TauRx Therapeutics Ltd
395 King Street, Aberdeen AB24 5RP
United Kingdom

The TRx-014-009 Clinical Study Report was finalized on 25 November 2011 and described the final safety data and provided data for all efficacy assessments, either in listings of individual patient data or in the datasets. Because the protocol for TRx-014-009 stated that "individual patient data from TRx-014-009 will be amalgamated with the data from TRx-014-001 to examine the long term potential of TRX0014 (MTC) to slow the rate of decline by comparison with historical controls", analysis of efficacy data was not completed at that time. Additionally, analyses of secondary variables were not planned in the original analyses. Thus, an addendum was prepared to include complete analyses of the primary and secondary variables.

As such, the provided summary report for Study TRx-014-009 includes the following:

- Synopsis from TRx-014-009 Clinical Study Report dated 25 November 2011
- Title page from TRx-014-009 Study Report Addendum 1: Efficacy dated 29 April 2012
- Efficacy conclusions from TRx-014-009 Study Report Addendum 1: Efficacy dated 29 April 2012

2 SYNOPSIS

Name of Sponsor Company TauRx Therapeutics Ltd.	**Individual Study Table Referring to Part of the Dossier**	**(For National Authority Use Only)**
Name of Finished Product Methylthioninium chloride (MTC)	**Volume** **Page**	

Study Number: TRx-014-009	
Study Title: An Open-Label, Continuation Study of the Effects of MTC 30 mg *t.i.d.* and 60 mg *t.i.d.* in Patients with Alzheimer's Disease	
Principal Investigator: Dr. Peter Bentham	
Study Centres: 12 sites in the UK and 1 site in Singapore	
Publication Reference: None.	
Study Period: 13 September 2007 – 2 December 2010	**Phase of Development:** Phase II (open-label extension of Study TRx-014-001)
Objectives: To extend Study TRx-014-001, thereby providing patients continued access to therapy, and allowing investigation of long-term safety, tolerability and efficacy of MTC.	
Methodology: Open-label extension study with visits approximately every 3 months (13 weeks). Baseline assessments for this study were based on the final study visit in the double-blind study, Study TRx-014-001. If there was a sufficient intervening period of time between the final TRx-014-001 visit and the start of TRx-014-009, assessments were to be repeated. Patients electing to enrol were to continue on MTC, without interruption, at an assigned dose of either MTC 30 mg *t.i.d.* or 60 mg *t.i.d.*, depending on their prior treatment in TRx-014-001.	
Number of Subjects (planned and analysed): The study was open to all 118 patients ongoing in Study TRx-014-001 when that study closed; of these 111 patients elected to continue in TRx-014-009 (10 treated with MTC 30 mg *t.i.d.* and 101 treated with MTC 60 mg *t.i.d.*).	
Diagnosis and Main Criteria for Inclusion: Patients with mild or moderate dementia of the Alzheimer type at enrolment into Study TRx-014-001 and who were ongoing in Study TRx-014-001 when that study was closed at his or her site of participation were eligible to enrol.	
Study Product: Methylthioninium Chloride (MTC), TRx0014, 30 mg capsule (as the chloride salt, delivering 23 mg methylthioninium)	
Comparator Product: None.	
Duration of Treatment: Treatment was to continue in this study as long as there was a perceived benefit to the patient in the opinion of the Investigator. The protocol was amended at 12 month intervals to allow continued treatment.	
Criteria for Evaluation: **Efficacy:** The primary efficacy variable in Study TRx-014-009 was the change over time in ADAS-Cog, the same as it had been in Study TRx-014-001. The secondary efficacy assessments in Study TRx-014-001, including the short CAMDEX (inclusive of MMSE), NPI, ADFACS, and CDR, were also to continue in Study TRx-014-009. All efficacy assessments were to be measured every 26 weeks (approximately every 6 months) until the final scheduled visit. **Safety:** Safety monitoring included evaluation and recording of adverse events at each visit, clinical laboratory testing every 3 months (haematology and clinical chemistry), and vital sign measurements (blood pressure, pulse, and body weight) every 6 months throughout.	
Statistical Methods: This report describes the final safety data. Because the protocol for TRx-014-009 stated that "individual patient data from TRx-014-009 will be amalgamated with the data from TRx-014-001 to examine the long term potential of TRX0014 (MTC) to slow the rate of decline by comparison with historical controls", analysis of efficacy data is not completed as of this writing. Thus, an addendum to the study report will be prepared that includes analyses of the primary and secondary efficacy variables when they become available. Data for all efficacy assessments are provided in listings of individual patient data. Two approaches to analysis of safety data have been taken. First, data obtained in Study TRx-014-009 are presented	

using descriptive statistics, beginning with Visit 0 as the Baseline; absolute values and change from baseline are calculated for laboratory results and vital sign measurements. For adverse events in TRx-014-009, the incidence of study-emergent AEs is presented (*i.e.*, events not present at entry into TRx-014-009) and the prevalence of all AEs (*i.e.*, events present at entry into TRx-014-009 as well as those that emerged during the study). (All adverse events ongoing at the final visit for Study TRx-014-001were to be recorded on the AE CRF.) As all subjects had had a substantial duration of exposure to MTC prior to entry into Study TRx-014-009, selected data are also presented showing results encompassing all exposure to MTC. Analyses of change from baseline in laboratory results and vital sign measurements are primarily based on change relative to the start of MTC. The combined analyses allow a comparison of efficacy with continued treatment (relative to the observations in the double-blind TRx-014-001 study) as well as a more comprehensive overall summary of the safety profile of long-term treatment with MTC using a relevant baseline.
No inferential statistics were planned nor have they have been used to compare the two dose levels. Doses were not allocated randomly and there are too few patients in one of the two dose groups for meaningful statistical analysis.

SUMMARY CONCLUSIONS

111 patients entered TRx-014-009, 59 women and 52 men. The mean age was 71.4 years ± 9.69. As to race, there were 97 Caucasian and 14 Asian patients. The majority (71.2%) had been treatment naïve with respect to anticholinesterase inhibitors or memantine use and continued to be throughout participation in TRx-014-001. At entry into TRx-014-009, the mean MMSE was 18.1, ranging from 4 to 28.

A total of 68 patients permanently discontinued study drug before the study was closed administratively. Based on the Sponsor review of all CRF sources of information pertaining to reason for discontinuation, the most common reason was lack of efficacy (23 patients or 20.7%), followed by withdrawal of consent (14 patients or 12.6%, with general deterioration in cognition cited as a secondary reason in most of these). Adverse events resulted in the discontinuation of 12 patients or 10.8%.

Efficacy Results: Analysis of efficacy is underway and a summary will be provided as an addendum to this report once available.

Safety Results: In Study TRx-014-009, 105 patients (94.5%) experienced at least one adverse event starting in this study. Of these, 42 patients (37.8%) had an event judged possibly or probably related to study drug. The number of patients in the 30 mg *t.i.d.* dose group was too small to draw any meaningful conclusion. Most events were mild or moderate in intensity; 30 patients 27.0%) experienced a severe adverse event. Overall, 42 patients (37.8%) experienced at least one adverse event that met the regulatory definition of serious (many of these were also judged severe in intensity). Forty-five patients (40.5%) had an adverse event leading to dose interruption, alteration, or discontinuation. All adverse events ongoing at the final visit for Study TRx-014-001were to be recorded on the AE CRF. When accounting for ongoing and new events, 107 patients (96.4%) experienced adverse events.

No new safety issues were identified in this study. The most common AEs pertained to the urinary tract (pollakiuria, UTI, incontinence); urinary AEs were present in 50.5% of the patients (new onset in TRx-014-009 in 37.8%); such events resulted in the discontinuation of 2.7% of patients. Gastrointestinal events such as diarrhoea and dyspepsia were also common: 32.4% of patients (new onset in 25.2%). Diarrhoea resulted in the discontinuation of 2.7%. Anaemia was present in 30.6% (new onset in 21.6%), dizziness/falls/injuries were present in 27.9% (new onset in 26.1%). Non-exfoliative rash was present in 13.5% (new onset in 9.9%). Also, these adverse events had been identified in the double-blind, placebo-controlled Study TRx-014-001 as more common on MTC than placebo, thus likely attributable to study drug. Psychiatric and nervous system events were also common, however, interpretation of these events is confounded by the introduction in this study of a separate CRF onto which worsening dementia symptoms were to be collected; this form rather than the AE CRF was the source for most of these events. Overall, 65.8% of patients had psychiatric disorders and 53.2% had nervous system disorders.

There were a total of 9 deaths: 6 patients died while participating in the study or shortly (within days) after discontinuing MTC, 1 patient in the MTC 30 mg *t.i.d.* group and 5 patients in the MTC 60 mg *t.i.d.* group and 3 additional patients were reported to have died several months after discontinuation from the study. None were attributed to study drug. Non-fatal SAEs were reported in 37 patients in this study. The most common events were urinary tract infection and fall, each occurring in 4 patients (3.6%), followed by syncope and aggression each occurring in 3 patients (2.7%) and myocardial infarction, diarrhoea, head injury, cerebrovascular accident,

convulsion, TIA, agitation, and confusional state each in 2 patients (1.8%). Only 4 patients had SAEs judged by the Investigator as related to MTC (in all cases they were considered possibly related): diarrhoea; exacerbation of psoriasis; aggression (resulted in discontinuation); and urinary tract infection (resulted in discontinuation).

Patients were reviewed for other significant adverse events, including cardiac events and signs and symptoms of serotonin toxicity. There were no cardiac events suggestive of a treatment effect. There were no adverse event reports of serotonin toxicity reported during the trial. Review of individual patient data did not identify any cases suggestive of serotonin toxicity arising from concomitant administration of MTC and other serotonergic medications.

MTC produced small but consistent reductions in total WBC, neutrophil, and lymphocyte counts from the start of Study TRx-014-009 and from the start of MTC treatment in Study TRx-014-001, although mean values remained consistent and within the reference range. Seven patients had at least one decreased WBC or neutrophil count that met criteria for possibly clinically significant during Study TRx-014-009. Of these, 3 patients had neutrophil counts consistent with significant neutropenia. However, in each case the low counts were an isolated occurrence. Eosinophil counts showed slight fluctuations on treatment but did not increase over time. Six patients in Study TRx-014-009 had a possibly clinically significant value associated with high eosinophil counts. None was reported as an AE. None were associated with rash. All AEs resolved without sequelae with or without discontinuation of study drug. Differential blood counts at regular intervals were shown to be an adequate means for medical monitoring for these MT effects.

The effects observed on Hb and Hct are consistent with the known effects of MT on the haematological system. While males appeared to be more susceptible, the changes seen were limited in extent for both genders and a trend according to exposure time was not detectable.

During this study, there were no Heinz bodies observed or adverse events suggestive of methaemoglobinaemia.

Clinical blood chemistry parameters were generally unaffected during the study. Mean parameters reflective of hepatic and renal function remained stable with long-term exposure.

Vital sign data were reviewed and no additional potential risks associated with MTC were identified.

Conclusions:
MTC has been safely used in this study and the long-term safety profile in AD patients is consistent with the known safety profile of MT. No new safety issues were identified. Long-term exposure to MT (for up to 5.9 years inclusive of both TRx-014-001 and TRx-014-009 [approximately 4 years on average) was shown to be safe in doses of 30 mg and 60 mg *t.i.d.* for long durations of time.

Date of Final Report: 25 November 2011

1. TITLE PAGE

Study Title: An Open-Label, Continuation Study of the Effects of MTC 30 mg *t.i.d.* and 60 mg *t.i.d.* in Patients with Alzheimer's Disease

Report Version: Addendum 1 to the Final Study Report: Analysis of Efficacy

Study Code: TRx-014-009

EudraCT Number: 2007-002470-59

Study Indication: Mild or moderate dementia of the Alzheimer type (at enrolment into the initial double-blind study TRx-014-001)

Investigational Product: Methylthioninium chloride (TauRx product code: TRx0014)

4.4.7. Efficacy Conclusions

Overall, after an initial improvement early in treatment relative to baseline, the mean scores indicate a gradual worsening of dementia over the course of the long-term study. With the diminishing sample sizes near the end of participation, variability increases. Results should be interpreted with caution, however, as this represents only 78% of the patients who entered TRx-014-009. A number of the patients with missing or incomplete data can be presumed to have had worsening scores as they either discontinued due to lack of efficacy without a subsequent rating, were unable to provide a total score, or could no longer ingest the study medication.

It is noted that many patients (21%) either did not provide efficacy data (as they discontinued or were unable to complete the scale); overall, an additional 14% of the patients discontinued due to lack of efficacy. The remaining 43% who did not complete the study either discontinued due to an adverse event or died, withdrew consent (without a clear alternate reason), were lost to follow-up, or were non-compliant.

These efficacy data following long-term exposure[5] to MTC are not compared to other dementia populations (historical controls) on the basis of possible biases due to other factors, including treatment, that may have changed over time.

[5] On average, since the start of MTC (Study TRx-014-001), patients had been exposed to MTC for 3.61 years, with exposure ranging from 1.19 to 5.90 years by the end of TRx-014-009.