TauRx Pharmaceuticals
Innovation in neurodegeneration

INTERVIEW WITH THE CHAIRMAN

3rd March 2017

In this interview, TauRx's Executive Chairman and co-founder, Professor Claude Wischik, responds to questions concerning the LMTX® Phase 3 study results.

Q. Now that you and your team have had time to analyse and consider the Phase 3 study results in more detail, what are your primary conclusions?

When I consider the results of the two Phase 3 clinical studies in Alzheimer's disease (AD), I draw the following conclusions:

- I see a clear and consistent signal of potential treatment benefit across the monotherapy groups with the same pattern of results demonstrated in Study 015 in mild/moderate subjects and in Study 005 in very mild/mild subjects.
- These treatment effects do not appear to be explicable by baseline differences between patients taking and not taking standard AD treatments.
- The 8 mg/day dose has performed as well as the higher doses (150, 200 and 250 mg/day) over 15 – 18 months, and has a better tolerability and safety profile.
- The apparent treatment effect sizes are larger than for currently available standard of care and last longer.

These studies have provided evidence that LMTX®, when taken as monotherapy, has the potential to delay the clinical progression of AD and to delay the progression of brain atrophy. These effects

were demonstrated in the revised primary analyses defined prior to database lock in Study 005 and confirmed the earlier results seen in Study 015. Therefore, including the earlier Phase 2 study's encouraging clinical and functional imaging outcomes, we now have three independent studies confirming the potential usefulness of the methylthioninium moiety (MT) in the treatment of mild to moderate AD.

Q. How sure are you that those patients recruited to your studies who were not on current standard of care (i.e. approved symptomatic treatments for Alzheimer's disease), who therefore took LMTX® as a monotherapy, really had the disease?

In Study 005, the initial rate of progression of brain atrophy in monotherapy patients was indistinguishable from the rates reported for mild AD in unselected patients in the ADNI program (Alzheimer's Disease Neuroimaging Initiative) as measured by MRI (magnetic resonance imaging). However, by the time our monotherapy patients reached the second year of our study, their rate of progression of whole brain atrophy had reverted to that reported for the normal (without AD) elderly control cohort in the ADNI program and in an independent UK/Dutch cohort. This implies that patients taking LMTX® as monotherapy physically revert to an earlier stage of their illness as demonstrated by MRI. By contrast, patients taking LMTX® in combination with standard AD treatments showed either continuation or acceleration in the rate of brain atrophy, as reported for mild AD. There is currently no drug available or in prospect for the treatment of AD capable of producing these benefits in mild to moderate AD.

The results seen in both studies cannot be explained by the confounding effect of comparing patients taking or not taking standard AD treatments. We have found in a recent analysis of data (from ADNI patients in the same MMSE range of severity as in Study 005) that the differences in the rate of disease progression (as measured on the ADAS-cog scale over 18 months) between those taking or not taking either an acetylcholinesterase inhibitor (AChEI) or memantine was determined largely by differences in severity at baseline. When the same correction for baseline differences between patients taking and not taking AD treatments was applied to our trial data, the treatment effects remained significant. So the apparent treatment effects cannot be explained by differences at baseline between patients taking and not taking the standard AD treatments.

Q. What were the Phase 3 trial outcomes that most surprised you?

There were two major surprises arising from the Phase 3 study data:

a) the impact that current approved symptomatic treatments for AD (AChEIs and memantine) have on the efficacy of LMTX® in subjects with AD

b) the potential efficacy of the 8 mg/day dose that had been intended as control.

Let me examine each of these in turn.

a) AChEI/Memantine Impact

A key question arising out of the Phase 3 study results is the nature of the negative interaction between LMTX® and AChEIs and memantine in AD. A large body of preclinical research work has already started at TauRx that aims to answer these questions and some results are already available which shed light on the trial results.

b) Dose-response and efficacy of the 8 mg/day dose

Our published work shows that, at low doses, more LMTX® is taken up into brain than MTC. Recent preclinical research work using radioactive LMTX® suggests that a low dose simulating the 8 mg/day dose used in the trials reaches the brain in sufficient quantity to have efficacy. Further population pharmacokinetic analyses and preclinical studies aim to support the theory of potential accumulation of the MT moiety in deep compartments (including brain) during repeated dosing with LMTX®.

Q. With the Phase 3 trial results now available, what are the likely next steps for TauRx?

The many, highly statistically significant differences in study outcomes in favour of LMTX® when taken as monotherapy are very encouraging and the scale of the effects seen is clinically meaningful. However, these trials were not designed and randomized to test for differences between monotherapy and add-on therapy effects and, while encouraging, the results do not establish a causal link between monotherapy and beneficial effects.

TauRx now aims to develop LMTX® as a monotherapy treatment of mild to moderate AD to reduce the rate of clinical decline and reduce the rate of progression of brain atrophy as measured by MRI. The dose at which we plan further development is 8 mg/day, given as 4 mg tablets taken twice daily, and we plan to initiate one or more appropriately randomized studies of LMTX® in AD patients later in 2017.