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TauRx Adds to Growing Body of Evidence Supporting Tau Aggregation Inhibition With Publication of Six New Journal Articles

ABERDEEN, Scotland and SINGAPORE, 1 June 2015 – With the publication of a key article in *The Journal of Biological Chemistry*, TauRx Pharmaceuticals Ltd. continues to build a growing body of evidence supporting the rationale for tau aggregation inhibition in the treatment of neurodegenerative diseases such as Alzheimer's Disease (AD) and Frontotemporal Dementia (FTD). This latest of six connected papers, five of them published in the past six months describes the robust scientific research programme behind the development of LMTX™, the second-generation tau aggregation inhibitor (TAI) currently in three large global Phase 3 clinical trials.

"Taken together, these six papers reflect more than 10 years of clinical and preclinical research dedicated to discovering more about the genesis and relentless spread of the tau pathology through the brain of AD patients," said Dr. Charles Harrington, Chief Scientist of TauRx and lead author of the latest article, "Cellular models of aggregation-dependent template-directed proteolysis to characterize tau aggregation inhibitors for treatment of Alzheimer's Disease" (Harrington et al., *Journal of Biological Chemistry* 2015, 290/17: 10862-10875). "Together, they provide a strong basis for our belief that LMTX™ should be capable of affecting the course of the disease, reducing the rate of spread of the pathology and potentially permitting an improved quality of life to these patients as well as to their immediate families and their caregivers."

Professor Claude Wischik, co-founder and Executive Chairman of TauRx and lead author of two of the articles, said: "Since the completion of our Phase 2 studies and the announcement of our highly promising results back in 2008, we have been working towards our goal of bringing forward a tau-targeted approach into final stage clinical trials. Now these publications provide the long-awaited data from our efforts, which collectively chronicle that journey."

Despite the strong efficacy signals seen on clinical and functional molecular imaging endpoints at the minimum effective dose in the Phase 2 study, a major confounding issue was the apparent failure of response at the highest dose. "This took a considerable body of work to resolve, and publishing the

Phase 2 results without fully explaining the dose-response problem would simply have clouded the issue," he explained. "As we have now shown in Baddeley et al. (2015), the underlying problem is that the bioavailability of the active methylthioninium (MT) moiety is limited when it is dosed in the oxidised MT^+ form, as we did using the chloride salt (methylthionium chloride, MTC, commonly known as 'methylene blue'). With further work, we were able to show that the minimum effective dose of 138 mg MT/day was simply the highest bioavailable dose administered in the Phase 2 study. Solving this problem then permitted us to publish the Phase 2 data in full as Wischik et al. in the *Journal of Alzheimer's Disease* (2015)."

This then led to the question of how to provide MT in a form with better bioavailability and tolerability. "We were able to show that the problem is the redox state of the MT moiety, and we had to discover how to produce MT in a stable reduced form, which we have done with LMTX™," he said. "This is a novel chemical entity that is able to deliver MT to the brain more efficiently." The discovery, synthesis and biological characterisation of LMTX™ forms the main subject of the most recent paper (Harrington et al., 2015). "We were also able to define for the first time the critical concentration of MT required for it to act as a Tau Aggregation Inhibitor (TAI)." It turns out that this concentration (~ 0.15 µM) is very close to the steady state brain concentration the team reported in Baddeley et al. (2015) at the minimum effective dose of 138 mg MT/day (0.18 µM). This concentration also overlaps the brain concentrations required to reverse both the pathology and the behavioural deficits in the two new tau transgenic mouse models they developed and reported (Melis et al., 2015a, b).

"The story we have to tell is unavoidably complex and the amount of research work that our multidisciplinary scientific team has undertaken to understand and explain the story has been enormous," Professor Wischik said. "Rather than send this information out in parts over an extended period of time through several disconnected updates, we made a conscious decision to wait until we could assemble the critical pieces of the jigsaw into a coherent whole. The body of papers we have now published supports our central contention that abnormal aggregation of tau protein is the main driver of clinical dementia, and that LMTX™ provides the first fully viable TAI as a novel basis for treatment and prevention of AD."

He added: "In about one year's time, we should know whether the first two of our three Phase 3 studies to complete have generated the data that will support our claim that LMTX™ could be the first truly disease-modifying drug for AD. Looking forward to what we believe will be a successful outcome, 2015

will be the last year in which it is possible to argue a strong version of the amyloid-β theory, and 2016 will mark a need for a fundamental paradigm shift in regards to both treatment and prevention of AD. Until then, we plan to prepare the ground for this shift and to continue the task of sharing our research output with the AD research community via our 2015-2016 publication programme. We anticipate that this will comprise a further 4-5 papers covering additional work in the areas of the pharmacokinetics and mechanism of action of LMTX™."

The six publications, now available on the TauRx website at www.taurx.com, are as follows:

1. Wischik *et al.*, Tau aggregation inhibitor therapy for Alzheimer's disease, *Biochemical Pharmacology* 2014; 88: 529-539. A review article commissioned by the journal for a special AD supplement. Set against the background of repeated failures of treatment approaches based on the amyloid-β theory of AD, the article sets out the TauRx approach based on TAI therapy as the way forward.

2. Wischik *et al.,* Tau aggregation inhibitor therapy: an exploratory Phase 2 Study in mild or moderate Alzheimer's disease, *Journal of Alzheimer's Disease* 2015; 444:705-720. This formal publication of the Phase 2 study results reflects the original 6-month study duration with two blinded extension phases to 2 years. The article shows that treatment at the minimum effective dose of 138 mg/day of methylthioninium (MT) met the primary pre-specified efficacy endpoint at 6 months, stopped decline on the functional molecular imaging outcome and achieved a 90% reduction in the rate of clinical progression of the disease over 12 months in mild/moderate AD. It also shows that this level of efficacy can be achieved safely with MT.

3. Baddeley *et al.*, Complex disposition of methylthioninium redox forms determines efficacy in tau aggregation inhibitor therapy for Alzheimer's disease, *Journal of Pharmacology and Experimental Therapeutics* 2015; 352:1-9. This article presents the four Phase 1 studies and two preclinical studies that were required to get to the bottom of the bioavailability limitations of the form of MT tested in the Phase 2 trial and sets out the basis for proceeding into Phase 3 with LMTX™.

4. Melis *et al.*, Different pathways of molecular pathophysiology underlie cognitive and motor tauopathy phenotypes in transgenic models for Alzheimer's disease and frontotemporal lobar degeneration, *Cellular and Molecular Life Sciences* 2015; 72:2199-2222. This article covers two transgenic mouse models that TauRx has developed in order to develop a better understanding of tau pathology; the differences between clinical presentations of tauopathies as either emotional/motor (as is the case in the fronto-temporal syndromes) or cognitive (as in AD) are shown

to depend on different but convergent pathways of tau pathology that do not require amyloid-β as an explanation.

5. Melis *et al.*, Effects of oxidized and reduced forms of methylthioninium in two transgenic mouse tauopathy models, *Behavioural Pharmacology* 2015; 26:353-368. An analysis of results from the use of MTC and LMTX™ in the two transgenic models described in the CMLS paper above and defines the brain concentration range for TAI activity of MT in vivo as 0.13 – 1.38 µM.

6. Harrington *et al*, Cellular models of aggregation-dependent template-directed proteolysis to characterize tau aggregation inhibitors for treatment of Alzheimer's Disease, *Journal of Biological Chemistry* 2015; 290(17): 10862-10875. This final paper in the series discloses the primary synthesis and characterisation of LMTX™, the critical concentration required for dissolution of tau aggregates isolated from AD brain tissues, and two cellular models developed to measure the prion-like processing of tau protein in living cell systems and measurement of TAI activity of novel drug candidates.

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About TauRx Pharmaceuticals Ltd

TauRx Pharmaceuticals 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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