Synopsis – Study 14603A

Study Title Interventional, randomised, double-blind study to evaluate the safety and tolerability of once daily versus twice daily memantine treatment in patients with dementia of Alzheimer's type and MMSE range 5-18
Investigators 6 principal investigators at 6 sites in China *Signatory investigator* – [redacted]
Study Sites 6 sites in China
Publications None (as of the date of this report)
Study Period *First patient first visit* – 22 October 2015 (the date when the first *Informed Consent Form* was signed) *Last patient last visit* – 25 July 2016 (the date of the last protocol-specified contact with any patient)
Objectives • *Primary objective*: – to evaluate the safety and tolerability of a 20 mg once daily dose of memantine (OD) compared with 10 mg given twice daily (BID) in patients with dementia of Alzheimer's type and Mini Mental State Examination (MMSE) score in the range 5 to 18 • *Secondary objective*: – to assess the efficacy of 20 mg memantine once daily *versus* 10 mg memantine twice daily on global clinical impression using the Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change (ADCS-CGIC)
Study Methodology • This was an interventional, prospective, multi-site, randomised, double-blind, parallel-group, fixed-dose study. • The study consisted of: – Screening Period – 1-week period from screening to randomisation – Treatment Period – 12-week double-blind treatment period with either once daily or twice daily memantine – Safety Follow-up Period – 4-week period after completion of the study or after withdrawal from the study • Eligible patients were randomised (1:1) at the Baseline Visit to either treatment with memantine 20 mg once daily or memantine 10 mg twice daily for 12 weeks. • Efficacy and safety data were collected throughout the study.
Number of Patients Planned 60 patients were planned for randomisation: 30 in the 20 mg memantine once daily group and 30 in the 10 mg memantine twice daily group
Diagnosis and Main Selection Criterion Outpatients with a primary diagnosis of probable Alzheimer's disease consistent with the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's disease and Related Disorders Association criteria, who: • had a MMSE total score ≥5 and ≤18 at the Screening Visit • were ≥50 years of age • had been treated daily with memantine for ≥4 months prior to the Screening Visit. The dose of memantine had been stable at 20 mg once daily for ≥3 months prior to the Screening Visit

Investigational Medicinal Product, Dose and Mode of Administration, Batch Number

Memantine – 20 mg/day; tablets, orally; batch No. 2384673/31241 (10 mg)

Reference Therapy, Dose and Mode of Administration, Batch Number

Placebo – tablets, orally; batch No. 2386617/31207

Duration of Treatment

12 weeks of treatment

Efficacy Assessment

- ADCS-CGIC

Safety Assessments

- Adverse events (AEs), clinical safety laboratory tests, vital signs, weight/BMI, electrocardiograms (ECGs), physical and neurological examinations

Endpoints

- *Primary endpoints*:
  - safety and tolerability:
    - adverse events
    - absolute values and changes from screening/baseline in clinical safety laboratory tests, vital signs, and weight
    - potentially clinically significant (PCS) clinical safety laboratory test values, vital signs, and weight changes
    - ECG clinical evaluations
- *Secondary endpoint*:
  - global clinical impression:
    - ADCS-CGIC score at Week 12

Statistical Methodology

- The following analysis sets were used:
  - *all-patients-randomised set* (APRS) – all randomised patients
  - *all-patients-treated set* (APTS) – all patients in the APRS who took at least one dose of IMP
  - *full-analysis set* (FAS) – all patients in the APTS who had a valid baseline assessment and at least one valid post-baseline assessment of the ADCS-CGIC
  - *completer set* (CS) – all patients in the FAS who completed the study; a study completer was defined as a patient who completed 12 weeks of treatment with IMP and had valid assessments of ADCS-CGIC at all planned visits
- Unless otherwise indicated, the efficacy analyses were based on the FAS and the safety analyses were based on the APTS.
- The overall incidences of adverse events, serious adverse events (SAEs), and adverse events leading to withdrawal were summarised by treatment group. The incidences of treatment-emergent AEs (TEAEs), SAEs, and adverse events leading to withdrawal were summarised by system organ class (SOC) and preferred term. *Post-hoc* analyses comparing the two treatment groups were performed using Fisher's exact test for TEAEs with an incidence ≥5% in either treatment group and for *related* TEAEs.
- Absolute values and changes from baseline in clinical safety laboratory tests, vital signs, and weight (BMI) were summarised by visit and last assessment using descriptive statistics. Changes from baseline in vital signs to all assessment time points were analysed *post-hoc* by an ANCOVA using OC with treatment and site as fixed factors, and baseline as a covariate. PCS values were flagged and summarised by treatment group.
- ECG status was summarised by counts and percentages as well as shift tables.

Statistical Methodology (continued)

- The efficacy endpoint, ADCS-CGIC score, was analysed based on the FAS and CS:
  - per visit presenting the distribution (using bar charts) and descriptive statistics (n, mean, standard deviation, minimum, and maximum) by treatment group
  - based on an analysis of covariance (ANCOVA) of ADCS-CGIC score at Week 12, with treatment and site as fixed factors, and baseline score as a covariate using observed cases (OC)
  - using the Wilcoxon's rank test for ADCS-CGIC score at Week 12
- As a sensitivity analysis, the ADCS-CGIC was analysed using a mixed model for repeated measurements (MMRM).
- All the p-values of the efficacy analyses are based on two-sided tests; the confidence intervals (CIs) are two-sided.

Patient Disposition and Analysis Sets

- Patient disposition is summarised below:

	BID		OD		Total	
	n	(%)	n	(%)	n	(%)
Patients randomised	32		30		62	
Patients treated (all-patients-treated set [APTS])	32		30		62	
Patients completed	29	(91)	28	(93)	57	(92)
Patients withdrawn	3	(9)	2	(7)	5	(8)
Primary reason for withdrawal:						
Adverse event(s)	1	(3)	2	(7)	3	(5)
Lost to follow-up	1	(3)	0		1	(2)
Administrative reason(s)	1	(3)	0		1	(2)
Analysis sets:						
APTS	32		30		62	
Full-analysis set (FAS)	32		30		62	
Completer set (CS)	29		28		57	

Demography and Baseline Characteristics of the Study Population

- The treatment groups were comparable with respect to age, duration of Alzheimer's disease, and sex distribution: the mean age was 70 years, the mean duration of Alzheimer's disease was 2.2 years, and there were slightly more women than men (55% *versus* 45%). All the patients were Chinese.
- In accordance with the selection criteria, the MMSE score in both treatment groups ranged from 5 to 18; the mean MMSE score at baseline was 11.4 points in both treatment groups. The mean modified Hachinski ischemia score in both treatment groups was ≤4 which ruled out vascular dementia, thus suggesting dementia of Alzheimer's type as more probable; the mean score was 1.8 points in the BID group and 1.6 points in the OD group.
- There was no clinically relevant difference in the mean ADCS-CGIC score at baseline between the treatment groups. The mean ADCS-CGIC score was 4.4 points in both treatment groups and indicated that patients were *moderately* to *markedly ill*.
- There were no clinically relevant differences between the treatment groups with regard to medical history or use of recent and concomitant medications.

Efficacy Results

- The mean ADCS-CGIC score was maintained during the Treatment Period. In the BID group, the mean score was 3.66 points at Week 4 and 3.55 points at Week 12 while in the OD group, the mean score was 3.90 points at Week 4 and 3.86 points at Week 12.
- There was no statistically significant difference between the treatment groups in the mean ADCS-CGIC score at Week 12 (ANCOVA, FAS, OC). Similar results were obtained when analysed using ANCOVA, CS, OC or using non-parametric analyses using FAS or CS. These results were supported by sensitivity analysis using MMRM (FAS).

Safety Results

- The adverse event incidence in the Treatment Period is summarised below:

	BID		OD	
	n	(%)	n	(%)
Patients treated	32		30	
Patients who died	0		0	
Patients with treatment-emergent serious AEs (SAEs)	1	(3.1)	0	
Patients with treatment-emergent adverse events (TEAEs)	16	(50.0)	15	(50.0)
Patients with AEs leading to withdrawal	1	(3.1)	2	(6.7)
Total number of SAEs	1		0	
Total number of TEAEs	28		23	
Total number of AEs leading to withdrawal	1		2	

- In both treatment groups, the adverse event profile suggests that memantine was safe and tolerable. Half of the patients in each treatment group had TEAEs. The TEAEs were either *mild* or *moderate*; there were no *severe* TEAEs. In general, the TEAEs were typical for the population of patients studied.
- No deaths occurred during the study. No TEAEs was reported in more than 2 patients in either treatment group. The TEAEs reported in 2 patients in either treatment group comprised: *hypertension* (OD group), *sinus bradycardia* (OD group), *white blood cell count decreased* (OD group), and *urinary incontinence* (BID group).
- In the Treatment Period, 1 SAE (*spinal compression fracture* in the BID group) was reported; the event was considered *not related* to IMP by the investigator.
- A total of 3 patients had adverse events leading to withdrawal; 2 patients had *agitation* (1 patient in each treatment group) and 1 patient had *vomiting* (OD group).
- There were no statistically significant differences between the treatment groups in the mean changes from baseline in vital signs. There were no clinically relevant differences between the treatment groups in the clinical safety laboratory values, weight, or ECG status.

Conclusions

- In Chinese patients with dementia of Alzheimer's type and an MMSE score of 5 to 18, once daily dosing with memantine 20 mg was safe and well tolerated, and had a similar tolerability profile compared with twice daily dosing with memantine 10 mg.
- Based on the ADCS-CGIC, the therapeutic effect of memantine was maintained, whether administered once daily or twice daily.

Report Date

28 October 2016

This study was conducted in compliance with the principles of *Good Clinical Practice*.