ABERDEEN, Scotland and Singapore, 17th December 2016 – Top-line results from TauRx Therapeutics Ltd.'s second Phase 3 study in Alzheimer's disease, study TRx-237-005, were presented on 8th December at the 9th Clinical Trials on Alzheimer's Disease (CTAD) 2016 meeting in San Diego, CA, USA[1]. The study investigated the efficacy and safety of LMTX® in 800 patients with mild Alzheimer's disease at a dose of either 100 mg or 4 mg (intended as the control dose) twice daily over an 18-month treatment period.

The first Phase 3 study (TRx-237-015; recently published in The Lancet [Gauthier *et al.*, 2016[2]]) which compared two higher doses (75 mg twice daily and 125 mg twice daily) with the same intended control dose of 4 mg twice daily found no difference between either of the two higher doses and the intended control. In prespecified *post hoc* analyses, this earlier study showed significant differences in favour of the two higher doses taken as monotherapy compared with the intended control (which included patients taking the 4 mg dose alone or as add-on to approved treatments for Alzheimer's disease). In a further analysis, the same difference in favour of 4 mg twice a day as monotherapy was found compared with the same dose taken as add-on to existing treatments. There was no difference in the apparent treatment effect between the higher doses and the 4 mg dose, and also no evidence of any potential benefit at any dose in patients taking LMTM as an add-on to approved treatments for Alzheimer's disease (cholinesterase inhibitors and/or memantine).

In light of these results, the primary analyses of TRx-237-005 were modified prior to database lock and unblinding to compare 100 mg twice a day as monotherapy with the intended control, and 4 mg twice a day as monotherapy with the same dose as add-on. This was to test the hypotheses arising from the earlier study in a manner that provided strong control against potential statistical error. Both of these analyses, which were required to reach a statistical threshold of 0.025 for both the cognitive (ADAS-cog) and functional (ADCS-ADL) outcomes, again demonstrated better outcomes within the monotherapy subgroups and met all of the required levels of significance. The same was true for the

principal measure of brain atrophy (lateral ventricular volume). In a *post-hoc* analysis, it was also shown that the subgroup receiving the high dose as monotherapy had significantly better outcomes than the subgroup taking the same dose as add-on treatment. Therefore, this study confirmed in a prespecified manner the results seen in the earlier study.

Whilst these analyses were all positive on the modified primary outcomes, the change in the analysis plan resulted in the study being analysed as an observational cohort study, and not as randomized. There were no significant differences between 100 mg and 4 mg twice a day in the originally intended, as-randomised analyses. Since all of the differences in favour of LMTM as monotherapy depend on comparing patients taking and not taking approved AD treatments, it is possible that the differences simply reflect differences between these patient populations. Such differences in rate of progression have been reported (Schneider *et al.*, 2011[3]), but only in mild cognitive impairment (not in mild Alzheimer's disease) and particularly for patients taking a combination of a cholinesterase inhibitor and memantine. When the patients taking this combination of approved treatments were removed from the analysis, the significant differences in favour of LMTM monotherapy remained.

There were very few differences at baseline between patients taking and not taking approved Alzheimer's disease treatments that might account for the large differences seen in treatment outcome, and correcting for these did not remove the significant differences in favour of LMTM monotherapy. More importantly, patients entering the study on monotherapy showed rates of progression of whole brain atrophy very similar to those reported for mild Alzheimer's disease for the first 6 months (ADNI data, Leung *et al.*, 2013[4]). These patients went on to have a significantly reduced rate of progression by the time they reached 12 – 18 months, when the rates of atrophy progression became indistinguishable from those seen as part of the normal aging process in people without Alzheimer's disease (Leung et al., 2013[4]). In contrast, the patients receiving LMTM as add-on treatment progressed as expected for mild Alzheimer's disease with significant acceleration of brain atrophy on some measures.

Gastrointestinal and urinary effects were the most common adverse events, occurring in more patients receiving the high dose than in those receiving the 4 mg dose.

Results from both Phase 3 studies suggest that the dose of 4mg LMTX® twice daily, which had originally been intended as a control in both studies, is associated with slower progression of Alzheimer's disease and with better safety and tolerability than higher doses. On the basis of these encouraging data, a further study of LMTX® is now planned in which the 4mg twice daily dose will be compared with placebo in patients with Alzheimer's disease not receiving cholinesterase inhibitors or memantine.

It is TauRx's intention to publish the results of study TRx-237-005 shortly.

About Study TRx-237-005

Approximately 800 patients were enrolled in this Phase 3, randomised, controlled, double-blind trial, across 98 sites in 12 countries. Co-primary efficacy outcomes were scores on the Alzheimer's Disease Assessment Scale–cognitive subscale (ADAS-Cog) and the Alzheimer's Disease Co-operative Study–Activities of Daily Living (ADCS-ADL); secondary outcomes included changes in lateral ventricular volume in order to assess potential therapeutic effect on the rate of brain atrophy. The trial is part of the Phase 3 programme of LMTX® in Alzheimer's disease and behavioural variant frontotemporal dementia.

About Alzheimer's disease

Alzheimer's disease (AD) is a progressive neurologic disease of the brain that causes damage to neurons - the specialized cells of the nervous system that enable the flow of information, thoughts and memories in the brain. When Alzheimer's damages neurons it leads to loss of memory and reasoning, which can affect a person's ability to interact socially or function at work. No treatment yet exists to halt the progression of Alzheimer's-related dementia, delay its onset, or prevent it from occurring. Currently available drugs only temporarily treat the symptoms.[5]

About tau aggregation inhibitors

TauRx's tau aggregation inhibitors (TAIs) have arisen from nearly 30 years of research. TAIs work by undoing the tau tangles that cause dementia, thereby potentially slowing and even arresting memory loss.[6] LMTX® is a stable reduced form of methylthioninium. The first-generation TAI, rember® was a

patented, highly-purified version of methylthioninium chloride (methylene blue), a compound previously used to treat a variety of conditions.

About TauRx Therapeutics Ltd

TauRx Therapeutics Ltd is a member of the TauRx Pharmaceuticals group which is developing technology spun-out from the University of Aberdeen, Scotland, and was established in Singapore in 2002 with the aim of developing new treatments and diagnostics for a range of neurodegenerative diseases. The company's tau aggregation inhibitor, LMTX®, targets aggregates of abnormal fibres of tau protein that form inside nerve cells in the brain, giving rise to 'tau tangles'. TauRx's headquarters are in Singapore and its primary research facilities are based in Aberdeen. For more information, please visit: http://www.taurx.com.

References

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