AstraZeneca

Clinical Study Report Synopsis

Drug Substance	ZD4054
Study Code	D4320C00017
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A Phase I, Double-blind, Double-dummy, Placebo-controlled, Randomised, Four-period Crossover Study to Assess the Effects of Single Oral Doses of ZD4054 (10 mg and 30 mg) on QTc Interval Compared to Placebo, Using AVELOX (Moxifloxacin) as a Positive Control, in Healthy Volunteers Aged 18 to 45 Years

Study dates: First healthy volunteer enrolled: 30 June 2008
Last healthy volunteer completed: 19 November 2008

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)

The study was conducted at a single centre in the United Kingdom.

Publications

None at the time of writing this report.

Objectives

Primary objective

The primary objective of this study was to assess the maximum of the mean changes in time-matched QT interval corrected for heart rate using a study-specific correction factor (QTcX) after ZD4054 administration (10 mg and 30 mg) compared to placebo.

Secondary objectives

The secondary objectives of the study were:

1. To assess the maximum of the mean changes in time-matched QT interval, QT interval corrected for heart rate using the Bazett formula (QTcB), QT interval corrected for heart rate using the Fridericia formula (QTcF) and QT interval corrected for heart rate using a subject-specific correction factor (QTcI) after ZD4054 administration (10 mg and 30 mg) compared to placebo

2. To assess the maximum of the mean changes in time-matched QTcX, QT, QTcB, QTcF and QTcI intervals after moxifloxacin administration compared to placebo

3. To examine the pharmacokinetics (PK) of ZD4054 by assessment of maximum plasma concentration (C_{max}), time to reach maximum concentration (t_{max}), area under plasma concentration-time curve from zero to time of last measurable concentration (AUC_{0-t}), area under plasma concentration-time curve from zero to infinity (AUC), terminal rate constant (λ_z), terminal half life ($t_{1/2}$), apparent plasma clearance (CL/F), apparent volume of distribution at steady state (Vss/F) and mean residence time (MRT)

4. To explore the relationship between plasma concentration and the cardiac ventricular repolarisation effect on the heart after a single oral dose of ZD4054 by assessments of plasma concentrations of ZD4054 and digital electrocardiograms

5. To further assess the safety and tolerability of ZD4054 by assessment of adverse events (AEs), laboratory variables and vital signs.

Exploratory objective

The exploratory objective of this study was to collect an optional pharmacogenetic sample from consenting healthy volunteers for exploratory investigation to determine whether

variability in PK or safety parameters could be explained by differences in the healthy volunteer's genotype.

Study design

The study consisted of an open-label tolerability assessment, where healthy volunteers received a single dose of ZD4054 10 mg, followed by a 4-period crossover section, where healthy volunteers were randomly assigned to receive 1 of 4 treatment sequences (1:1:1:1) in a double blind, double-dummy, placebo-controlled fashion. Each treatment sequence comprised 4 treatments ie, ZD4054 30 mg, ZD4054 10 mg, moxifloxacin 400 mg and placebo.

Target healthy volunteer population and sample size

Male healthy volunteers aged between 18 and 45 years, with a body mass index between 18 and 28 kg/m^2 were eligible for enrolment in this study. It was planned that approximately 50 healthy volunteers would enter the tolerability assessment section of the study and receive a single dose of ZD4054 10 mg; 40 of the healthy volunteers who tolerated ZD4054 10 mg were then to be randomly assigned to receive 1 of 4 treatment sequences (1:1:1:1) during the 4-period crossover section of the study. For the primary comparison (the test of non-inferiority of ZD4054 compared with placebo), a 1-sided 0.05 level paired t-test with 90% power required 36 evaluable healthy volunteers.

In total, 52 healthy volunteers were assessed for tolerability, and of the 43 healthy volunteers who tolerated ZD4054 10 mg and were eligible, 41 healthy volunteers received randomised treatment.

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

ZD4054 (10 mg and matching placebo tablets) was manufactured and supplied by AstraZeneca. Moxifloxacin (400 mg tablets) was commercially available; AstraZeneca encapsulated the 400 mg tablets and manufactured matching placebo capsules. The batch numbers were: 51224C07 for ZD4054 10 mg, 51255J07 for ZD4054 placebo, 07-010709AZ for moxifloxacin 400 mg and 07-010710AZ for moxifloxacin placebo. In order to improve tolerability of ZD4054 in this study, healthy volunteers received prophylactic paracetamol (500 mg, manufactured by Numark) in all treatment periods.

On Day 1 of each treatment period, healthy volunteers took investigational product orally under fasted conditions with 200 mL purified water (fasting from 10 hours before until 4 hours after administration, and, other than the 200 mL mentioned, no water from 1 hour before until 2 hours after administration). The tablets were swallowed whole and not divided, chewed or crushed.

Duration of treatment

For all study periods (tolerability assessment period and each of the 4 periods during the crossover section of the study), healthy volunteers received a single dose of the protocolled

study medication on Day 1 of the period. A washout period of at least 7 days was scheduled between each dose of study medication.

Criteria for evaluation - pharmacodynamics and pharmacokinetics (main variables)

The pharmacodynamic (PD) variables were:

- QTcX intervals for ZD4054 30 and 10 mg compared with placebo (primary variable)
- QT, QTcB, QTcF and QTcI intervals for ZD4054 30 and 10 mg compared with placebo
- QTcX, QT, QTcB, QTcF and QTcI intervals for moxifloxacin 400 mg compared with placebo

The PK variables were:

- C_{max}, t_{max}, AUC_{0-t}, AUC, λ_z, $t_{1/2}$, CL/F, Vss/F and MRT for ZD4054

The PK/PD variables were:

- Analysis of the RR, QT, QTcX, QTcF, QTcI and QTcB intervals matched to PK sampling times for ZD4054 to allow determination of any PK/PD effect.

Analysis of the pharmacogenetic objective will be reported separately.

Criteria for evaluation - safety (main variables)

The safety variables were:

- AEs, laboratory variables, electrocardiograms and vital signs.

Statistical methods

Statistical analyses were done using a repeated measures analysis of covariance model with fixed effects: baseline QT/QTc, period, treatment, time, interaction between period and time, and interaction between treatment and time. Subject was a random effect. Least squares mean differences between treatments and 2-sided 90% confidence intervals (CIs), based on the treatment-by-time interaction term, were reported at each sampling time.

Subject population

Fifty-two healthy volunteers were enrolled in the study (excluding screen failures) and took part in the tolerability assessment; of whom, 2 healthy volunteers were withdrawn due to poor tolerance of the ZD4054 10 mg tolerability dose (both developed study-specific discontinuation criteria: common terminology criteria [CTC] Grade 2 headache) and 9 healthy volunteers tolerated ZD4054 10 mg but were not randomised to the crossover section of the

study due to safety reasons, incorrect enrolment, withdrawal of consent, or because they were surplus to requirements (4, 2, 1 and 2 healthy volunteers, respectively).

Thus, 41 healthy volunteers were randomised to receive 1 of the 4 treatment sequences, of whom 37 healthy volunteers (90.2%) completed the study. Four healthy volunteers terminated the study prematurely: 1 healthy volunteer received disallowed concomitant medication (piriton and hydrocortisone cream) and 3 healthy volunteers terminated the study because of an AE (erythema of eyelid and lip swelling; transaminases increased; ventricular extrasystoles).

All 52 healthy volunteers were included in the safety analysis set and all 41 randomised healthy volunteers were included in the randomised safety analysis set. Four healthy volunteers (1 in each treatment sequence) were excluded from the PD analysis set; 2 of the 4 healthy volunteers were also excluded from the PK analysis set (1 healthy volunteer from each of the CDAB and DBCA treatment sequences). Thus a total of 37 healthy volunteers were included in the PK/PD analysis set. Healthy volunteers were excluded from these analysis sets because they did not satisfy the criteria of the PD or PK analysis sets; this decision was made prior to unblinding of the data.

The mean age of the study population was 32.5 years; all healthy volunteers were male and the majority were White (90.2%). Overall, the treatment sequences were well balanced with regards to key baseline and demographic characteristics.

Summary of pharmacodynamic results

The maximum placebo-corrected, baseline-adjusted, mean effect of ZD4054 10 mg and 30 mg for QTcX was 4.4 ms at 4 hours (90% CI upper bound: 7.1 ms) and 5.9 ms at 24 hours (90% CI upper bound: 8.6 ms), respectively. The results from the analysis of the effect of ZD4054 10 mg and 30 mg for QTcX met the International Conference on Harmonisation (ICH) E14 criteria for a negative thorough QT study.

The maximum placebo-corrected, baseline-adjusted, mean effect of ZD4054 10 mg and 30 mg for:

- QT was -1.1 ms at 0.5 and 2 hours (upper 90% CI: 2.5 and 2.6 ms, respectively) and -1.0 ms at 2 hours (upper 90% CI: 2.7 ms), respectively.
- QTcB was 13.7 ms at 4 hours (upper 90% CI: 17.0 ms) and 19.5 ms at 24 hours (upper 90% CI: 22.8 ms), respectively.
- QTcF was 8.3 ms at 4 hours (upper 90% CI: 11.0 ms) and 11.5 ms at 24 hours (upper 90% CI: 14.2 ms), respectively.
- QTcI was 4.6 ms at 4 hours (upper 90% CI: 7.3 ms) and 5.6 ms at 4 and 24 hours (upper 90% CI: 8.4 ms), respectively.

The results from the analysis of the effect of ZD4054 10 mg and 30 mg on QTcB and QTcF did not meet the ICH E14 criteria for a negative thorough QT study.

The maximum placebo-corrected, baseline-adjusted, mean effect of moxifloxacin 400 mg for QTcX was 9.9 ms at 3 hours (lower 90% CI: 7.2 ms). Results for the analysis of QT, QTcB, QTcF and QTcI were consistent with those for QTcX. The average 1 to 4 hours effect of moxifloxacin on the placebo-corrected, baseline-adjusted QTcX was 7.8 ms (lower 90% CI: 5.8 ms). Because this lower bound value was >5 ms (pre-defined), assay sensitivity was demonstrated.

Assessment of mean RR interval versus time showed that, for placebo and moxifloxacin, the RR interval was relatively stable for the first 4 hours after dosing, whereas the RR interval was decreased (by 80 to 100 ms) by both the 10 mg and 30 mg doses of ZD4054.

Summary of pharmacokinetic results

Exposure to ZD4054 was demonstrated in all healthy volunteers after dosing at 10 and 30 mg. Overall exposure in terms of AUC was approximately proportional for the 2 doses. The shapes of the plasma concentration-time curves for ZD4054 were the same for both the 10 and 30 mg dose levels. The CL/F, Vss/F, $t_{1/2}$ and MRT were similar for the 2 dose levels.

Summary of pharmacokinetic/pharmacodynamic relationships

Plots of AUEC versus AUC and C_{max} for ZD4054 did not demonstrate any apparent relationships between exposure and QTcB, QTcF, QTcX or QTcI. Further assessment of the relationship between QTcX and QTcF with plasma concentrations of ZD4054 demonstrated that both QTcX and QTcF showed an increase with plasma concentration of ZD4054. For the mean C_{max} from a ZD4054 30 mg dose, the mean change in QTcX compared with placebo would be 3.3 ms (90% CI: 1.7 ms, 4.9 ms) and the mean change in QTcF compared with placebo would be 7.5 ms (90% CI: 5.9 ms, 9.1 ms).

Summary of safety results

During the tolerability assessment period, 14 healthy volunteers (26.9%) reported at least 1 AE and 9 healthy volunteers (17.3%) had an AE that the investigator considered to be causally related to investigational product; no serious adverse event (SAEs), AEs leading to discontinuation of investigational product or AEs of CTC Grade 3 or higher were reported during this period. The AEs reported were consistent with the known safety profile for ZD4054.

A higher percentage of healthy volunteers reported AEs while receiving ZD4054 30 mg (84.2%) compared with while they were receiving ZD4054 10 mg (57.9%); AEs were more commonly reported on ZD4054 than on moxifloxacin 400 mg (38.5%) or placebo (28.2%).

The most commonly reported AE for healthy volunteers while on ZD4054 was headache (73.7% and 42.1% on ZD4054 30 mg and 10 mg, respectively); nausea, dizziness and vomiting were also commonly reported on ZD4054 30 mg (23.7%, 10.5% and 7.9%

respectively), and application site rash and contusion were also commonly reported on ZD4054 10 mg (10.5% and 7.9%, respectively). Although reported at a lower frequency, headache was also 1 of the most commonly reported AEs for healthy volunteers on moxifloxacin 400 mg and placebo (10.3% and 5.1%, respectively), along with application site rash (12.8% and 5.1%, respectively). All AEs of application site rash were associated with study procedures.

Few AEs of CTC Grade 3 or higher were reported: 2 healthy volunteers had CTC Grade 3 headache on ZD4054 30 mg and 1 healthy volunteer had CTC Grade 3 myalgia on placebo.

There were no deaths, SAEs, or other significant adverse events in the study. In total, 2 healthy volunteers discontinued study treatment due to AEs: 1 healthy volunteer due to ventricular extrasystoles during his first randomised treatment period (placebo) and 1 healthy volunteer due to transaminases increased following his first randomised treatment period (ZD4054 10 mg). In addition, 1 healthy volunteer discontinued the study due to AEs (lip swelling, erythema of eyelid) during the moxifloxacin 400 mg treatment period, and 1 healthy volunteer discontinued the study due to an AE-related issue (received disallowed concomitant medication [piriton and hydrocortisone cream] for application site rash) during their second randomised treatment period (placebo).