminary unadjusted analysis

APOE e4 Carriers

- Change from Baseline
  - ADCS-ADL
  - (Mean ±SE)

- Month

- Tarenflurbil
  - (n = 348)
  - 58.1%
  - e4 Carriers

- Placebo
  - (n = 335)

APOE e4 Non-carriers

- Change from Baseline
  - ADCS-ADL
  - (Mean ±SE)

- Month

- Tarenflurbil
  - (n = 253)
  - 41.9%
  - e4 Non-carriers

- Placebo
  - (n = 240)

Tarenflurbil
## Overall Adverse Events (0-18 months)

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=821)</th>
<th>800 mg BID (n=860)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects w/ AE</td>
<td>85.7% 704</td>
<td>88.5% 761</td>
</tr>
<tr>
<td>Discontinued for AE</td>
<td>11.6% 95</td>
<td>18.4% 158</td>
</tr>
<tr>
<td>Subjects w/ SAE</td>
<td>19.9% 163</td>
<td>22.7% 195</td>
</tr>
<tr>
<td>Deaths</td>
<td>2.2% 18</td>
<td>2.8% 24</td>
</tr>
</tbody>
</table>

Preliminary analysis
Key Safety Findings

- AEs in general reflect the expected symptom profile of a population with Alzheimer’s disease
  - In most, AEs were well balanced between tarenflurbil and placebo

- However, there were a few signals for increased AEs:

<table>
<thead>
<tr>
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<th>Placebo (n=821)</th>
<th>800 mg BID (n=860)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>4.5%</td>
<td>9.7%</td>
</tr>
<tr>
<td>Infection (pneumonia, H. zoster, sepsis)</td>
<td>2.9%</td>
<td>6.9%</td>
</tr>
<tr>
<td>Gastrointestinal Ulcer</td>
<td>0.4%</td>
<td>1.7%</td>
</tr>
</tbody>
</table>

- We have yet to examine correlations between AEs, concomitant medication use and/or pre-existing conditions

Preliminary analysis
Conclusions

◦ Well-powered, well-designed, and well-conducted trial in mild AD (MMSE 20-26)
  - Treatment groups were well matched at baseline
  - Placebo decline rates were as expected for 18 months
    • ADAS-cog 7.1 points (SD 9.2)
    • ADCS-ADL 9.8 points (SD 14.0)
    • CDR-sb 2.5 points (SD 3.1)

◦ No difference in outcomes for the efficacy parameters
  - Subgroup and sensitivity analyses consistent with primary analysis

◦ Tarenflurbil was generally well tolerated
  - Slightly higher incidence of anemia, infections and GI ulcers vs placebo
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