AstraZeneca

Clinical Study Report Synopsis

Drug Substance	TC-5214
Study Code	D4130C00008
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An Open-Label, Multi-Center, Phase I Study To Compare the Pharmacokinetics of a Single Oral Dose of TC-5214 (S-Mecamylamine) in Subjects with Renal Impairment with Subjects with Normal Renal Function

Study dates: First subject enrolled: 12 November 2010
Last subject last visit: 19 July 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 S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To assess the pharmacokinetics of a single dose of TC-5214 in subjects with renal impairment and to compare the results with those in subjects with normal renal function	AUC, $AUC_{(0-t)}$, $AUC_{(0-72)}$, $AUC_{(4-8)}$, $AUC_{(72-76)}$, C_{max}, t_{max}, λ_z, $t_{1/2,\lambda z}$, CL/F, and V_z/F in all subjects $Ae_{(0-t)}$, f_e, and CL_R in Groups 1 to 3	Pharmacokinetic
Secondary	**Secondary**	
To assess the effect of hemodialysis on TC-5214 pharmacokinetics	$Ad_{(4-8)}$, $fd_{(4-8)}$, and CL_D, in Group 5 during Part 1, Period 2 $Ad_{(72-76)}$, $fd_{(72-76)}$, and CL_D for subjects in Group 5, Part 2	Pharmacokinetic
To assess the safety and tolerability of TC-5214 in subjects with renal impairment compared with those subjects with normal renal function	Adverse events, clinical laboratory tests, physical examinations, 12-lead electrocardiograms, vital signs, and Columbia Suicide Severity Rating Scale	Safety
Exploratory[a]	**Exploratory**	
To collect samples for potential pharmacogenetic testing, which will allow future investigation of the influence of genotype on drug disposition and pharmacodynamic response	Pharmacogenetic testing	Pharmacogenetic

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

Study design

This was a Phase 1 single dose, multicenter, open-label study designed to evaluate the safety, tolerability, and pharmacokinetics of TC-5214 in renally impaired subjects compared with subjects with normal renal function.

Based on an interim review of the safety and pharmacokinetic data of 2 subjects with moderate impairment and 2 subjects with end-stage renal disease, subjects with severe renal impairment were not recruited for this study and the study was conducted in 2 parts. The interim pharmacokinetic analysis of the data from the first 4 subjects demonstrated renal impairment reduces the plasma clearance of TC-5214 in accord with what might be predicted for a drug cleared predominantly via renal elimination. In addition, the limited interim pharmacokinetic data showed an increase in the half-life of TC-5214 by approximately 3- and 10-fold, respectively as compared to the mean terminal half-life ($t_{1/2,\lambda z}$) of TC-5214 in human

plasma available at the time of the interim analysis (eg, 8 to 9 hours). Therefore, the study design was updated for Groups 1 to 3 to ensure the adequate characterization of TC-5214 pharmacokinetics and patient safety.

Part 1 included subjects who had completed the study prior to the interim analysis (including 3 subjects each in the mild and moderately impaired renal groups and 4 subjects with end-stage renal disease) and Part 2 included the remainder of study participants.

Subjects were enrolled into 1 of 4 groups in parallel, according to their degree of renal impairment based on their estimated glomerular filtration rate, determined using the abbreviated, 4-variable Modification of Diet in Renal Disease formula as follows:

> Group 1: control subjects with normal renal function; estimated glomerular filtration rate greater than 80 mL/min
>
> Group 2: mild renal impairment; estimated glomerular filtration rate between 50 and 80 mL/min, inclusive
>
> Group 3: moderate renal impairment; estimated glomerular filtration rate from at least 30 to less than 50 mL/min
>
> Group 5: end-stage renal disease, currently receiving dialysis; estimated glomerular filtration rate less than 30 mL/min,

Subjects in Groups 1 through 3 reported to the clinic on Day -1 (or Day -2 at the discretion of the Investigator) and received a single, oral dose of 8 mg (normal and mild groups) or 2 mg (moderate group) TC-5214 on Day 1. For Part 1, pharmacokinetic sampling was conducted through 72 hours postdose and subjects were released from the clinic after completion of Day 4 procedures. For Part 2, pharmacokinetic sampling was performed through 120 hours postdose and subjects remained in the clinic until completion of Day 6 procedures. For both parts, subjects returned to the clinic 7 to 10 days after discharge for follow-up assessments.

Part 1, Group 5: The first 4 subjects enrolled into Group 5 participated in 2 treatment periods, and received a single oral dose of 2 mg TC-5214 on each occasion. During Period 1, subjects received a single dose of TC-5214 on Day 1 after completion of a dialysis session and remained in the clinic for pharmacokinetic sample collections and safety assessments until the start of their next dialysis session. There was a washout period of at least 2 weeks between treatment periods. Subjects in Treatment Period 2 received a single dose of TC-5214 on Day 1, at 4 hours prior to the start of a dialysis session. Subjects remained in the clinic until the start of their next dialysis session. Blood samples for pharmacokinetic assessments were collected prior to dialysis, during the entire dialysis session, and until the start of their next dialysis session. Dialysis fluid was collected in 1-hour intervals. Subjects returned to the clinic for a follow-up visit 7 to 10 days following discharge from the clinic.

Part 2, Group 5: The remainder of subjects enrolled into Group 5 participated in 1 treatment period, received a single oral dose of 2 mg TC-5214 on Day 1 after completion of their first

inpatient dialysis session, and remained in the clinic until the completion of the study assessments and procedures scheduled on Day 6. The inpatient treatment period included a second dialysis session scheduled between 72 and 76 hours postdose. Pharmacokinetic blood samples were collected through 72 hours postdose (assessment between dialysis) and between 72 and 120 hours (including samples during the 4-hour dialysis). Pharmacokinetic urine samples were collected for up to 120 hours postdose from subjects who were able to produce urine. Dialysis fluid was collected in 1-hour intervals between 72 and 76 hours postdose. Subjects returned to the clinic for a follow-up visit 7 to 10 days following discharge from the clinic.

Target subject population and sample size

The target population included male and nonpregnant, nonlactating female subjects with normal renal function, mild and moderate renal impairment, and end-stage renal disease on dialysis, aged 18 to 80 years with a body mass index between 19 and 40 kg/m^2. The demographics of healthy subjects with normal renal function were matched for age ±10 years, and body mass index ±3 kg/m^2, to the mean age and body mass index of subjects across the 3 renal impairment groups. Sex was matched to achieve similar distribution between male and female subjects.

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

Investigational product was supplied as tablets for oral use in strengths of 2 and 4 mg. Subjects with normal renal function and mild renal impairment received single oral doses of 8 mg (two 4-mg tablets); subjects with greater degrees of renal impairment received oral doses of 2 mg TC-5214. Batch numbers WK90573.001 and WK90573.002 for the 2 and 4 mg tablets, respectively.

Duration of treatment

Subjects in the normal, mild, and moderate renal groups as well as subjects in the end-stage renal disease group who participated in Part 2 received a single, oral dose of TC-5214. Subjects with end-stage renal disease who participated in Part 1 received study medication on 2 occasions. Including screening, treatment, and follow-up periods, the duration of study participation for individual subjects was up to 47 days for those who participated in a single treatment period and up to 62 days for those who participated in 2 treatment periods.

Statistical methods

Regression models were used to assess and quantify the relationship between renal function, as measured by the eGFR, and TC-5214 dose-normalized primary pharmacokinetic parameters (C_{max} and AUC). The initial model specified a linear relationship between primary pharmacokinetic parameters and the eGFR, and was estimated using ordinary least squares. Log-transformations were used to improve model fit and accommodate the log normal distribution typical for C_{max} and AUC. Model parameters, 90% confidence intervals, and p-values were reported. From the final models, estimates of the mean pharmacokinetic parameters and 90% confidence intervals were made at the median estimated glomerular

filtration rate of each of the renal function groups, as were the differences (or ratios) and 90% confidence interval relative to the control subjects with normal renal function.

As an exploratory analysis, the renal function groups were compared using a one-way analysis of variance model on the log-transformed dose-normalized primary pharmacokinetic parameters (C_{max} and AUC). The renal impairment groups were compared to the control subjects with normal renal function, with the latter as reference. Geometric least-squares means with corresponding 95% confidence intervals and ratios of geometric least-squares with corresponding 90% confidence intervals were presented. While this study was not statistically powered in terms of claiming no effect of renal impairment on TC-5214 exposure, interpretation of the effect of renal impairment was based on point estimates and associated 90% confidence intervals.

Subject population

There were 32 study participants (8 subjects per renal function group). Two subjects withdrew from the study at their discretion; the remaining 30 subjects completed the study. All subjects were included in the pharmacokinetic and safety analysis sets. Subjects in the end-stage renal disease group were slightly younger (mean age of 48 years) than the other groups (mean ages from 59 to 68 years); otherwise, demographic characteristics between the renal function groups were generally comparable. Subjects in the normal renal function group were considered healthy and without significant ongoing medical conditions. Subjects in the renal impairment groups demonstrated mild or moderate renal impairment or end-stage renal disease, based on the estimated glomerular filtration rates at screening.

Summary of pharmacokinetic results

This study confirms renal impairment reduces the plasma and renal clearance of TC-5214 with increases in systemic plasma exposure linearly related to a decline in renal function. An increase in eGFR by 10 units is associated with an 11% mean decrease in dose-normalized AUC or $AUC_{(0-72)}$ (a decrease of -0.120 on the natural log scale).

Table S2 Statistical comparison of TC-5214 key pharmacokinetic parameters between renal groups (Pharmacokinetic analysis set)

Parameter	Renal group	N	Geometric LS mean	Comparison to normal renal function group (Group 1)	
				Ratio (%)	90% CI
AUC/Dose (ng·h/mL)	Normal	8	71.38		
	Mild	8	100.6	140.96	(129.64, 153.25)
	Moderate	7	129.0	180.73	(162.35, 201.20)
$AUC_{(0-72)}$/Dose (ng·h/mL)	Normal	8	67.21		
	Mild	8	95.91	142.71	(135.28, 150.55)
	Moderate	8	124.1	184.63	(174.87, 194.93)
	ESRD	7	186.0	276.73	(257.77, 297.09)
C_{max} (ng/mL)	Normal	8	4.145		
	Mild	8	3.943	95.12	(90.96, 99.46)
	Moderate	8	3.803	91.73	(87.70, 95.96)
	ESRD	8	3.589	86.58	(81.96, 91.47)

CI confidence intervals, eGFR estimated glomerular filtration rate; ESRD end-stage renal disease; LS least-squares. Results based on linear regression with log-transformed dose-normalized pharmacokinetic parameter as the dependent variable and eGFR determined on Day -1 as the independent variable, including the Normal, Mild, and Moderate Groups, and the End-stage group, (Treatment Period 1 only). Estimates are for the median eGFR value for each group.

Table S3 Key TC-5214 pharmacokinetic parameters by renal group

Parameter		Normal Renal Function	Mild Renal Impairment	Moderate Renal Impairment	End-stage Renal Disease
CL/F (L/h)	n	8	8	7	ND
	Geomean	14.9	11.2	7.36	ND
	CV%	18.1	28.1	60.8	ND
CL_R (L/h)	n	8	8	8	ND
	Geomean	11.3	9.21	4.69	ND
	CV%	21.3	35.0	65.9	ND
$fe_{(0-72)}$ (%)	n	8	8	8	ND
	Geomean	74.1	78.3	54.9	ND
	CV%	14.1	16.1	22.2	ND
$fe_{(0-120)}$ (%)	n	8	4	5	ND
	Geomean	75.2	76.0	61.5	ND
	CV%	14.9	15.1	19.8	ND

Geomean geometric mean; ND not determined.

The median TC-5214 t_{max} for normal, mild, moderate, and end-stage renal disease groups was 1.78, 2.25, 2.25, and 3.00 hours respectively. Maximum exposure (C_{max}) following a single oral dose of TC-5214 was not affected by the degree of renal impairment.

Plasma clearance of TC-5214 in subjects with end-stage renal disease appeared negligible, with flat plasma concentration-time profiles leading to unreliable estimates for AUC, with individual plasma half-life estimates ranging from 96.9 to 282 hours. These estimates were based on a sampling period much shorter than the estimated $t_{1/2,\lambda z}$ values. The TC-5214 $t_{1/2,\lambda z}$ for normal, mild, and moderate groups was 10.4, 14.0, and 26.4 hours, respectively.

The average renal clearance in subjects with mild renal impairment and moderate renal impairment was only 81.5% and 41.5% of the CL_R in normal subjects. Urine was only available, and CL_R determined for 1 subject with ESRD, with a negligible CL_R of 0.0483 L/h.

The geometric mean percent of TC-5214 unbound in plasma was within a narrow range of 76.8% to 82.3% across both sampling time points and renal function groups.

The dialysis clearance of TC-5214 was 10.5 L/h, with approximately 10% of a dose removed during a standard 4-hour hemodialysis session.

Summary of safety results

There were no deaths or discontinuations from the study due to adverse events. There were 4 serious adverse events reported in 2 subjects (1 each from the moderate [angina pectoris] and end-stage renal disease [abdominal pain, hyperhydrosis, and syncope] groups); none of which were assessed by the Investigator as causally related to investigational product. Following dosing, 14 subjects overall had adverse events; 5 subjects in the mild renal group and 3 each in the normal, moderate, and end-stage renal disease groups. The most frequent adverse events were orthostatic hypotension in 7 subjects and abdominal pain in 2 subjects. The serious adverse event of syncope as well as 2 adverse events of orthostatic hypotension (mild renal group) and an adverse event of muscle spasms (moderate renal group) were of severe intensity.

Six events of orthostatic hypotension occurred in the normal (2 events) and mild (4 events) renal groups following administration of 8 mg TC-5214. The onset of these 6 events ranged from 3.75 to 4.75 hours following dosing and the durations ranged from 0.75 to 29.5 hours. The 2 adverse events in the normal renal function group were of moderate intensity and in the mild renal groups, 2 events were moderate and 2 were severe. Two subjects in the mild renal group (1 moderate and 1 severe episode) were given intravenous sodium chloride, which resolved their adverse events of orthostatic hypotension.

Decreases in mean blood pressure were noted at 4 hours postdose, which were most pronounced in the normal and mild renal groups, who received 8 mg TC-5214, and in the standing position. Smaller decreases in blood pressure were noted at 4 hours postdose for the moderate renal group who received 2 mg TC-5214; however changes in mean blood pressure for the end-stage renal disease group who received 2 mg TC-5214 after dialysis were minimal.

For all renal groups and in all positions, improvement in mean blood pressure was noted at the next scheduled evaluation at 24 hours postdose.

Following dosing, there were no clinically relevant changes or trends in mean or median laboratory or electrocardiogram variables measured in subjects exposed to TC-5214.