Second Phase 3 Study Results for LMTX® published in the *Journal of Alzheimer's Disease*

ABERDEEN, Scotland and Singapore, 27th November 2017 – TauRx Therapeutics Ltd today reported the full results from its second Phase 3 clinical study of LMTX®, the first tau aggregation inhibitor in Alzheimer's disease, published online in the *Journal of Alzheimer's Disease*.

Results from this study (TRx-237-005) are consistent with those from the first Phase 3 study, recently published in *The Lancet* [(TRx-237-015) Gauthier *et al.* 2016[1]] in mild to moderate Alzheimer's disease, in supporting the hypothesis that LMTX® might be effective as monotherapy at a dose as low as 4 mg twice daily.

The latest study (TRx-237-005) 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 results of the earlier study showed significant differences in favour of two higher doses of LMTX® (75 mg and 125 mg twice daily) when taken as monotherapy compared with the intended 4 mg control dose taken as monotherapy or as add-on therapy to currently approved treatments for Alzheimer's disease in prespecified *post hoc* analyses. In a further analysis, the same difference in favour of monotherapy compared with add-on treatment was found in patients taking the 4 mg twice daily dose.

Therefore, prior to database lock and unblinding, the primary analyses of TRx-237-005 were modified to compare 100 mg LMTX® twice daily as monotherapy with the intended control, and 4 mg twice daily as monotherapy compared with the same dose as add-on therapy as non-randomised cohort analyses. The aim was to test whether the findings from the first study could be confirmed as primary outcomes in a second independent study with strong controls against statistical error.

Results of the second study showed the same significant differences in favour of LMTX® monotherapy at the required statistical threshold of $p < 0.025$ in both comparisons on the co-primary clinical efficacy endpoints for the cognitive (ADAS-cog) and functional (ADCS-ADL) outcomes.

In both the LMTX® monotherapy and add-on therapy groups, whole brain atrophy (measured via MRI scans) initially progressed as expected for patients with mild Alzheimer's disease. However, after 9 months of treatment, the annualised rate of whole brain atrophy in monotherapy patients reduced significantly and became typical of that reported in normal elderly controls without Alzheimer's disease. The comparable rate seen in the add-on therapy group progressed as reported for patients with mild Alzheimer's disease.

Similarly, additional findings from FDG-PET scans in TRx-237-005 indicated that the decline in temporal lobe glucose uptake in those patients receiving LMTX® monotherapy was significantly less than that typically reported for patients with mild Alzheimer's disease.

When the various analyses were corrected for potential differences in severity or diagnosis at baseline between monotherapy and add-on therapy cohorts, the results remained robustly significant.

"While the monotherapy subgroups in the first and second Phase 3 LMTX® studies remain small – 15% and 20% respectively – the confirmation of the same pattern of results in the second independent study means they are unlikely to be a chance finding," said Prof. Claude Wischik, of Aberdeen University and executive chairman of TauRx Therapeutics Ltd.

"The overall retention rates in the second study were similar in both monotherapy and add-on treatment groups, so differential withdrawal rates cannot be the explanation. Likewise, seeing the same results in the second study conducted only in North America, Western Europe and Australia means that the first study was not atypical in some way through its inclusion of non-western countries. Finding the same pattern of results in the clinical and imaging outcomes also means that they cannot be explained as placebo effects in patients coming into a treatment setting for the first time."

Prof. Wischik went on to comment: "Although these results come from non-randomised cohort analyses, a number of things point to real treatment effects and not just differences between patients taking or not taking the standard treatments. The analysis showing a slow-down in the brain atrophy rate is a before-and-after analysis in which the monotherapy patients were their own controls, and so does not depend on a comparison with add-on therapy patients. We are also starting to understand the pharmacologic basis of the negative interaction between LMTX® and the standard treatments since we have now seen the same thing happening in an animal model of tau protein aggregation."

"These highly significant results support further validation of tau-based therapy in Alzheimer's disease," said George Perry, Dean of Sciences, University of Texas at San Antonio and Editor-in-Chief of the Journal of Alzheimer's Disease.

The lead author of the study, Gordon Wilcock, Emeritus Professor of Geratology and Honorary Clinical Senior Research Fellow in the Nuffield Department of Clinical Neurosciences at the University of Oxford, commented: "These data indicate the need for a further randomised controlled trial to evaluate efficacy of low dose LMTX® in patients not taking current treatments."

Further randomised controlled studies of LMTX® are set to commence shortly in which the 4 mg twice daily dose will be compared with placebo in patients with Alzheimer's disease who are not receiving other approved treatments for this condition (cholinesterase inhibitors and/or memantine).

For further information on the Journal of Alzheimer's Disease publication of study TRx-237-005 visit https://content.iospress.com/download/journal-of-alzheimers-disease/jad170560?id=journal-of-alzheimers-disease%2Fjad170560

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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 regional brain volumes (as measured by

MRI) to assess potential therapeutic effects on the rate of brain atrophy, and changes in brain glucose uptake (as measured by FDG-PET) to assess effects on brain function. The trial is the second of two Phase 3 trials of LMTX® in Alzheimer's disease that reported top-line results in 2016.

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 treat the symptoms temporarily.[2]

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.[3] 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. LMTX® is a stable reduced form of methylthioninium which is better absorbed and is better tolerated than methylene blue.

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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2. Alzheimer's Association. 2015 Alzheimer's disease facts and figures. Available at: http://www.alz.org/facts/downloads/facts_figures_2015.pdf Accessed 20 October 2017.
3. Wischik CM, et al. Tau-aggregation inhibitor therapy for Alzheimer's disease. *Biochem Pharmacol* 2014; 88:529–39.

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