Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

Application	NDA 22,307
Brand Name	Effient
Generic Name	Prasugrel
Sponsor	Eli Lilly
Indication	Reduction of atherothrombotic events in acute coronary syndrome
Dosage Form	Tablet
Drug Class	Platelet aggregation inhibitor
Therapeutic Dose	60 mg loading dose; then 5 or 10 mg once daily maintenance dose
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	80 mg single dose
Application Submission Date	12/26/2007
Review Classification	Priority NDA
Date Consult Received	1/22/2008
Clinical Division	Division of Cardiovascular and Renal Products
PDUFA Date	6/26/2008

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No significant effect of prasugrel (80 mg which is 1.3-and 8-fold the loading and maintenance dose, respectively) was detected in this TQT study. There were limitations in the present TQT study which are described below.

1. Choice of 80-mg prasugrel dose: The 80-mg dose does not cover worst-case scenarios (based on intrinsic and extrinsic factors) when compared with 60-mg loading dose. This dose does, however, cover the expected high exposure scenario for the 5-or 10-mg maintenance dose.
2. Sampling schedule for ECG: The t_{max} of metabolites (except R-106583), which is essential for E-14 analysis, was not captured.
3. The time-matched baseline was collected only on Day -1 (1, 2 and 6 h) prior to period 1 and used for all the periods in the analysis such that it cancels out in any double-delta analysis. Therefore, the present double-delta analysis reduces to a single-delta analysis.

The largest upper limits of the two-sided 90% CI for the mean difference between prasugrel and placebo was below 10 ms, the threshold for regulatory concern as described in ICH E14 guideline.

This was a single-center, randomized, three-period crossover study in which 60 healthy subjects received placebo or a 80-mg single dose of prasugrel. Subjects also received a single oral dose of moxifloxacin 400 mg administered open label. Overall findings are summarized in the following table.

FDA Analysis: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Prasugrel 80 mg and Largest Lower Bounds for Moxifloxacin.

Treatment	Time (h)	ΔQTcF	90% CI
Prasugrel 80 mg	24	2.1	(-1.3, 5.40)
Moxifloxacin 400 mg	1	10.7	(8.3, 13.0)*

* After Bonferroni correction.

1.2 RESPONSES TO QUESTIONS POSED BY REVIEW DIVISION

1.2.1 Was TAAP acceptable in terms of TQT design?

There are several limitations with respect to study design:

- The 80 mg single dose was not sufficient to cover worst case scenarios after a 60-mg loading dose (See section 5.2).
- ECG sampling times were not adequate to capture t_{max} for three of the metabolites (See section 4.2.6.4).
- Time-matched baseline (1, 2 and 6 h only) was captured only prior to period 1 and was used for all periods in double- delta analysis. Therefore the present double-delta analysis (change from placebo adjusted for baseline) was equivalent to a single-delta analysis (change from placebo).

1.2.2 Was TAAP performed adequately?

TAAP study was performed adequately. The largest lower bound of the two sided 90% CI for ΔQTcF for moxifloxacin was greater than 5 ms indicating that the study was adequately designed to detect an effect on the QT interval.

Complete information regarding ECG acquisition and interpretation is not available (See Section 4.2.7).

1.2.3 Do you agree with the sponsor's conclusion that TAAP is a negative QT study?

Yes, even though the study design had several limitations, lack of positive signal from the concentration-QT modeling together with comparable levels of at least two metabolites in TAAP and Phase III trial (TAAL) suggest that prasugrel may not prolong QT at clinically relevant exposures. Moreover, since a 60-mg loading dose would be given once only at the start of treatment and will be administered in a controlled and monitored inpatient setting followed by the 10-mg maintenance dose (See Page 15, H7T-EW-TAAP), it would be reasonable to compare the exposures achieved by an 80-mg single dose of prasugrel to a 10-mg maintenance dose to interpret the effect of prasugrel on QT interval.

In that case the 80-mg dose (8-fold higher than the maintenance dose) covers the exposures achieved by a 10-mg maintenance dose.

1.2.4 What do you think of the concentration QT relationships for the metabolites?

Based on concentration-QT modeling, prasugrel metabolites do not exhibit any significant slope (See Section 5.2).

2 PROPOSED LABEL

The sponsor did not include any information regarding the TQT study in the label.

3 BACKGROUND

Prasugrel (CS-747, LY640315) is a member of the thienopyridine class of antiplatelet agents. Prasugrel is an orally bioavailable prodrug metabolized to an active adenosine diphosphate (ADP) receptor antagonist, which is a potent inhibitor of platelet activation and aggregation mediated by the P2Y12 ADP receptor. The proposed therapeutic indication for Prasugrel (EFFIENT™) is for the reduction of atherothrombotic events and the reduction of stent thrombosis in acute coronary syndromes.

3.1 MARKET APPROVAL STATUS

Prasugrel is not approved for marketing in the USA or elsewhere.

3.2 PRECLINICAL INFORMATION

Source: Non-Clinical Summary

> "The potential for prasugrel to inhibit cardiac repolarization was evaluated by examining the effect of 3 prasugrel metabolites on potassium currents in hERG transfected cells. Prasugrel was not evaluated in this assay since this prodrug is rapidly metabolized and systemic exposures are negligible. The metabolites R-138727 and R-106583 were evaluated because these are the active and most abundant nonactive human metabolites, respectively, and R-95913 was evaluated because it is the intermediary step between prasugrel and the active metabolite. No significant effects on the potassium currents in hERG-transfected CHO-K1 cells were observed at up to the highest concentrations tested (30 μM for R106583 and R138727; 15 μM for R-95913) which were greater than 485 times the expected free Cmax values following a clinical loading dose of 60-mg. Therefore, the hERG data for prasugrel metabolites do not suggest a potential impact of prasugrel on cardiac repolarization due to inhibition of potassium currents. Furthermore, quantitative electrocardiograms were evaluated in 3- and 9-month repeat-dose studies in dogs and no effects on QT-interval were observed up to the maximum dose of 20 mg/kg, approximately 9 times the clinical loading dose on a mg/m^2 basis."

3.3 PREVIOUS CLINICAL EXPERIENCE

Source: Summary of Clinical Safety

> "The Summary of Clinical Safety is based on data accumulated as of 20 September 2007.

- "The primary safety database (H7T-MC-TAAL [TAAL]) includes data from 13457 treated subjects (6741 treated with prasugrel, 6716 treated with clopidogrel) with acute coronary syndromes (ACS) undergoing percutaneous coronary intervention (PCI) who were treated with prasugrel or clopidogrel, co-administered with aspirin for up to 15 months.
- "The secondary safety database includes data from integrated safety observations from 4 smaller completed studies grouped into All but TAAL (ABT). The total number of prasugrel-treated subjects was 940 in the 4 studies mentioned above, and 6741 in Study TAAL.
- "The tertiary safety database comprises the safety data from multiple clinical pharmacology studies involving healthy subjects and subjects from special populations (renal and hepatic impairment) exposed to prasugrel as a single dose, multiple doses, or loading dose followed by daily maintenance dose for up to 21 days (total number of treated subjects with prasugrel was 975).

"No statistically significant differences were seen between treatment groups for CV, or non-CV deaths in the All ACS, UA/NSTEMI, and STEMI populations of the primary safety database. There were more deaths due to hemorrhage (both ICH and non-ICH) in subjects randomized to prasugrel compared to clopidogrel.

"In the primary safety database, the number of subjects experiencing SAEs included in the cluster of Torsade de Pointes/QT Prolongation was similar between treatment groups. The largest proportion of subjects experienced "Ventricular Tachycardia" (24 out of 25 with prasugrel, 25 out of 26 with clopidogrel). One clopidogrel-treated subject died suddenly and the death was reported as an SAE because it was considered possibly related to study drug.

"Two prasugrel-treated subjects and 1 clopidogrel-treated subject each experienced 1 episode of Torsade de Pointes. Both subjects treated with prasugrel experienced 1 episode of Torsade de Pointes and episodes of ventricular fibrillation and/or ventricular tachycardia within 3 days following an apparently successful PCI and exposure to the drug. Complex ventricular arrhythmias were converted to sinus rhythm by electrical and pharmacological therapy. Study drug was continued and further recurrences were not observed. One prasugrel-treated subject died about 20 days after the event due to hypoxic brain damage. In both cases, Torsade de Pointes was deemed by the investigator unrelated to study drug, but rather to the underlying ischemic heart disease."

Reviewer's Comment: Previous Clinical experience is not suggestive of increased AEs related to QT-prolongation compared to active comparator.

3.4 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of prasugrel's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The sponsor submitted the study report for H7T-EW-TAAP including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

The title of the study is 'A Placebo-Controlled Study of the Electrophysiological Effects of a Single 80 mg Prasugrel Dose on the QT Interval Healthy Subjects.'

4.2.2 Protocol Number

The protocol number of this study is H7T-EW-TAAP.

4.2.3 Study Dates

The study was conducted from April 15, 2005 to October 12, 2005.

4.2.4 Objectives

The primary objective of this study was to evaluate the effect of prasugrel on ventricular repolarization as assessed by QT/QTc interval when given as a single 80-mg dose.
The secondary objectives were:

- to evaluate the safety and tolerability of prasugrel when given as a single 80-mg dose
- to assess the relationship between plasma concentrations of R-138727 (the active metabolite of prasugrel), R-95913 (the primary metabolite of prasugrel), and R-106583 and R-119251 (two inactive metabolites of prasugrel) to potential QTc changes after a single 80-mg dose of prasugrel
- to assess exposure to R-138727, R-95913, R-106583 and R-119251 after a single 80-mg dose of prasugrel.

4.2.5 Study Description

4.2.5.1 Design

This was a single-centre, randomized, three-period (with an additional fixed sequence baseline visit to collect baseline control ECGs), crossover study in healthy male and female subjects.

4.2.5.2 Controls

The Sponsor use both placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding

Investigators and subjects were blinded to prasugrel and placebo, however, moxifloxacin was administered open-label.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

All subjects received the following treatments on three separate occasions:
Treatment 1: single oral dose of placebo

Treatment 2: single oral dose of 80-mg prasugrel

Treatment 3: single oral dose of 400-mg moxifloxacin (positive control).

For Period 1 only, subjects were admitted to the Clinical Research Unit (CRU) on Day -2, and baseline electrocardiogram (ECGs) measurements were taken on Day -1. Baseline ECG measurements were performed on the day prior to the first period in order that a drug-free time-matched baseline could be used for comparative purposes. For Periods 2 and 3, subjects were admitted to the CRU on Day -1. For all three periods, subjects received study drug on Day 1 and were discharged on Day 2, approximately 24 hours post-dose. Each treatment period was separated by a washout of at least 10 days.

4.2.6.2 Sponsor's Justification for Doses

Sponsor states in the TQT report (See Page 32-33, H7T-EW-TAAP) that

> "The primary use of the concentration data was to correlate concentrations to any observed change in QT/QTc interval. The concentration-time data were not intended to accurately quantify the overall exposures to prasugrel metabolites after an 80-mg dose of prasugrel.
>
> "The calculated exposures to prasugrel metabolites were quantified from only five samples collected over 24 hours, which is too infrequent a sampling scheme to accurately quantify noncompartmental pharmacokinetic parameter estimates. However, even considering this limitation, exposures to the four prasugrel metabolites were consistent with expected exposures based on previous studies in healthy subjects. Table TAAP.9.1 lists AUC, Cmax and tmax estimates from two previous studies: H7T-EW-TAAK (TAAK), which measured all four metabolites after a single 60-mg prasugrel dose to healthy subjects, and H7T-EW-TAAJ (TAAJ), a large Phase 1 study that measured only the active prasugrel metabolite after a single 60-mg dose of prasugrel. The mean AUCs of prasugrel's four metabolites in the current study are 20% to 60% larger than those in TAAK, which, given the infrequent sampling scheme in the current study and the inherent variability across each of the three studies being compared, is not inconsistent with the 33% higher dose in the current study. Similarly, the mean AUC of the active metabolite (R-138727) in the present study was approximately 29% greater than that in study TAAJ."

Table TAAP.9.1. Comparison of Prasugrel Metabolite Exposures in Healthy Subjects in Previous Studies

	Geometric Mean (%CV)							
	H7T-EW-TAAP (80 mg single dose) (N=50-56)a			H7T-EW-TAAK (60 mg single dose) (N=16-18)b		H7T-EW-TAAJ (60 mg single dose) (N=66)c		
	C1hr (ng/mL)	AUC(0-tlast) (ng•h/mL)	C max (ng/mL)	AUC(0-24) (ng•h/mL)	t max (h) (median)	C max (ng/mL)	AUC(0-24) (ng•h/mL)	t max (h) (median)
R-95913	186	497	193	338	0.50	NC	NC	NC
	(43.3)	(38.1)	(56.3)	(43.5)	(0.50-1.00)			
R-138727	449	679	465	452	0.50	515	527	0.50
	(44.8)	(37.3)	(32.0)	(22.9)	(0.50-1.00)	(48.7)	(35.1)	(0.25-1.02)
R-119251	227	468	309	391	0.50	NC	NC	NC
	(43.7)	(37.2)	(28.3)	(18.4)	(0.50-1.00)			
R-106583	555	3370	383	2110	0.50	NC	NC	NC
	(40.1)	(31.3)	(21.2)	(24.9)	(0.50-1.50)			

NC = not calculated

a from current study report, Table TAAP.7.1 AUC(0-24) was not reported as it was in TAAK and TAAJ,
but it was closely approximated by AUC(0-tlast)

b from H7T-EW-TAAK Final Study Report, Table TAAK.11.1 (R-138727) and Table TAAK.11.6 (R-95913, R-119251 and R-106583). Includes only data from subjects not taking ketoconazole.

c from H7T-EW-TAAJ Final Study Report, Table TAAJ.11.1"

Sponsor states in the TQT report (See Page 15, H7T-EW-TAAP) that

> "The prasugrel loading dose of 60 mg has been studied extensively in healthy subjects, in subjects with stable atherosclerosis and in subjects undergoing PCI. The 60 mg loading dose was shown to be safe and well tolerated. In clinical practice, the loading dose will be given once only at the start of treatment and will be given in a controlled and monitored inpatient setting, for example, prior to elective or urgent PCI. This study was conducted with a single prasugrel dose of 80 mg, a dose comparable to the highest prasugrel dose of 75 mg previously shown to be safe and well tolerated in healthy subjects (Study 15878/H7T-MC-S001). The 80 mg dose is 33% higher than the 60 mg loading dose and 8 times higher than the 10 mg maintenance dose undergoing clinical testing in the Phase III study. Using pharmacokinetic data from study H7T-EW-TAAK, it was estimated that the single 80 mg dose of prasugrel used in this study would produce metabolite exposures approximately 10 to 11 times those expected during 10 mg maintenance dosing in clinical testing."

Reviewer's comments: There are several scenarios possible after clinical 60-mg loading dose which might result in higher exposures for some of the metabolites than observed by single 80-mg prasugrel dose in the present QT study (See Section 5.2 for details). The scenarios are:

- *Higher exposures in subjects with bodyweight < 60 kg.*

- *Higher exposures in Asian subjects.*
- *Higher exposures for R-95913 and R-119521 in moderate hepatic impaired individuals.*
- *Higher exposure for R-95913 after co administration with ketoconazole.*

4.2.6.3 Instructions with Regard to Meals

All doses of placebo, prasugrel and moxifloxacin were administered in fasted state. As per study (H7T-EW-TAAF Main Report), the C_{max} of all the studied metabolites were lowered with food, thus the 80-mg dose is comfortably above the exposures which might be achieved by a 60-mg loading dose if administered with food.

4.2.6.4 ECG and PK Assessments

Table 1: Sampling Schedule

Study Day	-1 (for Period 1 Only)	1
Intervention	No treatment (Baseline)	Single dose
12-Lead ECGs	1, 2 and 6 h*	1, 2, 6 and 24 h post dose
PK Samples for drug	None collected	Predose and1, 2, 6, 12, 24 h post dose

* Collected only prior to period 1.

Sponsor did not collect PK and ECG at 0.5 h which is the median t_{max} for three metabolites R138727, 95913 and 119251. The justification provided by the sponsor for this study design is as follows:

> "The choice of ECG and pharmacokinetic assessment times was made after considering many factors, among them the advantages and disadvantages of having closely spaced ECG readings during the first hour post dose, the possibility of hysteresis between plasma concentrations and QT/QTc, and the effect of variability in plasma concentrations on QT/QTc interval if prasugrel metabolites were to affect QT/QTc interval. Given the results of the study, the number and timing of ECG assessments were confirmed to be adequate to support the study's conclusions. The schedule of ECG assessments was based on pharmacokinetic data from two previous studies in healthy subjects, TAAJ and TAAK, both of which included sampling times of 0.25, 0.5, 1.0 and 1.5 hours. In study TAAJ, the tmax in individual subjects ranged from 0.25 to 0.27 hours in 4 subjects, from 0.50 to 0.57 hours in 49 subjects, and from 1.00 to 1.02 hours in 13 subjects. The distribution of tmax in TAAK was similar to that in TAAJ for the active metabolite, R-95913 and R-119251, but was a little later for R-106583. The tmax of R-106583 in individual subjects was 0.5 hours in 6 subjects, 1.0 hour in 19 subjects, and 1.5 hours in 11 subjects. Combined across all four metabolites in study TAAK, the tmax ranged from 0.25 to 0.3 hours a total of 7 times, from 0.50 to 0.53 hours a total of 79 times, from 1.0 to 1.03 hours a total of 43 times, and was 1.5 hours a total of 11 times. Given these data, an ideal ECG schedule would have included assessments at 0.5 and 1.0 hours, which would have encompassed the median tmax of each metabolite. However, two ECG assessments so closely spaced seemed redundant, and therefore a single time point of 1.0 hour was chosen for several reasons:

- "The major metabolite is R-106583, the tmax of which has been 1.0 hour in previous studies. The AUC for this metabolite is five times the AUC for the metabolite with the next highest AUC, R-138727. Although R-106583 is inactive for platelet binding, a lack of effect on QT/QTc interval could not be assumed.
- "Given the pharmacokinetic sampling scheme in studies TAAJ and TAAK, the true median t_{max} for R-95913, R-138727, and R-119251 appeared to be somewhere between 0.5 and 1 hours, albeit closer to 0.5 hours.
- "If a QT/QTc effect were present, an ECG assessment slightly before tmax would probably be associated with higher variability in metabolite concentrations than would an assessment slightly after the tmax. This is because the slope of the concentration-time curve before t_{max} is considerably steeper than the slope after tmax, and therefore an assessment before the t_{max} could be taken when the plasma concentrations of metabolites are considerably below t_{max}.
- "If any hysteresis were to exist between plasma concentrations and the effect of metabolites on QT/QTc, then assessing QT interval slightly later than the median tmax would be more likely to capture the maximum pharmacodynamic effect. □A single ECG assessment at 0.5 hours would probably miss any effect of the major metabolite R-106583, whose median t_{max} has been 1.0 hour in previous studies."

Reviewer's comments: Despite of above reasoning which the sponsor gives, it would have been helpful to have both 0.5 and 1 h for PK and ECG so that it could cover possible C_{max} ranges of all the metabolites and had provided more information for the analysis. It is very important to capture t_{max} to interpret E-14 analysis. Moreover, hysteresis as the reason for justification of selection of time points is inappropriate as it is not an established fact in this context.

4.2.6.5 Baseline

Patients' baseline electrocardiogram (ECGs) measurements were taken on Day -1, the day prior to the first period in order that a drug-free time-matched baseline could be used for comparative purposes.

4.2.7 ECG Collection

Source: Study Protocol

> "Three replicate 12-lead ECGs at 1-minute intervals will be recorded at baseline and post-dose in periods 1, 2 and 3 at the time points specified above. At each time point, sequential ECGs will be recorded until the investigator determines that three ECGs are suitable for measurement of the QT interval. As described below, an additional fourth ECG will be recorded for safety assessment.
>
> "Replicate ECGs for QT measurement will be sent to an ECG vendor designated by Lilly. The vendor cardiologist will only measure and report designated cardiac intervals.
>
> "Safety Assessment: Twelve-lead ECGs will be recorded for safety assessment as follows- In all three study periods, including the baseline at the same times that the three replicate ECGs are recorded for QT measurement, a fourth replicate ECG will be recorded for safety assessment. At approximately 24 hours post-dose a single safety ECG will be collected prior to discharge from the Unit. Additional

(unscheduled) ECGs may be recorded for safety assessment, if clinically indicated."

Reviewer's comments: Per study report "The 12-lead ECGs for QT measurements were sent electronically to an independent cardiologist who was blinded to all study treatments. The QT and QTc intervals were measured electronically from three replicate ECGs". Additional information about ECG acquisition and interpretation are not available in the study report. It is not clear if the reader was blinded to subject and time. It is also unclear if the core lab addressed inter-reader variability by having a subset of tracings read by a second reader

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

A total of 60 healthy subjects, 30 males and 30 females, aged 18 to 63 years, inclusive with a normal baseline ECG and BMI between 19-32kg/m^2 participated in the study. All subjects completed the study.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The sponsor used the method outlined by Dmintrienko and Smith (2002 & 2003) as the primary method for examining prasugrel's effect on the QT intervals. A linear mixed effect model was implemented only with placebo and prasugrel data with ΔQT as the dependent variable; ΔRR as a covariate; treatment, time, and treatment-by-time interaction as fixed effects; subject, subject-by-treatment, and subject-by-time as random effects; and a random error term, as shown in the following model:

ΔQT=ΔRR + treatment + time + treatment*time + subject + subject*treatment + subject*time + random error

The least squares (LS) mean ΔQT for each treatment at each scheduled time point was estimated when ΔRR equal to zero. The LS mean ΔQT difference between prasugrel and placebo at each scheduled time point, the resulting 90% confidence intervals (CI), and p-values were reported.

For QTcF, QTcB and QTcI, the statistical analysis model was nearly identical to the ΔQT analysis except that the change from baseline in RR interval was not used as a covariate, for example:

ΔQTcF=treatment + time + treatment*time + subject + subject*treatment + subject*time + random error

The control (placebo and moxifloxacin) data were used in the above model to perform the sensitivity analysis.

The sponsor's analysis results for QT, QTcB, QTcF and QTcI are shown in Table 2 for the comparison between prasugrel and placebo and Table 3 for the comparison between moxifloxacin and placebo.

Table 2 Sponsor's Analysis Results for Time-Matched Changes from Baseline in QT and QTc Intervals between Prasugrel and Placebo

Parameter		Least squares mean time-matched change from baseline (Period 1, Day -1)		Prasugrel - Placebo	
(ms)	Time (h)	80 mg prasugrel	Placebo	Difference (90% CI)	P-value
QT	1	-2.12	-0.727	-1.39 (-3.35, 0.567)	0.242
	2	-2.93	-1.76	-1.17 (-3.14, 0.798)	0.327
	6	-1.22	-1.26	0.0429 (-1.91, 2.00)	0.971
QTcB	1	0.200	-1.80	2.00 (-0.266, 4.27)	0.146
	2	0.133	-2.82	2.95 (0.684, 5.22)	0.0326
	6	2.15	-0.850	3.00 (0.734, 5.27)	0.0298
QTcF	1	-1.45	-1.02	-0.433 (-2.30, 1.43)	0.702
	2	-2.12	-2.02	-0.100 (-1.97, 1.77)	0.930
	6	-0.300	-1.02	0.717 (-1.15, 2.58)	0.527
QTcI	1	-1.75	-0.583	-1.17 (-3.24, 0.902)	0.353
	2	-2.12	-1.28	-0.833 (-2.90, 1.24)	0.507
	6	-0.867	-0.267	-0.600 (-2.67, 1.47)	0.632

Sponsor's Table TAAP. 7.2.

Table 3 Sponsor's Analyses Results for Time-Matched Changes from Baseline in QT and QTc Intervals Between Moxifloxacin and Placebo

Parameter		Least squares mean time-matched changes from baseline (Period 1, Day -1)		Moxifloxacin - Placebo	
(ms)	Time (h)	400 mg moxifloxacin	Placebo	Difference (90% CI)	P-value
QT	1	9.38	-0.727	10.1 (8.15, 12.1)	<0.001
	2	8.59	-1.76	10.4 (8.41, 12.3)	<0.001
	6	7.52	-1.26	8.79 (6.84, 10.7)	<0.001
QTcB	1	10.8	-1.80	12.6 (10.3, 14.9)	<0.001
	2	7.08	-2.82	9.90 (7.63, 12.2)	<0.001
	6	7.23	-0.850	8.08 (5.82, 10.3)	<0.001
QTcF	1	9.65	-1.02	10.7 (8.80, 12.5)	<0.001
	2	8.15	-2.02	10.2 (8.30, 12.0)	<0.001
	6	7.52	-1.02	8.53 (6.67, 10.4)	<0.001
QTcI	1	9.58	-0.583	10.2 (8.10, 12.2)	<0.001
	2	8.80	-1.28	10.1 (8.01, 12.2)	<0.001
	6	7.70	-0.267	7.97 (5.90, 10.0)	<0.001

Sponsor's Table TAAP.7.3.

Based on the sponsor's analysis results, the time-matched changes from baseline for QTcB were statistically greater for prasugrel compared to placebo at 2 and 6 hours post dose, although the mean difference between the treatments was small (3.0 ms) and the increase from baseline was low (0.1 and 2.2 ms, respectively). There was no statistical difference between prasugrel and placebo for time-matched changes from baseline for QT, QTcF and QTcI at all time points. The mean time-matched changes from baseline for QT, QTcB, QTcF and QTcI were less than 5 ms for prasugrel compared to placebo, and the upper limits of the two-sided 90% CI for the mean differences were less than 10 ms, and thus, within the limits set for clinical relevance in regulatory guidelines.

The mean time-matched changes from baseline for QT, QTcB, QTcF and QTcI were statistically greater for moxifloxacin compared to placebo at all time points, and exceeded the limits set for clinical relevance in regulatory guidelines. The sponsor concluded that the study was able to detect clinically relevant changes in QT/QTc if they existed.

4.2.8.2.2 Categorical Analysis

The sponsor summarized the number and percentage of subjects who had QTcF and QTcI intervals greater than 450 ms for males and 470 ms for females at each scheduled time point for each treatment. They also summarized the number and percentage of subjects who had a change from baseline in QTcF and QTcI intervals greater than 30 mg and 60 mg at any scheduled time point for each treatment.

Based on the sponsor's analysis results shown in Table 4, no female subjects showed QTcF and QTcI intervals exceeding 450 ms or 470 ms. Only one male showed QTcI intervals exceeding 450 ms at 1 and at 2 hours after receiving prasugrel. Also one subject had showed QTcI value exceeding 470 ms at 2 hours after receiving moxifloxacin.

Table 4 Sponsor's Analysis Results for Frequency of 12-Lead ECG QTc Intervals >450 ms (for Males) and >470 ms (for Females)

		Number [%] of males >450 ms and females >470 ms	
Treatment	Time (h)	QTcF	QTcI
Baseline	1	0 [0]	0 [0]
(N=60)	2	0 [0]	0 [0]
	6	0 [0]	0 [0]
80 mg prasugrel	1	0 [0]	1 [2]
(N=60)	2	0 [0]	1 [2]
	6	0 [0]	0 [0]
Placebo	1	0 [0]	0 [0]
(N=60)	2	0 [0]	0 [0]
	6	0 [0]	0 [0]
400 mg moxifloxacin	1	0 [0]	0 [0]
(N=60)	2	0 [0]	1 [2]
	6	0 [0]	0 [0]

N = Number of subjects studied

Sponsor's Table TAAP.7.4.

Based on the sponsor's analysis results shown in Table 5, no subject showed a time-matched increase from baseline in QTcF and QTcI of >30 ms following the administration of prasugrel or placebo. Following administration of moxifloxacin, two female subjects showed a time-matched increase from baseline in QTcI of >30ms.

Table 5 Sponsor's Analysis Results for Frequency of Time-Matched Increases from Baseline (Period 1, Day -1) in 12-Lead ECG QTc Intervals >30 ms and >60 ms

		Number [%] of subjects			
		QTcF		QTcI	
Treatment	Time (h)	>30 ms	>60 ms	>30 ms	>60 ms
80 mg prasugrel	1	0 [0]	0 [0]	0 [0]	0 [0]
(N=60)	2	0 [0]	0 [0]	0 [0]	0 [0]
	6	0 [0]	0 [0]	0 [0]	0 [0]
Placebo	1	0 [0]	0 [0]	0 [0]	0 [0]
(N=60)	2	0 [0]	0 [0]	0 [0]	0 [0]
	6	0 [0]	0 [0]	0 [0]	0 [0]
400 mg moxifloxacin	1	0 [0]	0 [0]	1 [2]	0 [0]
(N=60)	2	0 [0]	0 [0]	0 [0]	0 [0]
	6	0 [0]	0 [0]	2 [3]	0 [0]

N = Number of subjects studied

Sponsor's Table TAAP 7.6

4.2.8.2.3 Additional Analyses

The sponsor did not perform any additional analysis.

4.2.8.3 Safety Analysis

There were no deaths or SAEs or discontinuations due to an AE.

The most frequently reported drug-related adverse events following administration of prasugrel were contusion (bruising), dizziness (including postural dizziness) and nausea.

The incidence of other bleeding-related adverse events (post procedural haemorrhage and skin laceration) was low following administration of prasugrel. Following administration of placebo, the incidence of all bleeding-related adverse event was low, and no bleeding-related adverse events were reported following the administration of moxifloxacin.

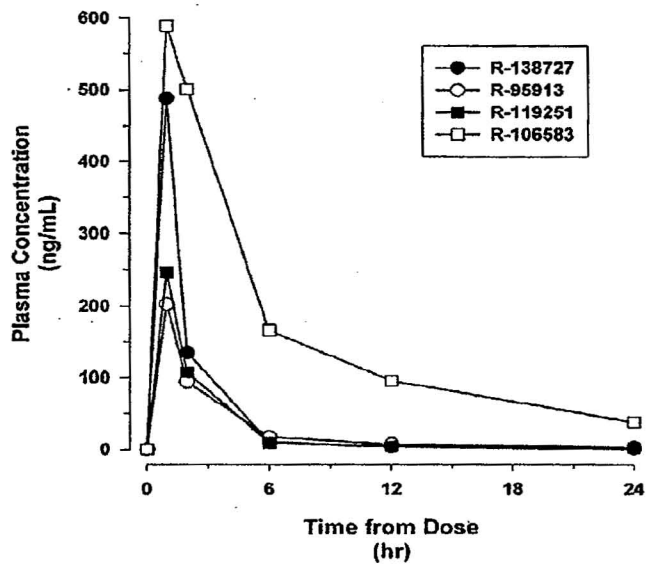
There were no clinically significant findings in safety 12-lead ECGs for individual subjects following administration of prasugrel, placebo and moxifloxacin.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

Mean concentration time profiles of prasugrel metabolites are shown in Figure 1 below. Non compartmental parameter estimates for R-138727, R-95913, R-119251 and R-106583 following single oral dose of 80-mg prasugrel are presented in Table 6.

Figure 1: Mean concentration-time profiles of prasugrel metabolites



Sponsor's Figure TAAP 7.1