AstraZeneca

Clinical Study Report Synopsis

Drug Substance	TC-5214
Study Code	D4130C00013
Edition Number	1
Date	15 September 2011

A Phase I, Double-blind, Placebo-controlled, Parallel Group Study to Assess the Safety, Tolerability and Pharmacokinetics of TC-5214 Given as Multiple Ascending Oral Doses in Medically Stable Elderly Subjects

Study dates: First subject enrolled: 17 January 2011
Last subject last visit: 25 May 2011

Phase of development: Clinical pharmacology (I)

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

Study centre(s)

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 multiple ascending oral doses of TC-5214 compared to placebo in medically stable elderly subjects	AEs, neurological examinations, visual acuity tests, vital signs (orthostatic blood pressure [supine, sitting and standing] and pulse, oral temperature and respiration rate), physical examinations, laboratory parameters, ECGs, and suicidality as assessed by the C-SSRS	Safety
Secondary	**Secondary**	
To characterize the PK of TC-5214 in elderly subjects	*Following a single dose of TC-5214 (Day 1) over a 12-hour sampling period:* Plasma: C_{max}, t_{max}, $AUC_{(0-12)}$ *Following multiple doses of TC-5214 (Day 5) over a 72-hour sampling period:* Plasma: $C_{ss,max}$, $t_{ss,max}$, $C_{ss,min}$, $C_{ss,avg}$, $t_{ss,min}$, $t_{½\lambda z}$, λ_z, $AUC_{ss,(0-12)}$, fluctuation ratio, and CL_{ss}/F. $R_{ac(Cmax)}$ and $R_{ac(AUC[0-12])}$ were assessed between Day 1 and Day 5 Urine (Day 5 only): $A_{e(0-12),ss}$ $A_{e(0-t),ss}$ $A_{e(0-72),ss}$, $f_{e,ss}$ (% dose) and $CL_{R,ss}$	PK
Exploratory	**Exploratory**	
To collect samples for potential PGx testing, which will allow future investigation of the influence of genotype on TC-5214 disposition and safety	DNA/genotype (optional)	PGx
To compare PK parameter data from the elderly subjects in the present study to data from healthy younger subjects in the MAD study (D4130C00006)	To be determined	PK

AE: Adverse event, $A_{e(0-12),ss}$: Cumulative amount of drug excreted unchanged into urine from zero to 12 hours at steady state, $A_{e(0-72),ss}$: Cumulative amount of drug excreted unchanged into urine from zero to 72 hours at steady state, $A_{e(0-t),ss}$: Cumulative amount of drug excreted unchanged into urine from zero to time t at steady state, $AUC_{(0-12)}$: Area under the plasma concentration-time curve from zero to 12 hours, $AUC_{ss,(0-12)}$: Area under the plasma concentration-time curve from zero to the end of the 12 hours dosing interval at steady state, $CL_{R,ss}$: Renal clearance at steady state, CL_{ss}/F: Apparent clearance at steady state, C_{max}: Maximum plasma concentration, $C_{ss,avg}$: Average plasma concentration at steady state, $C_{ss,max}$: Maximum plasma concentration at steady state, $C_{ss,min}$: Minimum plasma concentration at steady state, C-SSRS: Columbia Suicide Severity Rating Scale, ECG: Electrocardiogram, $f_{e,ss}$; Fraction of dose excreted unchanged into urine at steady state, λ_z: Terminal rate constant, PGx: Pharmacogenetic(s), PK: Pharmacokinetic(s), $R_{ac(Cmax)}$: Accumulation ratio for C_{max} (ratio of $C_{ss,max}$ on Day 5 to C_{max} on Day 1) $R_{ac(AUC[0-12])}$: Accumulation ratio for $AUC_{(0-12)}$ (ratio of $AUC_{ss,(0-12)}$ on Day 5 to $AUC_{(0-12)}$ on Day 1), t_{max}: Time to C_{max}, $t_{ss,max}$: Time to $C_{ss,max}$, $t_{ss,min}$: Time to $C_{ss,min}$, $t_{½\lambda z}$: Terminal half-life.

Study design

This was a Phase I, randomized, double-blind, placebo-controlled, parallel group study to assess the safety, tolerability and PK of TC-5214 following oral MAD administration to medically stable elderly subjects. The study included 3 visits and 4 cohorts. Eight subjects participated in each cohort and received either TC-5214 or placebo, randomized 6:2.

The subjects received TC-5214 twice daily (every 12 hours) on Days 1 to 4 and as a single morning dose on Day 5. The starting dose of TC-5214 among elderly subjects aged 65 to 74 years in Cohort 1 was 2 mg. In Cohort 2, dose escalation continued as planned with the pre-defined dose level, 4 mg. The starting dose of TC-5214 among the elderly subjects aged 75 years or older in Cohort 3 was 1 mg. In Cohort 4, dose escalation continued as planned with the pre-defined dose level, 2 mg.

Target subject population and sample size

Thirty-two medically stable elderly subjects were planned for inclusion in the study. Eight subjects were planned in each cohort. Elderly subjects aged 65 to 74 years comprised Cohorts 1 and 2. Elderly subjects aged 75 years or older comprised Cohorts 3 and 4.

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

Investigational product (IP) was administered orally as TC-5214 tablets or matching placebo (Table S2).

Table S2 Details of investigational product and other study treatments

IP	Dosage form, strength, and route of administration	Manufacturer	Formulation number	Batch number
TC-5214	Tablet, 1 mg, oral	Patheon	3800001800	CXWG
TC-5214	Tablet, 2 mg, oral	Patheon	3800001803	CBWG
TC-5214	Tablet, 4 mg, oral	Patheon	3800001805	CBWH
Placebo	Tablet, oral	Patheon	3800001793	CBWC

Duration of treatment

The subjects received TC-5214 or placebo administered twice daily (12 hours apart) on Days 1 to 4 and as a single morning dose on Day 5.

Statistical methods

The sample size was not based on formal statistical considerations, but was based on experience from previous similar Phase I studies with other compounds.

Safety, tolerability and PK data were summarized using descriptive statistics. Confidence intervals (CIs) for the PK analysis were calculated only for descriptive purposes. The difference in exposure parameters (C_{max} and $AUC_{(0-12)}$ for TC-5214 between Day 1 and Day 5

in each dose group and age group were assessed for accumulation using a linear mixed model with a fixed and repeated effect for study day (Days 1 and 5).

The time to reach steady state was assessed graphically and statistically using a repeated measures linear mixed model with treatment day as a fixed and repeated effect and Helmert contrasts.

Subject population

In total, 75 medically stable white elderly male and female subjects were enrolled (consented) to participate in the study. Thirty-two subjects were randomized to treatment in the study, which was performed at 2 study sites in Sweden. Overall, 31 subjects completed the study and received all doses of IP according to the Clinical Study Protocol. One subject in Cohort 2 (elderly aged between 65 and 74 years) was discontinued from IP due to an AE (postural dizziness) on Day 2 after receiving 4 mg TC-5214 twice daily on Day 1 (every 12 hours) and once in the morning of Day 2. The safety analysis set included all randomized subjects, and the PK analysis set included all 24 subjects who received TC-5214.

Overall, demographic characteristics were comparable between the cohorts in each age group, but there were slight differences in mean body mass index, estimated glomerular filtration rate (eGFR) and calculated creatinine clearance between the treatment and age groups.

Summary of pharmacokinetic results

Visual examination of the trough concentrations on Days 3, 4 and 5 indicated that steady state was achieved on Day 3 after twice daily dosing. The plasma concentration profile of TC-5214 at steady state in elderly subjects was characterized by a median t_{max} of 1.50 to 2.26 hours, a mono-exponential decline with a geometric mean $t_{½\lambda z}$ of 12.5 to 16.0 hours and a CL_{ss}/F of 9.15 to 15.9 L/h. A correlation between kidney function and TC-5214 plasma exposure, accumulation, and urinary recovery was indicated among the elderly subjects. The fraction of dose excreted in urine during 12 hours at steady state was 61 to 93% and $CL_{R,\,ss}$ ranged between 7.61 to 9.73 L/h. The accumulation ratio was 1.76 to 2.38 for $AUC_{(0\text{-}12)}$ and 1.67 to 2.25 for C_{max}. Overall, the exposure of TC-5214 appeared to be dose proportional in elderly subjects, when renal function is taken into account.

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

Table S3 Summary of TC-5214 selected PK parameters on Day 1 and Day 5

		65 to 74 years		>=75 years	
Parameter	**Day**	**2 mg TC-5214 N=6**	**4 mg TC-5214 N=6**	**1 mg TC-5214 N=6**	**2 mg TC-5214 N=6**
$AUC_{(0-12)}$ (h*ng/mL)	1	81.2 (18.8)	173 (6.5)	35.8 (18.6)	91.8 (14.4)
$AUC_{ss,(0-12)}$ (h*ng/mL)	5	177 (17.7)	360 (20.4)	62.9 (21.9)	219 (33.3)
C_{max} (ng/mL)	1	9.63 (21.4)	20.2 (5.6)	4.35 (21.1)	10.7 (15.8)
$C_{ss,max}$ (ng/mL)	5	18.9 (17.4)	39.7 (13.6)	7.25 (19.3)	24.0 (20.9)
CL_{ss}/F (L/h)	5	11.3 (17.7)	11.1 (20.5)	15.9 (21.8)	9.15 (33.5)
$t_{1/2\lambda z}$ (h)	5	13.9 (21.8)	12.5 (14.9)	12.9 (12.7)	16.0 (41.9)
$f_{e\ (0-12),ss}$ (%)	5	70.6 (26.1)	68.5 (18.0)	61.2 (29.6)	92.8 (18.6)
eGFR (mL/min/ 1.73m^2)	-1	75 (68, 84)	80 (61, 97)	83 (69, 104)	69 (62, 83)
Dose adjusted parameter					
$AUC_{(0-12)}$ (h*ng/mL)	1	40.6 (18.8)	43.2 (6.5)	35.8 (18.6)	45.9 (14.4)
C_{max} (ng/mL)	1	4.81 (21.4)	5.05 (5.6)	4.35 (21.1)	5.33 (15.8)
$C_{ss,max}$ (ng/mL)	5	9.43 (17.4)	9.92 (13.6)	7.25 (19.3)	12.0 (20.9)
$AUC_{ss,(0-12)}$ (h*ng/mL)	5	88.7 (17.7)	90.0 (20.4)	62.9 (21.9)	109 (33.3)
$C_{ss,min}$ (ng/mL)	5	5.45 (18.9)	5.38 (25.6)	3.50 (24.2)	6.62 (48.3)

Geometric Mean (CV%) except for eGFR where the mean and range are shown. eGFR estimated glomerular filtration rate

Summary of safety results

No major safety or tolerability concerns were identified in this study up to the pre-defined dose levels of 2 mg twice daily (elderly aged ≥75 years) and 4 mg twice daily (elderly aged 65 to 74 years) administered for 5 days. The AE profile was similar in the two age groups receiving the same dose. There were no serious AEs or other significant AEs, but one subject in the 65 to 74 year-old group discontinued due to an AE (postural dizziness). The most common AEs that were judged by the Investigator to be related to treatment were constipation and postural dizziness. The frequency of AEs increased in a dose-dependent manner. All

AEs were of mild or moderate intensity, except 3 events of postural dizziness among the 65 to 74 year-old subjects who received TC-5214 that were of severe intensity.

In general, no clinically significant effects were observed for neurological examination items, visual acuity tests, physical examination items, laboratory variables, ECGs, and suicidality.