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First Evidence of Potential Efficacy of Tau Aggregation Inhibitor Therapy in Alzheimer's Disease – TauRx Publishes Positive Results of Phase II Clinical Trial in the Journal of Alzheimer's Disease

ABERDEEN, Scotland and SINGAPORE, 20 January 2015 – The *Journal of Alzheimer's Disease* has published today the results of the first clinical trial of a Tau Aggregation Inhibitor (TAI) in Alzheimer's disease (AD).[1] This Phase II clinical trial, conducted by TauRx Therapeutics Ltd (a Singapore incorporated spinout from the University of Aberdeen), provided the basis and rationale for subsequent Phase III clinical trials of a TAI in AD currently in progress.

The double-blind dose-finding Phase II clinical trial involved 321 patients in 16 clinical research centres in the UK and one centre in Singapore and tested three doses of the drug. The study met its predefined primary efficacy endpoint at 24 weeks on the standard scale most commonly used to measure cognitive decline in clinical trials (ADAS-cog) at the 138 mg / day dose. The primary result was also supported by benefit on two other clinical scales. The effect sizes seen were statistically significant and clinically meaningful in moderate subjects at 24 weeks. The clinical results were also supported by brain scan evidence of arrest of decline over the same period in mild subjects at the same dose. The beneficial effect was sustained to 50 weeks in both mild and moderate subjects at this dose, with 90% reduction in the rate of cognitive decline overall.

This is the first ever clinical trial which has attempted to target directly the hallmark neurofibrillary tangle pathology of AD. Tangles were originally discovered by Alois Alzheimer in 1906 and this discovery gave the disease its name. Tangles were found to be composed of abnormal filaments largely made up of a short fragment of the protein Tau in 1988 by Professor Claude Wischik (co-founder of TauRx Therapeutics Ltd) and colleagues in Cambridge, UK. The spread and density of tangles in the brain are known to be highly correlated with the clinical severity of dementia. They are also correlated with the extent of abnormal aggregation of Tau protein and loss of neuronal function seen on brain scans in those brain regions where tangles typically form. Wischik and colleagues went on to report in 1996 that the chemical substance methylthioninium (MT), used in medicine for the last 100 years, dissolves tangle filaments isolated from the human brain by selectively blocking a critical step in the process required to form the rogue filaments.

The encouraging efficacy signals seen in the TauRx trial at the minimum effective dose of 138 mg / day were first announced in a preliminary form at the Alzheimer's Association International Conference on Alzheimer's Disease in Chicago, USA, in July 2008. However, the surprising observation that the top dose of 228 mg /day had reduced efficacy has taken TauRx scientists a further 4 years to unravel. The results of these studies have also been reported in parallel in the *Journal of Pharmacology and Experimental Therapeutics*.[2]

The form of MT that has been used in medicine for the last 100 years (a chloride salt of the oxidised MT^+ form of the molecule, denoted MTC, and commonly known as "methylene blue") is poorly tolerated

without food, so taking it with food has been recommended traditionally. However, TauRx scientists discovered that MTC suffers from dose-dependent impairment in absorption when taken with food. This is due to the fact that the oxidised MT^{+} form needs to be actively converted to the reduced LMT form in the gut before it can be absorbed as LMT. In other words, MTC is a pro-drug for LMT, and food interferes with the conversion and absorption process. Since MTC was given with food in the Phase II trial to maximise tolerability for patients, only 109 mg / day of the intended 228 mg dose was available for absorption. Therefore, the minimum effective dose of 138 mg / day identified in the trial was simply the highest available dose tested.

In order to go forward into Phase III testing, TauRx scientists have developed an entirely new form of the molecule which keeps MT in the LMT form and therefore permits it to be absorbed directly without need for active conversion in the gut. This new form is denoted LMTX® for the present and is better absorbed and tolerated than MTC. This has enabled Phase III trials to test whether an even higher level of efficacy can be achieved without significant loss of tolerability and safety. The ongoing trials are testing MT delivered as LMTX® in the dosage range of 150 – 250 mg / day.

The full results now published in the *Journal of Alzheimer's Disease* were previously available only as reports supporting regulatory filings for global confirmatory Phase III clinical trials in 22 countries. These trials are now fully recruited and the first results are expected in the first half of 2016. If the Phase III clinical trials confirm a level of efficacy and safety similar to that seen in the Phase II trial reported in the *Journal of Alzheimer's Disease*, a treatment targeting the Tau aggregation pathology of AD could be on the market as early as 2017.

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About TauRx Therapeutics Ltd

TauRx Therapeutics Ltd is a spin-out company 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®, is currently in global Phase III clinical trials for Alzheimer's and Frontotemporal Dementia (FTD). LMTX® targets aggregates of abnormal fibres of tau protein that form inside nerve cells in the brain, giving rise to 'tau tangles'. TauRx's primary research facilities are headquartered in Aberdeen. For more information, please visit: http://www.taurx.com.

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