AstraZeneca

Clinical Study Report Synopsis

Drug Substance	TC-5214
Study Code	D4130C00009
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A Randomised, Double-blind, Placebo-controlled, Phase I Study in 2 Parts: Part A to Assess a Safe and Tolerable Supratherapeutic Dose of TC-5214 after Single Ascending Oral Doses in Healthy Male Subjects, Followed by Part B: a 4-period Double-dummy Crossover Study to Investigate the Effect of 2 Single Doses (Therapeutic and Supratherapeutic) of TC-5214 on the QT/QTc Interval, Compared to Placebo, using Moxifloxacin (Avelox®) as a Positive Control, in Healthy Male Subjects

Study dates: First subject enrolled: 7 September 2011
Last subject last visit: 2 April 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**
Part A Primary	Safety	To assess the safety and tolerability of TC-5214 following administration of single ascending doses by assessment of adverse events, vital signs, physical examination, laboratory parameters, ECGs, ECG real-time display, and suicidal ideation as assessed by C-SSRS	Adverse events
			Laboratory variables
			Vital signs: blood pressure, pulse rate, body temperature
			ECG and ECG real-time display
			Physical examination
			C-SSRS
		To establish a single tolerable supratherapeutic dose of TC-5214 that may be utilised for investigation in Part B (thorough QT/QTc) of this study	ECG and ECG real-time display
Part B Primary	Pharma-codynamic	To assess the maximum of the mean change in time-matched QTc intervals after administration of a supratherapeutic and assumed therapeutic dose of TC-5214 compared with placebo	12-lead Holter ECG/QTcI
Part A Secondary	Pharmaco-kinetic	To evaluate and characterise the PK of TC-5214 in plasma and urine in healthy volunteers following SAD administration	C_{max}, t_{max}, $t_{1/2\lambda z}$, λ_z, $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}24)}$, AUC, CL/F, V_z/F, $Ae_{(0\text{-}t)}$, f_e, and CL_R
Part B Secondary	Pharma-codynamic	To assess the maximums of the mean change in time-matched QT, QTcB (QT interval corrected for heart rate according to Bazett), and QTc (either QTcF or QTcI) intervals after administration of TC-5214 supratherapeutic and assumed therapeutic doses compared with placebo	Continuous digital ECG data on the parameters RR, PR, QRS, and QT intervals and QTcF, QTcB, and QTcI

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
		To assure assay sensitivity by assessing the effect of moxifloxacin 400 mg on QTcF compared to placebo	Continuous digital ECG data on the parameter QTcI
		To assess the effect of TC-5214 on the following ECG parameters: PR, RR, and QRS intervals	Continuous digital ECG data on the parameters RR, PR, and QRS
		To assess the PK of TC-5214 in plasma in healthy male volunteers	C_{max}; t_{max}; $AUC_{(0-24)}$
		To explore the relationship between TC-5214 plasma concentrations and the QT interval during the first 24 hours after a single oral dose of TC-5214 in healthy volunteers	Continuous digital ECG data on the parameters QT intervals and QTcF, QTcB, and QTcI
		To examine the safety and tolerability of TC-5214 by assessment of adverse events, vital signs, physical examinations, laboratory parameters, ECGs, and suicidality as assessed by C-SSRS	Adverse events, laboratory variables, vital signs, physical examination, ECG, and C-SSRS
Part B Exploratory[a]	Pharma-codynamic	To collect 12-lead Holter data for the exploratory evaluation of uncorrected QT intervals, estimated through Holter-bin method.	-

[a] If performed, this will be reported separately from this Clinical Study Report.

λ_z: terminal rate constant; $Ae_{(0-t)}$: cumulative amount of drug excreted unchanged into the urine from zero to time t hours; AUC: area under the plasma concentration-time curve from zero to infinity; $AUC_{(0-24)}$: area under the plasma concentration-time curve from zero to 24 hours postdose; $AUC_{(0-t)}$: area under the plasma concentration-time curve from zero to the time of the last quantifiable concentration; C-SSRS: Columbia-Suicide Severity Rating Scale; CL/F: apparent plasma clearance; CL_R: renal clearance; C_{max}: maximum plasma concentration; ECG: electrocardiogram; f_e: fraction of dose excreted as unchanged drug into urine; PK: pharmacokinetic(s); QTcB: QT interval corrected for heart rate according to Bazett; QTcF: QT interval corrected for heart rate according to Fridericia; QTcI: QT interval corrected for individual heart rate; SAD: single ascending dose; $t_{1/2\lambda z}$: terminal half-life; t_{max}: time to maximum plasma concentration; V_z/F: apparent volume of distribution.

Study design

This Phase I study was conducted in 2 parts at 2 study centres. This study was terminated during Part B, after completion of Part A, and all healthy volunteers still in the study were withdrawn.

Part A

Part A was a randomised, double-blind, placebo-controlled single ascending dose (SAD) study in healthy male volunteers.

A dose of 20 mg was administered to the first sentinel group of 4 healthy volunteers (20 mg TC-5214 to 3 healthy volunteers and placebo to 1 healthy volunteer). While supine, the investigational product was well tolerated, but when the healthy volunteers were asked to stand for scheduled assessments at 7 hours postdose, they experienced hypotension, tachycardia, and dizziness. Though the stopping criteria were not met, the SRC recommended that a new cohort of 12 healthy volunteers be enrolled and the starting dose decreased to 16 mg.

Subsequently, in this SAD study, the lowest dose of TC-5214 was 16 mg and dose escalation continued until 28 mg. After each cohort (16 mg, 20 mg, 24 mg, and 28 mg), a Safety Review Committee (SRC) evaluated the safety, tolerability, and the pharmacokinetics (PK) of TC-5214 and decided on the next dose. A single cohort of 12 healthy male volunteers were to be randomised to receive 3 of the 4 TC-5214 doses (planned: 20 mg, 24 mg, 28 mg, and 32 mg; actual: 16 mg, 20 mg, 24 mg, and 28 mg) and 1 dose of placebo on 4 separate occasions.

Part B

Part B was a double-blind, double-dummy, randomised, placebo-controlled, 4-way crossover thorough QT/QTc study to evaluate single oral doses of TC-5214 (supratherapeutic and therapeutic doses) compared with placebo and a single oral dose of moxifloxacin 400 mg as a positive control in healthy male volunteers.

All healthy volunteers were to receive each of the following 4 treatments in a randomized sequence in 4 treatment periods: Treatment A: 28 mg TC-5214 (and moxifloxacin placebo); Treatment B: 8 mg TC-5214 (and moxifloxacin placebo); Treatment C: 400 mg moxifloxacin (and TC-5214 placebo); and Treatment D: placebo (TC-5214 placebo and moxifloxacin placebo). Treatment D was also administered on Day -1 of each treatment period. Each dose was separated by a wash-out period of at least 7 days.

Target subject population and sample size

Healthy male volunteers aged 18 to 50 years (inclusive) with a body mass index of 19 to 30 kg/m^2 who provided written informed consent.

Planned: 12 healthy volunteers in Part A and 52 healthy volunteers in Part B

Randomised: 16 healthy volunteers in Part A and 48 healthy volunteers in Part B

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

Table S2 Details of the investigational products

Investigational product	Dosage form and strength	Manufacturer	Batch number
TC-5214	4 mg oral tablets	Patheon	11-001437AZ 12-000515AZ
TC-5214 placebo	Tablets to match TC-5214	Patheon	11-001339AZ 12-000514AZ
Moxifloxacin	400 mg film-coated tablets, encapsulated in a Swedish orange DB AAEL capsule	Bayer; encapsulated by AstraZeneca	11-004515AZ 10-004515AZ
Moxifloxacin placebo	Swedish orange DB AAEL capsule containing microcrystalline cellulose and magnesium stearate	AstraZeneca	11-004632AZ 10-004623AZ

Duration of treatment

Four single doses of different treatments in 4 treatment periods.

Statistical methods

Pharmacokinetic parameters were determined for Part A and Part B separately. Dose proportionality was assessed for Part A using a random-coefficients linear mixed model for log-transformed parameters (AUC and C_{max}) on log dose level. For Part B TC-5214 pharmacokinetic parameters were determined and compared to the exposure obtained at the equivalent doses for Part A.

For Part B, analyses of change-from-baseline QTc metrics were carried out using a repeated measures linear mixed model with fixed effects for period, treatment, time, interaction of treatment by time, interaction of period by time and baseline as a continuous covariate. Subject was treated as a random effect. The correlation between repeated measurements on a subject within a treatment period will be accounted for with a first-order autoregressive covariance structure. Each subject available for analysis contributed up to four sets of QT/QTc measurements, one for each treatment period. Least squares (LS) means and two-sided 95% confidence intervals (CIs), based on the treatment-by-time interaction term, were reported at each of the post-dose time points of electrocardiogram (ECG) recordings.

Three different contrasts (TC-5214 high dose versus placebo; TC-5214 low dose versus placebo; moxifloxacin versus placebo) were estimated from the same model at each of the post-dose time points. Graphs of the LS mean differences relative to placebo with 90% CI were presented for each active treatment separately.

The primary analysis tested the treatment effect of TC-5214 on the primary QTc interval with the upper bounds of the 2-sided 90% CI evaluated against the 10 ms threshold under an inter-section-union test for each dose level. The secondary analysis tested the effects of TC-5214 on the secondary ECG intervals in a similar fashion.

Assay sensitivity was tested by evaluating the primary QTc interval with a linear contrast comparing moxifloxacin versus placebo for the mean QTc over the 1 to 4-hour post-dose interval estimated and a 2-sided 90% confidence intervals presented. This analysis was repeated for secondary QTc and other ECG intervals.

A model based analysis was conducted to support the primary analysis, which allowed the statistical model to correct the QT intervals for on-treatment RR intervals.

The analyses of safety, tolerability, pharmacokinetics and pharmacodynamics were summarised descriptively including tables, listings and graphs as appropriate.

Subject population

All healthy volunteers who received any investigational product in this study were eligible to be enrolled and randomised.

Part A

In total, 16 healthy male volunteers were randomised in Part A. Four healthy volunteers (25.0%) were withdrawn upon recommendation from the SRC. One healthy volunteer (6.3%) was withdrawn due to physician decision (following AEs of abdominal pain, nausea, vomiting, and malaise) and 1 healthy volunteer (6.3%) was withdrawn due to an AE (dizziness). A total of 10 healthy volunteers (62.5%) received all the investigational product administrations and completed Part A.

Part B

In total, 48 healthy male volunteers were randomised in Part B. Two healthy volunteers (4.2%) withdrew consent, 1 healthy volunteer (2.1%) was withdrawn due to physician decision, 1 healthy volunteer (2.1%) was withdrawn due to an AE (atrial fibrillation), and 36 healthy volunteers (75.0%) were withdrawn due to sponsor decision. A total of 8 healthy volunteers (16.7%) received all the investigational product administrations and completed Part B.

Summary of pharmacokinetic results

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

Table S3 Summary of Key TC-5214 Plasma Parameters - Part A

Parameter (Units)	Geometric Mean CV% 16 mg Dose (N=9)	20 mg Dose (N=12)	24 mg Dose (N=9)	28 mg Dose (N=7)
AUC (ng·h/mL)	1510	1700	2250	2560
	16.9	21.3	23.5	21.3
C_{max} (ng/mL)	67.4	80.5	93.6	113
	16.4	18.1	14.7	12.3
t1/2 λz (h)	12.0	11.2	11.7	12.3
	22.4	20.3	19.3	17.9

The median t_{max} ranged from 1.50 to 2.52 across dose levels. Exposure increased with dose, appeared proportional graphically and established proportional statistically for AUC with a slope estimate (90% CI) of 1.05 (0.883, 1.22).

Geometric mean CL_R and $fe_{(0-72)}$ urine parameters were similar across treatments, ranging from 7.13 L/h to 7.73 L/h and 64.5 to 69.0%, respectively.

A summary of key TC-5214 pharmacokinetic parameters for Part B is presented in Table S4.

Table S4 Summary of Key TC-5214 Plasma Parameters – Part B

Parameter		8 mg (N=25)	28 mg (N=27)
$AUC_{(0-24)}$ (ng•h/mL)	n	25	27
	Geometric mean	426	1700
	CV%	17.6	13.7
C_{max} (ng/mL)	n	25	25
	Geometric mean	33.5	118
	CV%	17.4	15.9
t_{max} (h)	n	25	25
	Median	1.53	1.52
	(Min, Max)	(1.02, 7.02)	(1.00, 7.03)

At the planned supratherapeutic dose of 28 mg the $AUC_{(0-24)}$ estimate was similar to the estimate of 1770 ng*h/mL obtained after dose escalation to 28 mg TC-5214 in Part A. Likewise the C_{max} estimate was similar to the estimate of 113 ng/mL obtained after dose escalation to 28 mg TC-5214 in Part A.

Summary of pharmacodynamic results

In the primary comparison of QTcI of TC-5214 at 8 mg and 28 mg versus placebo, the upper bound of the 2-sided 90% CI did not exceed 10 ms at any time point postdose. The maximum placebo-subtracted mean change from baseline in QTcI (ΔΔQTcI) at 8 mg and 28 mg were -1.4 ms and 1.4 ms with upper bounds of the 2-sided 90% CI of 1.6 ms and 4.4 ms, respectively.

Both QTcI and QTcF were correlated with RR. Neither correction factor nor model based QTc adequately corrected for RR.

The lower limit of the 2-sided 90% CI for the difference of moxifloxacin versus placebo in ΔQTcI over the interval of 1 to 4 hours postdose was greater than 5 ms (lower limit of 7.2 ms).

Changes in QTcI from baseline to the observed maximum at any time point over the 24-hour period after dosing exceeded 30 ms for 1 healthy volunteer receiving 8 mg TC-5214 (41 ms at 2.5 hours) and 1 healthy volunteer who received moxifloxacin 400 mg (30 ms at 3 hours) (Appendix 12.2.6.2 and Table 11.3.9.4.2). There were no volunteers with absolute QTcI values above 450 ms.

There were no volunteers with changes in QTcF from baseline to the observed maximum at any time point over the 24-hour period after dosing exceeded 30 ms, and none with absolute QTcF values above 450 ms.

Summary of safety results

The highest incidence of healthy volunteers with at least 1 adverse event (AE) in Part A was reported after the 16 mg dose. At least 1 AE was reported for 8 healthy volunteers (88.9%) after 16 mg, 10 healthy volunteers (83.3%) after 20 mg, 5 healthy volunteers (55.6%) after 24 mg, 2 healthy volunteers (28.6%) after 28 mg, and 2 healthy volunteers (18.2%) after placebo. The most frequently reported AE was dizziness, most of the dizziness events were reported on the same day as the investigational product administration and all of the events were considered to be related to the investigational product administration. Two healthy volunteers were withdrawn from the study due to AEs, both after 20 mg TC-5214. One healthy volunteer was withdrawn due to moderate dizziness, considered related to the investigational product and one healthy volunteer due to moderate abdominal pain, nausea, vomiting, and malaise, all considered related to the investigational product.

The highest incidence of healthy volunteers with at least 1 AE in Part B was reported after 28 mg TC-5214. At least 1 AE was reported for 17 healthy volunteers (63.0%) after 28 mg TC-5214, for 9 healthy volunteers (36.0%) after 8 mg TC-5214, for 11 healthy volunteers (39.3%) after moxifloxacin, and for 5 healthy volunteers (19.2%) after placebo. The most

frequently reported AE was abdominal pain, most of the abdominal pain events were reported within 2 days of investigational product administration and of the abdominal pain events were considered to be related to the investigational product administration. One healthy volunteer was withdrawn due to a serious adverse event (SAE) of moderate atrial fibrillation, considered not related to the investigational product.

No clinically relevant laboratory measurements were reported in either Part A or Part B. Decrease in mean and median supine systolic blood pressure (SBP) was reported and no clinically relevant vital signs measurements were reported in Part B. A clinically significant abnormal ECG was reported as an SAE (considered unrelated to the investigational product) of atrial fibrillation for 1 healthy volunteer in Part B. No change from normal at baseline to abnormal at postbaseline in physical examination findings and no suicidal ideation, behaviour, or attempts were reported in either Part A or Part B.