AstraZeneca

Clinical Study Report Synopsis	
Drug Substance	AZD3480
Study Code	D3690C00004
Edition Number	1
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A Double-blind, Randomised, Multicentre, Placebo-controlled, 4-Ways Crossover Study to Investigate the Effect on the QT/QTc Interval of Repeated and Escalating Doses of AZD3480 during 6 Days, using Moxifloxacin as a Positive Control, in Healthy Male Volunteers (CYP2D6 Extensive and Poor Metabolisers) after an Open Single Oral Dose Phase for Phenotyping in Poor Metabolisers

Study dates:	First healthy volunteer enrolled: 14 January 2008 Last healthy volunteer completed: 14 August 2008
Phase of development:	Clinical pharmacology (I)

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

Study centres

This study was conducted at 3 centres in Sweden:
AstraZeneca Clinical Pharmacological Unit, AstraZeneca R&D, Lund.
AstraZeneca Clinical Pharmacological Unit, Sahlgrenska University Hospital, Gothenburg.
AstraZeneca Clinical Pharmacological Unit, Karolinska University Hospital, Huddinge.

Publications

None at the time of writing this report.

Objectives

Primary objectives

The primary objective of this study was to evaluate the effects on cardiac repolarisation of supratherapeutic doses of AZD3480, by analysing the mean changes in time-matched QTcX interval on the 6th day of repeated escalating dosing compared to placebo in healthy male volunteers, sub-grouped as Extensive Metabolisers (EMs) and Poor Metabolisers (PMs) according to CYP2D6 metabolic capacity, using moxifloxacin as positive control for assay sensitivity.

Secondary objectives

To evaluate the effects on cardiac repolarisation of assumed therapeutic dose of AZD3480, by analysing the mean changes in time-matched QTcX interval on the 6th day of repeated dosing compared to placebo in healthy male volunteers, sub grouped as EMs and PMs according to CYP2D6 metabolic capacity.

To evaluate the potential for AZD3480 to impact cardiac electric activity as assessed by the ECG variables PR, QRS and RR-intervals, as well as possible morphologic and rhythm deviations of clinical significance captured by the ECG recordings.

To evaluate plasma concentration-effect relationship regarding effect on the heart after repeated assumed therapeutic dose/concentration range and escalating supratherapeutic oral doses of AZD3480, by assessments of the plasma concentration of AZD3480, its metabolites comprising TC 1784 and QT/QTc interval and other ECG variables as applicable. If such comparison suggests a possible effect on the ECG variables, pharmacokinetic/pharmacodynamic (PK/PD) modelling will be used to further explore the relationship between AZD3480 and its metabolites and the effect on the heart.

To evaluate the safety and tolerability of AZD3480 by assessment of adverse events (AEs), ECG, blood pressure (BP), pulse rate, and laboratory variables.

To evaluate the pharmacokinetics (PK) of AZD3480 by assessment of AUCτ, (AUCss), Cmax (Cssmax), tmax (tssmax) and t½λz , its metabolite TC-1784 and possibly other metabolites.

Study design

This study consisted of two parts (Parts A and B) separated by at least 14 days wash out period.

Part A (phenotyping visit) was an open part of the study where PMs received a single 75mg dose of AZD3480 and blood was collected for PK analysis and phenotyping in order to facilitate prediction of individualised dosing in the subsequent Thorough QT (TQT) study (Part B).

Part B (TQT study), in both EMs and PMs, was a randomised, multicentre, double-blind, double-dummy, placebo controlled, 4-way crossover study (4 treatment sequences) using moxifloxacin as positive control. Each of the four treatment periods consisted of 6 days of drug/placebo administration followed by washout periods of at least 14 days length from the last dosing day (Day 6).

Target healthy volunteer population and sample size

Healthy male volunteers aged 20 to 60 years with a BMI of 19-30 kg/m^2, genotyped to EMs with two or more functional CYP2D6 alleles or PMs with no functional CYP2D6 allele.

Based on existing non-clinical and clinical study data (IB), the hypothesis tested in this study was that the supratherapeutic dose of AZD3480 did not have an effect of regulatory concern on QTcX. The residual standard deviations in the mixed effects models used for power calculations for PMs and EMs, respectively, was assumed to be 8.5 ms. Under the assumption of no difference in QTcX between supratherapeutic dose and placebo: if there were 28 complete subjects in each of the sub-analyses, then there is a 90% probability in each sub-analysis that all of the 9 confidence intervals are less than +10 ms. To counteract dropouts and occasional missing ECGs, a total of up to 40 randomised subjects were targeted for inclusion in each metabolic sub-group.

Investigational product and comparators: dosage, mode of administration and batch numbers

In Part A where only PMs participated, 35 PMs received a single 75 mg dose of AZD3480.

AZD3480 was administered as opaque white, hard gelatine capsules of the 4-hydroxybensoate salt (TC-1734-226), for which 1 mg corresponds to 0.629 mg free base. The capsule strengths were 10 mg (batch no. H 1828-02-01-01), 25 mg (batch no. H 1812-02-01-01) and 50 mg (batch no. H 1813-02-01-01) of the salt, containing 6.3 mg, 15.7 mg, 31.5 mg of free base, respectively.

In Part B, all healthy volunteers received oral study medication for 6 days; escalating AZD3480 supratherapeutic dose (PMs 50 to 200 mg and EMs 250 mg), AZD3480 assumed therapeutic dose (20 mg) and placebo (batch nos. H 1814-02-01-01 and H 1791-01-01-03). Moxifloxazin capsule 400 mg (batch no. H 1790-01-01-02) was administered as a single dose at day 6.

When plasma concentrations were evaluated in a blinded manner it became evident that PMs had exceeded the predefined exposure limits. A decision was taken to reduce individual escalating supratherapeutic dose regimen in 7 subjects. The planned and actual dose regimes are shown in Table 1.

Table 1 Escalating supratherapeutic dose regimens in PMs

Options		Study days						No. planned	No. treated
		1	2	3	4	5	6		
1	Dose (mg)	50	75	75	75	75	75 + moxifloxacin/ placebo	0	4
2		75	100	100	100	100	100 + moxifloxacin/ placebo	0	3
3		75	100	125	125	125	125 + moxifloxacin/ placebo	7	3
4		75	100	125	150	150	150+ moxifloxacin/ placebo	10	7
5		75	100	125	150	175	175+ moxifloxacin/ placebo	10	8
6		100	125	150	175	200	200 + moxifloxacin/ placebo	8	7

Duration of treatment

The study was a 4-way crossover study (4 treatment sequences) using moxifloxacin as positive control. Each of the four treatment periods consisted of 6 days of drug/placebo administration followed by washout periods of at least 14 days length from the last dosing day (Day 6).

Criteria for evaluation - pharmacodynamics and pharmacokinetics (main variables)

Primary pharmacodynamic variable: QTcX interval
Supportive pharmacodynamic variables: Subject specific correction of QT, QTcF and QTcB
Other pharmacodynamic variables: PR, QRS and RR-intervals
Pharmacokinetic variables: AUCτ, (AUCss), Cmax, (Cssmax) tmax (tssmax) and t1/2λZ for AZD3480 and its metabolite TC-1784

Criteria for evaluation - safety (main variables)

Adverse events, blood pressure, pulse rate, ECG, and clinical laboratory test

Statistical methods

Analysis was performed in a fixed order: therapeutic dose vs placebo first, supratherapeutic dose vs placebo second. The prerequisite for analysis of the supratherapeutic dose vs placebo was that the analysis of the therapeutic dose vs. placebo showed no prolongation of QT. The primary analysis focused on the comparison of the supratherapeutic dose of AZD3480 and placebo, analysis was performed by the metabolic capacity sub-groups PMs and EMs.

Moxifloxacin was compared to placebo to address assay sensitivity, this analysis was not part of the fixed testing sequence described above.

The basic model for analysis of the primary objective, was a linear mixed effects model with QTcX as dependent variable and treatment, study period, and time as fixed factors and baseline QTcX as covariate as well as the interaction between time and treatment and the interaction of time and period. Subject was a random factor.

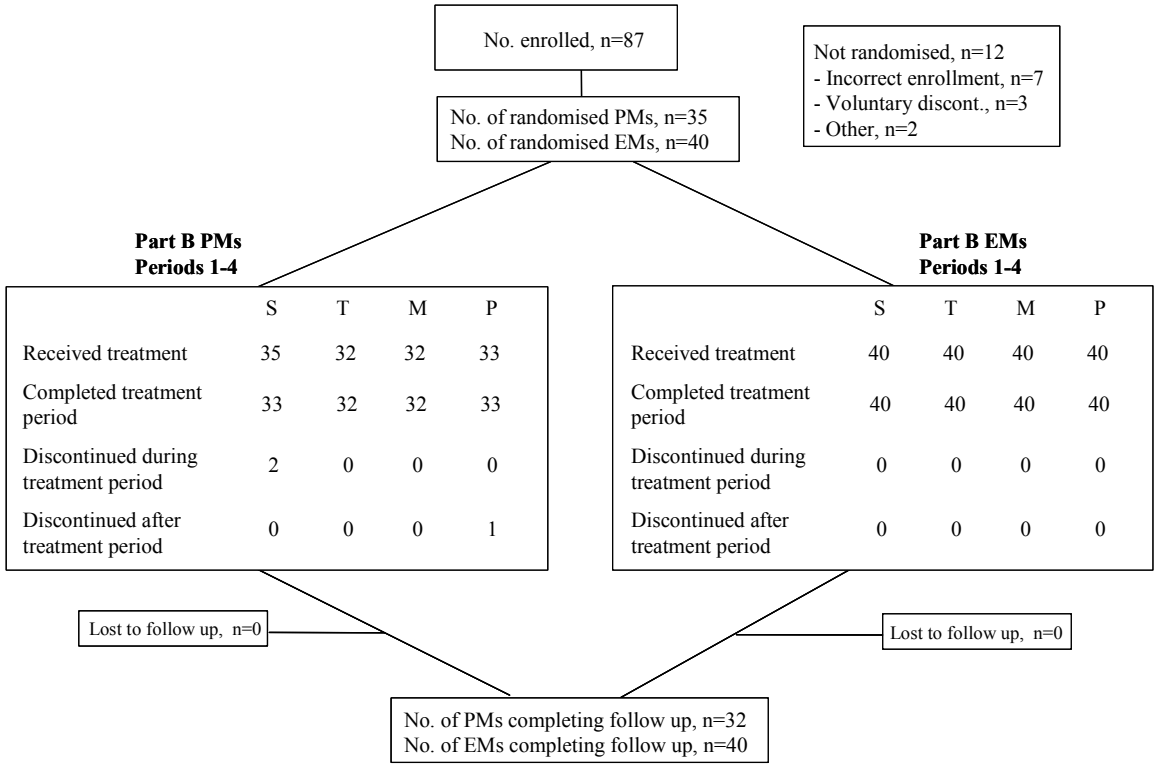
A decreasing correlation with duration of time was assumed for the QTcX values and a first-order autoregressive covariance structure was used in the model.

Based on this model, one-sided 95% confidence intervals (corresponding to two-sided 90% confidence intervals) were computed for the 9 comparisons (different time points) for supratherapeutic dose versus placebo. The criterion for no effect of regulatory concern of supratherapeutic dose on QTcX was that the upper limit of the one-sided 95% confidence interval for the mean difference between supratherapeutic dose and placebo for each time point was less than +10 ms. Categorical analysis of QTcX changes was analysed using descriptive statistics and graphs.

Subject population

A total of 35 PMs were randomised. 33 out of 35 PMs who were treated with the supratherapeutic dose of AZD3480 (20 to 200 mg/day) completed the treatment period. These 33 PMs also completed the placebo treatment period. After completing the placebo period one PM decided to discontinue the study. The remaining 32 PMs completed Part B of the study (Figure 1). A total of 40 EMs were randomised. All EMs completed all treatment periods (Figure 1).

Figure 1 Subject disposition



S= AZD3480 (supratherapeutic dose): PMs Escalating individual doses predicted not to exceed exposure limit at Day 6 treatment and EMs escalating up to 250mg at Day 6
T=AZD3480 (assumed therapeutic dose):20mg Day 1 to 6
M= Moxifloxacin 400mg only at Day 6 (placebo Day 1 to Day 5)
P = Placebo Day 1 to 6

In total 3 PMs decided to discontinue from the study during Part B. Changes in job situation made subject E0003006/507 discontinue the study after receiving 3 days treatment with supratherapeutic dose and subject E0003015/110 after receiving all supratheraeputic doses and all placebo doses. Subject E0001014/104 decided to discontinue after 4 days of supratherapeutic dose treatment after reporting a feeling of "shut in" which was noted as severe anxiety in the CRF.

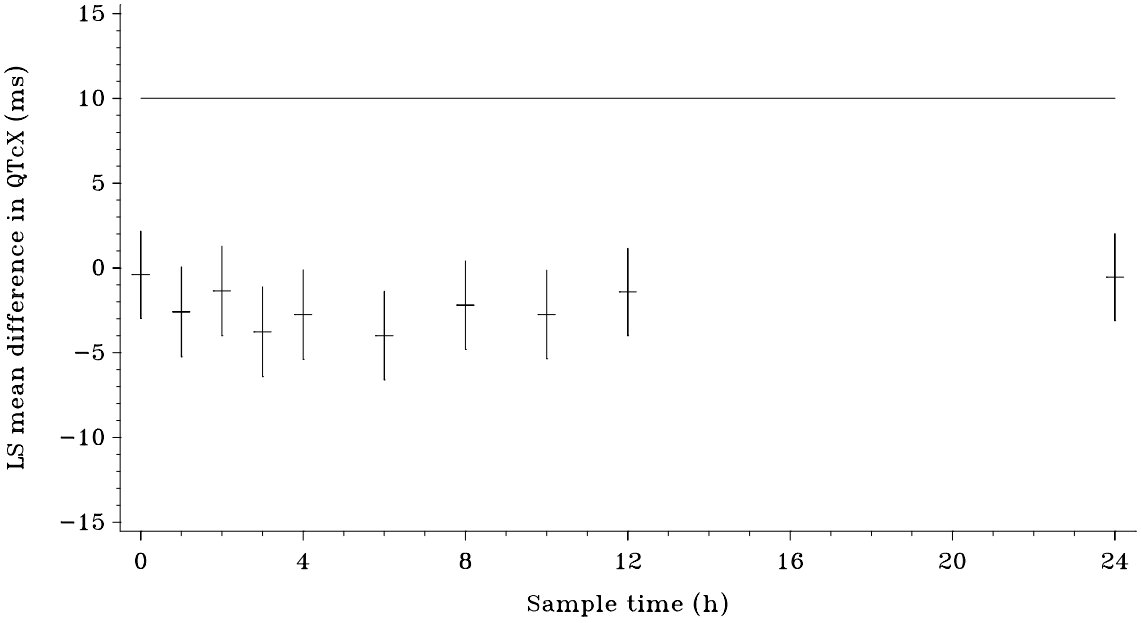
There were no imbalances with regards to demographics in the PM and EM groups. The protocol deviations and concomitant medications taken were considered unlikely to have influenced the measurement or analysis of PK and PD parameters. The treatment groups were comparable and the number in each analysis set was adequate to give valid and reliable results this TQT study.

Summary of pharmacodynamic results

Assay sensitivity was demonstrated in the study and according to the fixed order of analysis, no prolongation of QT was observed after assumed therapeutic dose (20 mg).

There was no effect on cardiac repolarisation meeting the threshold level of regulatory concern of an escalating supratherapeutic dose of AZD3480, as measured by placebo subtracted LS mean difference in QTcX and 90% two-sided CI by sample time and dose. At no time point the upper limit of the two-sided 90% CI exceeded 10 ms (corresponding to one-sided 95% CI) in either PMs (Figure 2) or EMs. Placebo subtracted LS mean difference varied between –0.4 (predose) and –4.0 ms (6h) in PMs.

Figure 2 **Placebo subtracted LS mean difference in QTcX and 90% two-sided CI by sample time and AZD3480 50-200mg (Day 6[a]) (PM PD analysis set)**



[a] The period of time from administration of Investigational Product at 0h (Day 6) up to and including 24h (Day 7)
SOURCE DOCUMENT: F_ECG_LS_QTCX_SUPRA_PM.SAS GENERATED: 14:28:24 22OCT2008 DB version prod: 4

There were no PMs or EMs with a QTcX increase of >30 ms compared to study baseline or a QTcX value >450 after escalating supratherapeutic dose of AZD3480 at any time point over 24 hr period after dose on Day 6.

There was no effect of supratherapeutic dose of AZD3480 on cardiac repolarisation meeting the threshold level of regulatory concern seen in QTcF.

There was no effect on cardiac repolarisation meeting the threshold level of regulatory concern of an assumed therapeutic dose of AZD3480 (20 mg), as measured by placebo

subtracted LS mean difference in QTcX and QTcF, and 90% two-sided CI by sample time and dose.

Summary of pharmacokinetic results

The maximum plasma concentration of AZD3480 in PMs and EMs on Day 6 was reached at a median time of 3 and 2 h, respectively, following both escalating supratherapeutic doses up to 50-200 mg and an assumed therapeutic dose of AZD3480 (20 mg).

In PMs, the geometric mean C_{max} was 1506 nmol/L and AUC_{τ} was 21968 h*nmol/L following escalating supratherapeutic doses up to 50-200 mg. There were 18 subjects in whom the exposure limit of 1700 nmol/L for C_{max} was exceeded, and for AUC_{τ}, the maximum exposure limit of 26400 nmolh/L was exceeded in 20 subjects. Following an assumed therapeutic dose of AZD3480 (20 mg) the geometric mean C_{ssmax} was 147 nmol/L and AUCτ was 2104 h*nmol/L. Clearance (CL/F) was higher after the 20 mg dose than after the supratherapeutic doses, 25.5 L/h vs 15.6 L/h, indicating non-linear PK.

In EMs, the geometric mean C_{max} was 348 nmol/L and AUC_{τ} was 1654 h*nmol/L following escalating supratherapeutic doses up to 50-200 mg. Following an assumed therapeutic dose of AZD3480 (20 mg) the geometric mean C_{ssmax} was 6.5 nmol/L and AUC_{ss} was 36 h*nmol/L. Thus, $AUC_{\tau/ss}$ after a 20 mg dose was approximately 60 times higher in PMs than EMs. As expected, CL/F in EMs was much higher after the 20 mg dose than after the supratherapeutic dose, 1501 L/h vs 371 L/h (geometric mean).

Summary of pharmacokinetic/pharmacodynamic relationships

There was no effect of plasma concentration of AZD3480 or TC-1784 on QTcX after escalating supratherapeutic dose or assumed therapeutic dose in PMs or EMs.

Summary of safety results

Despite the high exposure levels, especially during supratherapeutic dosing, there were no serious adverse events and in total only 10 adverse events of severe intensity were reported.

There were only small differences between PMs and EMs in AE incidence when treated with assumed therapeutic dose of AZD3480 (20 mg), moxifloxacin and placebo. A higher incidence (80 and 83% in PMs and EMs, respectively) was seen during treatment with supratherapeutic doses than with the other treatments. The majority of AEs were of mild intensity. The most commonly reported AEs during treatment with AZD3480 were dizziness, headache and nausea, which is in agreement with previous studies.

A slight tendency for increased P-creatinine levels (comparing baseline with Day 6, 24 hrs) was observed, in particular during supratherapeutic dosing in PMs (on average close to the maximum exposure limit extended to Cmax of 3160 nmol and AUC of 41419 nmolh/L at highest). However, P-creatinine levels were still within the normal range and the increase was reversible. A competitive inhibition of P-creatinine secretion at supratherapeutic dosages of AZD3480 can not be excluded.

Otherwise, no clinically relevant treatment related findings or trends were seen in haematology, clinical chemistry, urinalysis, vital signs or ECG in male PMs or EMs exposed to escalating supratherapeutic or assumed therapeutic oral doses of AZD3480.