2 SYNOPSIS

Name of Sponsor Company: TauRx Therapeutics Ltd (TauRx)	
Name of Finished Product: Leuco-methylthioninium bis(hydromethanesulfonate) (LMTM, TRx0237) Tablets, 125 mg	
Name of Active Ingredient: Methylthioninium (MT)	
Study Number: TRx-237-008	
Study Title: A Double-Blind, Placebo-Controlled, Randomized, 4-Week Safety and Tolerability Study of LMTM in Subjects with Mild to Moderate Alzheimer's Disease on Pre-Existing Stable Acetylcholinesterase Inhibitor and/or Memantine Therapy	
Principal Investigators: Dr. Mark Dale (United Kingdom); Dr. Alexander Kurz (Germany)	
Study Centers: 8 sites in the United Kingdom and 5 sites in Germany	
Publication Reference: None	
Study Period: Date of First Enrollment: 4 September 2012 Date of Last Subject Last Visit: 6 March 2013	**Phase of Development:** Phase 2
Objectives: The primary objective of this study was to assess the safety and tolerability of LMTM 250 mg daily when coadministered with an AChEI and/or memantine to subjects with mild to moderate Alzheimer's disease (AD). Exploratory assessments included cognitive function (ADAS-Cog_{11}) for information only; MT concentration data for cross-study population pharmacokinetic analysis; pharmacodynamic assessments for MAO inhibition; and measurement of plasma AChEI and/or memantine concentrations (to be analyzed only as needed to aid in safety assessment).	
Methodology: This was a randomized, double-blind, placebo-controlled, parallel group, 4-week study in subjects with mild to moderate AD receiving a stable regimen of an AChEI (*i.e.*, donepezil, galantamine, or rivastigmine) and/or memantine. Subjects were to receive study drug twice daily (*b.i.d.*) for 4 weeks, with the first dose to be administered in the clinic on Day 1 (Visit 2). Thereafter, dosing was to be on an outpatient basis. The study was to consist of seven visits over a 12-week period; outpatient study visits during the treatment period were to occur at time points approximately 3 days and 1, 2, and 4 weeks after Baseline. Safety assessments were to be performed at each visit. The ADAS-Cog_{11} was to be performed at Baseline and at the end of 4 weeks of treatment (Visit 6) or upon early termination. Blood samples were to be collected at Visits 2 through 6 for analysis of MT plasma concentrations, at Visits 2 and 3 for assessment of the effect of LMTM on markers of MAO inhibition, and at Visits 2 through 7 for analysis of AChEI and/or memantine plasma levels.	
Number of Subjects (planned and analyzed): Originally it was planned to enroll 60 subjects. The study was terminated by the Sponsor prior to the planned completion for administrative reasons. Nine subjects were enrolled and received at least one dose of study treatment.	
Diagnosis and Main Criteria for Inclusion: Subjects were to have a clinical diagnosis according to NIA/AA criteria of all cause dementia and probable Alzheimer's disease. At screening, they were to have mild to moderate dementia as determined by a MMSE score of 14-26 (inclusive) and a modified Hachinski ischaemic score of ≤ 4. Cognitive impairment was to have been present for at least 6 months. Subjects were to be currently taking an AChEI (*i.e.*, donepezil, galantamine, or rivastigmine) and/or memantine for ≥ 3 months; the current dosage regimen and dosage form must have been within the locally approved dose range and must have remained stable for ≥ 6 weeks before Baseline (Visit 2). It must have been planned that the dosage regimen would remain stable throughout participation in the study. In addition, they were to be able to give written informed consent and be supervised by a competent caregiver willing to participate in the study. **Key exclusion criteria:** • Significant CNS disorder other than Alzheimer's disease.	

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- Subjects in whom baseline MRI was contraindicated. MRI demonstrating significant intracranial pathology other than probable Alzheimer's disease or > 4 cerebral microhemorrhages, single area of superficial siderosis, or evidence of a prior macrohemorrhage.
- Clinical evidence or history of (within a specified period): cerebrovascular accident, transient ischemic attack, significant head injury with associated loss of consciousness, skull fracture or persisting cognitive impairment, or other unexplained or recurrent loss of consciousness.
- Epilepsy
- DSM-IV-TR criteria met for: current major depressive disorder; schizophrenia or other psychotic disorders, bipolar disorder, or substance (including alcohol) related disorders within the past 5 years.
- Residence in a hospital or continuous care facility
- History of swallowing difficulties
- Pregnant or breastfeeding
- History of significant hematological abnormality or current acute or chronic clinically significant abnormality, including history of hereditary or acquired methemoglobinemia or baseline measurement of MetHb > 2.0%; hemoglobinopathy, myelodysplastic syndrome, hemolytic anemia, or splenectomy; G6PD deficiency; or baseline hemoglobin value below age/sex appropriate lower limit.
- Abnormal serum chemistry laboratory value at Screening deemed to be clinically relevant.
- Clinically significant cardiovascular disease or abnormal assessments.
- Pre-existing or current signs or symptoms of respiratory failure.
- Concurrent acute or chronic clinically significant immunologic, renal, hepatic, or endocrine disease (not adequately treated) and/or other unstable or major disease other than Alzheimer's disease.
- Prior intolerance to MT-containing drug or any of the excipients.
- Treatment currently or within 3 months before Baseline with any of the following medications (unless otherwise noted): moderate to strong inhibitors of CYP1A2; tacrine; anxiolytics and/or sedatives/hypnotics (with exceptions); antipsychotics (clozapine, chlorpromazine, thioridazine, or ziprasidone; other antipsychotics initiated within 3 months before Baseline or used in a regimen that had not been stable for at least 3 months); carbamazepine; drugs associated with methemoglobinemia; warfarin (and other coumadin derivates).
- Prior participation in a clinical trial of a drug, biologic, or device in which the last dose was received within 28 days prior to Baseline.

Study Product: LMTM tablet containing 125 mg LMTM (Batch No. B00377FC, Piramal, UK), administered orally, *b.i.d.*

Placebo: Placebo tablet containing 4 mg LMTM (Batch No. B00780FC, Piramal, UK), administered orally, *b.i.d*., which was indistinguishable in appearance from the LMTM tablet but contained a small amount of LMTM in order to prevent inadvertent unblinding that might otherwise occur because of a known effect of LMTM to cause urine and/or fecal coloration.

Duration of Treatment: 4 weeks

Criteria for Evaluation:

Efficacy:

Not applicable.

Safety:

- Adverse events
- Clinical laboratory tests, including hematology, blood chemistry, urinalysis, and troponin-I
- Vital signs (temperature, respiratory rate, blood pressure, pulse)
- Weight
- Methemoglobin
- 12-lead ECGs
- Physical and neurological examinations

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- Serotonin toxicity assessments
- Columbia Suicide Severity Rating Scale

Statistical Methods: All 9 subjects who were enrolled into this study were treated with at least one dose of study drug and thus all data from each subject for the exploratory assessment of cognitive function (*i.e.*, ADAS-Cog_{11}) and safety assessments (including assessments of serotonin toxicity and suicidal behavior) are presented in the subject data listings. The statistical analyses performed on data from the 9 enrolled subjects are curtailed compared to the statistical analyses planned in the protocol due to the early termination of the study.

SUMMARY - CONCLUSIONS

The mean age of the 9 subjects was 74.2 years, ranging from 61 to 83 years. There were slightly more females than males, 55.6% *versus* 44.4%. All were Caucasian. All subjects were receiving an AChEI. At Baseline, the ADAS-Cog_{11} total score ranged from 14 to 48. The MMSE score at Screening ranged from 15 to 21; duration of AD diagnosis ranged from < 1 year up to approximately 6 years. There were 4 subjects randomized to placebo and 5 subjects randomized to LMTM. Two LMTM-treated subjects withdrew prematurely, with the remaining subjects completing the study. Compliance was high for both treatment groups (94-100%).

Exploratory Assessments: The ADAS-Cog_{11}, is included for informational purposes only. As expected given the short duration of the study, the individual subjects' changes in ADAS-Cog_{11} scores from Baseline over the 4-week assessment period were variable and unlikely influenced by treatment. MT plasma concentrations are reported; population pharmacokinetic data were not generated. Pharmacodynamic (PD) assessments of MAO A activity were not pursued to completion, due primarily to the small number of samples available. PD assessments of MAO B activity were completed; however, due to problems with platelet sample preparation or sample instability and assay accuracy, the results are considered unreliable and are not discussed.

Safety Results: Overall, 4 (100%) placebo-treated subjects and 4 (80%) LMTM-treated subjects experienced at least one TEAE. None was severe or serious. None resulted in dose interruption or reduction. Two LMTM-treated-subjects had AEs that resulted in study drug withdrawal. One subject had "electrocardiogram QT prolonged" reported as an AE at Visit 3 (Day 4) based on values reported by central ECG (collected at Visit 2 pre- and post-dose but reviewed during Visit 3; the decision to initiate dosing was based on the machine-read ECG results). The subject was removed from further study participation. In the second subject, increased TpI occurred on Day 4; the subject's family subsequently withdrew consent.

Laboratory data were reviewed and no other treatment-emergent abnormalities were apparent, as no abnormality was reported as a TEAE by the Investigator or flagged as clinically significant.

Orthostatic hypotension did not occur in any subject.

No cases of serotonin toxicity were reported with LMTM alone or in combination with a concomitant serotonergic medication (3 LMTM-treated subjects were taking a concomitant SSRI).

One subject informed the Investigator retrospectively of an episode of self harm with worsening depression that occurred 6 days after the last dose of a 4-day regimen of study drug (7 doses). There was no indication of suicidal ideation, intent, or action on the C-SSRS rated at any of the other visits for this subject. No other subject had a positive response on the C-SSRS at any visit.

Conclusion: Study drug was safely used in 9 subjects with mild to moderate Alzheimer's disease, 5 of whom were randomized to LMTM. The safety profile seen with exposure to MT, either as placebo (LMTM 8 mg) or LMTM 250 mg daily coadministered with AChEI treatment, is consistent with the known

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profile to date.
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