AstraZeneca

Clinical Study Report Synopsis

Drug Substance	TC-5214
Study Code	D4131C00002
Edition Number	1
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A Phase I, single center, randomised, double-blind, placebo-controlled study to assess the safety, tolerability and pharmacokinetics of a single dose and multiple doses of TC-5214 (S-Mecamylamine) in healthy male Japanese subjects

Study dates: First subject enrolled: 17 July 2010
Last subject last visit: 1 October 2010

Phase of development: Clinical pharmacology (I)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To assess the safety and tolerability of single and multiple ascending oral doses of TC-5214 compared to placebo in Japanese healthy subjects.	-Adverse events (AEs) -Laboratory variables -Physical examination: Brief neurological examinations, Visual acuity test -Electrocardiograms (ECGs) -Vital signs: Blood pressure, Pulse, Body temperature -Columbia Suicide Severity Rating Scale (C-SSRS)	Safety
Secondary	**Secondary**	
To characterize the pharmacokinetics (PK) of TC-5214 in plasma and urine.	AUC, C_{max}, t_{max}, CL/F, λz, AUMC, MRT, V_{ss}/F, A_e, F_e, CL_R, $C_{ss,max}$, C_{min}, $t_{ss,max}$, $t_{½λz}$, AUC_{ss}, $R_{ac(Cmax)}$, $R_{ac(AUC)}$, $R_{ac(Cmin)}$, LI	PK
To assess the standard electroencephalograms (EEGs).	EEGs	Safety
Exploratory	**Exploratory**	
To explore the pharmacodynamics (PD) effects of TC-5214 on selected psychometric assessments.	Bond and Lader Visual Analogue Scale (VAS)	PD
To collect blood samples for exploratory genetic research, if consent given, in order to identify and explore genetic variations that may affect PK & PD, safety and tolerability related to TC-5214 treatment.	An optional blood samples for DNA extraction	PGX*

*: No genotyping results are presented in this CSR.

Study design

This study was a randomized, double-blind, placebo-controlled, single-center Phase I study to assess the safety, tolerability and PK of TC-5214 following a single ascending dose and multiple ascending oral doses to healthy male Japanese subjects. This study consisted of two study parts, ie, typical single ascending dose (SAD) study and multiple ascending dose (MAD) study. In each study part, dose was gradually escalated and administration of the next

and subsequent doses of TC-5214 were based on review of available safety data from the previous doses. The planned number of subjects receiving TC-5214 or placebo was as follows: TC-5214 (n=9) and placebo (n=3) per dose panel.

Target subject population and sample size

Forty-eight healthy Japanese male subjects aged 20-55 years.

Investigational product and comparator(s): dosage, mode of administration

A single and multiple oral dose of TC-5214/placebo were given as tablet. Four dose panels (2, 4, 8 and 16 mg) were conducted. As a comparator, placebo to match TC-5214 was administered.

In 1st (2 mg) and 4th (16 mg) dose panels, subjects received a single dose of TC-5214/placebo in the SAD part. In 2nd (4 mg) and 3rd (8 mg) dose panels, subjects received a single dose of TC-5214/placebo in the SAD part. Then the subjects received multiple oral dose of TC-5214/placebo (4 mg bid [twice a day] for 2nd dose panel, 8 mg bid for 3rd dose panel) in the MAD part.

Duration of treatment

In the SAD part, the subjects received a single dose of TC-5214/placebo.

In the MAD part, the subjects received a single dose of TC-5214/placebo in the SAD part, and after at least two days of washout period following discharge, the subjects received multiple dose of TC-5214/placebo for 6 days (twice daily for 5 days and a single dose on the last dosing day).

Statistical methods

No formal statistical hypothesis testing was performed. The analyses of safety, tolerability, PK and PD data were summarised descriptively including tables, listings and graphs.

Subject population

A total of 48 Japanese healthy male subjects were randomized to the study at one center in Japan. All 48 randomized subjects completed the study. All the subjects met the criteria for eligibility. No major protocol deviations were found in this study. None of the subjects were excluded from the safety, PK, or PD analysis sets.

Overall, mean age was 22.9 years old; mean weight, 61.6 kg; and mean body mass index (BMI), 21.2 kg/m^2. The treatment groups were demographically similar to each other in terms of mean age, weight and BMI.

Summary of pharmacokinetic results

Following single administration, TC-5214 was rapidly absorbed with median t_{max} of 1.0 hours. The geometric mean $t_{½λz}$ was 6.9 to 7.7 hours. The geometric mean AUC and C_{max} of TC-5214 both appeared to be dose-proportional within the examined dose range of 2 to 16 mg.

Following multiple administration, TC-5214 was rapidly absorbed with t_{max} of 1.0 hours. The geometric mean $t_{½\lambda z}$ was 7.4 to 7.5 hours. Plasma concentration of TC-5214 seems to already achieve to steady state at 24 hours after beginning of bid dose.

TC-5214 was mainly excreted in urine as unchanged drug (geometric mean F_e: 80.5 to 86.5% after single dose and 68.1 to 69.5% after multiple dose).

C_{max} and AUC were increased dose proportionally up to 16 mg after single dose (Coefficient "β" in the power model for C_{max} and AUC were 0.94 (95% confidence interval [CI]: 0.86 to 1.01) and 1.06 (0.97 to 1.14), respectively). After bid dose for 6 days, C_{max}, $AUC_{(0-12)}$ and C_{min} increased by 1.34 to1.41 folds, 1.48 to 1.51 folds and 1.48 to 1.49 folds, respectively but there was observed no marked time dependency (linearity index: 0.858 to 0.897).

Summary of pharmacodynamic results

There were no clinically relevant changes from baseline of Bond-Lader VAS parameter scores (alertness, contentedness and calmness) at any measurement time during the study.

Summary of safety results

There were no deaths, other serious adverse events (SAEs), discontinuations of investigational product due to adverse events (DAEs), or any other significant adverse event (OAEs) in the study. Most AEs were of mild intensity. Two moderate AEs (pericoronitis [2 mg single dose] and dizziness [16 mg single dose]) were also reported. Most common AEs receiving TC-5214 were dizziness and orthostatic hypotension. All AEs, except for pericoronitis, were developed just after the measurement of blood pressure and/or heart rate at standing position. Frequency of the AEs increased at the 16 mg single dose and the 16 mg multiple dose (8 mg bid) group.

There were no clinically relevant changes in supine systolic blood pressure (SBP) and diastolic blood pressure (DBP) at single dose and in supine pulse, SBP and DBP at multiple dose. Trend to a dose related increase of supine pulse at 2 to 6 hours after single dose was found. Decrease of SBP and DBP at standing (1 and 3 minute) was found at higher dose levels (8 and 16 mg single dose and 16 mg multiple dose [8 mg bid]) compared to placebo. Compensatory increase of pulse at standing was also found.

There were no clinically relevant changes in the laboratory after single and multiple oral doses of TC-5214. There were no abnormal findings in ECG, brief neurological examination, EEG, visual acuity test, and C-SSRS.