Azeliragon (TTP488): From Futility to Fast Track

An examination of the risks of futility analysis and the precautions that should be taken when executing and interpreting these analyses

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Disclosures

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AZELIRAGON INHIBITS THE RECEPTOR FOR ADVANCED GLYCATION ENDPRODUCTS (RAGE)

- Role of RAGE
  - Pre- and post-natal neuronal development
  - Low expression under normal conditions

- RAGE is a key upstream factor that we believe is responsible for progression of AD
  - Increased expression observed in autopsies of human AD brains
  - Higher levels of RAGE expression correlated with disease severity and progression
  - Affects neuronal, microglial and endothelial cells

- RAGE knockout mice resist Aβ plaque formation but otherwise normal

Select RAGE Ligands:
- Advanced Glycation Endproducts (AGEs)
- HMGB1
- Aβ
- S100 Proteins

Azeliragon inhibits RAGE

- Aβ Production (β, γ secretase)
- Aβ Transport
- Amyloid Deposition
- Vascular Dysfunction

- Metabolic Dysregulation
- Tau Phosphorylation and Aggregation
- Cytokine Release and Chronic Inflammation

Neurotoxicity and Synaptic Loss

Alzheimer’s Disease and Degenerative Brain Disease
Azeliragon Phase 2b Study Design

- Randomized, double-blind, placebo-controlled trial
- Mild to moderate AD (MMSE 14-26); N=399
  - Power of 80% to detect a treatment benefit of 3 points on the ADAS-COG
- Stable background therapy with cholinesterase inhibitors and/or memantine
- Three arms (1:1:1)
  - 60mg/d x 6 days, 20 mg/day x 18 months
    - Discontinued due to increase incidence of confusion, falls and greater ADAS-cog decline not seen with 5 mg/d or placebo
  - 15 mg/d x 6 days, 5 mg/day x 18 months
  - Placebo x 18 months

- Objectives:
  - ADAS-COG after 18 months of treatment with azeliragon vs placebo
  - Safety/tolerability of treatment with azeliragon vs placebo

- Otherwise known as TTP488, PF-04494700
Azeliragon Phase 2b Analysis

- Pre-specified interim analyses
  - Safety: 50% of subjects completed 6 months; 100% completed or withdrew prior to 12 months
  - Futility: 12 months after all subjects randomized

- Primary analysis specified in protocol and SAP
  - Analysis of covariance (ANCOVA) with multiple imputation (MI)

- Supportive pre-planned analyses, using different methodologies to cope with missing data
  - Complete cases ANCOVA
  - Last observation carried forward (LOCF) ANCOVA
  - Generalized estimating equations (GEE)
  - Mixed model repeated measures (MMRM)
18 month data used to assess probability of rejecting null hypothesis at the end of trial

- Single-criterion conditional power computed based on assumed continuation of observed trend
Conditional probability = 9.3%

- Decision made to terminate study with subjects to discontinue dosing at next scheduled visit
- While not a consideration in the futility decision algorithm, 5mg/day was associated with numerical favorable difference versus placebo based on median values

| ADAS-COG\textsubscript{11} Change from Baseline at 18 months |
|-----------------|-----|-----|-----|
|                 | N   | Mean| SD  | Median |
| Placebo         | 40  | 11.17| 8.92| 10.33 |
| 5 mg/d          | 44  | 10.18| 9.81| 8     |

- Had conditional probability reached 10%, 12 month ADAS-COG\textsubscript{11} change from baseline difference between 5 mg/day and placebo = 1.34; study would have continued

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>107</td>
<td>6.4</td>
<td>6.95</td>
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<tr>
<td>5 mg/d</td>
<td>102</td>
<td>5.06</td>
<td>7.24</td>
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</table>
Protocol-planned analyses, using different methodologies to cope with missing data, all show statistically significant differences in ADAS-COG\textsubscript{11} favoring 5 mg/d versus placebo.

Statistical Methodology | p-value  \\
--- | ---  \\
Primary analysis specified in protocol and SAP | 0.008  \\
  - ANCOVA with MI imputation  \\
Supportive Analyses |   \\
  - Complete Cases ANCOVA | 0.02  \\
  - LOCF ANCOVA | 0.03  \\
  - GEE | 0.03  \\
  - MMRM (random effects) | 0.04
Azeliragon Phase 2b On-Treatment Analysis

- On-treatment analysis included all available on-treatment data where “on-treatment” defined as date of last dose plus 45 days (taking into account half-life of ~18 days)
  - Note: the 6 subjects receiving 5 mg/d excluded from this analysis had measureable azeliragon concentrations at 18 months, supporting use of the ITT analysis as on-treatment

- Significant 2.7 point difference from placebo at 18 months

Burstein et al. BMC Neurology 2014
Evaluation shows more pronounced efficacy in mild AD patients, including statistically significant improvement in both ADAS-COG$_{11}$ and CDR-SB.

ADAS-COG$_{11}$ Change from Baseline

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<tr>
<th>Month of Treatment</th>
<th>Placebo</th>
<th>5 mg/d</th>
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<tbody>
<tr>
<td>0</td>
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<tr>
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<td>-11.0</td>
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<tr>
<td>18</td>
<td>-12.0</td>
<td>-13.0</td>
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</table>

CDR-SB Change from Baseline

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<th>Month of Treatment</th>
<th>Placebo</th>
<th>5 mg/d</th>
</tr>
</thead>
<tbody>
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<tr>
<td>18</td>
<td>11.0</td>
<td>13.0</td>
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</tbody>
</table>

$Δ = 4.0, p = 0.018$

$Δ = 1, p = 0.02$
Futility Analysis

- The discordance between the positive results of the final analysis and the prediction from the futility analysis is most likely resolved understanding the specific attributes of the futility analysis.

- Data were used only from patients who had completed 18 months of treatment at the time of the analysis.
  - On only ~1/3 of patients with data available (40 in 5 mg/day, 44 in placebo).

- This analysis was based on a single snapshot, a single variable, and a single statistical model different than protocol planned final analysis.
  - Futility analyses, if performed, should consider including several variables or dimensions to protect against premature termination.
  - Statistical model used for the futility analysis was different from the statistical model used for the protocol planned final analysis.

- Conducted on preliminary dynamic ADAS-COG$_{11}$ data.
  - Post hoc attempts to replicate futility analysis based on snapshot of final database conclude study should have continued (i.e. >20% conditional probability).
STEADFAST Study: Phase 3 Clinical Trial Under SPA

- Randomized, double-blind, parallel group, 18-month trial in 800 patients with mild AD (MMSE 21-26)
  - Enrollment commenced in April 2015

- Two independently powered sub-studies (sub-study A and sub-study B) under a single protocol:
  - Each study (n=400) will have 2 arms: 5 mg/day of azeliragon and placebo
  - All patients will remain on standard of care: AChEI ± memantine

- Co-Primary Endpoints: ADAS-COG\textsubscript{11} and CDR-SB

- Secondary Endpoints:
  - Imaging: MRI volumetric measures, FDG-PET
  - ADCS-ADL, NPI, MMSE, COWAT, CFT, RUD, DEMQOL
  - Biomarkers: Plasma Aβ
Conclusions

- Futility analyses in AD trials may be misleading and argue for conducting the full analysis plan even when futility criteria are met.

- The results of the ITT analysis, the four sensitivity analyses, the on-treatment analysis and the mild sub-group analysis justify further investigation of low dose azeliragon in Phase 3.

- Phase 3 STEADFAST Study initiated in April 2015 under an FDA-agreed SPA.

www.steadfastalzheimers.com
ClinicalTrials.gov identifier: NCT02080364