Design considerations for the first Tau-based Phase III trial in AD with LMTX

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& Chairman TauRx Therapeutics
**β-Amyloid Dominant Theory for last 20 years: but string of trial failures has lead field to re-evaluate**

19 Phase 2 or 3 trials testing various aspects of amyloid hypothesis have failed\(^1\) despite estimated spend of US$ 15 billion

<table>
<thead>
<tr>
<th>β-Amyloid Drug/Company</th>
<th>Phase/Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tarenflurbil/ Myriad</td>
<td>2 &amp; 3/failed</td>
</tr>
<tr>
<td>Lipitor/ Pfizer</td>
<td>3/failed</td>
</tr>
<tr>
<td>Avandia/ GSK</td>
<td>3/failed</td>
</tr>
<tr>
<td>Alzhemed/ Bellus</td>
<td>2 &amp; 3/failed</td>
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<tr>
<td>Semagacestat/ Lilly</td>
<td>3/failed</td>
</tr>
<tr>
<td>AN1792/ J&amp;J/ Elan</td>
<td>2/failed</td>
</tr>
<tr>
<td>PBT2/ Prana</td>
<td>2/failed</td>
</tr>
<tr>
<td>Tramiprosate/ Neurochem</td>
<td>3/failed</td>
</tr>
<tr>
<td>Huperzine/ Neuro-Hitech</td>
<td>3/failed</td>
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<tr>
<td>Dimebon/Medivation/ Pfizer</td>
<td>3/failed</td>
</tr>
<tr>
<td>Gammagard/Baxter</td>
<td>3/failed</td>
</tr>
<tr>
<td>ELND005/J&amp;J/Transition</td>
<td>3/stopped</td>
</tr>
<tr>
<td>Bapineuzumab/J&amp;J/Elan</td>
<td>3/stopped</td>
</tr>
<tr>
<td>ACC-001/J&amp;J/Elan</td>
<td>2/stopped</td>
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<tr>
<td>m266/Lilly</td>
<td>2/stopped</td>
</tr>
<tr>
<td>Solaneuzumab/Lilly</td>
<td>3/failed</td>
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<tr>
<td>Avagacestat /BMS</td>
<td>2/failed/stopped</td>
</tr>
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</tbody>
</table>

The Time for Tau is Now

The Tau pathology is very extensive and destructive in AD and a range of other neurodegenerative disorders in the absence of $\beta$-amyloid.

Image\(^1\) from AD brain using mAb 6.423 which detects C-terminally truncated aggregated Tau\(^2\)

1. Image from: Wischik et al., 2001, Neurobiology of Alzheimer’s Disease Eds. Dawbarn & Allen) OUP 103-206
Relationship between brain scan, MMSE and Braak

Scan deficits correlate with Braak stage¹

<table>
<thead>
<tr>
<th>Braak</th>
<th>Mild AD MMSE ≥ 24</th>
<th>Moderate AD MMSE 15-23</th>
<th>Severe AD MMSE ≤ 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-4</td>
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<tr>
<td>4-6</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Clinical progression correlates with Braak stage²

1. Jobst et al., 1992, J Neurol Neurosurg Psychiat
2. Bradley et al., 2002, Br J Radio
52% of over-45 population (63 / 122m) have some degree of tau aggregation pathology in the brain.

Of these:

<table>
<thead>
<tr>
<th>Braak Stage</th>
<th>Percentage</th>
<th>Peak Age</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25%</td>
<td>53</td>
<td>31m</td>
</tr>
<tr>
<td>2</td>
<td>11%</td>
<td>63</td>
<td>13m</td>
</tr>
<tr>
<td>3</td>
<td>10%</td>
<td>70</td>
<td>12m</td>
</tr>
<tr>
<td>4+</td>
<td>6%</td>
<td>87</td>
<td>7m</td>
</tr>
<tr>
<td></td>
<td>54%</td>
<td></td>
<td>63m</td>
</tr>
</tbody>
</table>

Inhibition/prevention of tau aggregation pathology is a valid pharmaceutical target irrespective of amyloid.
Core-oligomer of the PHF is proteolytically stable and self-replicating\textsuperscript{1}: ie prion-like

\textsuperscript{1} Wischik et al., PNAS, 1996
Tau aggregation is highly correlated with clinical dementia in AD

Tau aggregation is self-propagating, recruiting normal Tau and spreading pathology throughout the brain in a stereotyped cascade

MT is the first Tau Aggregation Inhibitor (TAI) in clinical development

MT dissolves and enhances clearance of pathological Tau polymers and oligomers isolated from AD brain

Therefore treatment with MT has potential as a Tau-based disease-modifying treatment for AD as an alternative to amyloid-based approaches

MT converts proteolytically stable Tau aggregates into proteolytically susceptible monomers by ‘melting’ the para-crystalline Tau polymer (Wischik et al., 1996, PNAS 93:11213)
TauRx Phase 2 data – mild/moderate AD (12m), 321 subjects
FDA analysis model (mixed effects, mITT, no imputation, unstructured correlation matrix)

- Placebo decline (50 weeks) = 4.26 ± 0.94
- Effect size = 3.63 ± 1.29  p = 0.0053
- Effect size as % placebo decline = 85.1% ± 30.3%

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Regional Cerebral Flow

Mild subjects

ROI\(^1\) – Region of Interest Analysis

Nested imaging study in 100 mild AD cases at 6m\(^1\):
Treatment eliminates the scan decline seen in controls

L- Left, R-Right, FL- frontal lobe, OL- occipital lobe, PL-parietal lobe, TL-temporal lobe.

a, indicates a significant difference (P<0.05) in change in rCBF between placebo and All MTC; b, indicates a significant difference (P<0.05) in change in rCBF between placebo and MT 138 mg/day; the results are expressed as mean values with standard error bars.

Presented at ICAD, Chicago, 2008, Alzheimer's and Dementia 4, T775
Clinical Development Strategy
Uncertainty over effect size – mild AD

Observed effect size and expected placebo decline are the major determinant of Phase 3 trial success probability

Effect size as % placebo decline  = 85.1% ± 30.3%

Amyloid passive immunotherapy
22% reduction in slope weeks 40 - 80
6.7 → 5.2 ADAS-cog units per annum

Tau Aggregation Inhibitor
91% reduction in slope weeks 40 – 80
6.7 → 0.8 ADAS-cog units per annum
Uncertainty over expected placebo decline in mild/moderate AD over 12 months – ADAS-cog
Example: single outcome success probability for TRx005 with N=700:
- there is 90% probability that effect fraction ≥ 25%
- there is only 50% probability effect fraction ≥ 65%

Success probability for single outcome depends on two probability distributions:
- (1) that the effect fraction is of at least a given size
- (2) the corresponding trial success probability

Absolute success probability is calculated by integrating across both distributions.
Two-arm study

To achieve >90% absolute power, TauRx is able to plan study size 700 subjects in mild AD because effect-fraction observed in Phase 2 was 93% (se 38%)

If observed effect-fraction had been 34% (se 26%), then study size would need to be > 2,000 to achieve absolute power ~ 75%
Summary of TauRx Clinical Development Program

**TRx-237-005 (in competent imaging centres)**

- 18-month study in 700 patients with mild Alzheimer’s disease
- LMTM 200 mg/day *versus* placebo (8 mg/day)
- Primary endpoints: ADAS-cog and ADCS-CGIC; FDG-PET
- Secondary endpoints: ADCS-ADL, Volumetric MRI

**TRx-237-015 (diagnostic imaging only, broader recruitment base)**

- 15-month study in 833 subjects with mild-moderate Alzheimer’s disease
- LMTM 150 mg/day *versus* LMTM 250 mg/day *versus* placebo (8 mg/day)
- Primary endpoints: ADAS-cog and ADCS-CGIC;
- Secondary endpoints: ADCS-ADL, FDG-PET (150 subset), Volumetric MRI

**TRx-237-007**

- 12-month study in 180 patients with bvFTD
- LMTM 200 mg/day *versus* placebo (8 mg/day)
- Primary endpoints: ACE-R and ADCS-CGIC
Global trial sites for TauRx Phase 3 program - Worldwide Clinical Trials is main global CRO
Current status of LMTX Phase 3 AD trials:

• 1100 / 1533 randomised in AD

• Expect to complete recruitment:
  • TRx-015 by June/July 2014
  • TRx-005 by August/September 2014

• Expect first top-line from TRx-015 Q1 2016
TauRx Phase 3 program – timelines

LMTX is intended to be first-in-class tau-based treatment for mild/moderate AD with potential for use in preclinical prevention of tau aggregation pathology and AD.