Table 6. Non-compartmental parameter estimates for R-138727, R-95913, R-119251 and R-106583 following single oral dose of 80 mg prasugrel

Geometric Mean (%CV)				
Parameter	R-138727	R-95913	R-119251	R-106583
C1hr	449	186	227	555
(ng/mL)	(44.8)	(43.3)	(43.7)	(40.1)
AUC(0-tlast)	679	497	468	3370
(ng•h/mL)	(37.3)	(38.1)	(37.2)	(31.3)
AUC(0-∞)	700a	546b	526c	3830
(ng•h/mL)	(38.0)	(34.0)	(32.5)	(33.3)
T1/2	6.83a	7.40b	7.45c	8.61
(h)	(14.5)	(13.0)	(11.2)	(20.5)
N	60	60	60	60

Abbreviations: AUC(0-tlast) = area under the plasma concentration-time curve from time zero to the last quantifiable plasma concentration; AUC(0-∞)= area under the plasma concentration-time curve from time zero to infinity; C_{1hr} = plasma concentration measured 1 hour post dose; N = number of subjects used in parameter estimation; $T_{1/2}$ = apparent terminal elimination half-life

a N = 55

b N = 56

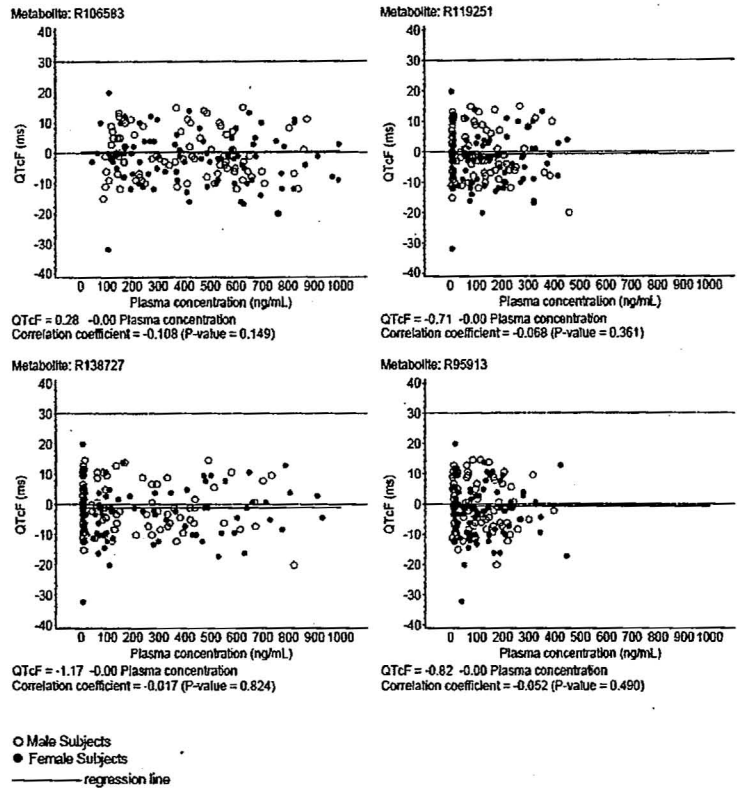
c N = 50

Sponsor's Table TAAP 7.1

4.2.8.4.2 Exposure-Response Analysis

Sponsors explored relationships of absolute QTcF and QTcI intervals and time-matched change from baseline versus plasma concentrations of all four prasugrel metabolites (R-138727, R-95913, R-106583 or R-119251). The time-matched changes from baseline in QTcF and QTcI intervals versus plasma concentrations of R-138727, R-95913, R-106583 and R-119251 profiles showed regression slopes close to zero for each metabolite over the entire range of concentration. (See H7T-EW-TAAP Main Report). These results indicate that there was no correlation between plasma concentrations of prasugrel metabolites and changes in QTc interval. Shown below are the plots for time-matched change from baseline versus plasma concentrations of all the metabolites using QTcF correction criteria (as QTcF was found to be more appropriate than QTcI; See section 5.1 and 5.2). (See Reviewer's assessment for exposure response analysis in Section 5.2)

Figure 2. Sponsors plasma concentration-QTcF relationships



Sponsor's TAAP Appendix 11.4.3

5 REVIEWERS' ASSESSMENT

5.1 STATISTICAL ASSESSMENTS

It appears that the sponsor's individual correction method did not sufficiently correct for heart rate (Figure). QTcF seems to be a better correction method (Figure). Therefore, this reviewer used QTcF as the primary endpoint. The statistical reviewer used an ANCOVA model by considering treatment, sequence, and period as covariates.

Table 7 shows the analysis results for both ΔΔQTcI and ΔΔQTcF. For the comparison between prasugrel and placebo after baseline adjustment, none of the upper limits of the one-sided 95% CI exceeds 10 ms. For the comparisons between moxifloxacin and placebo, the largest lower bound is greater than 5 ms after Bonferroni adjustment (97% CI). Therefore, this reviewer confirmed the sponsor's analysis results.

Table 7 Statistical Reviewer's Analysis Results for ΔΔQTcF and ΔΔQTcI

Time	Prasugrel vs. Placebo		Moxifloxacin vs Placebo		
	LS Mean	90% C.I.	LS Mean	90% C.I.	97% C.I.*
QTcF					
1	-0.43	(-2.80, 1.93)	10.67	(8.30, 13.03)	(7.54, 13.79)
2	-0.10	(-2.35, 2.15)	10.17	(7.92, 12.42)	(7.19, 13.14)
6	0.72	(-1.83, 3.26)	8.53	(5.99, 11.08)	(5.17, 11.90)
24**	2.07	(-1.25, 5.40)	4.35	(1.02, 7.67)	(-0.06, 8.75)
QTcI					
1	-1.17	(-3.56, 1.22)	10.17	(7.78, 12.56)	(7.00, 13.33)
2	-0.83	(-3.10, 1.44)	10.08	(7.81, 12.36)	(7.07, 13.09)
6	-0.60	(-3.13, 1.93)	7.97	(5.43, 10.50)	(4.62, 11.32)

- After Bonferroni correction.

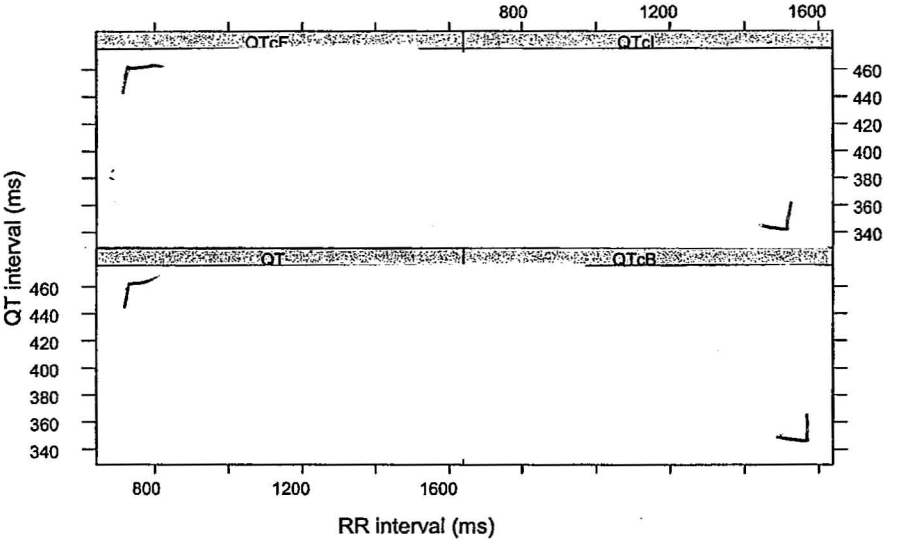
** At hr 24, there was only one measurement; whereas at other time points, there were 3 replicates.

Note: In this review, double delta, ΔΔ actually is just the single-delta difference between the two treatment arms of interest (prasugrel vs. placebo or moxifloxacin vs. placebo). The baseline values are cancelled out since all the treatments share the same baseline.

5.2 Clinical Pharmacology Assessments

The relationship between QT and RR with different correction methods is illustrated in figure below. The Fridericia,s correction method was found to be reasonable for further analysis.

Figure 3. QT (Raw QT measurements, Bazzet, Fridericia and individually corrected QT)-RR interval relationship



b(4)

The time course of mean ΔΔQTcF for R-138727 following 80-mg prasugrel and moxifloxacin (400 mg) is illustrated below in Figure 4. There seems to be no significant relationship between R-138727 exposure and ΔΔQTcF from Figure 5. The similar pattern for concentration- ΔΔQTcF was observed for other metabolites as well.

Figure 4. Time course of mean ΔΔQTcF

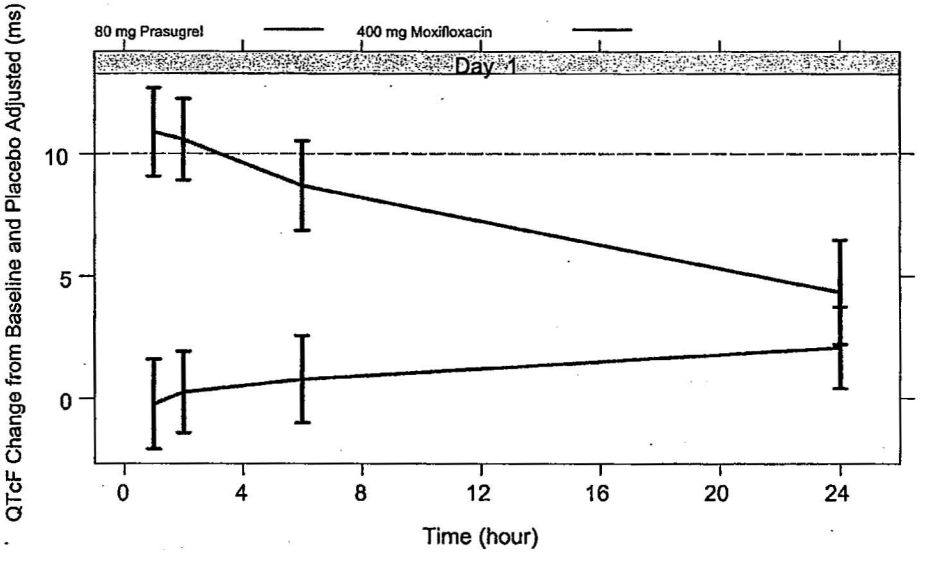
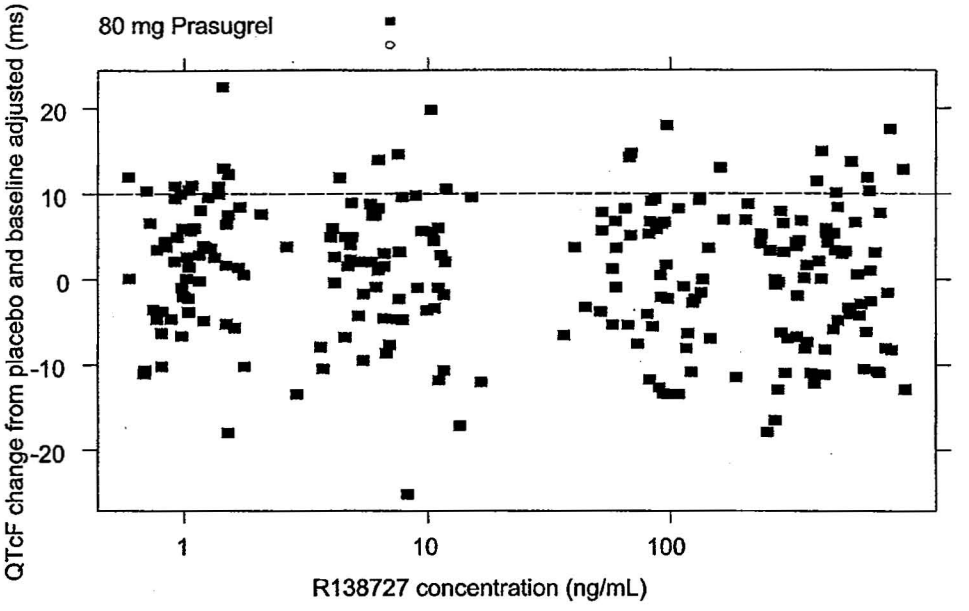


Figure 5. Log concentration-ΔΔQTcF relationship for R-138727



The Sponsor used a single 80-mg prasugrel dose as their only active treatment in the present TQT study TAAP. Use of single oral dose is justified with respect to accumulation as there is no accumulation expected and also because the maintenance dose is 10-mg ($1/8^{th}$ of the current TQT studied dose). The sponsor compares the exposures achieved by the four metabolites in the present study to that possible in worst-case scenarios after a 10-mg maintenance dose in clinical setting, and concludes that the latter are obviously much lower. However, as the dosing regimen proposed is a 60-mg loading dose followed by a 10-mg maintenance dose, it would also be relevant to compare the worst case scenarios of the metabolites with the clinical 60-mg loading dose. According to the PK metanalysis of various studies it was shown that the C_{max} increases with decrease in body weight with 60 kg as the threshold limit below which the maintenance dose should be decreased to 5-mg. Since the loading dose did not change, the C_{max} with the loading dose of 60-mg for the active metabolite (R-138727) may go as high as 1200 ng/ml (See 2.7.2. Summary-Clin Pharm, Page 91) which is not covered by the 80-mg prasugrel dose. In study TABZ (H7T-EW-TABZ Main Report), geometric mean of R-138727 C_{max} in Asians ranged from 565-614 ng/ml which is higher than the mean C_{1h} (449 ng/ml) achieved in the present study. The median C_{max} in Asians is around 600 ng/ml (approximate range 200-1400 ng/ml, Figure 2.7.2.23 in Summary-Clin Pharm). Also for metabolite R-95913 exposure in the Chinese group was higher (geometric mean 260 ng/ml, H7T-EW-TABZ Main Report, Pg 37) which is higher than the mean C_{max} (186 ng/ml) achieved with the 80-mg prasugrel dose in the present study. Compared to Caucasians, R-119251 exposure was higher in Asians (geometric mean C_{max} from 262 to 316 ng/ml) compared to 227 ng/ml achieved in the TQT study. Exposures for 1068583 were similar between Asians and Caucasians and should be covered by the mean C_{max} of 555 ng/ml in the TQT study. So overall for most of the metabolites,

exposures in Asians were on an average higher than observed in the present study signifying that the dose may not be large enough to produce the exposures of the metabolites expected in Asians. It is however important to note that the high exposures expected in TABZ when compared with the present TQT study may also be a consequence of an incorrect sampling scheme (see section 4.2.6.4). There was no effect of age on exposure of metabolites as evident from TACG study (H7T-EW-TACG Main Report, Page 32-37) which was also supported by population analysis of TAAD, TABR, TAAL. (See Summary-ClinPharm, Page 99). Exposures of R-138727 did not change significantly in moderately hepatic impaired individuals. C_{max} for 1068583 and 95913 decreased slightly but geometric mean for R-95913 was 209 ng/ml which is higher than 186 ng/ml obtained after 80-mg prasugrel. Exposure for R-119521 was increased in moderately hepatic impaired individuals (C_{max} geometric mean-296 ng/ml) which is higher than 227 ng/ml observed in TQT study (See H7T-EW-TABV Main Report, Pg 24-32). Exposures of all the metabolites decreased in ESRD subjects and no clinically significant scenarios were evident as a result of interaction with the strong 3A4 inducer rifampicin. With respect to drug interaction with ketoconazole, the exposure for metabolite 95913 doubled (geometric mean C_{max} -330 ng/ml) which is higher than that observed in the TQT study while for other three metabolites, the exposure lowered which is well within limits of exposures achieved in the present TQT study (See study H7T-EW-TAAK Main Report, Pg 41, 48).

Considering the fact that the insignificance in exposure-response relationship may be due insufficient information because of an inappropriately designed study with respect to selection of dose and time of sample collection, it was decided to look at the exposures achieved in a large Phase III clinical study TAAL. In TAAL only R119521 and R106583 were measured. The exposures in TAAL after a 60-mg loading dose were found to be much lower for R-106583 and similar for R-119521. In the population PK study of TAAL (1159 subjects) fewer than 2% of the subject had exposures of R-119521 higher than that observed in the QT study. With this information it could be said that the exposures of R-119521 were good enough in the present QT study to rule out any exposure-response relationship for R-119521 in spite of predicting the scenarios which might have higher exposure than in the present QT study. Furthermore, considering, that the 60-mg loading dose will be given inpatient under clinical supervision, it would be reasonable to compare exposures of metabolites in this TQT study (80-mg prasugrel) to that following a10-mg maintenance dose. In this case, the 80-mg dose would comfortably cover the exposures expected after a 10-mg maintenance dose. Moreover, no relationship was observed between concentration-$\Delta\Delta$QTcF for any of the metabolites in the observed concentration ranges. Thus it can be said that prasugrel is unlikely to prolong QT interval after clinically relevant exposures.

5.3 CLINICAL ASSESSMENTS

5.3.1 Safety Assessments

None of the events identified to be of clinical importance per the ICH E-14 guidelines (i.e. death, significant ventricular arrhythmia, seizures and syncope) occurred in this study.

5.3.2 ECG assessments

Waveforms submitted to the ECG warehouse were reviewed. ECG acquisition appears acceptable. The core lab used the 12 lead overlay method for QT measurement, which is acceptable (same method for baseline and treatment ECGs). However, QT analysis scores cannot be computed by the ECG warehouse in this case.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	60 mg LD, 10 mg MD. A 5 mg MD is recommended for subjects who weigh <60 kg and may be considered for subjects who are 75 years.	
Maximum tolerated dose	The highest single dose given to humans was 80 mg given in Study TAAP. This dose was well tolerated.	
Principal adverse events	The most frequently reported adverse events in clinical pharmacology studies were bruising and/or bleeding related to study procedures, headache, contusion, dizziness, nausea, and epistaxis.	
Maximum dose tested	Single Dose	80 mg
	Multiple Dose	25 mg/ day up to 10 days, 15 mg/day up to 28 days
Exposures Achieved at Maximum Tested Dose	Single Dose	For active metabolite C1h was 449 ng/mL (44.8%) and AUC0-tlast was 679 ng·hr/mL (37.3%). The plasma concentration was measured at 1 hour instead of at the typical Tmax of 30 minutes.
	Multiple Dose	Mean Cmax was 105 ng/ml and AUC0-tlast was 101 ng·hr/mL.
Range of linear PK	5 mg – 60 mg	
Accumulation at steady state	none	
Metabolites	The prasugrel active metabolite is R-138727. In vivo studies have identified the following additional prasugrel mebabolites: R-95913, R-100932, R-104434, R-106583, R-118443, and R-119251. While R-138727 inhibits platelet aggregation in a concentration dependent manner, the other prasugrel metabolites are inactive.	
Absorption	Absolute/Relative Bioavailability	We have not conducted an absolute bioavailabiliy study. Based on a 14C study, at least 79% of the

		prasugrel dose was absorbed.
	Tmax	The tmax range was 0.25 hours to 2.25 hours. The tmax range for metabolites was 0.5 hours – 1 hour.
Distribution	Vd/F or Vd	Vd/F is 44.2 liters (standard error = 7.13 %).
	% bound	Because the active metabolite of prasugrel is unstable in plasma, its binding to plasma proteins could not be determined. However, binding was 98% in a 4% human serum albumin solution in phosphate buffer at pH 7.4.
Elimination	Route	Approximately 95% of a [14C]prasugrel dose was recovered after oral administration (Study TAAB). About 68% and 27% of the dose was recovered in urine and feces, respectively, indicating that urinary excretion is the major pathway for the elimination of prasugrel metabolites.
	Terminal t½	7.4 hours
	CL/F or CL	CL/F is 123 L/hr (standard error is 3.98%).
	Age	The point estimate for a comparison of AUC between subjects 65 years and subjects <40 years was 0.92 (0.79, 1.07). The point estimate for Cmax was 0.93 (0.71, 1.22) (Tables TACG.7.2)
	Sex	The geometric mean of AUC(0-tlast) for the comparison of females to males was 1.01 (0.956, 1.07)
	Race	The effect of ethnic origin was assessed in a PK meta-analysis of 16 clinical pharmacology studies. The analysis showed that AUC(0-tlast) in subjects of African and Hispanic descent was comparable to those in Caucasians. The geometric mean of AUC(0-tlast) for the comparison of subjects of East Asian ethnicity to Caucasian subjects was 1.193 (1.111, 1.281).
	Hepatic & Renal Impairment	The geometric mean of AUC(0-tlast) for the comparison of subjects with end stage renal failure to healthy subjects was 0.579 (0.457, 0.733). The geometric mean of AUC(0-tlast) for the comparison of subjects with moderate hepatic impairment to healthy subjects was 1.08 (0.76, 1.54).
	Drug interactions	Drug interaction studies were conducted with prasugrel and aspirin, ketoconazole, rifampicin, and atorvastatin. These analyses detected no clinically relevant drug

		interactions.
	Food Effects	A high fat, high calorie meal did not affect the AUC of prasugrel's active metabolite after a single dose of prasugrel.HCl, but it decreased Cmax by 49% and delayed the tmax from 0.5 to 1.5 hours.
Expected High Clinical Exposure Scenario	Although low body weight (<60 kg) is associated with the highest exposure to the prasugrel active metabolite, the recommended adjustment from a 10 mg MD to a 5 mg MD will lower exposure in this population below the median across all subjects. Therefore, the worst case scenario during clinical use is expected to be in subjects of pure East Asian descent. After adjusting for body weight, exposure is expected to be about 20% compared to Caucasians. This increase is covered by 80 mg dose given in Study TAAP.	

6.2 TABLE OF STUDY ASSESSMENTS

Period Day	12-lead ECG	Physical Exam	Medical History	Clinical Lab Tests	Admit to CRU	Study Drug	Discharge from CRU	Vital signs	Height and Weight	Urine Drug Screen	Blood ET-OH /Breath Test	PK Sampling (hours)h
Screening	X	X	X	X				X	X	X	X	
PERIOD 1												
-2				X	X			X	Xe	X	X	
-1	Xa,f							X				
1	Xa,f					X		Xc				Xb
2	Xd	X					X	Xd				Xd
Washout g												
PERIOD 2												
-1				X	X			X	Xe	X	X	
1	Xa,f					X		Xc				Xb
2	Xd	X					X	Xd				Xd
Washout g												
PERIOD 3												
-1				X	X			X	Xe	X	X	
1	Xa,f					X		Xc				Xb
2	Xd	X						Xd				Xd
Follow-up	X	X		X			X	X	Xe			

a Taken at: 1, 2, and 6 hours

b Taken at Predose, 1, 2, 6, and 12 hours postdose

c Measured at: predose and 4 hours postdose

d Taken/Measured at: 24 hours postdose

e Weight only

f One additional safety ECG

g Minimum of 10 days

h PK samples will only be taken during placebo and prasugrel dosing periods

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Suchitra Balakrishnan
4/4/2008 02:30:42 PM
MEDICAL OFFICER

Yeh-Fong Chen
4/4/2008 02:34:47 PM
BIOMETRICS

Joanne Zhang
4/4/2008 02:38:36 PM
BIOMETRICS

Nitin Mehrotra
4/7/2008 09:45:05 AM
BIOPHARMACEUTICS

Christine Garnett
4/9/2008 12:46:08 PM
BIOPHARMACEUTICS

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-307

Eli Lilly and Company
Attention: Elizabeth C. Bearby, Pharm.D.
Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Bearby:

Please refer to your new drug application (NDA) dated December 26, 2007, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, for Effient (prasugrel) 5 mg and 10 mg Tablets.

We also refer to your submissions dated February 25 and 28, 2008.

During our filing review of your application, we identified the following potential review issues:

1. In Study TAAL, one of the key secondary objectives is the risk of definite or probable stent thrombosis per Academic Research Consortium (ARC) definition at study end; however, in the Clinical Study Report, definite stent thrombosis is described angiographically only. This definition is different than that proposed by Cutlip *et. al.* and the Academic Research Consortium,[1] which indicates definite stent thrombosis may be confirmed angiographically or pathologically.

    a. Please clarify the definition of definite stent thrombosis used for this trial.
    b. Please clarify whether or not autopsies were utilized to confirm stent thrombosis and indicate which patients had autopsy evidence of stent thrombosis.
    c. Please describe the materials used in the adjudication of the stent thrombosis endpoint (*e.g.*, coronary angiograms, reports of coronary angiograms, imaging studies, reports of imaging studies, autopsy reports, etc.). Please explain and justify the procedures used in the adjudication of the stent thrombosis endpoint.

2. Please provide a diagram for site of lesion (PCI/LESITE) for the PCI.XPT data set, or indicate where this diagram is located in the submission.

3. We still appear to have problems with the raw data for this submission. An example is case 01001012123 in TAAL. In the CRFs, this case has an adverse event of "Bilateral

[1]Cutlip DE, et. al., *Circulation* 2007;115:2344-2351.

Metastasis" (event code E13) noted on two occasions. However, in the SAS datasets this adverse event is recorded as "BRAIN CANCER" in variables AEMODIFY (described in the DEFINE.PDF file as "CRF Page 10, CRF Page 26. Investigator verbatim term.") and AETERM (identical to AEMODIFY). The CEC notes state that "THE PATIENT'S PRIMARY SITE WAS LUNG". The data clarification forms do document that your pharmacovigilance staff interacted with the investigator to change the AE to "BRAIN CANCER". However, we would like the original investigator recordings for all AEs. Please address the following requests:

a. Please explain why this case was not coded as a lung cancer.
b. Please provide a SAS file with the original investigator verbatim terms for all adverse events.
c. Please provide a SAS file with the original investigator verbatim terms for all adverse events for which the term was changed during the data clarification process and including a comment variable explaining why the change was made.
d. Please address whether any of the investigators' original endpoint categorizations changed through your data clarification process. If any were changed, please provide a SAS file with the original investigator categorizations for all endpoints changed during the data clarification process, including a comment variable explaining why the change was made.

4. There appear to be increased rates of cancer with prasugrel compared to clopidogrel. The documentation provided is brief and coding is sometimes inadequate for cancer cases, as illustrated in the case referenced in item 3. For some cases, the only information we have been provided in the SAS files is that there was a "PULMONAR LESION" or "GASTROINTESTINAL CANCER". Access to detailed and accurate information on all diagnosed or potential neoplasms is essential for a complete review of this submission. Please submit the following:

a. Please provide narratives and complete case report forms (including CEC dossiers when applicable) for all diagnosed or potential neoplasms.
b. For any case for which the available information is inconclusive regarding the malignancy status and site, *e.g.,* the "PULMONAR LESION" and "GASTROINTESTINAL CANCER" referenced above, please follow up as necessary to confirm the diagnosis, preferably documented by procedure and histology reports, and submit all copies of all communications and documentation obtained.
c. You should obtain long-term follow-up for vital status and, if dead, cause of death for all cancer cases.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We have also reviewed your proposed labeling and have several comments. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, these comments are recommendations only. Please submit the following formatting changes to the label:

1. Per 21 CFR 201.57(d)(8), the Highlights section should be in 8-point font. This may allow the Highlights and Table of Contents to fit on the same page. If not, insert the Table of Contents on page 2 of the labeling.
2. The Highlights section must be limited in length to one-half page, in 8 point type, two-column format. You may change the margins to one-half inch in order to comply. If you are unable to fit Highlights on one-half page, you must request a waiver from this requirement. [See 21 CFR 201.57(d)(8)]
3. Please delete the first two bullets under USE IN SPECIFIC POPULATIONS in the Highlights section, as the information is included elsewhere in Highlights (WARNINGS AND PRECAUTIONS).
4. Remove the trade mark symbol from the Highlights section. You may use it one time in the Full Prescribing Information.
5. Since the route of administration is typical for the dosage form and is commonly understood, you may omit the route of administration ("for oral use").
6. Throughout Full Prescribing Information, change passive phrases to active voice (*e.g.*, "Effient should be initiated" to "Initiate Effient"; "Effient should be used with caution in patients with a known history…" to "Use Effient with caution…"
7. Per 21 CFR 201.57(c)(5), the Contraindication listed should clearly define, "active pathological bleeding" in a clinically meaningful way. Specify your clinical concern about what happens in this population and describe the type and nature of this concern. Also include the cross-reference to the more detailed information in the Clinical Pharmacology, or Clinical Studies section.
8. Per 21 CFR 201.57(c)(6), the Warnings and Precautions section should include laboratory tests to monitor patient response or to identify possible reaction. Also, the items in Warnings and Precautions (section 5) do not cross-reference the applicable sub-sections in section 8 (Use in Specific Populations). Please make them consistent with each other.
9. Per 21 CFR 201.57(c)(7), replace adverse event" with "adverse reaction" (refer to the "Guidance for Industry: Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products – Content and Format"
10. Per 21 CFR 201.57(c)(9)(v)(C)(2), we recommend you include what knowledge you have about potential kidney excretion.
11. Please change "Trial" to "Trials" in the section heading ("Clinical Trial Experience") for section 6, in both Contents and FPI.

Please submit these changes to the Prescribing Information (physician labeling rule) format by Monday, March 24, 2008. You must also update the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, please call:

Meg Pease-Fye, M.S.
Regulatory Health Project Manager
(301) 796 -1130

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Norman Stockbridge
3/7/2008 04:07:22 PM