AstraZeneca

Clinical Study Report Synopsis

Drug Substance TC-5214

Study Code D4130C00010

Edition Number 1

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A Phase I Randomised, Placebo-controlled, Double-blind Study in Hypertensive Patients of the Blood Pressure Interaction between TC-5214 and Anti-hypertensive Medications (Calcium Channel Blockers, Beta-blockers, and ACE Inhibitors)

Study dates: First subject enrolled: 10 October 2011
Last subject last visit: 2 May 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 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary Part 1	Pharmacodynamic	To determine if treatment with TC-5214 at 4 mg bid had an effect on sitting blood pressure in patients with chronic hypertension	Sitting SBP change from baseline at 2 hours postdose
Primary Part 2	Pharmacodynamic	To determine if treatment with TC-5214 at 4 mg bid combined with treatment with the common class of anti-hypertensive medications (calcium channel blockers, beta-blockers, and ACE inhibitors) had an effect on sitting blood pressure greater than that observed with treatment with just the anti-hypertensive medications in patients with chronic hypertension	Sitting SBP change from baseline at 2 hours postdose
Secondary	Pharmacodynamic	To determine if treatment with TC-5214 at 4 mg bid had an effect on supine and standing blood pressure in patients with chronic hypertension	Absolute and change from baseline seated DBP at 2 hours, sitting SBP and DBP at 4 hours, supine SBP and DBP, and standing SBP and DBP at 2 and 4 hours postdose
	Pharmacodynamic	To determine if treatment with TC-5214 at 4 mg bid combined with treatment with the common class of anti-hypertensive medications (calcium channel blockers, beta-blockers, and ACE inhibitors) had an effect on supine and standing blood pressure greater than that observed with treatment with just the anti-hypertensive medications in patients with chronic hypertension	Absolute and change from baseline seated DBP at 2 hours, sitting SBP and DBP at 4 hours, supine SBP and DBP, and standing SBP and DBP at 2 and 4 hours postdose

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
	Safety	To assess the safety and tolerability of multiple oral doses of TC-5214 in chronic hypertensive patients by assessment of adverse events, vital signs, physical examinations, laboratory parameters, electrocardiogram, and suicidality as assessed by Columbia-Suicide Severity Rating Scale	Adverse events, laboratory variables, vital signs, physical examination, electrocardiogram, and Columbia-Suicide Severity Rating Scale
	Pharmacokinetic	To compare exposure to TC-5214 when administered by itself and concurrently with calcium channel blockers, beta-blockers, and ACE inhibitors	TC-5214 concentrations on Days 7, 14, 21, and 28 at predose and 1, 1.5, 2, 2.5, 3, and 4 hours postdose
Exploratory	Pharmacogenetic	To collect samples for potential pharmacogenetic testing, which will allow future investigation of the influence of genotype on TC-5214 disposition and PD response	Not applicable

ACE: angiotensin converting enzyme; bid: twice daily; DBP: diastolic blood pressure; SBP: systolic blood pressure.

Study design

This study was conducted in 2 separate, independent parts. Approximately 80 patients with chronic hypertension were to be randomised into 4 different groups (Groups 1, 2, 3, and 4) of 20 patients each. Group 1 participated in Part 1 and Groups 2, 3, and 4 in Part 2.

Group 1: patients were to be tapered off from their usual anti-hypertensive medication and only use TC-5214/placebo while in the study

Group 2: patients were to use a calcium channel blocker in combination with TC-5214/placebo

Group 3: patients were to use an ACE inhibitor in combination with TC-5214/placebo

Group 4: patients were to use a beta-blocker in combination with TC-5214/placebo

Both parts had a randomised, placebo-controlled, double-blind, 2-way cross-over design. Each part consisted of 2 treatment periods.

Part 1 studied the effect of TC-5214 when administered as monotherapy to hypertensive patients who had been tapered off and discontinued from their usual anti-hypertensive medication.

Part 2 studied the effect of TC-5214 when administered to hypertensive patients in combination with their individual maintained and stabilised anti-hypertensive medication. Patients were divided into 3 groups according to their anti-hypertensive medication (calcium channel blockers, beta-blockers, and ACE inhibitors).

Target subject population and sample size

Male or female patients with chronic, stable hypertension treated for at least 1 month before screening with a calcium channel blocker, a beta-blocker, or an angiotensin converting enzyme (ACE) inhibitor, either as the only anti-hypertensive medication or concurrently with a diuretic. Patients in Part 1 were to have an average sitting systolic blood pressure (SBP) of ≤140 mmHg at screening and patients in Part 2 an average sitting SBP of ≤160 mmHg at screening. Patients were to be aged 18 to 65 years (inclusive), have a body mass index (BMI) of 19 to 35 kg/m^2, weigh at least 50 kg and should have provided written informed consent.

Groups 2, 3, and 4 were to have at least 20 evaluable patients in each group.

Planned: 80 patients

Randomised: 79 patients

Analysed: 74 patients (PD analysis set); 74 patients (PK analysis set); 79 patients (safety analysis set)

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

Table S2 Objectives and outcome variables

Investigational product	Dosage form and strength	Manufacturer	Batch number
TC-5214	2 mg oral tablets	Patheon	CYKY
TC-5214	4 mg oral tablets	Patheon	CYMB
Placebo	Matching oral tablets	Patheon	CBWC

Part 1

4 mg TC-5214 or placebo oral tablets twice daily (bid) (58 doses)

Period 1: dosing started in the morning of Day 0 and continued through the morning of Day 14 (29 doses).

Period 2: dosing started in the afternoon of Day 14 and continued through the morning of Day 28 (29 doses).

Part 2

Period 1: 2 mg TC-5214 bid from the morning of Day 0 through the morning of Day 7 (15 doses over 7.5 days), 1 additional dose of 2 mg TC-5214 approximately 4 hours after the 2 mg morning dose on Day 7; followed by 4 mg TC-5214 bid from the evening of Day 7 through the morning of Day 14 (14 doses over 7 days) and in

Period 2: placebo bid from the afternoon of Day 14 (2 doses) through the morning of Day 28 with the exception of Day 21. On Day 21, 3 placebo doses were to be administered approximately 4 and 8 hours apart, or

Placebo bid in Period 1; from the morning of Day 0 through the morning of Day 14 with the exception of Day 7 which included 3 placebo doses administered approximately 4 and 8 hours apart) and in

Period 2: 2 mg TC-5214 bid from the afternoon of Day 14 through the morning of Day 21 [15 doses over 7.5 days]), and 1 additional dose of 2 mg TC-5214 approximately 4 hours after the 2 mg morning dose on Day 21; followed by 4 mg TC-5214 oral tablets bid from the evening of Day 21 through the morning of Day 28 [14 doses over 7 days]).

Duration of treatment

Period 1: bid administrations from Day 0 to the morning of Day 14

Period 2: bid administrations from the afternoon of Day 14 to the morning of Day 28

Statistical methods

The primary analysis in Part 1 compared the changes in sitting blood pressure from baseline to the 2 hour measurement, between TC-5214 and placebo using a linear mixed model to estimate the effect of TC-5214 on blood pressure in hypertensive patients when administered alone. Similarly, the primary analysis in Part 2 compared the changes in sitting blood pressure from baseline to the 2 hour measurement, to estimate the effect of TC-5214 on blood pressure in hypertensive patients when administered in combination with stable anti-hypertensive treatment. The secondary pharmacodynamic (PD) endpoints (sitting vital signs at 4 hours, plus supine and standing vital signs at all time points) were analysed using the same method.

Adverse events (AEs) were summarised by Preferred Term and System Organ Class using the Medical Dictionary for Regulatory Activities by treatment and anti-hypertensive drug class and across all treatments/drug classes. Furthermore, listings of SAEs and AEs that led to withdrawal were made and the number of patients who had any AEs, SAEs, and AEs that led to withdrawal were summarised. Tabulations and listings of data for vital signs and clinical laboratory tests were presented by treatment and anti-hypertensive drug class. Electrocardiogram (ECG) readings, physical examination findings, and Columbia-Suicide Severity Rating Scale (C-SSRS) results were presented in the data listings.

Plasma concentrations were summarised using descriptive statistics and figures over time, part, treatment, and anti-hypertensive drug class.

Subject population

A total of 79 patients were randomised, 20 patients (25.3%) did not complete the study due to AEs, withdrawal criteria met, non-compliance to the Clinical Study Protocol, unapproved concomitant medication, lost to follow-up, sponsor decision, withdrawal of consent, and other reasons.

The age of the patients ranged from 25 to 65 years (mean 52 years), the minimum weight was 57.0 kg, and the BMI ranged from 21 to 35 kg/m^2 (mean 29 kg/m^2), all in accordance with the inclusion criteria. None of the differences between the groups in the demographics and baseline characteristics or the use of concomitant medication had a potential effect on the outcome of the study or the interpretation of the results.

Summary of pharmacokinetic results

Similar mean TC-5214 steady-state plasma concentrations were observed for each anti-hypertensive treatment groups at each respective dose level (2 mg and 4 mg TC-5214). Mean TC-5214 plasma concentrations appeared to increase in proportion to dose with the increase in dose from TC-5214 2 mg bid to TC-5214 4 mg bid.

Summary of pharmacodynamic results

The primary PD analysis variable was the sitting 2 hour postdose SBP measurement.

Table S3 Primary statistical comparison of change from baseline in sitting systolic blood pressure (mmHg) 2 hours postdose (PD analysis set)

							Comparison to placebo		
Part/ Group	Day/ Dose Level	Predose Baseline SBP mmHg (SD) [n]	TRT [a]	n	TRT SBP mmHg (SD)	LS mean CFB	Diff	90% CI	P-value
1/1	7 / 4 mg	134 (13)	Active	15	124 (10)	-8.0	-10.3	(-15.9, -4.6)	0.0020
		[20]	Placebo	14	134 (11)	2.3			
	14 / 4 mg		Active	11	124 (11)	-5.1	-3.2	(-9.8, 3.4)	0.3203
			Placebo	13	129 (13)	-1.9			
2/2	7 / 2 mg	132 (10)	Active	9	123 (7)	-11.1	-9.4	(-18.6, -0.3)	0.0459
		[12]	Placebo	9	133 (10)	-1.7			
	14 / 4 mg		Active	8	124 (6)	-11.9	-10.3	(-16.5, -4.1)	0.0039
			Placebo	8	135(11)	-1.6			
2/3	7 / 2 mg	131 (8)	Active	19	116 (15)	-14.9	-8.3	(-15.0, -1.7)	0.0159
		[22]	Placebo	21	125 (9)	-6.5			
	14 / 4 mg		Active	18	115 (14)	-16.5	-12.7	(-16.8, -8.5)	<0.0001
			Placebo	19	127 (11)	-3.9			
2/4	7 / 2 mg	133 (12)	Active	19	123 (13)	-9.9	-3.9	(-8.5, 0.8)	0.0964
		[20]	Placebo	19	126 (13)	-6.1			
	14 / 4 mg		Active	18	122 (12)	-11.5	-3.1	(-7.0, 0.9)	0.1202
			Placebo	19	124 (13)	-8.4			

CI: confidence interval; Diff: difference; LS: least squares; n: Number of patients; SBP systolic blood pressure; TRT treatment.

[a] Part 1 / Group 1: TC-5214 versus placebo
Part 2 / Group 2: TC-5214 + calcium channel antagonist versus Placebo + calcium channel antagonist
Part 2 / Group 3: TC-5214 + ACE inhibitor versus Placebo + ACE inhibitor
Part 2 / Group 4: TC-5214 + beta-blocker versus Placebo + beta-blocker
During Part 1, the active treatment consisted of TC-5214 4 mg bid throughout the entire period. During Part 2, for the active treatment, subjects received TC-5214 2 mg bid prior to the Day 7 assessment and TC-5214 4 mg bid prior to the Day 14 assessments.

For Part 1, a statistically significant reduction in sitting SBP of -10.3 mmHg was noted for TC-5214 4 mg administered bid compared to placebo on Study Day 7, 2 hours postdose. Other reductions noted were not statistically significant ranging from -3.2 mmHg to -7.0 mmHg compared to placebo.

The results from Part 2 suggest TC-5214 can lower seated SBP to similar extent over and above the baseline pressure reductions elicited by stable background anti-hypertensive therapy alone. For the seated assessment this was on the order of approximately 10 mmHg when combined with a calcium channel antagonist or ACE inhibitor by 2 hours postdose, and up to approximately 5 mmHg when combined with a beta-blocker at around 4 hours postdose.

In general the trend of lower blood pressures noted with TC-5214 treatment was more marked for standing assessments and more modest for supine assessments.

Table S4 Primary statistical comparison of change from baseline in sitting diastolic blood pressure (mmHg) 2 hours postdose (PD analysis set)

							Comparison to placebo		
Part/ Group	**Day/ Dose Level**	**Predose Baseline DBP mmHg (SD) [n]**	**TRT [a]**	**n**	**TRT DBP mmHg (SD)**	**LS mean CFB**	**Diff**	**90% CI**	**P-value**
1/1	7 / 4 mg	87 (9)	Active	15	82 (9)	-6.3	-2.8	(-6.6, 1.1)	0.1458
		[20]	Placebo	14	85 (9)	-3.5			
	14 / 4 mg		Active	11	79 (9)	-5.7	-1.8	(-9.0, 5.4)	0.5977
			Placebo	13	83 (10)	-3.9			
2/2	7 / 2 mg	86 (8)	Active	9	80 (6)	-8.2	-3.0	(-7.1, 1.1)	0.1259
		[12]	Placebo	9	83 (6)	-5.2			
	14 / 4 mg		Active	8	83 (6)	-5.8	-1.9	(-5.7, 1.9)	0.2634
			Placebo	8	85 (7)	-3.9			
2/3	7 / 2 mg	87 (8)	Active	19	74 (11)	-13.2	-4.9	(10.2, 0.3)	0.0636
		[22]	Placebo	21	79 (8)	-8.2			
	14 / 4 mg		Active	18	75 (11)	-12.0	-4.0	(-9.1, 1.0)	0.1101
			Placebo	19	79 (9)	-8.0			
2/4	7 / 2 mg	87 (11)	Active	19	80 (10)	-6.8	-2.3	(-5.6, 1.0)	0.1647
		[20]	Placebo	19	82 (10)	-4.5			
	14 / 4 mg		Active	18	79 (9)	-7.7	-1.6	(-3.8, 0.6)	0.1342
			Placebo	19	80 (10)	-6.0			

CI: confidence interval; DBP diastolic blood pressure; Diff: difference; LS: least squares; n: Number of patients; TRT treatment.
[a] Part 1 / Group 1: TC-5214 versus placebo
Part 2 / Group 2: TC-5214 + calcium channel antagonist versus Placebo + calcium channel antagonist

Part 2 / Group 3: TC-5214 + ACE inhibitor versus Placebo + ACE inhibitor
Part 2 / Group 4: TC-5214 + beta-blocker versus Placebo + beta-blocker
During Part 1, the active treatment consisted of TC-5214 4 mg bid throughout the entire period. During Part 2, for the active treatment, subjects received TC-5214 2 mg bid prior to the Day 7 assessment and TC-5214 4 mg bid prior to the Day 14 assessments.

For the individual treatment groups comparisons, for the sitting and supine assessments of DBP, there were no statistically significant postdose reductions in DBP, at either TC-5214 dose level or timepoint.

No clear dose related trends in the blood pressure effect were evident.

TC-5214 4 mg bid administered alone had no effect on pulse rate. The combined analysis of all 3 antihypertensive groups in Part 2 suggests TC-5214 4 mg bid coadministered with an antihypertensive has the potential to increase pulse rate approximately 5 beats per minute compared to a background antihypertensive alone. Individual group assessments indicated largely consistent statistically significant differences in pulse rate attributable to the combination with a beta-blocker (Group 4).

Variability in orthostatic vital signs was high. Notably when TC-5214 was combined with an ACE inhibitor (Group 3), the largest mean orthostatic decreases in SBP were observed, at the 4 mg dose level (Day 14), at 2 hours postdose (-6 mmHg [SD=10 mmHg] orthostatic decrease; -10 mmHg [12] orthostatic CFB).

Summary of safety results

No deaths or SAEs were reported. Investigational product administration was discontinued for 5 patients (6.3%) due to AEs (3 patients on TC-5214 and 2 patients on placebo). The AEs leading to discontinuation of the investigational product were: moderate gastroenteritis (not related, placebo) for Patient E0002006; mild pruritus (related, TC-5214) for Patient E0003034; moderate constipation (related, TC-5214) and moderate dyspepsia (related, TC-5214) for Patient E0006020; moderate diarrhoea (not related, TC-5214) and moderate diverticulitis (related, TC-5214) for Patient E0006023; and moderate tooth abscess (not related, placebo) for Patient E0004005.

The highest proportion of patients with at least 1 AE while on TC-5214 was reported in Group 2 (81.8%) and the lowest in Group 1 (23.5%).

The most frequently reported AE was constipation (20 patients [25.3%] overall). At least 1 event was reported for 19 patients (26.4%) on TC-5214 and 1 patient (1.4%) on placebo, with the highest proportion of patients in Group 3 (ACE inhibitor) (43.5%). All of the constipation events were considered related to the investigational product by the Investigator.

At least 1 AE considered to be related to the investigational product were reported for 3 patients (17.6%) on TC-5214 and 2 patients (11.8%) on placebo in Part 1 and for 27 patients

(49.1%) on TC-5214 and 7 patients (12.3%) on placebo in Part 2. No severe AEs were reported.

Two AEs were ongoing at the end of the study: mild upper respiratory tract infection (not related) in Group 4 on placebo and moderate diverticulitis (related) in Group 3 on TC-5214.

No relevant trends in mean and median laboratory measurements over time and between treatments were noted. Variation in mean and median vital signs measurements for safety monitoring over time and between groups and treatments were noted. No abnormal, clinically significant (as judged by the Investigator) ECG findings were reported. No relevant abnormal physical examination findings were reported and no suicidal behaviour or attempts were reported, as assessed by C-SSRS.