LMTX® – TauRx's leading tau aggregation inhibitor

LMTX® is TauRx's leading tau-aggregation inhibitor (TAI) and was the first TAI to enter Phase 3 clinical studies in Alzheimer's disease. TauRx's TAIs have arisen from nearly 30 years of research and work on undoing the tau tangles that cause dementia, thereby potentially slowing and even arresting memory loss.[1]

A growing body of evidence supports the tau tangle pathway as the main driver of Alzheimer's disease.[2] In this pathway, abnormal aggregation of sub-units of tau protein into paired helical filaments ultimately leads to the formation of tangles of such filaments within nerve cells in the brain. The tangles first destroy nerve cells in the part of the brain critical for memory and then neurons in other parts of the brain as the tau aggregation process spreads from neuron to neuron. Typically, tau tangles first appear some 20 years before Alzheimer's symptoms are apparent, and form the earliest detectable stages of the disease; there are well-established correlations between tau pathology, progressive destruction of neurons and Alzheimer's severity.[1] Please follow this link for further information on Alzheimer's disease and tau as a new therapeutic target.

Background

The results of TauRx's Phase 2 trials with rember® (reported in 2008) showed that the active moiety MT had significant disease-retarding potential.[3] The trial also revealed that absorption of the specific form of MT present in rember® was not ideal, particularly in the presence of food. This led TauRx researchers to develop LMTX® as a second-generation TAI with a different chemical structure that delivers the same active moiety into the body as rember®, providing enhanced tolerability and bioavailability.

LMTX® has now been tested in Phase 3 clinical trials, involving over 1,900 patients and comprising three separate studies: two (TRX-005 and TRX-015) in Alzheimer's disease and one (TRX-007) in the rare neurodegenerative disorder, behavioural variant frontotemporal dementia (bvFTD). These three studies

completed in 2016. The trials missed the primary endpoints for which they were originally designed, but demonstrated promising results which warrant further investigation.

Study TRX-015

This 15-month study took place at 116 clinical sites in 16 countries. Of the 891 subjects randomized:

- 549 (61%) had moderate AD and 342 (39%) had mild AD;
- 755 (85%) were taking LMTX® as an add-on therapy and 136 (15%) were taking LMTX® as monotherapy;
- 357 (40%) were randomized to the control arm (8 mg/day, given as 4 mg twice daily), 268 (30%) were randomized to the lower dose arm (150 mg/day, given as 75 mg twice daily) and 266 were randomized to the higher dose arm (250 mg/day, given as 125 mg twice daily).

The modified intent-to-treat population (all patients taking the drug and having at least one post-baseline efficacy assessment) was 855 and the overall retention rate was 65%.

An abstract was presented at the 2016 Alzheimer's Association International Conference (AAIC) in Toronto, Canada on 27th July and results were published in *The Lancet* in November 2016.[4]

Study TRX-005

This 18-month study took place at 98 clinical sites in 12 countries. All 800 subjects were randomized but 1 site was removed from the study for compliance reasons, reducing the intent-to-treat population to 795 of which:

- 497 (63%) had very mild AD (CDR 0.5) and 298 (37%) had mild AD (CDR 1.0);
- 620 (78%) were taking LMTX® as an add-on therapy and 175 (22%) were taking LMTX® as monotherapy;
- 396 (50%) were randomized to the control arm (8 mg/day, given as 4 mg twice daily, and 399 (50%) were randomized to the treatment arm (200 mg/day, given as 100 mg twice daily).

The modified intent-to-treat population (all patients taking the drug and having at least one post-baseline efficacy assessment) was 761 and the overall retention rate was 66%.

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An abstract of the second study, in patients with mild Alzheimer's disease, was presented at the 9th Clinical Trials on Alzheimer's Disease (CTAD) on 8th December 2016.[5] TauRx will shortly submit a paper containing more detailed results and analyses for publication in a peer-reviewed journal.

Study TRX-007

This 12-month study took place at 69 clinical sites in 12 countries. Of the 220 subjects randomized:

- 45 (20%) were taking LMTX® as an add-on to approved AD treatments even though there is evidence that these have no effect in bvFTD, and 175 (80%) were taking LMTX® as monotherapy;
- 111 (50%) were randomized to the control arm (8 mg/day, given as 4 mg twice daily), and 109 (50%) were randomized to the treatment arm (200 mg/day, given as 100 mg twice daily).

The modified intent-to-treat population was 214 and the overall retention rate was 74%.

This is the largest reported randomized controlled trial in bvFTD carried out to date. Results for the Phase 3 trial in bvFTD were reported for the first time at the 10th International Conference on Frontotemporal Dementias (ICFTD), 31st August-2nd September 2016. There is at present no treatment available in bvFTD.

Future development programme

Building on the promising Alzheimer's disease data emerging from both Phase 3 trials, TauRx hopes to initiate additional clinical studies with LMTX® as a monotherapy for patients with mild to moderate forms of the disease, details of which will be shared by the company when appropriate.

TauRx also intends to further investigate LMTX® in behavioural variant frontontemporal dementia.

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