AstraZeneca

Clinical Study Report Synopsis

Drug Substance	TC-5214
Study Code	D4131C00003
Edition Number	1
Date	20 February 2012

A Phase I, single center, randomized, double-blind, placebo-controlled parallel-group study to assess the safety, tolerability and pharmacokinetics of single and multiple ascending doses of TC-5214 in Japanese healthy elderly male and female volunteers

Study dates: First subject enrolled: 16 July 2011
Last subject last visit: 24 October 2011

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 S 1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To assess the safety and tolerability of TC-5214 during single and multiple ascending oral doses to Japanese healthy elderly volunteers compared to placebo.	Adverse events (AEs), Laboratory variables, Physical examinations, Brief neurological examinations, Eye symptoms question, ECG, Vital signs: Blood pressure, Pulse, Body temperature, and Columbia Suicide Severity Rating Scale (C-SSRS)	Safety
Secondary	**Secondary**	
To characterize the pharmacokinetics (PK) of TC-5214 in plasma and urine.	C_{max}, t_{max}, C_{12hr}, C_{last}, t_{last}, λ_z, $t_{½\lambda z}$, $AUC_{(0-12)}$, $AUC_{(0-t)}$ AUC, % AUC_{ex}, AUMC, MRT, CL/F, V_z/F, A_e, F_e, CL_R, $C_{ss,max}$, $t_{max,ss}$, $C_{ss,last}$, $t_{last,ss}$, $C_{ss,min}$, $C_{ss,avg}$, $\lambda_{z,ss}$, $t_{½\lambda z,ss}$, $AUC_{ss,(0-12)}$, $AUC_{ss,(0-t)}$ AUC_{ss}, % $AUC_{ex,ss}$, $AUMC_{ss}$, MRT_{ss}, CL_{ss}/F, $V_{z,ss}$/F, C_{min}, $R_{ac(Cmax)}$, $R_{ac(AUC)}$, $R_{ac(Cmin)}$, LI, $A_{e,ss}$, $F_{e,ss}$ and $CL_{R,ss}$.	PK
Exploratory*	**Exploratory**	
To collect samples for potential pharmacogenetic testing, which will allow future investigation of the influence of genotype on TC-5214 (disposition, safety, tolerability and efficacy).	An optional blood samples for DNA extraction	DNA/ genotype testing
To compare PK data from Japanese healthy elderly volunteers in the present study with those of Japanese healthy young volunteers in the JSAD/MAD study (D4131C00002).		PK

*: With regard to the exploratory objectives, no results are presented in this CSR.

Study design

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

Japanese healthy elderly male and female volunteers aged 65 years or older.

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

Both the single and multiple doses of TC-5214/placebo were given as oral tablets. Four dose panels (1, 2, 4 and 8 mg) were conducted. As a comparator, placebo tablet to match TC-5214 was administered.

In the 1st, 2nd and 3rd dose panels of the SAD part, the same healthy volunteers were randomized to receive a single oral dose of TC-5214 on Day 1 (1 mg, 2 mg and 4 mg). After at least two days of washout period following discharge, the healthy volunteers started the multiple dosing (MAD part), 1 mg bid for the 1st dose panel, 2 mg bid for the 2nd dose panel and 4 mg bid for the 3rd dose panel. In the 4th and last dose panel of the SAD part, healthy volunteers were randomized to receive only a single oral dose of TC-5214 (8 mg)."

Duration of treatment

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

The washout period between the SAD and the MAD parts was at least 2 days.

In the MAD part, the subjects received multiple dose of TC-5214/placebo for 6 days (twice daily for 5 days and a single dose on the last day).

Statistical methods

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

Subject population

A total of 48 Japanese healthy elderly male and female subjects were randomized to the study at one center in Japan. All 48 randomized subjects completed the study. All of the subjects met the criteria for eligibility. No major protocol deviations were identified in this study. None of the subjects were excluded from the safety or PK analysis sets. There were no subjects who met the stopping criteria for dose escalation in the study.

Overall, mean age was 70 years; mean weight, 58 kg; and mean body mass index (BMI), 22.9 kg/m^2. The dose panel groups were demographically similar to each other in terms of age, weight, BMI, creatinine clearance and estimated glomerular filtration rate (eGFR). The 8 mg single dose panel consisted predominantly of female (8 versus 1).

Summary of pharmacokinetic results

The plasma concentration time-curves of TC-5214 were assessed up to 72 hours following a single dose on Day 1 of the SAD part, up to 12 hours following the morning dose on Day 1 of the MAD part and up to 72 hours following the morning dose on Day 6 of the MAD part. Furthermore, the trough plasma concentrations of TC-5214 were assessed from Day 1 to Day 6 of the MAD part for all dose panels.

A summary of key pharmacokinetic parameters of TC-5214 following a single dose on Day 1 of the SAD part and following the morning dose on Day 6 of the MAD part are presented below in Table S 2 and Table S 3.

Table S 2 Condensed summary of pharmacokinetic parameters of TC-5214 following a single oral dose of 1, 2, 4 and 8 mg of TC-5214 to health elderly subjects on Day 1 of the SAD part, along with renal function parameters (PK analysis set)

Treatment	1 mg (N=9)		2 mg (N=9)		4 mg (N=9)		8 mg (N=9)	
Variable	Geometric mean	CV (%)	Geometric mean	CV (%)	Geometric mean	CV (%)	Geometric mean	CV (%)
C_{max} (ng/mL)	6.45	12.0	12.41	17.7	25.61	20.5	58.47	25.9
t_{max} (hr)	1.5	1.0-3.0	1.0	1.0-6.0	1.0	1.0-4.0	1.0	1.0-1.5
$t_{1/2\lambda z}$ (hr)	11.0	16.5	11.2	19.4	10.9	11.5	9.3	11.4
AUC (ng·hr/mL)	101.5	15.7	200.5	13.0	393.3	11.4	798.3	19.3
CL/F (L/hr)	9.8	15.7	10.0	13.0	10.2	11.2	10.0	19.3
V_z/F (L)	156.4	15.0	160.7	13.7	160.0	14.4	134.2	21.6
F_e (%)	70.8	7.6	77.4	5.1	71.2	18.3	73.4	6.5
CL_R (L/hr)	6.98	16.4	7.73	14.7	7.24	14.1	7.36	19.6
eGFR (mL/min/1.73 m^2)	68	60-85	71	61-89	72	64-82	71	61-85

Geometric mean (CV%) except for t_{max} where median and range are shown, and eGFR where the mean and range are shown. eGFR estimated glomerular filtration rate.

Table S 3 Condensed summary of pharmacokinetic parameters of TC-5214 following the last dose (the morning dose on Day 6) of bid dosing of 1, 2 and 4 mg of TC-5214 to healthy elderly subjects along with renal function parameters (PK analysis set)

	1 mg bid (N=9)		2 mg bid (N=9)		4 mg bid (N=9)	
Variable	**Geometric mean**	**CV (%)**	**Geometric mean**	**CV (%)**	**Geometric mean**	**CV (%)**
$C_{ss,max}$ (ng/mL)	9.96	16.7	19.83	12.9	42.99	10.0
$t_{ss,max}$ (hr)	1.0	0.5-1.5	1.0	1.0-6.0	1.0	1.0-2.0
$AUC_{ss,(0-12)}$ (ng·hr/mL)	79.1	17.9	161.7	15.1	338.4	8.7
CL_{ss}/F (L/hr)	12.6	17.9	12.4	14.9	11.8	8.8
$V_{z,ss}/F$ (L)	188.0	14.1	189.9	15.3	170.5	10.8
$R_{ac(Cmax)}$	1.53	9.4	1.55	21.5	1.55	7.1
$R_{ac(AUC)}$	1.74	10.4	1.77	15.1	1.68	12.2
$F_{e,ss}$ (%)	70.1	17.2	79.8	10.5	79.9	13.6
$CL_{R,ss}$ (L/hr)	8.86	29.9	9.87	18.7	9.45	16.6
eGFR (mL/min/1.73 m^2)	76	61-97	79	62-102	80	66-94

Geometric mean (CV%) except for t_{max} where median and range are shown, and eGFR where the mean and range are shown. eGFR estimated glomerular filtration rate.
Linearity index=$AUCss_{,(0-12)}$ following the morning dose on Day 6 of the MAD part / AUC following the single dose on Day 1 of the SAD part

The plasma concentration profile of TC-5214 in elderly subjects was characterized by a median t_{max} of 1.0 to 1.5 hours, suggesting generally rapid absorption of this compound. The geometric mean of $t_{½}$ and CL/F ranged from 9.3 to 11.2 hours and from 9.8 to 12.6 L/hr, respectively. T_{max}, $t_{½\lambda z}$, CL/F and V_z/F were almost constant across dose levels. Based on the visual and statistical evaluation of the data, steady state was essentially reached within 2 days of bid dosing (pre-dose on Day 3 of the MAD part) for all three cohorts. Twice daily dosing resulted in accumulation of TC-5214, which was in the expected range based on $t_{½\lambda z}$ of TC-5214. C_{max} and AUC of TC-5214 increased dose proportionally up to 8 mg after a single dose, and $C_{ss,max}$ and $AUC_{ss,(0-12)}$ increased dose proportionally up to 4 mg after bid dosing, as demonstrated by the power model analysis and visual inspection of the data. A trend of lower plasma exposure of TC-5214 with higher renal function was suggested among the elderly subjects.

Summary of safety results

There were no deaths, discontinuations of investigational product due to adverse events (DAEs), or any other significant adverse events (OAEs) during the study. Only one serious adverse event (SAE) was reported (thoracic vertebral fracture) in the 2 mg bid group during

the MAD part of the study. The investigator considered the SAE not related to the investigational product due to the subject's medical history (old fractured compression L2).

A total of 3 of the 36 subjects with TC-5214-treated reported at least 1 AE during the study. The most common AE was orthostatic hypotension. A total of 4 cases of orthostatic hypotension were reported in 2 subjects in the 8 mg single dose group. All AEs of orthostatic hypotension were developed just after the measurement of blood pressure (BP) and pulse at standing position. These subjects' vital signs recovered to normal range in the supine position in a maximum of 5 minutes after onset of orthostatic hypotension. All AEs of orthostatic hypotension were considered mild in intensity and related to the investigational product (IP) by the investigator.

There were no clear trends in the mean changes in supine BP and pulse in the TC-5214 groups compared with the placebo group in either the SAD or the MAD part of the study. A decrease of standing systolic BP (SBP) and diastolic BP (DBP) (1 and 3 minute) at 1 to 4 hours after single dose were found in the 4 and 8 mg single dose group compared with placebo with compensatory increase of standing pulse. Likewise, decrease of standing SBP (1 and 3 minute) at 1 to 4 hours after multiple dose was found in the 4 mg bid group compared with placebo with compensatory increase of standing pulse.

There were no clinically relevant changes or trends in any laboratory values in either the SAD or the MAD part of the study except that CRP was elevated to 5.08 mg/dL (ULN=0.30 mg/dL) in the subject who experienced a SAE (thoracic vertebral fracture). There were no abnormal findings in ECG, brief neurological examination, eye symptoms question, modified discontinuation-emergent signs symptoms and C-SSRS.