AstraZeneca

Clinical Study Report Synopsis

Drug Substance	TC-5214
Study Code	D4130C00025
Edition Number	1
Date	15 May 2012

Phase I, Open-label, Randomized, Single-dose, Two-treatment (Fed Versus Fasted) Crossover Study to Assess the Effects of Food on the Pharmacokinetics of TC-5214 (S-Mecamylamine) in Healthy Subjects

Study dates: First subject enrolled: 3 November 2011
Last subject last visit: 16 January 2012

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 evaluate the effect of food, in comparison to fasting condition, on the extent and rate of absorption of TC-5214 following single oral dose administration to healthy subjects	AUC, C_{max}	Pharmacokinetic
Secondary	**Secondary**	
To assess the safety and tolerability of single oral doses of TC-5214	Adverse events, clinical laboratory tests, vital signs, electrocardiograms, physical examinations (including neurological examination), and Columbia-Suicide Severity Rating Scale assessments	Safety
To characterize the single-dose pharmacokinetics of TC-5214 in plasma and urine	$AUC_{(0-t)}$, $AUC_{(0-48)}$, $t_{1/2\lambda z}$, t_{max}, CL/F, V_z/F $Ae_{(0-t)}$, $fe_{(0-48)}$, and CL_R	Pharmacokinetic
Exploratory[a]	**Exploratory**	
To collect samples for potential pharmacogenetic testing, which will allow future investigation of the influence of genotype on TC-5214 disposition and pharmacodynamic response	Pharmacogenetic testing	Pharmacogenetic
To collect blood samples for safety biomarker testing that will allow future assessment of safety biomarkers	Biomarker testing	Biomarker

[a] Results of exploratory analyses, if performed, will be reported separately from the Clinical Study Report.

Study design

This was a Phase I, open-label, randomized, single-dose, 2-treatment (fed versus fasted) crossover study to assess the effects of food on the pharmacokinetics of TC-5214 (S-mecamylamine) in healthy volunteers. Each volunteer received 2 treatments in a randomized order: 4 mg TC-5214 commercial formulation administered once within 30 minutes after intake of a high-fat, high-calorie breakfast (Treatment A) and once after an overnight fast (Treatment B) in a 2-way crossover design. A washout period of at least 7 days separated the drug administrations.

Pharmacokinetic blood samples were collected prior to dosing and serially up to 72 hours following dosing in each treatment period. Urine samples for pharmacokinetic analysis were collected prior to dosing and up to 48 hours postdose.

Target subject population and sample size

Healthy male and nonpregnant, nonlactating female volunteers aged 18 to 55 years, inclusive, with a body mass index between 19 and 32 kg/m^2 and weight of at least 50 kg were eligible for study participation. Up to 18 volunteers were planned for enrollment to ensure a minimum of 14 evaluable volunteers.

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

Investigational product was supplied as TC-5214 commercial tablets for oral use in strengths of 4 mg. Volunteers received single oral doses of 4 mg on 2 separate occasions. Batch number: WK90806.002/DTWP.

Duration of treatment

The duration of each volunteer's participation was approximately 55 days including a screening period of up to 30 days, 2 residential treatment periods consisting of 5 days and 4 nights separated by a least a 7-day washout period between doses, and a follow-up visit 7 to 10 days after discharge from the second treatment period.

Statistical methods

Pharmacokinetic parameters and concentrations were summarized with descriptive statistics. For the statistical comparison between treatments, TC-5214 AUC and C_{max} were the primary pharmacokinetic analysis variables, $AUC_{(0-t)}$ was considered a secondary variable. The log-transformed parameter values of AUC, $AUC_{(0-t)}$, and C_{max} were analyzed using 2 mixed-effect models for each parameter. As a primary analysis, the treatment sequence, period, and treatment were treated as fixed effects, and volunteer within sequence was considered as a random effect. As a secondary analysis, the treatment sequence, period, treatment, and volunteer within sequence were all treated as fixed effects.

Treatment B (fasted) was considered the reference treatment and Treatment A (fed) was considered the test treatment. The least-squares means of each treatment and their 95% confidence intervals, the least-squares means for the differences between test treatment and the reference treatment, and the 90% confidence intervals were calculated from the mixed-effects models mentioned above. These least-squares means and their confidence intervals were then anti-log transformed to obtain the corresponding geometric means with 95% CIs, and ratio of geometric means with 90% CI (for fed treatment/fasted treatment). If the 90% CI for the geometric mean ratio between the test treatment and the reference treatment fell into the interval (80.00%, 125.00%), then equivalence between the test treatment and the corresponding reference treatment was to be concluded.

Subject population

There were 18 study participants; 1 volunteer was withdrawn at the discretion of the Investigator prior to receiving the fed treatment in Period 2 due to a previously undisclosed medical condition (mildly diffuse fatty liver infiltration). The remaining 17 volunteers completed the study as planned. Apart from the volunteer withdrawn, all volunteers were considered healthy and without significant ongoing medical conditions. Two volunteers received paracetamol for mild pain during study conduct; otherwise, no previous or concomitant medications were reported.

Summary of pharmacokinetic results

This study confirms that administration of TC-5214 after a high-fat, high-calorie meal does not affect TC-5214 plasma exposure or renal elimination.

Table S2 Statistical comparison of TC-5214 key plasma pharmacokinetic parameters (pharmacokinetic analysis set)

Parameter (unit)	Treatment	N	Geometric LS Mean	Ratio (%)	90% CI
AUC (ng·h/mL)	Fed	17	209.1		
	Fasted	18	221.3	94.51	(88.75, 100.66)
$AUC_{(0-t)}$ (ng·h/mL)	Fed	17	206.2		
	Fasted	18	218.7	94.30	(88.66, 100.29)
C_{max} (ng/mL)	Fed	17	15.91		
	Fasted	18	16.72	95.19	(87.09, 104.05)

CI confidence interval; LS least-squares. Estimates are based on a linear mixed model with treatment sequence, period, and treatment as fixed effects, and subject within sequence as a random effect.
Fed Treatment A: TC-5214 30 minutes after the start of a high-fat, high-calorie breakfast;
Fasted Treatment B: TC-5214 following a 10-hour fast.

The median (minimum, maximum) t_{max} under the fed condition was 2.50 hours (0.50, 4.02) compared to 1.68 hours (0.97, 4.03) when fasted. The geometric mean $t_{1/2,\lambda z}$ was 9.37 hours and 9.48 hours for the fed and fasted treatments, respectively.

The geometric mean TC-5214 CL_R and $fe_{(0-48)}$ were 15.8 L/h and 81.7% after a meal, and 15.6 L/h and 83.4% after a fast, respectively.

Summary of safety results

There were no deaths, serious adverse events, or adverse events leading to discontinuation of investigational product. One volunteer experienced adverse events of increased alanine aminotransferase and aspartate aminotransferase beginning at the follow-up evaluation, which were of severe intensity. Additional testing revealed reactive total hepatitis A antibody but nonreactive immunoglobulin M hepatitis A antibody, which was indicative of a remote (not acute) infection. Follow-up is ongoing at the time of this clinical study report. These events

were assessed by the Investigator as not related to investigational product. Following dosing, there were 13 adverse events in 8 (44.4%) volunteers overall; 5 (29.4%) volunteers had adverse events during Treatment A (fed) and 5 (27.8%) volunteers had adverse events during Treatment B (fasted). The most frequently reported adverse events overall were mild somnolence in 2 (11.1%) volunteers during Treatment A (fed) only and headache in 2 (11.1%) volunteers during Treatment B (fasted) only.

Following dosing, there were no clinically relevant changes or trends in mean or median clinical laboratory or vital sign variables measured in volunteers exposed to TC-5214. There were no changes following dosing in physical or neurological examinations or Columbia-Suicide Severity Rating Scale assessments.

One volunteer (a 50-year-old, white male) had orthostatic hypotension accompanied by postural dizziness approximately 48 hours after dosing in Period 1 (fasted treatment) and a second episode of orthostatic hypotension approximately 4 hours after dosing in Period 2 (fed treatment). All 3 adverse events were assessed by the Investigator as mild in intensity, at least possibly related to investigational product, and were resolved within approximately 1.5 to 2.5 hours after onset.