



## TauRx Previous Clinical Trials

### PHASE 2

TauRx evaluated its first-generation tau aggregation inhibitor (TAI), rember<sup>®</sup>, in a large, double-blind, long-duration, Phase 2 clinical trial in 321 patients with mild or moderate Alzheimer's disease. The purpose of the study was to identify the minimum effective dose for treatment of Alzheimer's disease. The study met its primary prespecified efficacy endpoint at a dose of 138 mg/day and provided the first clinical indication that treatment with TAIs holds promise in modifying the progression of the disease.

In this study, rember<sup>®</sup> showed statistically significant benefit relative to placebo at 26 weeks on the primary psychometric scale (ADAS-cog) and showed an 80% reduction in the rate of clinical decline over 50 weeks relative to controls, with benefit sustained over 2 years in patients continuing with treatment at the 138 mg/day dose.

Functional neuroimaging results from the trial supported the psychometric data: in patients taking rember<sup>®</sup>, the loss of function in the areas of the brain known to be particularly affected by the tau tangle pathology of disease was eliminated over 6 months in patients taking the 138 mg/day dose. Functional brain scan benefits seen at 6 months were predictive of clinical benefit at 12 months.

#### Phase 2 Results Lead to Second-Generation TAI Development

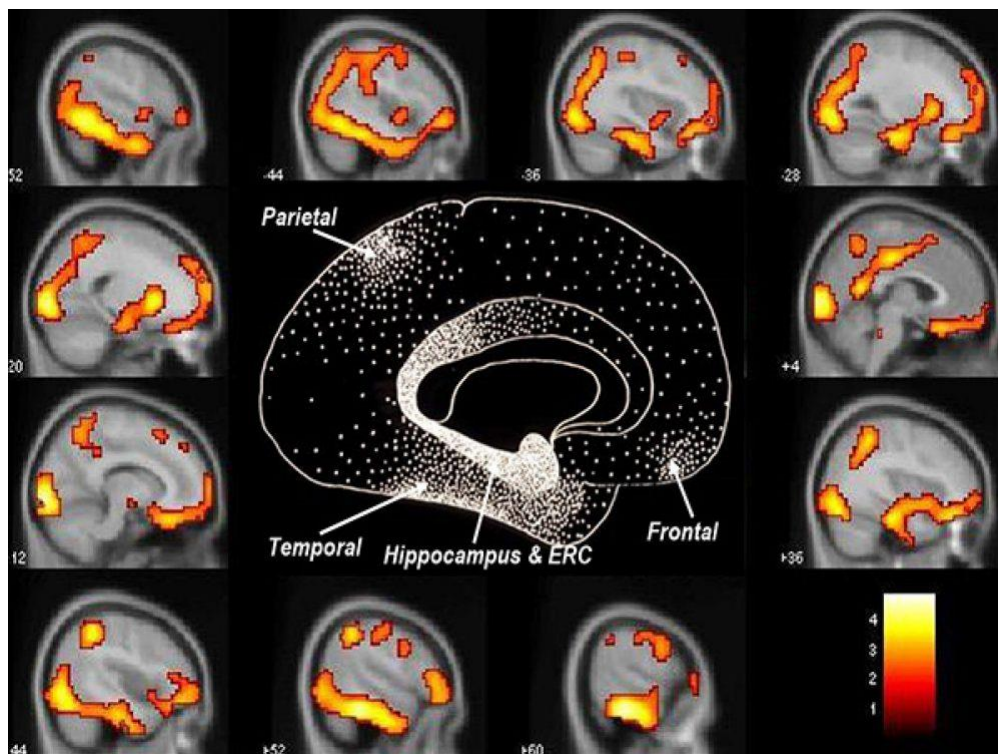
The Phase 2 study, and subsequent Phase 1 studies, also showed that there are limitations in the absorption of the active component of rember<sup>®</sup> (methylthioninium, MT) given in combination with food. The charged form of methylthioninium (MT<sup>+</sup>) present in rember<sup>®</sup> (as methylthioninium chloride, MTC) must be converted to the uncharged leuco-MT form (LMT) in the stomach to permit efficient absorption and distribution to the brain. This conversion is limited at doses higher than 138 mg/day when MTC is taken with food, which is needed to improve tolerability.

This finding led to the development of TauRx's second-generation TAI, which is a stable, reduced form that permits direct absorption of LMT without need for the conversion step. It has also been found recently that LMT is the active form of the drug at the tau aggregation site, and so a lower dose is needed for efficacy. In Phase 1 studies, our second-generation TAI was found to be well tolerated at much higher doses than rember<sup>®</sup>.



### Phase 2 Imaging Studies - Imaging Reveals Brain Regions Protected by TAIs

Molecular imaging (SPECT/PET) provided a key result in the Phase 2 rember® clinical trial by identifying regions within the brain that were protected by the drug. These regions coincided with areas known to be affected by Alzheimer’s neuropathology and provide significant support for the use of TAIs to treat the disease.



TauRx Clinical Phase 2 Imaging

In the images above, created using rCBF SPECT, the central figure demonstrates the locations of tau pathology in Alzheimer’s. The surrounding images show the locations that rember® appears to protect. The areas are the statistically significant regions of difference between the active and control groups.



### PHASE 3

The completed Phase 3 clinical trial program involving TauRx's second-generation tau aggregation inhibitor comprised two clinical trials (TRx-005 and TRx-015) in Alzheimer's disease and a further trial (TRx-007) in behavioural variant frontotemporal dementia (bvFTD; neurodegenerative orphan indication). These three studies were completed in 2016. All three studies tested the drug at doses in the range 150 – 250 mg/day against a low dose of 8 mg/day as an intended control. This dosing was selected in light of the Phase 2 results with rember® and before the superior absorption and efficacy properties of the second-generation drug were fully understood.

Study TRx-015 was the first study to report and showed promising results on clinical and brain imaging endpoints at doses of 150 and 250 mg/day. Surprisingly, the low dose of 8 mg/day appeared to show the same benefit as the higher doses. At all doses, the best results were seen in patients taking the drug as their only treatment (monotherapy) rather than in combination with the standard symptomatic treatments for Alzheimer's disease (cholinesterase inhibitors and/or memantine). In light of these outcomes, the analysis plan for the still ongoing Study TRx-005 was modified in order to focus on the monotherapy benefits of the drug. Study TRx-005 successfully met its modified primary prespecified outcomes and confirmed the results seen in Study TRx-015.

Recent work based on analysis of the blood levels of the drug in all the Phase 3 trial patients has uncovered highly significant concentration-response relationships on cognitive and brain imaging endpoints in patients taking the 8 mg/day dose as monotherapy or as add-on to standard symptomatic treatments for Alzheimer's disease. The same concentration-response relationship has also been found for monotherapy in bvFTD. These results have confirmed that 8 mg/day (taken as 4 mg twice daily) is the minimum effective dose for both diseases and that the best overall effects are seen when the drug is given as monotherapy. Ongoing studies in animals have identified likely mechanisms responsible for the negative interaction between the drug and symptomatic treatments in Alzheimer's disease.

TauRx's current clinical trial, LUCIDITY, uses FDG-PET imaging and a composite cognitive/functional clinical psychometric scale to confirm the efficacy of our second-generation TAI. In this study, the drug is given as a monotherapy at doses of 8 mg/day (taken as 4 mg twice daily), and a slightly higher dose of 16 mg/day (taken as 8 mg twice daily) which is considered to be the optimal dose, is also being tested. Both doses are compared with placebo. We hope that results of the blinded phase of the trial will be available by mid-2022.



## TRx-015

Study TRx-015 was designed to assess the safety and efficacy of our drug at three doses in 891 patients diagnosed with mild to moderate Alzheimer’s disease. The main measures of efficacy (“primary outcomes”) used in the study were:

1. The change in study subjects’ performance in two commonly used clinical assessments:
  - 2.1. The Alzheimer’s Disease Assessment Scale – Cognitive Subscale, known as ADAS-cog11
  - 2.2. The Modified Alzheimer’s Disease Cooperative Study – Activities of Daily Living, known as ADCS-ADL
3. The safety and tolerability of LMTM at doses of 150mg and 250mg per day given for up to 15 months were compared with a dose of 8mg per day

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 our drug as an add-on therapy and 136 (15%) were taking our drug 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%.

The results were published in The Lancet in November 2016.



### TRx-005

Study TRx-005 was designed to assess the safety and efficacy of the drug at two doses in 800 patients diagnosed with mild Alzheimer’s disease. The main measures of efficacy (“primary outcomes”) used in the study were:

The change in study subjects’ performance in two commonly used clinical assessments:

- 1a. The Alzheimer’s Disease Assessment Scale – Cognitive Subscale, known as ADAS-cog11
- 1b. The Modified Alzheimer’s Disease Cooperative Study – Activities of Daily Living, known as ADCS-ADL
2. The safety and tolerability of the drug at 200mg per day given for up to 18 months

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 our drug as an add-on therapy and 175 (22%) were taking our drug 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%.

The results were published in the Journal of Alzheimer’s Disease in November 2017.



### **TRx-007**

Study TRx-007 was designed as a double-blind, placebo-controlled study to evaluate the safety and efficacy of our drug in patients with behavioural variant frontotemporal dementia (bvFTD). The main measures of efficacy used in the study were the change in study subjects' performance at the beginning and the end of the study in two commonly used clinical assessments:

1. The Addenbrookes's Cognitive Examination (Revised), known as ACE-R
2. The Functional Activities Questionnaire, known as FAQ

In addition, the study assessed efficacy via the reductions seen in whole brain volume as measured by MRI.

This 12-month study took place at 69 clinical sites in 12 countries; 220 subjects were randomised.

This is the largest reported randomised controlled trial in bvFTD subjects carried out to date. There is at present no treatment available in bvFTD.