AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD6765
Study Code	D6702C00013
Edition Number	1.0
Date	02 October 2009

A Phase I, Single-center, Randomized, Double-blind, Placebo-controlled Single and Multiple Ascending Dose Study to Assess the Safety, Tolerability and Pharmacokinetics of AZD6765 in Healthy Male and Female Japanese and Caucasian Subjects

Study dates: First healthy volunteer/patient enrolled: 20 November 2008
Last healthy volunteer/patient completed: 05 March 2009

Phase of development: Clinical Pharmacology (1)

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

Study centre(s)

This study was conducted at a single center in the United States of America. The first healthy volunteer was enrolled on 20 November 2008. The last volunteer completed the study on 05 March 2009.

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**	
The primary objective of the study is to investigate safety and tolerability of AZD6765 in healthy male and female Japanese subjects when given in ascending single and multiple IV doses by assessment of adverse events (AEs), vital signs, physical examinations, electrocardiograms (ECGs) and clinical laboratory assessments.	Adverse events Clinical laboratory variables Vital signs: Blood pressure, heart rate; Body temperature, weight and height ECG: resting 12-lead ECG, real time telemetry Physical examination	Safety
Secondary	**Secondary**	
The secondary objectives were: • To characterize the PK of AZD6765 in healthy male and female Japanese subjects when given in ascending single and multiple IV doses by assessment of drug concentrations in plasma and urine. • To explore potential ethnic differences in the PK of AZD6765 between Caucasian and Japanese subjects when given in single and multiple intravenous (IV) doses.	Single dose PK parameters: C_{max} maximum plasma concentration t_{max} time to reach maximum plasma concentration $AUC_{(0-24)}$ area under the plasma concentration-time curve from zero to 24 hours $AUC_{(0-48)}$ area under the plasma concentration-time curve from zero to 48 hours $AUC_{(0-72)}$ area under the plasma concentration-time curve from zero to 72 hours $AUC_{(0-t)}$ AUC from zero to the time of the last quantifiable concentration AUC area under total plasma concentration-time curve from zero to infinity $t_{1/2}$ terminal elimination half-life CL total body clearance Vz volume of distribution during terminal phase Multiple dose PK parameters: $C_{ss,max}$ maximum plasma concentration at steady state $C_{ss,min}$ minimum plasma concentration at steady state $C_{ss,avg}$ average plasma concentration at steady state $T_{ss,max}$ time to steady state $C_{ss,max}$ $T_{ss,min}$ time to steady state $C_{ss,min}$ $AUC_{tau,ss}$ area under plasma concentration time curve from	PK

Objectives	Outcome variables	Type
	zero to the dosing interval tau at steady-state $AUC_{(0-48),ss}$ area under plasma concentration time curve from zero to 48 hours at steady-state CL_{ss} total body clearance at steady state V_{ss} volume of distribution at steady state $t_{1/2ss}$ terminal elimination half-life at steady state Linearity index (LI) calculated as $AUC_{tau,ss}/AUC_{Day\ 1}$ % fluctuation calculated as $100*(C_{ss,max} - C_{ss,min.})/(AUC_{tau,ss}/tau)$ Accumulation ratios based on AUC and C_{max}, ($Rac_{(AUC)}$, $Rac_{(Cmax))}$ will be calculated: $AUC_{tau,ss,Day\ 9}/AUC_{(0-24)Day\ 1}$ and $C_{ss,max,Day\ 9}/C_{max\ Day\ 1}$ Urine PK parameters: A_e cumulative amount of unchanged drug excreted into urine CL_R renal clearance of drug from plasma f_e fraction of drug systemically available that is excreted unchanged in urine (expressed as percentage) Summary statistics of these parameters were tabulated for each dose level.	
An exploratory object was to collect blood samples for optional exploratory genetic studies focusing on identification of genes that influence the disposition, efficacy, safety and tolerability of AZD6765	Voluntary sample donation; no results to be presented in this report.	PGX

PK – pharmacokinetics
PGX - pharmacogenetics

Study design

This was a Phase I, randomized, double-blind placebo-controlled, single and multiple ascending dose study in healthy Japanese and Caucasian male and female subjects conducted at a single center. Eight Japanese subjects participated in dose levels 40 mg, 80 mg and 150 mg and received either AZD6765 or placebo, randomized 3:1. The 120 mg dose level included 8 Japanese subjects and 8 Caucasian subjects; both ethnic groups received either AZD6765 or placebo, randomized 3:1.

Table S2 Planned dose levels

Dose levels[a]	1	2	3	4
Dose level A (Japanese) n=6+2[b]	40 mg, single administration at Day 1			
Dose level B (Japanese) n=6+2[b]		80 mg, single administration at Day 1 and once daily for 5 days at Day 5-9		
Dose level C (Japanese) n=6+2[b] + (Caucasian) n=6+2[b]			120 mg, single administration at Day 1 and once daily for 5 days at Day 5-9	
Dose level D (Japanese) n=6+2[b]				150 mg, single administration at Day 1

[a] Escalation will be guided by safety.
[b] n=active + placebo

Target subject population and sample size

Healthy Japanese male and female volunteers from 20 to 45 years of age were selected for this study.

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

Table S3 Details of investigational product and other study treatments

Investigational product or test drug	Dosage form, strength, and route of administration	Manufacturer	Lot number	Expiration date
AZD6765	15 mg/mL sterile solution for IV infusion	AstraZeneca	WK80323,001	11 March 2009
NaCl (Placebo)	9 mg/mL sterile solution for IV infusion	Baxter	P226134 P224030	01 August 2009 01 July 2009

Duration of treatment

Doses ranging from 40 mg to 150 mg AZD6765 were given to 24 healthy Japanese subjects, and placebo was given to 8 healthy Japanese subjects. Six healthy Caucasian male subjects were administered AZD6765 120 mg and 2 Caucasian male subjects were given placebo. All

subjects received a single dose of AZD6765 or placebo on study Day 1 and subjects in the 80 mg and 120 mg dose levels received AZD6765 or placebo on Days 5 through 9.

Statistical methods

All analyses were performed under the direction of the Biostatistics Group, AZ. All calculations were performed with the SAS® software, unless otherwise stated. Refer to Section 12 and 13 of CSP (Appendix 12.1.1) and to the statistical analysis plan (SAP; Appendix 12.1.9) for a more detailed description of the statistical and analytical methods

The safety population was defined as all healthy volunteers who received randomized investigational product (IP), AZD6765 or placebo, and for whom any post-dose data were available.

The pharmacokinetic analysis population included all subjects who satisfy all the following: (1) received at least 1 dose of study compound to be measured; (2) completed the study without any major protocol deviation thought to interfere with the ADME of the compound to be measured; (3) provided evaluable data in support of the pharmacokinetic analyses.

For those listings or data summaries where baseline and change from baseline measurements were presented, unless stated otherwise, the last observed measurement prior to the first dose of treatment medication was considered the baseline measurement.

Subject population

The first healthy volunteer entered the study on 20 November 2008, and the last healthy volunteer finished the study on 05 March 2009. In total, 20 Japanese male healthy volunteers, 12 Japanese female healthy volunteers, and 8 Caucasian male healthy volunteers were randomised into the study.

Several protocol deviations were reported in the study. There were no protocol deviations that led to exclusion of data from the PK, and the safety analysis included all randomized healthy volunteers. In a few instances, a safety measurement (ie, blood pressure measurement or ECG recording) at an isolated time point was obtained later than scheduled or not obtained due to management of an occurring AE; however, none to the extent that affected safety analysis or overall outcomes.

Demography and baseline characteristics were similar for the placebo, 80 mg, 120 mg Japanese and 150 mg active treatments. Height, weight and body mass index (BMI) were lowest for the 40 mg dose group, which contained the largest number of female subjects (5 of 6 subjects). While BMI was similar for the Caucasian subjects compared to Japanese subjects, the Caucasian males were taller and heavier than the Japanese subjects.

The study progressed through the dose escalation with none of the subjects fulfilling any of the stopping criteria.

Summary of pharmacokinetic results

Plasma AZD6765 PK parameters after single dose administration – Day 1

The plasma PK profile of AZD6765 was assessed from predose to 72 hours relative to start of infusion. PK parameters for subject 304 (120 mg dose level) were calculated with and without the 1.5 hour time point concentration due to an extremely high value (C1.5h = 3030 ng/mL, which is considered to be anomalous). The inclusion or exclusion of this value does not affect the overall conclusions of the study, thus results referenced in this report exclude the aberrant value.

Maximum concentrations of AZD6765 were achieved by the end of the 1-hour infusion. Median t_{max} ranged from 0.98 to 1.02 hours across the 40 mg to 150 mg dose levels in Japanese subjects.

AZD6765 exposure (C_{max}, $AUC_{(0-t)}$, $AUC_{(0-24)}$, $AUC_{(0-48)}$, $AUC_{(0-72)}$ and AUC) increased with each increasing dose level. Geometric mean C_{max} increased from 465 ng/mL to 1577 ng/mL and geometric mean AUC ranged from 5808 ng*h/mL to 17777 ng*h/mL across the dose levels for Japanese subjects. In Japanese subjects, AZD6765 plasma PK data variability (GCV%) ranged from 17 to 26% for C_{max} and 22 to 28% for AUC.

Geometric mean $t_{1/2}$ ranged from approximately 11 to 12 hours and geometric mean Vz ranged from 119 to 145 L for the 40 mg to 150 mg dose levels in Japanese subjects. Geometric mean CL after single dose ranged from approximately 6.9 to 8.4 L/h across the dose levels in Japanese subjects.

A comparison of the AZD6765 120 mg single dose PK results between the Japanese and Caucasian subjects showed C_{max} and AUC parameters for Caucasians to be comparable to Japanese subjects. Similarities were also observed in t_{max}, $t_{½}$, CL, and Vz parameters. C_{max} and AUC geometric mean values were 972 ng/mL and 12745 ng*hr/mL in Japanese subjects compared to 1041 ng/mL and 14237 ng*h/mL in Caucasian subjects, respectively. Median t_{max} was approximately 1 hour in both groups, geometric mean $t_{½}$ was approximately 12 hours in both groups, geometric mean CL was approximately 8 L/h in both groups, and geometric mean Vz was 145 L (Japanese) and 168 L (Caucasians).

Plasma AZD6765 PK parameters after multiple dose administration – Day 9

Subjects in the 80 mg and 120 mg (or placebo) dose levels were also dosed on Days 5 to 9.

Trough AZD6765 concentrations were measured on Days 6, 7, 8 and 9 and 24 hours after infusion on Day 9 to evaluate the attainment of steady state. Based on the Day 1 geometric mean $t_{½}$ of approximately 12 hours, steady state should have been attained after 4 days of dosing (study Day 8). Visual inspection of the plasma AZD6765 trough concentrations measured on Days 6, 7, 8 and 9 show that steady state was attained by Day 9.

Steady-state AZD6765 exposure ($C_{ss,max}$, $AUC_{tau,ss}$, and $AUC_{(0-48),ss}$) increased with ascending doses (80 mg to 120 mg) in the Japanese subjects. Geometric mean $C_{ss,max}$ was 947 ng/mL for 80 mg and 1221 ng/mL for 120 mg AZD6765. Geometric $AUC_{tau,ss}$ was 8550 ng*h/mL for

80 mg and 13262 ng*h/mL for 120 mg AZD6765. AZD6765 plasma PK data variability (GCV%) ranged from 20 to 30% for $C_{ss,max}$ and 21 to 33% for $AUC_{tau,ss}$ in Japanese subjects.

After multiple IV dosing in Japanese subjects, median t_{max} was approximately 1 hour, geometric mean $t_{1/2}$ was approximately 11 hours, geometric mean V_{ss} was approximately 136L, geometric mean CL was approximately 9 L/h for the 80 and 120 mg dose levels.

A comparison of the AZD6765 120 mg multiple dose PK results between the Japanese versus Caucasian subjects showed similarities in $C_{ss,max}$, $AUC_{tau,ss}$, $T_{ss,max}$, $t_{½,ss}$, CL_{ss}, and Vz_{ss} parameters. $C_{ss,max}$ and $AUC_{tau,ss}$ geometric mean values were 1221 ng/mL and 13262 ng*hr/mL compared to 1207 ng/mL and 11917 ng*h/mL, respectively, in Japanese and Caucasian subjects. Median $T_{ss,max}$ was approximately 1 hour in both groups, geometric mean $t_{½}$ was approximately 11 hours in both groups, geometric mean CL_{ss} was approximately 9 L/h in both groups, and geometric mean V_{ss} was approximately 136 L in both groups.

Comparative PK parameters were calculated to assess single dose versus multiple dose administration profiles. Geometric mean accumulation ratios suggest slight accumulation of AZD6765 in the plasma after multiple dosing in Japanese subjects. For the 80 mg and 120 mg dose levels, $Rac_{(AUC)}$ increased 15% and 23%, respectively, after steady state vs. single dosing. $Rac_{(Cmax)}$ increased 29% and 17% for the 80 mg and 120 mg, respectively, after steady state vs. single dosing.

$Rac_{(AUC)}$ was similar in Japanese vs. Caucasian subjects at the 120 mg dose level. After steady state dosing, AUC increased by 23% in Japanese subjects compared to 26% in Caucasians. $Rac_{(Cmax)}$ was lower in Japanese vs. Caucasian subjects. After steady state dosing, Cmax increased by 17% in Japanese subjects compared to 24% in Caucasians.

Geometric mean linearity index was close to 1.0 (0.90 for 80 mg and 0.93 for 120 mg for both Japanese and Caucasian subjects) suggesting time invariance of the PK for the once daily IV dosing regimen used in this study.

Results of the single dose proportionality assessment, utilizing the method of Smith et al 2000, a more formal statistical analysis with pre-specified intervals, were evaluated. The estimated slope values for C_{max} and AUC were less than 1 (0.87 and 0.84, respectively), and their corresponding 90% confidence intervals were not fully contained within the pre-specified intervals. Though, the results did not provide sufficient support to definitely confirm dose proportionality given the limited number of subjects (n=6 per dose group), gender and between-subject variability, the overall slope estimate values show that AZD6765 exposure increased in a roughly proportional and linear manner over the dose range studied, 40 mg to 150 mg.

Results of the dose normalized C_{max} and AUC show AZD6765 to be approximately dose proportional from 40 mg to 150 mg for C_{max} and dose proportional from 80 mg to 150 mg for AUC, but slightly less than dose proportional from 40 mg to 80 mg. The geometric mean (%CV) dose normalized exposure values at the 40, 80, 120 and 150 mg dose levels for C_{max} were 11.6, 9.19, 8.68 and 10.5 ng/mL (%CV ranged from 17.3 to 26.2%), respectively; and

for AUC, 145.2, 120.1, 118.6 and 118.5 ng*h/mL (%CV ranged from 21.6 to 27.7%), respectively.

The slightly higher exposure observed at the 40 mg dose level may be attributed to difference in body weight between the 40 mg dose level group (majority female subjects and mean body weight 55.4 kg) and the rest of the other dose level groups (majority males subjects and mean body weights 67.4, 67.1 and 60.7 kg, for the 80, 120 and 150 mg dose levels, respectively).

In the multiple ascending dose study only two dose levels were evaluated, 80 mg and 120 mg. The results of the multiple dose proportionality assessment, also utilizing the method of Smith et al 2000 with pre-specified intervals, were evaluated. The estimated slope value was less than 1 for C_{max} but was about 1 for AUC (0.63 and 1.08, respectively), and their corresponding 90% confidence intervals were not fully contained within the pre-specified intervals. Though, the results did not provide sufficient support to definitely confirm dose proportionality given the limited number of subjects (n=6 per dose group) and inter-subject variability, the overall slope estimate values show that AZD6765 exposure increased in a roughly proportional manner over the dose range studied, 80 mg to 120 mg.

Further, the geomean (%CV) dose normalized exposure values at the 80 mg and 120 mg dose levels for $C_{ss,max}$ were 11.8 ng/mL (29.9%) and 10.2 ng/mL (20.6%), respectively, and for $AUC_{tau,ss}$ 106.9 ng*hr/mL (33.2%) and 110.5 ng*hr/mL (21.0%), respectively. These values indicate that AZD6765 exposure increased in a roughly proportional manner with increase in dose, over the dose range studied.

Urine AZD6765 PK parameters after single dose administration

AZD6765 urine concentrations were measured from 0-72 hours relative to start of infusion. The geometric mean amount of unchanged drug excreted in urine (A_e) increased with each dose level after single dose administration to Japanese subjects; the range of values calculated from 0-48 h was 9.22 to 51.79 mg and from 0-72 h was 9.80 to 54.45 mg.

The geometric mean fraction of drug excreted into urine (f_e) ranged from 23% to 35% for 0-48 h and 24% to 36% for 0-72 h for the 40 mg to 150 mg dose levels given to Japanese subjects.

Renal clearance (CL_R) ranged from 1.7 to 3.1 L/h (for both the 0-48 h and 0-72 h calculations) across the 40 to 150 mg dose levels given to Japanese subjects.

Single dose urine PK parameters were similar in the Japanese and Caucasian subjects. Geometric mean $A_{e(0-48)}$ and $A_{e(0-72)}$ was 29.95 and 32.31 mg, respectively, for Japanese subjects and 26.39 and 28.20 mg, respectively in Caucasians. Geometric mean $f_{e(0-48)}$ and $f_{e(0-72)}$ was 24.95 and 26.92%, respectively in Japanese subjects and 21.99 and 23.50%, respectively, in Caucasians. Geometric mean $CL_{R(0-48)}$ and $CL_{R(0-72)}$ was 2.25 and 2.31 L/h, respectively, in Japanese subjects and 2.23 and 2.25 L/h, respectively, in Caucasians.

Urine AZD6765 PK parameters after multiple dose administration

AZD6765 urine concentrations were measured from 0-24 hours post-dose on Day 9. After steady state dosing, geometric mean A_e was 23.65 mg for 80 mg, 27.68 mg for 120 mg Japanese, and 31.52 mg for 120 mg Caucasian. The geometric mean CL_R was 2.76 L/h for 80 mg, 2.09 L/h for 120 mg Japanese, and 2.65 L/h for 120 mg Caucasians.

Summary of safety results

There were no deaths, serious AEs (SAEs), or other significant AEs (OAEs in the study.

The total number of AEs reported for Japanese and Caucasian subjects during both the single and multiple dose cohorts was 56 AEs reported by 22 subjects (73%) on active and 4 AEs were reported by 4 subjects (40%) on placebo. Fifty-six (93%) AEs were of mild intensity and 4 (7%) AEs were of moderate intensity. The 4 moderate AEs included 2 Japanese subjects who experienced a brief syncopal episode (< 3-minute duration) at 80 mg and 150 mg single dose levels, respectively; 1 Japanese subject who expressed "feeling drunk" after 80 mg multiple dose and 1 Japanese subject administered a single 150 mg dose who had orthostatic hypotension. There were no AEs of severe intensity. Of the 60 AEs reported, 82% (49 events) had at least a possible causality to study treatment. All treatment related AEs resolved by the completion of the study without medical intervention. Non-treatment related AEs also resolved by the end of the study; one subject (subject 503) received acetaminophen for relief of backpain.

The incidence of overall AE reporting increased with increasing AZD6765 dose in Japanese subjects. After single dose administration in Japanese subjects, the highest incidence of AE reporting (6 of 6 subjects [100%]) occurred at the 120 mg and 150 mg dose levels. The incidence of AE reporting was 25% for placebo; 17% for 40 mg, and 67% for 80 mg dose levels. The most commonly (more than 1 subject per dose) reported treatment related AEs after single dose to Japanese subjects were dizziness (83% for 120 mg), and feeling drunk (33% for 80 mg and 100% for 150 mg). The onset of these events occurred during the 60-minute infusion or within approximately one hour after infusion completion.

After multiple dosing in Japanese subjects, the incidence of AE reporting increased with increasing dose (0% for placebo, 50% for 80 mg, and 67% for 120 mg). After multiple dosing, the most commonly (more than 1 subject per dose) reported treatment related AEs by Japanese subjects were dizziness (67% for 120 mg) and feeling drunk (50% for 80 mg). The onset of these events occurred during the infusion on Day 5 or within approximately one hour following the completion of Day 5 infusion, with exception of the following: 1 event of feeling drunk reported during infusion of 80 mg on Day 7; 1 event of dizziness reported during infusion of 120 mg on Day 7, and 2 events of dizziness reported during infusion of 120 mg on Day 6.

Adverse event reporting differed in Japanese and Caucasians subjects. Following 120 mg single dose AZD6765 administration, 6 Japanese subjects (100%) and 4 Caucasian subjects (67%) reported AEs. After multiple 120 mg doses, 4 Japanese subjects (67%) and 5 Caucasian subjects (83%) reported AEs**.** As stated above, the most commonly reported

treatment related AE was dizziness in Japanese subjects at 120 mg dose level. For Caucasian subjects, the most commonly reported AEs after single dose 120 mg were feeling drunk (50%) and bradyphrenia (slowed thought processes) (33%), and the most commonly reported treatment related AEs after multiple dose were feeling drunk (67%), dizziness (33%), and bradyphrenia (33%).

For Caucasian subjects, contact dermatitis due to ECG lead placement was reported by 67% of subjects following multiple dose administration of 120 mg; these events were assessed as not related to IP.

None of the subjects had a clinically significant chemistry, hematology or urinalysis laboratory value. No AEs were related to abnormal laboratory values.

None of the clinical laboratory stopping criteria were met during the study. None of the subjects had a troponin T or troponin I that was out of normal range. None of the subjects had a bilirubin value > than 2x the ULN and none had an ALT > 2.5x the ULN.

One subject had an AST > 2.5x the ULN: subject 507 (120 mg Caucasian) had an AST of 1.79 ukat/L (reference range 0.2505-0.6179 ukat/L) at follow-up (8 days following last drug administration). Prior to the last dose, the subject had an AST of 0.234 ukat/L. The only other laboratory parameter for this subject that was out of range at follow-up was LDH = 5.49 ukat/L (reference range 1.67-3.173 ukat/L). The values were not considered AEs by the investigator.

The mean and mean change from baseline for supine and orthostatic vital signs were similar between the AZD6765 dose levels and placebo. There were no resting, supine pulse measurements > 125 bpm or < 30 bpm. There were three subjects with an AE related to vital signs measurements.

Subject 106, a 24 yr old Japanese female (40 mg single dose level) exhibited orthostatic hypotension after standing 5 min at the 15 min and 2 h relative to start of infusion measurements, which continued intermittently for approximately 11 hours. The event was considered mild and related. The maximum concentration of AZD6765 was at 1 h after the start of infusion (C_{max} = 527 ng/mL).

Subject 202, a 21 yr old Japanese male (80 mg single dose level) experienced syncope lasting 3 minutes at approximately 2 h relative to start of infusion. The event was considered moderate and related to treatment. The event resolved spontaneously without intervening treatment after resting supine. The maximum plasma concentration of AZD6765 was observed 1.0 h after the start of infusion (C_{max} = 710 ng/mL).

Subject 408, a 26 yr old Japanese female (150 mg single dose level) experienced a brief episode of syncope lasting 1 min at 2 h relative to start of infusion, and orthostatic hypotension upon standing for vital signs measurements from 2 h to 5.5 h relative to start of infusion. Both events were considered moderate and related. The maximum concentration of AZD6765 was observed 1.0 h after the start of infusion for this subject (C_{max} = 1930 ng/mL).

Mean observed and change from baseline resting ECG measurements and measurements obtained through continuous ECG monitoring after single and multiple dose administration were evaluated.

None of the abnormalities exhibited on resting ECG were assessed as clinically significant, at any time point for any subject. There were no AEs related to ECG measurements. For the resting ECGs, changes in QTcF were assessed; there were no resting QTcF > 450 msec. There was no increase from baseline > 30 msec in resting QTcF.

The mean maximum increase from baseline after single and multiple dose administration for continuous ECG parameters were summarized. Mean increases from baseline after single dose for QTcB and QTcF were not dose dependent. The mean maximum increase in QTcB was 11.5 msec for the 150 mg dose and 12.4 msec for placebo given to Japanese subjects. The mean maximum increase in QTcF was 8.2 msec for the 80 mg dose and 6.7 msec for placebo given to Japanese subjects. For Caucasian subjects the mean maximum increase in QTcB and QTcF was 9.0 msec and 5.1 msec, after a single 120 mg dose (compared to 10.7 msec and 6.4 msec in Japanese subjects). For Caucasian subjects the mean maximum increase in QTcB and QTcF was 4.2 msec and 2.0 msec, after placebo.

The mean maximum increases from baseline after multiple doses for QTcB and QTcF were not dose dependent. The mean maximum increase in QTcB was 13.1 msec for the 80 mg dose and 12.0 msec for placebo given to Japanese subjects. The mean maximum increase in QTcF was 11.7 msec for the 80 mg dose and 9.3 msec for placebo given to Japanese subjects. For Caucasian subjects the mean maximum increase in QTcB and QTcF was 8.2 msec and 4.1 msec (compared to 12.6 msec and 7.5 msec for Japanese subjects), after multiple 120 mg doses. For Caucasian subjects the mean maximum increase in QTcB and QTcF was 9.7 msec and 4.2 msec, after placebo.

For continuous ECG monitoring, a categorical summary of maximum increase from baseline for QT interval parameters showed no instances of increases from baseline > 30 msec for QTcB and QTcF intervals. None of the subjects exhibited a prolongation of QTcF or QTcB > 480 msec. For QT_{tang} 4 Japanese subjects (subjects 103 & 106 for 40 mg single dose; subject 207 for the 80 mg single dose, and subject 408 for the 150 mg dose) had at least one measurement > 450 msec and 1 subject (subject 207 for the 80 mg single dose) had 2 measurements > 480 msec. For QT_{tang} 1 Japanese subject (subject 207 for the 80 mg multiple dose) had at least one measurement > 480 msec. None of the QT_{tang} measurements were considered clinically significant by the investigator.