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Second Phase 3 study results for LMTX published

November 29 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. 20161] 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

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).

More information: Gordon K. Wilcock et al. Potential of Low Dose Leuco-Methylthioninium Bis(Hydromethanesulphonate) (LMTM) Monotherapy for Treatment of Mild Alzheimer's Disease: Cohort Analysis as Modified Primary Outcome in a Phase III Clinical Trial, *Journal of Alzheimer's Disease* (2017). DOI: 10.3233/JAD-170560

Provided by IOS Press