AstraZeneca

Clinical Study Report Synopsis

Drug Substance	TC-5214
Study Code	D4130C00006
Edition Number	1
Date	20 May 2011

A Phase I, Single Center, Double-blind, Randomized, Placebo-controlled, Parallel-group Study to Assess the Safety, Tolerability, and Pharmacokinetics of Oral TC-5214 (S-Mecamylamine) After Administration of Single and Multiple Ascending Doses for up to 8 Days in Healthy Male and Female Subjects

Study dates: First subject enrolled: 09 June 2010
Last subject last visit: 02 September 2010

Phase of development: Clinical pharmacology (I)

Study Site Quintiles Phase I Services, Overland Park, Kansas, United States

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

Publications

None at the time of this report.

Objectives and criteria for evaluation (Table S1)

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To investigate the safety and tolerability of TC-5214 following oral administration of single and multiple ascending doses compared to placebo	Adverse events, brief neurological examinations, visual acuity tests, vital signs[a], physical examinations, laboratory parameters, electrocardiograms[b], and suicidality as assessed by the Columbia-Suicide Severity Rating Scale	Safety
Secondary	**Secondary**	
To characterize the single- and multiple-dose pharmacokinetics of TC-5214 in plasma and urine[c]	Plasma: AUC, C_{max}, t_{max}, $t_{1/2\lambda z}$, CL/F, V_Z/F, $R_{ac}(C_{max})$, $R_{ac}(AUC_{(0-12)})$, and TCP Urine: $Ae_{(0-t)}$, f_e, and CL_R	PK
To assess the effect of food on the pharmacokinetics of TC-5214	Plasma: ratio of fed $AUC_{(0-12)}$/fasted $AUC_{(0-12)}$ and ratio of fed C_{max}/fasted C_{max}	PK
Exploratory	**Exploratory**	
To collect samples for potential pharmacogenetic testing	Pharmacogenetic exploratory research	DNA
To explore any potential metabolites of TC-5214 in plasma and urine	Metabolite exploratory research	Metabolites

DNA deoxyribonucleic acid; PK pharmacokinetic; TCP temporal change parameter (ie, linearity factor).

[a] Vital signs were measured after resting in a supine position for 10 minutes and after standing for 1 and 3 minutes.

[b] Digital electrocardiograms were obtained and read centrally using a validated automated system with a cardiologist over-reading.

[c] Plasma samples for PK were collected on Day 1 (predose to 48 hours postdose), Day 6 (predose to 12 hours postdose), and Day 8 (predose to 72 hours postdose). Predose blood samples to assess trough TC-5214 plasma concentrations were collected predose starting on Day 4 continuing through Day 8 for the 12 mg dose level. Predose trough samples at the 4 mg and 8 mg dose levels were only available on Days 6 through 8. Urine samples for PK were collected for 48 hours after the morning dose administered on Day 1 (-12 to 0, 0 to 12, 12 to 24, and 24 to 48), and for 72 hours postdose on Day 8 (-12 to 0, 0 to 12, 12 to 24, 24 to 48, and 48 to 72 hours).

Study design

This was a Phase I single center, double-blind randomized (within cohorts), placebo-controlled, parallel-group study in healthy volunteers. Six cohorts planned with 9 volunteers randomized to TC-5214 and 3 randomized to placebo within each cohort but only three cohorts studied.

The study was initially designed to use either a fixed-dosing or dose-titration regimen; however, only the fixed-dosing regimen was conducted. Volunteers received 4 mg TC-5214

or placebo as a single dose on Day 1, no dose on Day 2 and on Day 3 through the morning of Day 8 TC-5214 or placebo every 12 hours. On Day 6 volunteers received their morning dose 30 minutes after the start of a high-fat, high caloric breakfast.

Major changes to the conduct of the study

The initial planned doses were 4 mg, 8 mg, 16 mg, etc. Because of the presence of adverse events (mostly orthostatic changes and gastrointestinal adverse events) with the 8 mg bid dose, the 12 mg dose was studied instead of the 16 mg dose. With the 12 mg bid dosing the stopping criteria was met, therefore, the doses of TC-5214 administered were 4 mg, 8 mg, and 12 mg.

Termination of the study based on protocol-defined stopping criteria

The Safety Review Committee stopped further dose escalation due to 6 volunteers in the 12 mg bid treatment group meeting the criteria for orthostatic hypotension.

Target subject population and sample size

Thirty-six, healthy male and non-pregnant, non-lactating female volunteers aged 18 to 55 years were studied.

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

Doses of TC-5214 were administered orally as 4 mg tablets or matching placebo (Table S2).

Table S2 Details of investigational products

Investigational product	Dosage form and strength, route of administration, and dosing schedule	Manufacturer	Lot number
TC-5214	4 mg tablet, oral, qd (Days 1 and 8) and bid (Days 3 through 7)	Patheon (Mississauga, Ontario, Canada)	WK90436.017
Placebo to match	placebo tablet, oral, qd (Days 1 and 8) and bid (Days 3 through 7)	Patheon (Mississauga, Ontario, Canada)	WK90436.014

qd once daily; bid twice daily.

Duration of treatment

Each volunteer received a single dose on Day 1 and repeated dosing every 12 hours from Day 3 through 7 and morning of day 8 (5.5 days of multiple dosing).

Statistical methods

As an exploratory study, sample size was not based on formal statistical considerations and all statistical testing is considered exploratory.

Tabulations and listings of data for brief neurological examinations, visual acuity tests, vital signs, physical examinations, clinical laboratory tests, and digital electrocardiograms were presented. Results from the Columbia Suicide Severity Rating Scale were presented separately in a listing only. For clinical laboratory tests, listings of values for each volunteer were presented with abnormal or out-of-range values flagged.

Dose proportionality was assessed graphically and statistically using the power model approach. The degree of accumulation, the effect of food on TC-5214 pharmacokinetics, the dose and time dependency of TC-5214 pharmacokinetics parameters, and the time required to reach steady state were also assessed.

Subject population

The volunteer population consisted of 36 healthy volunteers, 24 (66.7%) male and 12 (33.3%) female volunteers with a mean age of 29 years. Thirty-four (34) volunteers completed the study. Two volunteers (E0001039 (placebo) and E0001072 (12 mg) completed all scheduled investigational product administration but did not complete follow-up. All 27 TC-5214-treated volunteers were included in the pharmacokinetic analyses.

Summary of pharmacokinetic results

Steady-state plasma concentrations of TC-5214 administered twice daily appeared to be reached 1 to 3 days after the start of multiple dosing.

The median TC-5214 t_{max} ranged from 1.50 to 3.00 hours. The geometric mean $t_{1/2\lambda z}$ was slightly higher on Day 8 (from 9.62 to 10.4 hours) compared to after a single dose (7.75 to 8.71 hours). This is likely due to a more accurate estimation of $t_{1/2\lambda z}$ over the longer blood sampling interval of 72 hours on Day 8 compared to the 48-hour sampling interval on Day 1.

A high-fat meal had no effect on TC-5214 systemic exposure ($C_{ss,max}$ and $AUC_{ss,(0-12)}$) compared to administration after a fast.

Systemic exposure (C_{max} and AUC) increased in proportion to TC-5214 dose after both a single dose on Day 1, and at steady state, with an accumulation ratio of approximately 1.80 for AUC and 1.70 for C_{max}. TC-5214 kinetics were time independent based on the ratio of $AUC_{ss,(0-12)}$ (Day 8)/AUC (Day 1).

The fraction of TC-5214 excreted renally unchanged after a single dose ranged from 66% to 72.5%, and after multiple dosing at steady state from 52% to 61.9%.

A summary of key TC-5214 pharmacokinetic parameters is presented in Table S3.

Table S3 Summary of TC-5214 C_{max} and AUC on Day 1, Day 6, and Day 8

		Geometric Mean (CV%)		
Parameter (units)	**Day**	**4 mg TC-5214 N=9**	**8 mg TC-5214 N=9**	**12 mg TC-5214 N=9**
AUC (ng*h/mL)	Day 1	229 (25.0)	456 (26.6)	687 (15.3)
$AUC_{(0-12)}$ (ng*h/mL)	Day 1	133 (22.8)	259 (21.6)	398 (11.2)
$AUC_{ss,(0-12)}$ (ng*h/mL)	Day 6	239 (21.0)	481 (17.6)	713 (16.4)
$AUC_{ss,(0-12)}$ (ng*h/mL)	Day 8	237 (17.9)	466 (31.6)	722 (17.1)
C_{max} (ng/mL)	Day 1	15.6 (26.3)	30.5 (21.8)	45.4 (21.0)
$C_{ss,max}$ (ng/mL)	Day 6	26.7 (17.6)	52.1 (16.2)	80.6 (19.0)
$C_{ss,max}$ (ng/mL)	Day 8	26.2 (14.2)	51.3 (33.0)	78.8 (17.0)

Summary of safety results

Four (4) mg bid of TC-5214 was well tolerated and 8 mg bid was moderately tolerated with moderate nausea with vomiting, and a near-syncopal episode. This led to the decision to only increase the TC-5214 dose to 12 mg bid for Group 3. The 12 mg bid was poorly tolerated due to orthostatic hypotension, abdominal discomfort, and visual disturbance requiring a number of the subjects to be treated with concomitant medication even though none of the subjects discontinued treatment. Six volunteers who received 12 mg bid met orthostatic hypotension stopping criteria that prevented further dose escalation, and therefore 12 mg bid could be considered to be the maximum tolerated dose in this study.

Overall, the most frequently reported adverse events (2 or greater in the TC-5214-treated volunteers) are displayed in Table S4.

Table S4 Number (%) of subjects with cardiac, eye, gastrointestinal, and nervous system disorder adverse events arranged by system organ class/preferred term

	Treatment			
System organ class/Preferred term	Placebo N=9	4 mg TC-5214 N=9	8 mg TC-5214 N=9	12 mg TC-5214 N=9
Subjects with any adverse event	7 (77.8%)	5 (55.6%)	6 (66.7%)	9 (100.0%)
Cardiac disorders	1 (11.1%)	1 (11.1%)	0	3 (33.3%)
Orthostatic tachycardia	0	1 (11.1%)	0	3 (33.3%)
Eye disorders	0	0	0	3 (33.3%)
Vision blurred	0	0	0	3 (33.3%)
Gastrointestinal disorders	1 (11.1%)	0	3 (33.3%)	8 (88.9%)
Constipation	0	0	3 (33.3%)	7 (77.8%)
Nausea	0	0	0	5 (55.6%)
Abdominal discomfort	0	0	0	4 (44.4%)
Abdominal distension	0	0	1 (11.1%)	3 (33.3%)
Nervous system disorders	5 (55.6%)	1 (11.1%)	2 (22.2%)	7 (77.8%)
Postural dizziness	1 (11.1%)	1 (11.1%)	2 (22.2%)	6 (66.7%)
Headache	2 (22.2%)	0	0	4 (44.4%)

Supine blood pressures were similar across all treatment groups and similar to placebo group but what appeared to be dose-related increase in pulse was observed. Orthostatic vital sign changes were observed in several volunteers throughout the study; 2 volunteers in the 4 mg bid cohort, 1 volunteer in the 8 mg bid cohort, and 6 volunteers in the 12 mg bid cohort.

The only laboratory observation of note was one volunteer (4 mg bid treatment group) had an elevation of the liver transaminases (alanine aminotransferase greater than 2.5 × the upper limit of normal; aspartate aminotransferase greater than 1.5 × upper limit of normal) that was recorded 3 days after last dose that resolved on follow-up.

There were no drug effects on the digital electrocardiograms with the Fredericia correction with no evidence of prolongation or change in the QT interval.

In testing of visual acuity, there were no clinically significant changes but 3 volunteers in the 12 mg bid cohort noticed blurred vision.

There were no clinically relevant changes in Columbia Suicide Severity Rating Scale.