CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 22-307/S008

Trade Name: Effient®

Generic Name: prasugrel

Sponsor: Eli Lilly and Company

Approval Date: 10/16/2013

Indication: Effient® is a $P2Y_{12}$ platelet inhibitor indicated for the reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with acute coronary syndrome who are to be managed with PCI as follows:

- Patients with unstable angina or, non-ST-elevation myocardial infarction (NSTEMI).
- Patients with ST-elevation myocardial infarction (STEMI) when managed with either primary or delayed PCI.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-307/S008

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
REMS	
Summary Review	**X**
Officer/Employee List	**X**
Office Director Memo	**X**
Cross Discipline Team Leader Review	**X**
Medical Review(s)	**X**
Chemistry Review(s)	
Environmental Assessment	
Pharmacology Review(s)	
Statistical Review(s)	**X**
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	**X**
Other Reviews	**X**
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-307/S008

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22307/S-008

SUPPLEMENT APPROVAL

Eli Lilly and Company
Attention: Peter Morrow, MS
Director, Global Regulatory Affairs - US
Lilly Corporate Center
Indianapolis, IN 46285

Dear Mr. Morrow:

Please refer to your Supplemental New Drug Application (sNDA) dated December 14, 2012, received December 17, 2012, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Effient (prasugrel hydrochloride) 5 mg and 10 mg Tablets.

We acknowledge receipt of your amendments dated January 31, February 5, 8, and 18, March 19, April 1, 23, and 26, May 3, 10, 17, and 31, June 28, July 9, September 25, and October 11, 2013.

This Prior Approval efficacy supplemental new drug application contained effectiveness, safety, and clinical pharmacology data from Study H7T-MC-TABY ("A Comparison of Prasugrel and Clopidogrel in Acute Coronary Syndrome (ACS) Subjects with Unstable Angina/Non-ST-Elevation Myocardial Infarction (UA/NSTEMI) Who are Medically Managed—The TRILOGY ACS Study"). This application did not seek any new indication (b) (4) this application proposed changes to the labeling based on results from four completed pharmacokinetic/pharmacodynamic studies. Lastly, the submission contained final reports for Postmarketing Requirement #2 (95-2) and Postmarketing Commitment #6 (95-6).

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text. (b) (4) we have updated the label in Section 12 with new pharmacokinetic/pharmacodynamic data.

We note that your October 11, 2013, submission includes final printed labeling (FPL) for your package insert and Medication Guide. We have not reviewed this FPL. You are responsible for assuring that the wording in this printed labeling is identical to that of the approved content of labeling in the structured product labeling (SPL) format.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Given the limited number of children with acute coronary syndrome, we are waiving the pediatric study requirement for this application because studies would be impossible or highly impracticable.

POSTMARKETING REQUIREMENTS UNDER 505(o)

We remind you of your post-marketing requirements listed in our action letter dated July 10, 2009. These requirements are listed below:

95-2 You will gather baseline cancer history and cancer adverse event data from the ongoing trial TRILOGY, a 10,300-subject trial being conducted in patients with acute coronary syndrome who are being managed medically (without coronary revascularization). The final report on cancers in this trial is to be submitted to IND 63,449.

The timetable you submitted on July 8, 2009 states that you will conduct this trial according to the following timetable:

Protocol Submission: Received 06/20/2008
Trial Completion Date: 12/2012
Final Report Submission: 01/2013

POSTMARKETING COMMITMENTS REPORTABLE UNDER SECTION 506B

We also remind you of your post-marketing commitment listed in our action letter dated July 10, 2009. This commitment is listed below:

95-6 You commit to the collection of samples at baseline for genotyping CYP450 enzymes in TRILOGY subjects, to allow a comparison of effectiveness and bleeding in prasugrel and clopidogrel subgroups by metabolizer status. These data will be submitted with the final study report of TRILOGY. The periodic reports will include the fraction of subjects who consented to genetic testing.

We understand that the protocols for these trials have been submitted.

Final Protocol Submission: Received 06/20/2008
Trial Completion Date: 12/2012
Final Report Submission: 01/2013

Submit clinical protocols to your IND (63,449) for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package

labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call:

Alison Blaus, RAC
Regulatory Project Manager
(301) 796-1138

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE:
Content of Labeling

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

/s/

NORMAN L STOCKBRIDGE
10/16/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-307/S008

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use EFFIENT safely and effectively. See full prescribing information for EFFIENT.

EFFIENT (prasugrel) tablets, for oral use

Initial U.S. Approval: 2009

WARNING: BLEEDING RISK

See full prescribing information for complete boxed warning.

- **Effient can cause significant, sometimes fatal, bleeding (5.1, 5.2, 6.1).**
- **Do not use Effient in patients with active pathological bleeding or a history of transient ischemic attack or stroke (4.1, 4.2).**
- **In patients ≥75 years of age, Effient is generally not recommended, except in high-risk patients (diabetes or prior MI), where its use may be considered (8.5).**
- **Do not start Effient in patients likely to undergo urgent coronary artery bypass graft surgery (CABG). When possible, discontinue Effient at least 7 days prior to any surgery (5.2).**
- **Additional risk factors for bleeding include: body weight <60 kg; propensity to bleed; concomitant use of medications that increase the risk of bleeding (5.1)**
- **Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, percutaneous coronary intervention (PCI), CABG, or other surgical procedures in the setting of Effient (5.1).**
- **If possible, manage bleeding without discontinuing Effient. Stopping Effient increases the risk of subsequent cardiovascular events (5.3).**

---------- RECENT MAJOR CHANGES ----------

Warnings and Precautions
General Risk of Bleeding (5.1) 11/2012

---------- INDICATIONS AND USAGE ----------

Effient® is a $P2Y_{12}$ platelet inhibitor indicated for the reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with acute coronary syndrome who are to be managed with PCI as follows:

- Patients with unstable angina or, non-ST-elevation myocardial infarction (NSTEMI) (1.1).
- Patients with ST-elevation myocardial infarction (STEMI) when managed with either primary or delayed PCI (1.1).

----------DOSAGE AND ADMINISTRATION----------

- Initiate treatment with a single 60-mg oral loading dose (2).
- Continue at 10-mg once daily with or without food. Consider 5-mg once daily for patients <60 kg (2).
- Patients should also take aspirin (75-mg to 325-mg) daily (2).

----------DOSAGE FORMS AND STRENGTHS----------

5-mg and 10-mg tablets (3)

---------- CONTRAINDICATIONS ----------

- Active pathological bleeding (4.1)
- Prior transient ischemic attack or stroke (4.2)
- Hypersensitivity to prasugrel or any component of the product (4.3)

----------WARNINGS AND PRECAUTIONS----------

- CABG-related bleeding: Risk increases in patients receiving Effient who undergo CABG (5.2).
- Discontinuation of Effient: Premature discontinuation increases risk of stent thrombosis, MI, and death (5.3).
- Thrombotic thrombocytopenic purpura (TTP): TTP has been reported with Effient (5.4).
- Hypersensitivity: Hypersensitivity including angioedema has been reported with Effient including in patients with a history of hypersensitivity reaction to other thienopyridines (5.5).

----------ADVERSE REACTIONS----------

Bleeding, including life-threatening and fatal bleeding, is the most commonly reported adverse reaction (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Eli Lilly and Company at 1-800-545-5979 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 10/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: BLEEDING RISK

- **Effient can cause significant, sometimes fatal, bleeding *[see Warnings and Precautions (5.1, 5.2) and Adverse Reactions (6.1)]*.**
- **Do not use Effient in patients with active pathological bleeding or a history of transient ischemic attack or stroke *[see Contraindications (4.1, 4.2)]*.**
- **In patients ≥75 years of age, Effient is generally not recommended, because of the increased risk of fatal and intracranial bleeding and uncertain benefit, except in high-risk situations (patients with diabetes or a history of prior MI) where its effect appears to be greater and its use may be considered *[see Use in Specific Populations (8.5)]*.**
- **Do not start Effient in patients likely to undergo urgent coronary artery bypass graft surgery (CABG). When possible, discontinue Effient at least 7 days prior to any surgery *[see Warnings and Precautions (5.2)]*.**
- **Additional risk factors for bleeding include: body weight <60 kg; propensity to bleed; concomitant use of medications that increase the risk of bleeding (e.g., warfarin, heparin, fibrinolytic therapy, chronic use of non-steroidal anti-inflammatory drugs [NSAIDs]) *[see Warnings and Precautions (5.1)]*.**
- **Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, percutaneous coronary intervention (PCI), CABG, or other surgical procedures in the setting of Effient *[see Warnings and Precautions (5.1)]*.**
- **If possible, manage bleeding without discontinuing Effient. Discontinuing Effient, particularly in the first few weeks after acute coronary syndrome, increases the risk of subsequent cardiovascular events *[see Warnings and Precautions (5.3)]*.**

1 INDICATIONS AND USAGE

1.1 Acute Coronary Syndrome

Effient® is indicated to reduce the rate of thrombotic cardiovascular (CV) events (including stent thrombosis) in patients with acute coronary syndrome (ACS) who are to be managed with percutaneous coronary intervention (PCI) as follows:

- Patients with unstable angina (UA) or non-ST-elevation myocardial infarction (NSTEMI).
- Patients with ST-elevation myocardial infarction (STEMI) when managed with primary or delayed PCI.

Effient has been shown to reduce the rate of a combined endpoint of cardiovascular death, nonfatal myocardial infarction (MI), or nonfatal stroke compared to clopidogrel. The difference between treatments was driven predominantly by MI, with no difference on strokes and little difference on CV death *[see Clinical Studies (14)]*.

It is generally recommended that antiplatelet therapy be administered promptly in the management of ACS because many cardiovascular events occur within hours of initial presentation. In the clinical trial that established the efficacy of Effient, Effient and the control drug were not administered to UA/NSTEMI patients until coronary anatomy was established. For the small fraction of patients that required urgent CABG after treatment with Effient, the risk of significant bleeding was substantial *[see Warnings and Precautions (5.2)]*. Because the large majority of patients are managed without CABG, however, treatment can be considered before determining coronary anatomy if need for CABG is considered unlikely. The advantages of earlier treatment with Effient must then be balanced against the increased rate of bleeding in patients who do need to undergo urgent CABG.

2 DOSAGE AND ADMINISTRATION

Initiate Effient treatment as a single 60-mg oral loading dose and then continue at 10-mg orally once daily. Patients taking Effient should also take aspirin (75-mg to 325-mg) daily *[see Drug Interactions (7.3) and Clinical Pharmacology (12.3)]*. Effient may be administered with or without food *[see Clinical Pharmacology (12.3) and Clinical Studies (14)]*.

Dosing in Low Weight Patients

Compared to patients weighing ≥60 kg, patients weighing <60 kg have an increased exposure to the active metabolite of prasugrel and an increased risk of bleeding on a 10-mg once daily maintenance dose. Consider lowering the maintenance dose to 5-mg in patients <60 kg. The effectiveness and safety of the 5-mg dose have not been prospectively studied *[see Warnings and Precautions (5.1), Adverse Reactions (6.1), and Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

Effient 5-mg is available as a yellow, elongated hexagonal, film-coated, non-scored tablet:

- debossed with "5 MG" on one side and "4760" on the other side (original formulation)

OR

- debossed with "5121" on one side and 3 parallel arched lines followed by a "5" on the other side (revised formulation)

Effient 10-mg is available as a beige, elongated hexagonal, film-coated, non-scored tablet:

- debossed with "10 MG" on one side and with "4759" on the other side (original formulation)

OR

- debossed with “5123” on one side and 3 parallel arched lines followed by a “10” on the other side (revised formulation)

4 CONTRAINDICATIONS

4.1 Active Bleeding

Effient is contraindicated in patients with active pathological bleeding such as peptic ulcer or intracranial hemorrhage *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*.

4.2 Prior Transient Ischemic Attack or Stroke

Effient is contraindicated in patients with a history of prior transient ischemic attack (TIA) or stroke. In TRITON-TIMI 38 (TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel), patients with a history of TIA or ischemic stroke (>3 months prior to enrollment) had a higher rate of stroke on Effient (6.5%; of which 4.2% were thrombotic stroke and 2.3% were intracranial hemorrhage [ICH]) than on clopidogrel (1.2%; all thrombotic). In patients without such a history, the incidence of stroke was 0.9% (0.2% ICH) and 1.0% (0.3% ICH) with Effient and clopidogrel, respectively. Patients with a history of ischemic stroke within 3 months of screening and patients with a history of hemorrhagic stroke at any time were excluded from TRITON-TIMI 38. Patients who experience a stroke or TIA while on Effient generally should have therapy discontinued *[see Adverse Reactions (6.1) and Clinical Studies (14)]*.

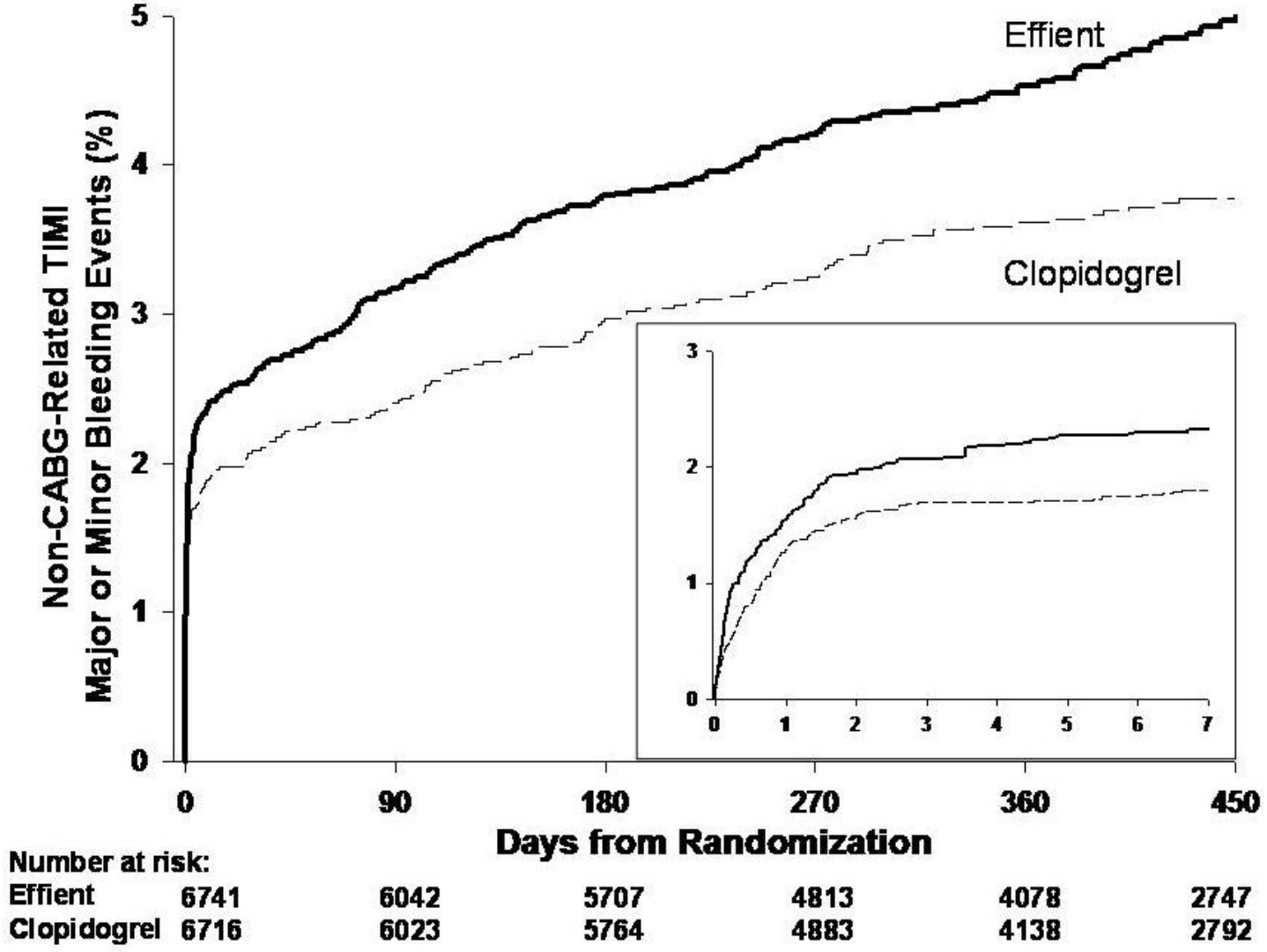
4.3 Hypersensitivity

Effient is contraindicated in patients with hypersensitivity (e.g., anaphylaxis) to prasugrel or any component of the product *[see Adverse Reactions (6.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 General Risk of Bleeding

Thienopyridines, including Effient, increase the risk of bleeding. With the dosing regimens used in TRITON-TIMI 38, TIMI (Thrombolysis in Myocardial Infarction) Major (clinically overt bleeding associated with a fall in hemoglobin ≥5 g/dL, or intracranial hemorrhage) and TIMI Minor (overt bleeding associated with a fall in hemoglobin of ≥3 g/dL but <5 g/dL) bleeding events were more common on Effient than on clopidogrel *[see Adverse Reactions (6.1)]*. The bleeding risk is highest initially, as shown in Figure 1 (events through 450 days; inset shows events through 7 days).



Number at risk:						
Effient	6741	6042	5707	4813	4078	2747
Clopidogrel	6716	6023	5764	4883	4138	2792

Figure 1: Non-CABG-Related TIMI Major or Minor Bleeding Events.

Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, PCI, CABG, or other surgical procedures even if the patient does not have overt signs of bleeding.

Do not use Effient in patients with active bleeding, prior TIA or stroke *[see Contraindications (4.1, 4.2)]*.

Other risk factors for bleeding are:

- Age ≥75 years. Because of the risk of bleeding (including fatal bleeding) and uncertain effectiveness in patients ≥75 years of age, use of Effient is generally not recommended in these patients, except in high-risk situations (patients with diabetes or history of myocardial infarction) where its effect appears to be greater and its use may be considered *[see Adverse Reactions (6.1), Use in Specific Populations (8.5), Clinical Pharmacology (12.3), and Clinical Trials (14)]*.
- CABG or other surgical procedure *[see Warnings and Precautions (5.2)]*.
- Body weight <60 kg. Consider a lower (5-mg) maintenance dose *[see Dosage and Administration (2), Adverse Reactions (6.1), and Use in Specific Populations (8.6)]*.
- Propensity to bleed (e.g., recent trauma, recent surgery, recent or recurrent gastrointestinal (GI) bleeding, active peptic ulcer disease, severe hepatic impairment, or moderate to severe renal impairment) *[see Adverse Reactions (6.1) and Use in Specific Populations (8.7, 8.8)]*.
- Medications that increase the risk of bleeding (e.g., oral anticoagulants, chronic use of non-steroidal anti-inflammatory drugs [NSAIDs], and fibrinolytic agents). Aspirin and heparin were commonly used in TRITON-TIMI 38 *[see Drug Interactions (7.1, 7.2. 7.3), and Clinical Studies (14)]*.

Thienopyridines inhibit platelet aggregation for the lifetime of the platelet (7-10 days), so withholding a dose will not be useful in managing a bleeding event or the risk of bleeding associated with an invasive procedure. Because the half-life of prasugrel's active metabolite is short relative to the lifetime of the platelet, it may be possible to restore hemostasis by administering exogenous platelets; however, platelet transfusions within 6 hours of the loading dose or 4 hours of the maintenance dose may be less effective.

5.2 Coronary Artery Bypass Graft Surgery-Related Bleeding

The risk of bleeding is increased in patients receiving Effient who undergo CABG. If possible, Effient should be discontinued at least 7 days prior to CABG.

Of the 437 patients who underwent CABG during TRITON-TIMI 38, the rates of CABG-related TIMI Major or Minor bleeding were 14.1% in the Effient group and 4.5% in the clopidogrel group *[see Adverse Reactions (6.1)]*. The higher risk for bleeding events in patients treated with Effient persisted up to 7 days from the most recent dose of study drug. For patients receiving a thienopyridine within 3 days prior to CABG, the frequencies of TIMI Major or Minor bleeding were 26.7% (12 of 45 patients) in the Effient group, compared with 5.0% (3 of 60 patients) in the clopidogrel group. For patients who received their last dose of thienopyridine within 4 to 7 days prior to CABG, the frequencies decreased to 11.3% (9 of 80 patients) in the prasugrel group and 3.4% (3 of 89 patients) in the clopidogrel group.

Do not start Effient in patients likely to undergo urgent CABG. CABG-related bleeding may be treated with transfusion of blood products, including packed red blood cells and platelets; however, platelet transfusions within 6 hours of the loading dose or 4 hours of the maintenance dose may be less effective.

5.3 Discontinuation of Effient

Discontinue thienopyridines, including Effient, for active bleeding, elective surgery, stroke, or TIA. The optimal duration of thienopyridine therapy is unknown. In patients who are managed with PCI and stent placement, premature discontinuation of any antiplatelet medication, including thienopyridines, conveys an increased risk of stent thrombosis, myocardial infarction, and death. Patients who require premature discontinuation of a thienopyridine will be at increased risk for cardiac events. Lapses in therapy should be avoided, and if thienopyridines must be temporarily discontinued because of an adverse event(s), they should be restarted as soon as possible *[see Contraindications (4.1, 4.2) and Warnings and Precautions (5.1)]*.

5.4 Thrombotic Thrombocytopenic Purpura

Thrombotic thrombocytopenic purpura (TTP) has been reported with the use of Effient. TTP can occur after a brief exposure (<2 weeks). TTP is a serious condition that can be fatal and requires urgent treatment, including plasmapheresis (plasma exchange). TTP is characterized by thrombocytopenia, microangiopathic hemolytic anemia (schistocytes [fragment red blood cells] seen on peripheral smear), neurological findings, renal dysfunction, and fever *[see Adverse Reactions (6.2)]*.

5.5 Hypersensitivity Including Angioedema

Hypersensitivity including angioedema has been reported in patients receiving Effient, including patients with a history of hypersensitivity reaction to other thienopyridines *[see Contraindications (4.3) and Adverse Reactions (6.2)]*.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

The following serious adverse reactions are also discussed elsewhere in the labeling:

- Bleeding *[see Boxed Warning and Warnings and Precautions (5.1, 5.2)]*
- Thrombotic thrombocytopenic purpura *[see Warnings and Precautions (5.4)]*

Safety in patients with ACS undergoing PCI was evaluated in a clopidogrel-controlled study, TRITON-TIMI 38, in which 6741 patients were treated with Effient (60-mg loading dose and 10-mg once daily) for a median of 14.5 months (5802 patients were treated for over 6 months; 4136 patients were treated for more than 1 year). The population treated with Effient was 27 to 96 years of age, 25% female, and 92% Caucasian. All patients in the TRITON-TIMI 38 study were to receive aspirin. The dose of clopidogrel in this study was a 300-mg loading dose and 75-mg once daily.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials cannot be directly compared with the rates observed in other clinical trials of another drug and may not reflect the rates observed in practice.

Drug Discontinuation

The rate of study drug discontinuation because of adverse reactions was 7.2% for Effient and 6.3% for clopidogrel. Bleeding was the most common adverse reaction leading to study drug discontinuation for both drugs (2.5% for Effient and 1.4% for clopidogrel).

Bleeding

Bleeding Unrelated to CABG Surgery - In TRITON-TIMI 38, overall rates of TIMI Major or Minor bleeding adverse reactions unrelated to coronary artery bypass graft surgery (CABG) were significantly higher on Effient than on clopidogrel, as shown in Table 1.

Table 1: Non-CABG-Related Bleeding[a] (TRITON-TIMI 38)

	Effient (%) (N=6741)	Clopidogrel (%) (N=6716)
TIMI Major or Minor bleeding	4.5	3.4
TIMI Major bleeding[b]	2.2	1.7
Life-threatening	1.3	0.8
Fatal	0.3	0.1
Symptomatic intracranial hemorrhage (ICH)	0.3	0.3
Requiring inotropes	0.3	0.1
Requiring surgical intervention	0.3	0.3
Requiring transfusion (≥4 units)	0.7	0.5
TIMI Minor bleeding[b]	2.4	1.9

[a] Patients may be counted in more than one row.
[b] See 5.1 for definition.

Figure 1 demonstrates non-CABG related TIMI Major or Minor bleeding. The bleeding rate is highest initially, as shown in Figure 1 (inset: Days 0 to 7) *[see Warnings and Precautions (5.1)]*.

Bleeding by Weight and Age - In TRITON-TIMI 38, non-CABG-related TIMI Major or Minor bleeding rates in patients with the risk factors of age ≥75 years and weight <60 kg are shown in Table 2.

Table 2: Bleeding Rates for Non-CABG-Related Bleeding by Weight and Age (TRITON-TIMI 38)

	Major/Minor		Fatal	
	Effient[a] (%)	Clopidogrel[b] (%)	Effient[a] (%)	Clopidogrel[b] (%)
Weight <60 kg (N=308 Effient, N=356 clopidogrel)	10.1	6.5	0.0	0.3
Weight ≥60 kg (N=6373 Effient, N=6299 clopidogrel)	4.2	3.3	0.3	0.1
Age <75 years (N=5850 Effient, N=5822 clopidogrel)	3.8	2.9	0.2	0.1
Age ≥75 years (N=891 Effient, N=894 clopidogrel)	9.0	6.9	1.0	0.1

[a] 10-mg Effient maintenance dose
[b] 75-mg clopidogrel maintenance dose

Bleeding Related to CABG - In TRITON-TIMI 38, 437 patients who received a thienopyridine underwent CABG during the course of the study. The rate of CABG-related TIMI Major or Minor bleeding was 14.1% for the Effient group and 4.5% in the clopidogrel group (*see* Table 3). The higher risk for bleeding adverse reactions in patients treated with Effient persisted up to 7 days from the most recent dose of study drug.

Table 3: CABG-Related Bleeding[a] (TRITON-TIMI 38)

	Effient (%) (N=213)	Clopidogrel (%) (N=224)
TIMI Major or Minor bleeding	14.1	4.5
TIMI Major bleeding	11.3	3.6
Fatal	0.9	0
Reoperation	3.8	0.5
Transfusion of ≥5 units	6.6	2.2
Intracranial hemorrhage	0	0
TIMI Minor bleeding	2.8	0.9

[a] Patients may be counted in more than one row.

Bleeding Reported as Adverse Reactions - Hemorrhagic events reported as adverse reactions in TRITON-TIMI 38 were, for Effient and clopidogrel, respectively: epistaxis (6.2%, 3.3%), gastrointestinal hemorrhage (1.5%, 1.0%), hemoptysis (0.6%, 0.5%), subcutaneous hematoma (0.5%, 0.2%), post-procedural hemorrhage (0.5%, 0.2%), retroperitoneal hemorrhage (0.3%, 0.2%), pericardial effusion/hemorrhage/tamponade (0.3%, 0.2%), and retinal hemorrhage (0.0%, 0.1%).

Malignancies

During TRITON-TIMI 38, newly-diagnosed malignancies were reported in 1.6% and 1.2% of patients treated with prasugrel and clopidogrel, respectively. The sites contributing to the differences were primarily colon and lung. In another Phase 3 clinical study of ACS patients not undergoing PCI, in which data for malignancies were prospectively collected,

newly-diagnosed malignancies were reported in 1.8% and 1.7% of patients treated with prasugrel and clopidogrel, respectively. The site of malignancies was balanced between treatment groups except for colorectal malignancies. The rates of colorectal malignancies were 0.3% prasugrel, 0.1% clopidogrel and most were detected during investigation of GI bleed or anemia. It is unclear if these observations are causally-related, are the result of increased detection because of bleeding, or are random occurrences.

Other Adverse Events

In TRITON-TIMI 38, common and other important non-hemorrhagic adverse events were, for Effient and clopidogrel, respectively: severe thrombocytopenia (0.06%, 0.04%), anemia (2.2%, 2.0%), abnormal hepatic function (0.22%, 0.27%), allergic reactions (0.36%, 0.36%), and angioedema (0.06%, 0.04%). Table 4 summarizes the adverse events reported by at least 2.5% of patients.

Table 4: Non-Hemorrhagic Treatment Emergent Adverse Events Reported by at Least 2.5% of Patients in Either Group

	Effient (%) (N=6741)	**Clopidogrel (%) (N=6716)**
Hypertension	7.5	7.1
Hypercholesterolemia/Hyperlipidemia	7.0	7.4
Headache	5.5	5.3
Back pain	5.0	4.5
Dyspnea	4.9	4.5
Nausea	4.6	4.3
Dizziness	4.1	4.6
Cough	3.9	4.1
Hypotension	3.9	3.8
Fatigue	3.7	4.8
Non-cardiac chest pain	3.1	3.5
Atrial fibrillation	2.9	3.1
Bradycardia	2.9	2.4
Leukopenia (<4 x 10^9 WBC/L)	2.8	3.5
Rash	2.8	2.4
Pyrexia	2.7	2.2
Peripheral edema	2.7	3.0
Pain in extremity	2.6	2.6
Diarrhea	2.3	2.6

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of Effient. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and lymphatic system disorders — Thrombocytopenia, Thrombotic thrombocytopenic purpura (TTP) *[see Warnings and Precautions (5.4) and Patient Counseling Information (17)]*

Immune system disorders — Hypersensitivity reactions including anaphylaxis *[see Contraindications (4.3)]*

7 DRUG INTERACTIONS

7.1 Warfarin

Coadministration of Effient and warfarin increases the risk of bleeding *[see Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)]*.

7.2 Non-Steroidal Anti-Inflammatory Drugs

Coadministration of Effient and NSAIDs (used chronically) may increase the risk of bleeding *[see Warnings and Precautions (5.1)]*.

7.3 Other Concomitant Medications

Effient can be administered with drugs that are inducers or inhibitors of cytochrome P450 enzymes *[see Clinical Pharmacology (12.3)]*.

Effient can be administered with aspirin (75-mg to 325-mg per day), heparin, GPIIb/IIIa inhibitors, statins, digoxin, and drugs that elevate gastric pH, including proton pump inhibitors and H_2 blockers *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B - There are no adequate and well-controlled studies of Effient use in pregnant women. Reproductive and developmental toxicology studies in rats and rabbits at doses of up to 30 times the recommended therapeutic exposures in humans (based on plasma exposures to the major circulating human metabolite) revealed no evidence of fetal harm; however, animal studies are not always predictive of a human response. Effient should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

In embryo fetal developmental toxicology studies, pregnant rats and rabbits received prasugrel at maternally toxic oral doses equivalent to more than 40 times the human exposure. A slight decrease in pup body weight was observed; but, there were no structural malformations in either species. In prenatal and postnatal rat studies, maternal treatment with prasugrel had no effect on the behavioral or reproductive development of the offspring at doses greater than 150 times the human exposure *[see Nonclinical Toxicology (13.1)]*.

8.3 Nursing Mothers

It is not known whether Effient is excreted in human milk; however, metabolites of Effient were found in rat milk. Because many drugs are excreted in human milk, prasugrel should be used during nursing only if the potential benefit to the mother justifies the potential risk to the nursing infant.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established *[see Clinical Pharmacology (12.3)]*.

8.5 Geriatric Use

In TRITON-TIMI 38, 38.5% of patients were ≥65 years of age and 13.2% were ≥75 years of age. The risk of bleeding increased with advancing age in both treatment groups, although the relative risk of bleeding (Effient compared with clopidogrel) was similar across age groups.

Patients ≥75 years of age who received Effient 10-mg had an increased risk of fatal bleeding events (1.0%) compared to patients who received clopidogrel (0.1%). In patients ≥75 years of age, symptomatic intracranial hemorrhage occurred in 7 patients (0.8%) who received Effient and in 3 patients (0.3%) who received clopidogrel. Because of the risk of bleeding, and because effectiveness is uncertain in patients ≥75 years of age *[see Clinical Studies (14)]*, use of Effient is generally not recommended in these patients, except in high-risk situations (diabetes and past history of myocardial infarction) where its effect appears to be greater and its use may be considered *[see Warnings and Precautions (5.1), Clinical Pharmacology (12.3), and Clinical Studies (14)]*.

8.6 Low Body Weight

In TRITON-TIMI 38, 4.6% of patients treated with Effient had body weight <60 kg. Individuals with body weight <60 kg had an increased risk of bleeding and an increased exposure to the active metabolite of prasugrel *[see Dosage and Administration (2), Warnings and Precautions (5.1), and Clinical Pharmacology (12.3)]*. Consider lowering the maintenance dose to 5-mg in patients <60 kg. The effectiveness and safety of the 5-mg dose have not been prospectively studied *[see Dosage and Administration (2) and Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

No dosage adjustment is necessary for patients with renal impairment. There is limited experience in patients with end-stage renal disease, but such patients are generally at higher risk of bleeding *[see Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)]*.

8.8 Hepatic Impairment

No dosage adjustment is necessary in patients with mild to moderate hepatic impairment (Child-Pugh Class A and B). The pharmacokinetics and pharmacodynamics of prasugrel in patients with severe hepatic disease have not been studied, but such patients are generally at higher risk of bleeding *[see Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)]*.

8.9 Metabolic Status

In healthy subjects, patients with stable atherosclerosis, and patients with ACS receiving prasugrel, there was no relevant effect of genetic variation in CYP2B6, CYP2C9, CYP2C19, or CYP3A5 on the pharmacokinetics of prasugrel's active metabolite or its inhibition of platelet aggregation.

10 OVERDOSAGE

10.1 Signs and Symptoms

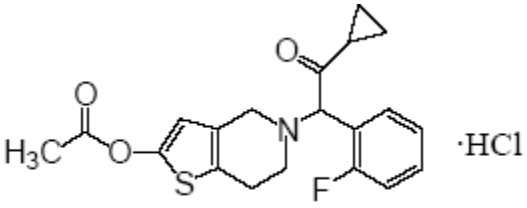
Platelet inhibition by prasugrel is rapid and irreversible, lasting for the life of the platelet, and is unlikely to be increased in the event of an overdose. In rats, lethality was observed after administration of 2000 mg/kg. Symptoms of acute toxicity in dogs included emesis, increased serum alkaline phosphatase, and hepatocellular atrophy. Symptoms of acute toxicity in rats included mydriasis, irregular respiration, decreased locomotor activity, ptosis, staggering gait, and lacrimation.

10.2 Recommendations about Specific Treatment

Platelet transfusion may restore clotting ability. The prasugrel active metabolite is not likely to be removed by dialysis.

11 DESCRIPTION

Effient contains prasugrel, a thienopyridine class inhibitor of platelet activation and aggregation mediated by the $P2Y_{12}$ ADP receptor. Effient is formulated as the hydrochloride salt, a racemate, which is chemically designated as 5-[(1RS)-2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl acetate hydrochloride. Prasugrel hydrochloride has the empirical formula $C_{20}H_{20}FNO_3S$•HCl representing a molecular weight of 409.90. The chemical structure of prasugrel hydrochloride is:



Prasugrel hydrochloride is a white to practically white solid. It is soluble at pH 2, slightly soluble at pH 3 to 4, and practically insoluble at pH 6 to 7.5. It also dissolves freely in methanol and is slightly soluble in 1- and 2-propanol and acetone. It is practically insoluble in diethyl ether and ethyl acetate.

Effient is available for oral administration as 5-mg or 10-mg elongated hexagonal, film-coated, non-scored tablets, debossed on each side. Each yellow 5-mg tablet is manufactured with 5.49 mg prasugrel hydrochloride, equivalent to 5-mg prasugrel and each beige 10-mg tablet with 10.98 mg prasugrel hydrochloride, equivalent to 10-mg of prasugrel.

Original Formulation

During manufacture and storage, partial conversion from prasugrel hydrochloride to prasugrel free base may occur. Other ingredients include mannitol, hypromellose, croscarmellose sodium, microcrystalline cellulose, and vegetable magnesium stearate. The color coatings contain lactose, hypromellose, titanium dioxide, triacetin, iron oxide yellow, and iron oxide red (only in Effient 10-mg tablet).

Revised Formulation

Other ingredients include mannitol, hypromellose, low-substituted hydroxypropyl cellulose, microcrystalline cellulose, sucrose stearate, and glyceryl behenate. The color coatings contain lactose, hypromellose, titanium dioxide, triacetin, iron oxide yellow, and iron oxide red (only in Effient 10-mg tablet).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Prasugrel is an inhibitor of platelet activation and aggregation through the irreversible binding of its active metabolite to the $P2Y_{12}$ class of ADP receptors on platelets.

12.2 Pharmacodynamics

Prasugrel produces inhibition of platelet aggregation to 20 µM or 5 µM ADP, as measured by light transmission aggregometry. Following a 60-mg loading dose of Effient, approximately 90% of patients had at least 50% inhibition of platelet aggregation by 1 hour. Maximum platelet inhibition was about 80% (*see* Figure 2). Mean steady-state inhibition of platelet aggregation was about 70% following 3 to 5 days of dosing at 10-mg daily after a 60-mg loading dose of Effient.

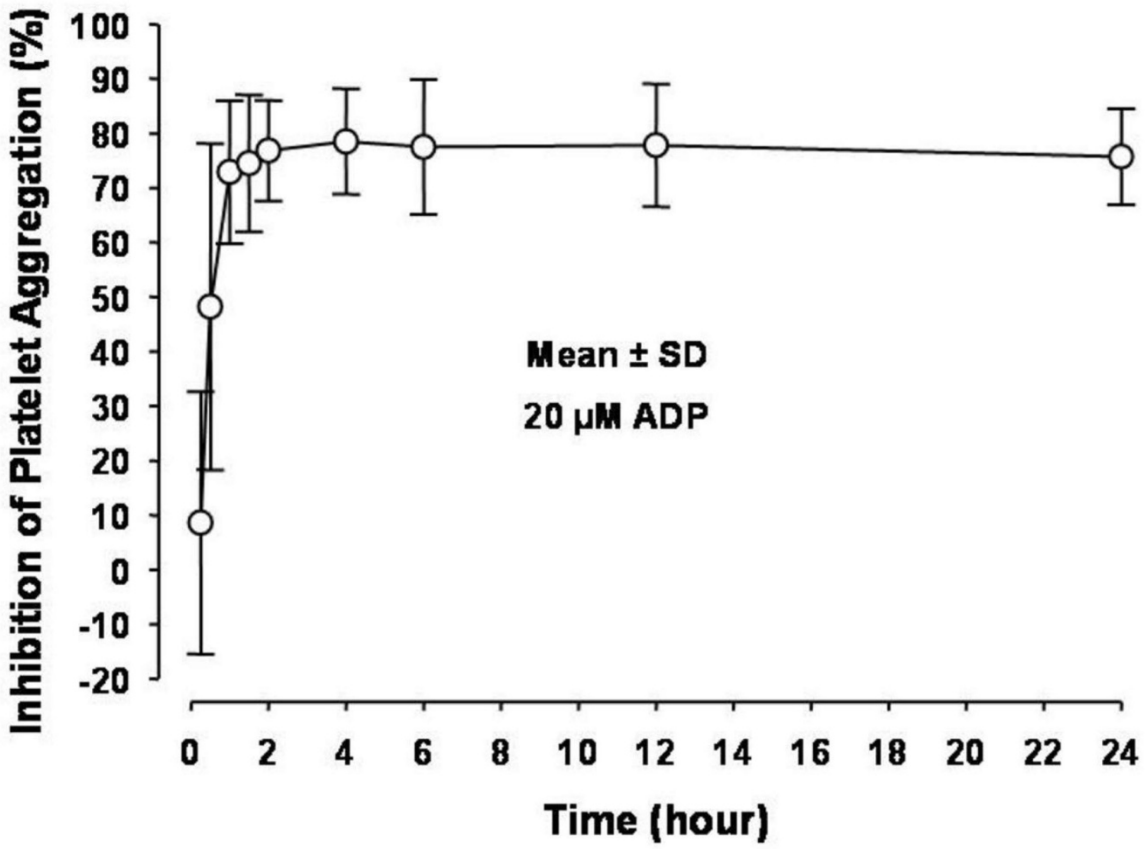


Figure 2: Inhibition (Mean±SD) of 20 µM ADP-induced Platelet Aggregation (IPA) Measured by Light Transmission Aggregometry after Prasugrel 60-mg.

Platelet aggregation gradually returns to baseline values over 5-9 days after discontinuation of prasugrel, this time course being a reflection of new platelet production rather than pharmacokinetics of prasugrel. Discontinuing clopidogrel 75-mg and initiating a prasugrel 10-mg maintenance dose with or without a prasugrel 60-mg loading dose results in a decrease of 14 percentage points in maximum platelet aggregation (MPA) by Day 7. This decrease in MPA is not greater than that typically produced by a 10-mg maintenance dose of prasugrel alone. The relationship between inhibition of platelet aggregation and clinical activity has not been established.

5-mg in Low Body Weight Patients - In patients with stable coronary artery disease, mean platelet inhibition in subjects <60 kg taking 5-mg prasugrel was similar to that of subjects ≥60 kg taking 10-mg prasugrel. The relationship between inhibition of platelet aggregation and clinical activity has not been established.

12.3 Pharmacokinetics

Prasugrel is a prodrug and is rapidly metabolized to a pharmacologically active metabolite and inactive metabolites. The active metabolite has an elimination half-life of about 7 hours (range 2-15 hours). Healthy subjects, patients with stable atherosclerosis, and patients undergoing PCI show similar pharmacokinetics.

Absorption and Binding - Following oral administration, ≥79% of the dose is absorbed. The absorption and metabolism are rapid, with peak plasma concentrations (C_{max}) of the active metabolite occurring approximately 30 minutes after dosing. The active metabolite's exposure (AUC) increases slightly more than proportionally over the dose range of 5 to 60-mg. Repeated daily doses of 10-mg do not lead to accumulation of the active metabolite. In a study of healthy subjects given a single 15-mg dose, the AUC of the active metabolite was unaffected by a high fat, high calorie meal, but C_{max} was decreased by 49% and T_{max} was increased from 0.5 to 1.5 hours. Effient can be administered without regard to food. The active metabolite is bound about 98% to human serum albumin.

Metabolism and Elimination - Prasugrel is not detected in plasma following oral administration. It is rapidly hydrolyzed in the intestine to a thiolactone, which is then converted to the active metabolite by a single step, primarily by CYP3A4 and CYP2B6 and to a lesser extent by CYP2C9 and CYP2C19. The estimates of apparent volume of distribution of prasugrel's active metabolite ranged from 44 to 68 L and the estimates of apparent clearance ranged from 112 to 166 L/hr in healthy subjects and patients with stable atherosclerosis. The active metabolite is metabolized to two inactive compounds by S-methylation or conjugation with cysteine. The major inactive metabolites are highly bound to human plasma proteins. Approximately 68% of the prasugrel dose is excreted in the urine and 27% in the feces as inactive metabolites.

Specific Populations

Pediatric - Pharmacokinetics and pharmacodynamics of prasugrel have not been evaluated in a pediatric population *[see Use in Specific Populations (8.4)]*.

Geriatric - In a study of 32 healthy subjects between the ages of 20 and 80 years, age had no significant effect on pharmacokinetics of prasugrel's active metabolite or its inhibition of platelet aggregation. In TRITON-TIMI 38, the mean exposure (AUC) of the active metabolite was 19% higher in patients ≥75 years of age than in patients <75 years of age. In a study in subjects with stable atherosclerosis, the mean exposure (AUC) to the active metabolite of prasugrel in subjects ≥75 years old taking a 5-mg maintenance dose was approximately half that seen in subjects 45 to 64 years old taking a 10-mg maintenance dose. *[See Warnings and Precautions (5.1) and Use in Specific Populations (8.5)]*.

Body Weight - The mean exposure (AUC) to the active metabolite is approximately 30 to 40% higher in subjects with a body weight of <60 kg than in those weighing ≥60 kg. In a study in subjects with stable atherosclerosis, the AUC of the active metabolite on average was 38% lower in subjects <60 kg taking 5-mg (N=34) than in subjects ≥60 kg taking 10-mg (N=38) *[see Dosage and Administration (2), Warnings and Precautions (5.1), Adverse Reactions (6.1), and Use in Specific Populations (8.6)]*.

Gender - Pharmacokinetics of prasugrel's active metabolite are similar in men and women.

Ethnicity - Exposure in subjects of African and Hispanic descent is similar to that in Caucasians. In clinical pharmacology studies, after adjusting for body weight, the AUC of the active metabolite was approximately 19% higher in Chinese, Japanese, and Korean subjects than in Caucasian subjects.

Smoking - Pharmacokinetics of prasugrel's active metabolite are similar in smokers and nonsmokers.

Renal Impairment - Pharmacokinetics of prasugrel's active metabolite and its inhibition of platelet aggregation are similar in patients with moderate renal impairment (CrCL=30 to 50 mL/min) and healthy subjects. In patients with end-stage renal disease, exposure to the active metabolite (both C_{max} and AUC (0-t_{last})) was about half that in healthy controls and patients with moderate renal impairment *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.7)]*.

Hepatic Impairment - Pharmacokinetics of prasugrel's active metabolite and inhibition of platelet aggregation were similar in patients with mild to moderate hepatic impairment compared to healthy subjects. The pharmacokinetics and pharmacodynamics of prasugrel's active metabolite in patients with severe hepatic disease have not been studied [*see Warnings and Precautions (5.1) and Use in Specific Populations (8.8)]*.

Drug Interactions

Potential for Other Drugs to Affect Prasugrel

Inhibitors of CYP3A - Ketoconazole (400 mg daily), a selective and potent inhibitor of CYP3A4 and CYP3A5, did not affect prasugrel-mediated inhibition of platelet aggregation or the active metabolite's AUC and T_{max}, but decreased the C_{max} by 34% to 46%. Therefore, CYP3A inhibitors such as verapamil, diltiazem, indinavir, ciprofloxacin, clarithromycin, and grapefruit juice are not expected to have a significant effect on the pharmacokinetics of the active metabolite of prasugrel *[see Drug Interactions (7.3)]*.

Inducers of Cytochromes P450 - Rifampicin (600 mg daily), a potent inducer of CYP3A and CYP2B6 and an inducer of CYP2C9, CYP2C19, and CYP2C8, did not significantly change the pharmacokinetics of prasugrel's active metabolite or its inhibition of platelet aggregation. Therefore, known CYP3A inducers such as rifampicin, carbamazepine, and other inducers of cytochromes P450 are not expected to have significant effect on the pharmacokinetics of the active metabolite of prasugrel *[see Drug Interactions (7.3)]*.

Drugs that Elevate Gastric pH - Daily coadministration of ranitidine (an H_2 blocker) or lansoprazole (a proton pump inhibitor) decreased the C_{max} of the prasugrel active metabolite by 14% and 29%, respectively, but did not change the active metabolite's AUC and T_{max}. In TRITON-TIMI 38, Effient was administered without regard to coadministration of a proton pump inhibitor or H_2 blocker *[see Drug Interactions (7.3)]*.

Statins - Atorvastatin (80 mg daily), a drug metabolized by CYP450 3A4, did not alter the pharmacokinetics of prasugrel's active metabolite or its inhibition of platelet aggregation *[see Drug Interactions (7.3)]*.

Heparin - A single intravenous dose of unfractionated heparin (100 U/kg) did not significantly alter coagulation or the prasugrel-mediated inhibition of platelet aggregation; however, bleeding time was increased compared with either drug alone *[see Drug Interactions (7.3)]*.

Aspirin - Aspirin 150 mg daily did not alter prasugrel-mediated inhibition of platelet aggregation; however, bleeding time was increased compared with either drug alone *[see Drug Interactions (7.3)]*.

Warfarin - A significant prolongation of the bleeding time was observed when prasugrel was coadministered with 15-mg of warfarin *[see Drug Interactions (7.1)]*.

Potential for Prasugrel to Affect Other Drugs

In vitro metabolism studies demonstrate that prasugrel's main circulating metabolites are not likely to cause clinically significant inhibition of CYP1A2, CYP2C9, CYP2C19, CYP2D6, or CYP3A, or induction of CYP1A2 or CYP3A.

Drugs Metabolized by CYP2B6 — Prasugrel is a weak inhibitor of CYP2B6. In healthy subjects, prasugrel decreased exposure to hydroxybupropion, a CYP2B6-mediated metabolite of bupropion, by 23%, an amount not considered clinically significant. Prasugrel is not anticipated to have significant effect on the pharmacokinetics of drugs that are primarily metabolized by CYP2B6, such as halothane, cyclophosphamide, propofol, and nevirapine.

Effect on Digoxin - The potential role of prasugrel as a Pgp substrate was not evaluated. Prasugrel is not an inhibitor of Pgp, as digoxin clearance was not affected by prasugrel coadministration *[see Drug Interactions (7.3)]*.

12.5 Pharmacogenomics

There is no relevant effect of genetic variation in CYP2B6, CYP2C9, CYP2C19, or CYP3A5 on the pharmacokinetics of prasugrel's active metabolite or its inhibition of platelet aggregation.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis - No compound-related tumors were observed in a 2-year rat study with prasugrel at oral doses up to 100 mg/kg/day (>100 times the recommended therapeutic exposures in humans (based on plasma exposures to the major circulating human metabolite). There was an increased incidence of tumors (hepatocellular adenomas) in mice exposed for 2 years to high doses (>250 times the human metabolite exposure).

Mutagenesis - Prasugrel was not genotoxic in two *in vitro* tests (Ames bacterial gene mutation test, clastogenicity assay in Chinese hamster fibroblasts) and in one *in vivo* test (micronucleus test by intraperitoneal route in mice).

Impairment of Fertility - Prasugrel had no effect on fertility of male and female rats at oral doses up to 300 mg/kg/day (80 times the human major metabolite exposure at daily dose of 10-mg prasugrel).

14 CLINICAL STUDIES

The clinical evidence for the effectiveness of Effient is derived from the TRITON-TIMI 38 (TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel) study, a 13,608-patient, multicenter, international, randomized, double-blind, parallel-group study comparing Effient to a regimen of clopidogrel, each added to aspirin and other standard therapy, in patients with ACS (UA, NSTEMI, or STEMI) who were to be managed with PCI. Randomization was stratified for UA/NSTEMI and STEMI.

Patients with UA/NSTEMI presenting within 72 hours of symptom onset were to be randomized after undergoing coronary angiography. Patients with STEMI presenting within 12 hours of symptom onset could be randomized prior to coronary angiography. Patients with STEMI presenting between 12 hours and 14 days of symptom onset were to be randomized after undergoing coronary angiography. Patients underwent PCI, and for both UA/NSTEMI and STEMI patients, the loading dose was to be administered anytime between randomization and 1 hour after the patient left the catheterization lab. If patients with STEMI were treated with thrombolytic therapy, randomization could not occur until at least 24 hours (for tenecteplase, reteplase, or alteplase) or 48 hours (for streptokinase) after the thrombolytic was given.

Patients were randomized to receive Effient (60-mg loading dose followed by 10-mg once daily) or clopidogrel (300-mg loading dose followed by 75-mg once daily), with administration and follow-up for a minimum of 6 months (actual median 14.5 months). Patients also received aspirin (75-mg to 325-mg once daily). Other therapies, such as heparin and intravenous glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors, were administered at the discretion of the treating physician. Oral anticoagulants, other platelet inhibitors, and chronic NSAIDs were not allowed.

The primary outcome measure was the composite of cardiovascular death, nonfatal MI, or nonfatal stroke in the UA/NSTEMI population. Success in this group allowed analysis of the same endpoint in the overall ACS and STEMI populations. Nonfatal MIs included both MIs detected solely through analysis of creatine kinase muscle-brain (CK-MB) changes and clinically apparent (investigator-reported) MIs.

The patient population was 92% Caucasian, 26% female, and 39% ≥65 years of age. The median time from symptom onset to study drug administration was 7 hours for patients with STEMI and 30 hours for patients with UA/NSTEMI. Approximately 99% of patients underwent PCI. The study drug was administered after the first coronary guidewire was placed in approximately 75% of patients.

Effient significantly reduced total endpoint events compared to clopidogrel (*see* Table 5 and Figure 3). The reduction of total endpoint events was driven primarily by a decrease in nonfatal MIs, both those occurring early (through 3 days) and later (after 3 days). Approximately 40% of MIs occurred peri-procedurally and were detected solely by changes in CK-MB. Administration of the clopidogrel loading dose in TRITON-TIMI 38 was delayed relative to the placebo-controlled trials that supported its approval for ACS. Effient produced higher rates of clinically significant bleeding than clopidogrel in TRITON-TIMI 38 *[see Adverse Reactions (6.1)]*. Choice of therapy requires balancing these differences in outcome.

The treatment effect of Effient was apparent within the first few days, and persisted to the end of the study (*see* Figure 3). The inset shows results over the first 7 days.

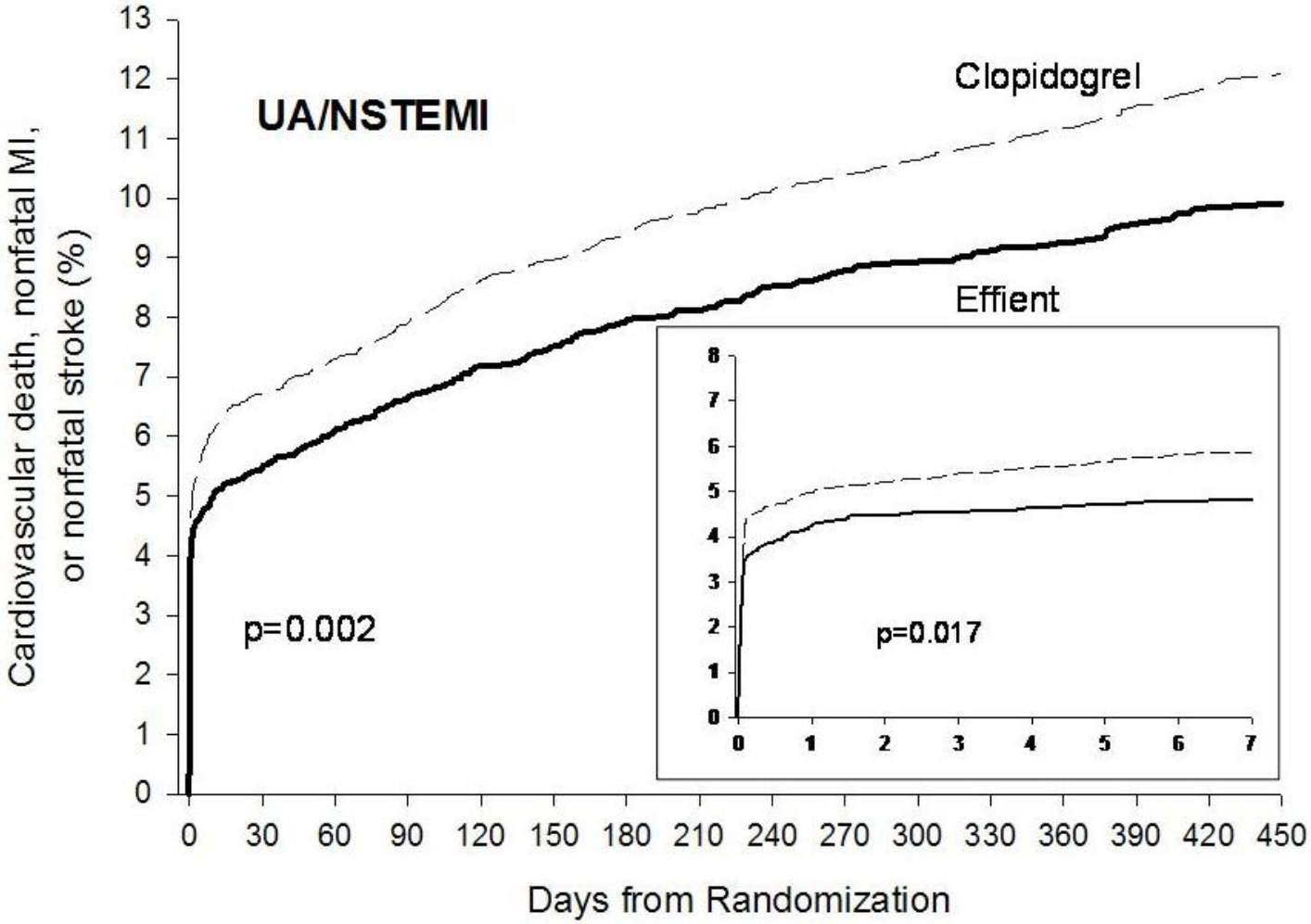


Figure 3: Time to first event of CV death, MI, or stroke (TRITON-TIMI 38).

The Kaplan-Meier curves (*see* Figure 3) show the primary composite endpoint of CV death, nonfatal MI, or nonfatal stroke over time in the UA/NSTEMI and STEMI populations. In both populations, the curves separate within the first few hours. In the UA/NSTEMI population, the curves continue to diverge throughout the 15 month follow-up period. In the STEMI population, the early separation was maintained throughout the 15 month follow-up period, but there was no progressive divergence after the first few weeks.

Effient reduced the occurrence of the primary composite endpoint compared to clopidogrel in both the UA/NSTEMI and STEMI populations (*see* Table 5). In patients who survived an on-study myocardial infarction, the incidence of subsequent events was also lower in the Effient group.

Table 5: Patients with Outcome Events (CV Death, MI, Stroke) in TRITON-TIMI 38

	Patients with events		**From Kaplan-Meier analysis**	
	Effient (%)	**Clopidogrel (%)**	**Relative Risk Reduction (%)[a] (95% CI)**	**p-value**
UA/NSTEMI	**N=5044**	**N=5030**		
CV death, nonfatal MI, or nonfatal stroke	9.3	11.2	18.0 (7.3, 27.4)	0.002
CV death	1.8	1.8	2.1 (-30.9, 26.8)	0.885
Nonfatal MI	7.1	9.2	23.9 (12.7, 33.7)	<0.001
Nonfatal Stroke	0.8	0.8	2.1 (-51.3, 36.7)	0.922
STEMI	**N=1769**	**N=1765**		
CV death, nonfatal MI, or nonfatal stroke	9.8	12.2	20.7 (3.2, 35.1)	0.019
CV death	2.4	3.3	26.2 (-9.4, 50.3)	0.129

Nonfatal MI	6.7	8.8	25.4 (5.2, 41.2)	0.016
Nonfatal Stroke	1.2	1.1	-9.7 (-104.0, 41.0)	0.77

[a] RRR = (1-Hazard Ratio) x 100%. Values with a negative relative risk reduction indicate a relative risk increase.

The effect of Effient in various subgroups is shown in Figures 4 and 5. Results are generally consistent across pre-specified subgroups, with the exception of patients with a history of TIA or stroke *[see Contraindications (4.2)]*. The treatment effect was driven primarily by a reduction in nonfatal MI. The effect in patients ≥75 years of age was also somewhat smaller, and bleeding risk is higher in these individuals *[see Adverse Reactions (6.1)]*. See below for analyses of patients ≥75 years of age with risk factors.

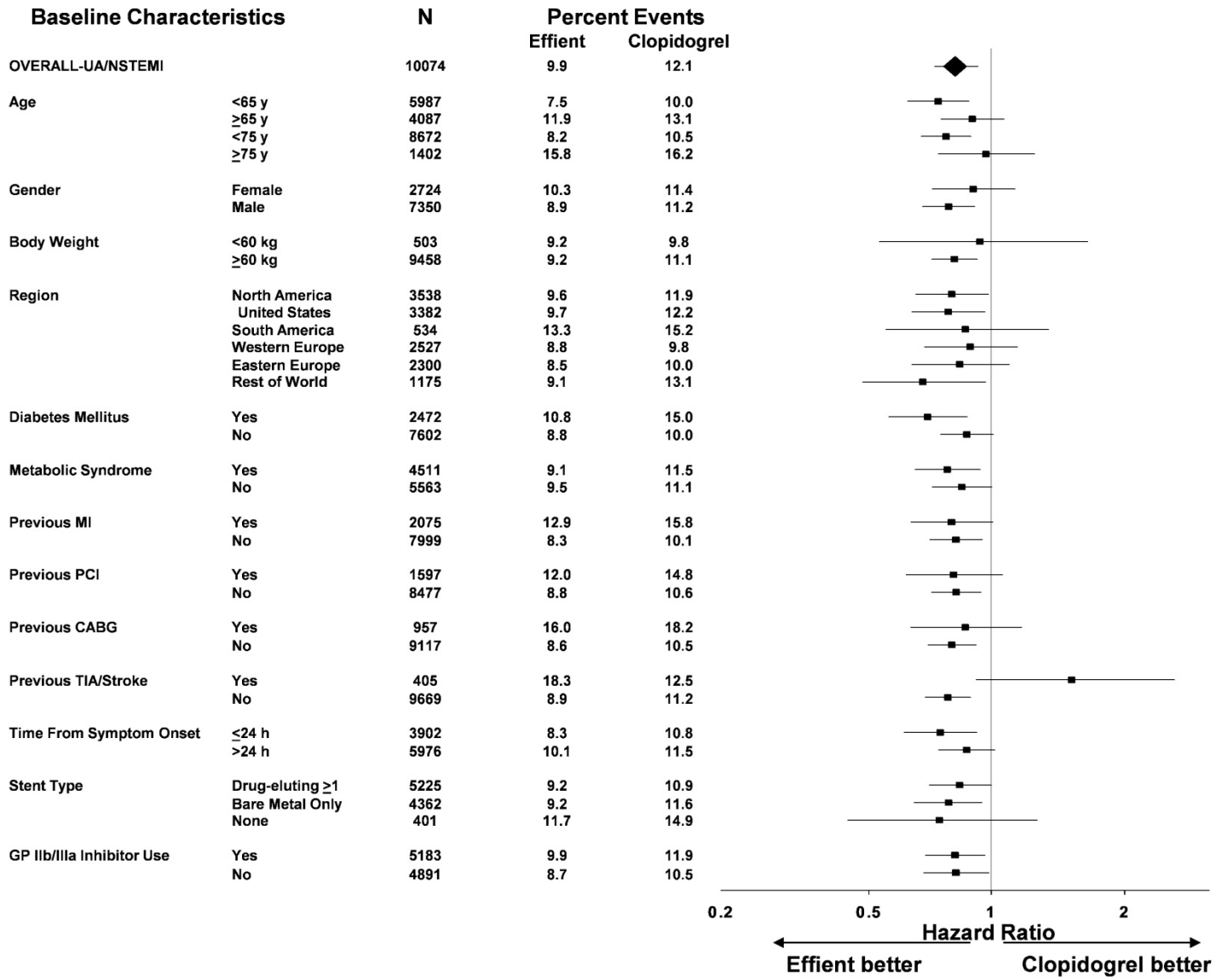


Figure 4: Subgroup analyses for time to first event of CV death, MI, or stroke (HR and 95% CI; TRITON-TIMI 38) – UA/NSTEMI Patients.

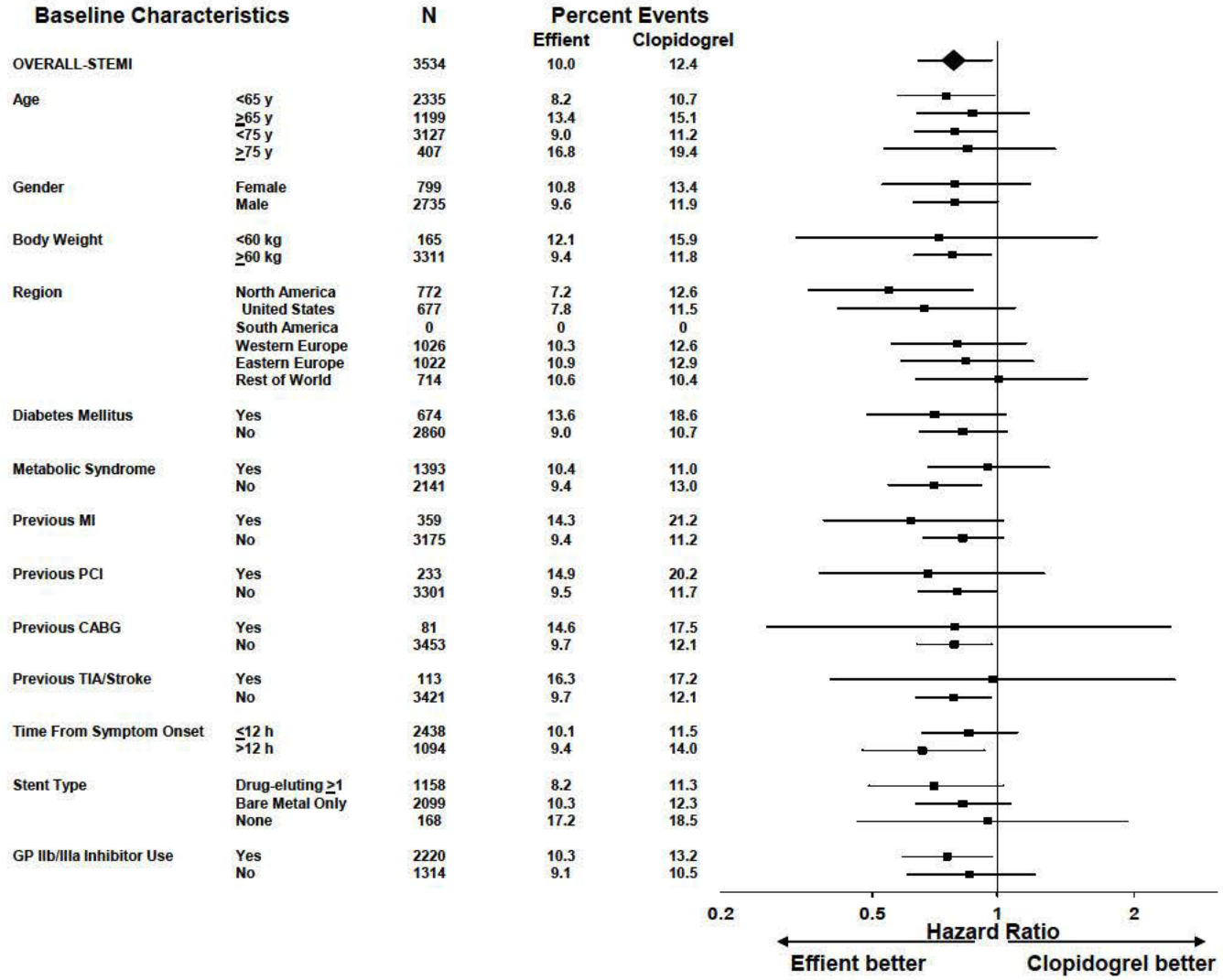


Figure 5: Subgroup analyses for time to first event of CV death, MI, or stroke (HR and 95% CI; TRITON-TIMI 38) – STEMI Patients.

Effient is generally not recommended in patients ≥75 years of age, except in high-risk situations (diabetes mellitus or prior MI) where its effect appears to be greater and its use may be considered. These recommendations are based on subgroup analyses (*see* Table 6) and must be interpreted with caution, but the data suggest that Effient reduces ischemic events in such patients.

Table 6: Subgroup Analyses for Time to First Event of CV Death, MI, or Stroke: Patients < or ≥75 Years of Age, ± Diabetes, ± Prior History of MI, All ACS Patient Population

	Effient		Clopidogrel		Hazard Ratio (95% CI)
	N	% with events	N	% with events	
Age ≥75					
Diabetes - yes	249	14.9	234	21.8	0.64 (0.42, 0.97)
Diabetes - no	652	16.4	674	15.3	1.1 (0.83, 1.43)
Age <75					
Diabetes - yes	1327	10.8	1336	14.8	0.72 (0.58, 0.89)
Diabetes - no	4585	7.8	4551	9.5	0.82 (0.71, 0.94)
Age ≥75					
Prior MI - yes	220	17.3	212	22.6	0.72 (0.47, 1.09)
Prior MI - no	681	15.6	696	15.2	1.05 (0.80, 1.37)
Age <75					
Prior MI - yes	1006	12.2	996	15.4	0.78 (0.62, 0.99)
Prior MI - no	4906	7.7	4891	9.7	0.78 (0.68, 0.90)

There were 50% fewer stent thromboses (95% C.I. 32% - 64%; p<0.001) reported among patients randomized to Effient (0.9%) than among patients randomized to clopidogrel (1.8%). The difference manifested early and was maintained through one year of follow-up. Findings were similar with bare metal and drug-eluting stents.

In TRITON-TIMI 38, prasugrel reduced ischemic events (mainly nonfatal MIs) and increased bleeding events *[see Adverse Reactions (6.1)]* relative to clopidogrel. The findings are consistent with the intended greater inhibition of platelet aggregation by prasugrel at the doses used in the study *[see Clinical Pharmacology (12.2)]*. There is, however, an alternative explanation: both prasugrel and clopidogrel are pro-drugs that must be metabolized to their active moieties. Whereas the pharmacokinetics of prasugrel's active metabolite are not known to be affected by genetic variations in CYP2B6, CYP2C9, CYP2C19, or CYP3A5, the pharmacokinetics of clopidogrel's active metabolite are affected by CYP2C19 genotype, and approximately 30% of Caucasians are reduced-metabolizers. Moreover, certain proton pump inhibitors, widely used in the ACS patient population and used in TRITON-TIMI 38, inhibit CYP2C19, thereby decreasing formation of clopidogrel's active metabolite. Thus, reduced-metabolizer status and use of proton pump inhibitors may diminish clopidogrel's activity in a fraction of the population, and may have contributed to prasugrel's greater treatment effect and greater bleeding rate in TRITON-TIMI 38. The extent to which these factors were operational, however, is unknown.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Effient (prasugrel) is available as elongated hexagonal, film-coated, non-scored tablets in the following strengths, colors, imprints, and presentations:

Features	**Strengths**	
	5-mg	**10-mg**
Tablet color	yellow	beige
Tablet imprint	5	10
Tablet imprint	5121	5123
Presentations and NDC Codes		
Bottles of 30	0002-5121-30	0002-5123-30
Blisters ID*24	0002-5121-52	NA
Blisters ID*90	NA	0002-5123-77

* Identi Dose®, unit dose medication, Lilly

16.2 Storage and Handling

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP controlled room temperature].

Dispense and keep product in original container. Keep container closed and do not remove desiccant from bottle. Do not break the tablet.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide)

Benefits and Risks

- Summarize the effectiveness features and potential side effects of Effient.
- Tell patients to take Effient exactly as prescribed.
- Remind patients not to discontinue Effient without first discussing it with the physician who prescribed Effient.
- Recommend that patients read the Medication Guide.

Bleeding

Inform patients that they:

- will bruise and bleed more easily.
- will take longer than usual to stop bleeding.
- should report any unanticipated, prolonged, or excessive bleeding, or blood in their stool or urine.

Other Signs and Symptoms Requiring Medical Attention

- Inform patients that TTP is a rare but serious condition that has been reported with Effient.
    - Instruct patients to get prompt medical attention if they experience any of the following symptoms that cannot otherwise be explained: fever, weakness, extreme skin paleness, purple skin patches, yellowing of the skin or eyes, or neurological changes.
- Inform patients that they may have hypersensitivity reactions including rash, angioedema, anaphylaxis, or other manifestations. Patients who have had hypersensitivity reactions to other thienopyridines may have hypersensitivity reactions to Effient.

Invasive Procedures

Instruct patients to:

- inform physicians and dentists that they are taking Effient before any invasive procedure is scheduled.
- tell the doctor performing the invasive procedure to talk to the prescribing health care professional before stopping Effient.

Concomitant Medications

Ask patients to list all prescription medications, over-the-counter medications, or dietary supplements they are taking or plan to take so the physician knows about other treatments that may affect bleeding risk (e.g., warfarin and NSAIDs).

Manufactured by Eli Lilly and Company, Indianapolis, IN, 46285

Marketed by Daiichi Sankyo, Inc. and Lilly USA, LLC

B4.0NL7802 AMP

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-307/S008

SUMMARY REVIEW

DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Regulatory Project Manager Review

NDA:	22307-S008
Drug:	**EFFIENT (prasugrel) Tablets**
Class:	$P2Y_{12}$ Platelet Inhibitor
Applicant:	Eli Lilly

Current Indication:

Acute Coronary Syndrome

Effient® is indicated to reduce the rate of thrombotic cardiovascular (CV) events (including stent thrombosis) in patients with acute coronary syndrome (ACS) who are to be managed with percutaneous coronary intervention (PCI) as follows:

- Patients with unstable angina (UA) or non-ST-elevation myocardial infarction (NSTEMI).
- Patients with ST-elevation myocardial infarction (STEMI) when managed with primary or delayed PCI.

Effient has been shown to reduce the rate of a combined endpoint of cardiovascular death, nonfatal myocardial infarction (MI), or nonfatal stroke compared to clopidogrel. The difference between treatments was driven predominantly by MI, with no difference on strokes and little difference on CV death *[see Clinical Studies (14)]*.

It is generally recommended that antiplatelet therapy be administered promptly in the management of ACS because many cardiovascular events occur within hours of initial presentation. In the clinical trial that established the efficacy of Effient, Effient and the control drug were not administered to UA/NSTEMI patients until coronary anatomy was established. For the small fraction of patients that required urgent CABG after treatment with Effient, the risk of significant bleeding was substantial *[see Warnings and Precautions (5.2)]*. Because the large majority of patients are managed without CABG, however, treatment can be considered before determining coronary anatomy if need for CABG is considered unlikely. The advantages of earlier treatment with Effient must then be balanced against the increased rate of bleeding in patients who do need to undergo urgent CABG.

New Proposed Dosing Information (in maroon):

Dosing in Low Weight Patients

Compared to patients weighing ≥60 kg, patients weighing <60 kg have an increased exposure to the active metabolite of prasugrel and an increased risk of bleeding on a 10 mg once daily maintenance dose. Consider lowering the maintenance dose to 5 mg in patients <60 kg. The effectiveness and safety of the 5 mg dose have not been prospectively studied (b) (4)

[redacted]

(b) (4)

Date of submission: 14 December 2012
FDA Received: 17 December 2012
Approval date: 16 October 2013
PDUFA date: 17 October 2013

❖ REVIEW TEAM

- Office of New Drugs, Office of Drug Evaluation I, Division of Cardiovascular & Renal Products
  - Cross-Discipline Team Leader and Primary Clinical Reviewer:
    - Karen Hicks, M.D.
  - Special Clinical Reviewer (Cancer)
    - Thomas Marciniak, M.D.
  - Regulatory Health Project Manager
    - Alison Blaus, RAC
- Office of Clinical Pharmacology
  - Martina Sahre, Ph.D. – Clinical Pharmacology Reviewer
  - Hobart Rogers, Ph.D., PharmD – Pharmacogenomics Reviewer
- Office of Biostatistics, Division of Biometrics I
  - Ququan (Cherry) Liu, Ph.D.
- Office of Medical Policy
  - Division of Drug Marketing, Advertising and Communications (DDMAC)
    - Zarna Patel, PharmD – Full Product Labeling

❖ BACKGROUND

We have met with the applicant on a few occasions & provided a number of correspondences regarding TRILOGY. Please refer to the preNDA advice letters dated 5 January 2012, 1 February 2012, and 19 June 2012 (there was no "pre-NDA" meeting for this supplement). Please also refer to the minutes from the top-line meeting with the sponsor on 8 August 2012 (minutes dated 28 August 2012). Lastly, the TRILOGY submission includes data related to the last two PMR/PMCs for EFFIENT as detailed in the initial 10 July 2009 Approval letter:

95-2 You will gather baseline cancer history and cancer adverse event data from the ongoing trial TRILOGY, a 10,300-subject trial being conducted in patients with acute coronary syndrome who are being managed medically (without coronary revascularization). The final report on cancers in this trial is to be submitted to IND 63,449 (PMR)

95-6 You commit to the collection of samples at baseline for genotyping CYP450 enzymes in TRILOGY subjects, to allow a comparison of effectiveness and bleeding in prasugrel and clopidogrel subgroups by metabolizer status. These data will be submitted with the final study report of TRILOGY. The periodic reports will include the fraction of subjects who consented to genetic testing (PMC)

❖ GENERAL APPLICATION HIGHLIGHTS

The review of this application proceeded relatively smoothly, meeting all major 21st century review timelines.

User Fee

The user fee for this application was paid in full on 6 December 2012, prior to the submission of the application (ID 3012896).

Pediatric Review Committee (PeRC)

The PeRC meeting to discuss this application was held on 14 August 2013. The PeRC and the Division agreed with the applicant that due to the limited number of children with acute coronary syndrome, studies would be impossible or highly impracticable.

Advisory Committee

It was decided at the filing meeting that an Advisory Committee would not be needed for this efficacy supplement.

❖ LABELING REVIEW

Labeling discussions began in September 2013 and were concluded on 16 October 2013. Please see the final label appended to the approval letter. The label was reviewed and commented on by SEALD. OPDP (DDMAC) did not review the label as the changes made were minimal.

❖ DISCIPLINE REVIEWS

Below are the conclusions reached by the AGGRASTAT team members, organized by role and/or discipline.

Divisional Memorandum (15 October 2013)

Dr. Stockbridge drafted and finalized a review on behalf of the Division on 15 October 2013 concurring with the primary clinical reviewer recommending approval for use as indicated in the agreed-upon labeling. He also noted a disagreement with Dr. Marciniak's final recommendations. Please see Dr. Stockbridge's review for his rationale. Lastly, Dr. Stockbridge also noted that both the PMR and PMC were deemed fulfilled.

Primary Clinical / Cross-Discipline Team Leader Review (dated 10 September 2013 and 17 September 2013)

Dr. Hicks agreed with the applicant that the labeling of the Study TADI supports current labeling to say, "consider lowering the maintenance dose to 5 mg in patients < 60 kg." (b) (4) Her recommendations are included in the agreed-upon labeling appended to approval letter. Finally, Dr. Hicks noted that both PMR/PMC 95-2 and 95-6 (noted in the Background section of this review) should be fulfilled.

Special Clinical Review - Cancer (dated 22 August 2013 and 19 September 2013)

In Dr. Marciniak's review, he noted that TRILOGY addresses a post-marketing requirement (PMR) to "gather baseline cancer history and cancer adverse event data" from it. He explained that the rationale for the PMR was due to an apparent increase in solid cancer rates with prasugrel that were

observed in the TRITON trial. In his opinion, he stated that the TRILOGY data as submitted do not show increased solid cancer rates with prasugrel. However, he relied more on the TRITON rather than the TRILOGY results because, "TRITON was more consistent with the increased solid cancer rates with increased bleeding in the recent anticoagulant trials and because TRILOGY has evidence for underreporting from Asia and Eastern Europe and a suspicious reversal of the increased cancer rates in the second half of the trial. Also, TRILOGY has unfavorable results in the US." In his review, Dr. Marciniak recommended the following:

- We do not include the TRILOGY cancer results in labeling.
- We proceed with a rigorous analysis of bleeding and cancer in all antiplatelet and anticoagulant outcome trials.

Clinical Pharmacology Review (dated 13 September 2013)
Dr. Sahre and Rogers authored a combined review of S008. In Dr. Sahre's portion of the review, she noted that the submission contains four clinical pharmacology studies, in addition to TRILOGY. The clinical pharmacology trials included assessment of the effect of age and body weight on pharmacokinetics and platelet aggregation markers in patients with stable coronary artery disease. Two other trials aimed to assess the effect on platelet aggregation markers when patients were switched from clopidogrel to prasugrel after a loading dose or a maintenance dose. Based on the results of the clinical pharmacology studies, there were proposed labeling changes (b) (4) After their review of the data and some back and forth with the applicant, an agreement was met on the appropriate labeling. This language is included in the label appended to the 16 October 2013 approval letter.

Dr. Rodger's review focused on the pharmacogenomic (PG) substudy of TRILOGY. As mentioned in the Background section of this RPM overview, the substudy fulfilled the requirement of the post marketing commitment #95-6. Upon review of S008, Dr. Rodgers noted that the PG substudy did not identify any associations between CYP2C19 genotype and efficacy or safety in either the clopidogrel- or prasugrel-treated arms of TRILOGY. (b) (4)

❖ CONSULT REVIEWS

Please see the following reviews and their corresponding dates:

- SEALD: 8 October 2013
- OPDP: 10 October 2013

❖ CONCLUSION

After taking into consideration all of the primary reviews, consults, and the applicant's additional analyses, the Agency issued an approval letter for sNDA 22307-S008 on 16 October 2013. A separate PMR/PMC Fulfillment letter for 95-2 and 95-6 will be drafted at a later date.

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

/s/

ALISON L BLAUS
10/17/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-307/S008

OFFICER/EMPLOYEE LIST

Officer/Employee List
Application: NDA 22307-S008
Product: EFFIENT (prasugrel) Tablets

The following officers or employees of FDA participated in the decision to approve this application and consented to be identified:

Norman Stockbridge
Thomas Marciniak
Karen Hicks
Edward Fromm
Alison Blaus
Ququan Liu
Michael Pacanowski
Hobart Rogers

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-307/S008

OFFICE DIRECTOR MEMO

DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Divisional Memo

NDA: 22307 S008 Effient (prasugrel).

Sponsor: Eli Lilly

Review date: 15 October 2013

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

Distribution: NDA 22307

This memo conveys the Division's recommendation to approve this application.

This application has been the subject of reviews of clinical pharmacology and biopharmaceutics (Sahre & Rogers, 19 August and 10 September 2013), cancer (Marciniak, 8 August 2013, updated 19 September 2013), and statistics (Liu, 9 September 2013). There is a comprehensive clinical review/CDTL memo (Hicks, 10 September 2013). I highlight a few matters here.

Current labeling says "consider lowering the maintenance dose [from 10] to 5 mg" in patients < 60 kg. This was explicitly tested the TADI PK study. This effectively moves most such patients from the uppermost quartile of exposure to the lowermost (initial review, p14). The exposure difference in this study did not result in measurable differences in platelet aggregation. I cannot determine from these data at what weight a dose reduction is in a patient's best interests. Existing labeling says "consider" lowering the dose; I think that suffices, as does the review team.

Age does not affect exposure to prasugrel. Study TACY confirms this in a comparison of subjects >75 to age 45-65. Halving the dose in patients >75 years old resulted in about 9% reduction in platelet inhibition. (b) (4)

A pharmacogenomics substudy (N=4094) of TRILOGY showed a tendency towards less benefit on prasugrel among reduced metabolizers, but neither the overall comparison nor any of the phenotype groups was even nominally statistically significant.

TRILOGY randomized 9326 subjects within 10 days (median of 4 days) of a UA/NSTEMI event that was managed without PCI to either clopidogrel (300 mg, then 75 mg/day) or to prasugrel (30 mg then [most subjects] 10 mg/day). Follow-up was a median of 14 months. All subjects received aspirin. The primary end point of first occurrence of adjudicated CV death, MI, or stroke was experienced by 1269 subjects; HR=0.96 (95% CI 0.86-1.07). No claim was requested by the sponsor.

TRITON (management by PCI) had a similar event rate of around 10% in the UA/NSTEMI subgroup (N=10074). Its lower bound for event reduction was about 7%, not inconsistent with TRILOGY's upper bound of a 14% risk reduction.

TRILOGY also addressed a PMR stemming from residual concern about cancer in the TRITON study. The sponsor's plan for this is described in a Malignancy Charter (15 July 2009), and included interrogation of subjects regarding new cancer at each visit, dedicated case report forms, a search for possible cancer cases in the adverse events

data, and formal adjudication. The intent was to detect new primary cancers and new metastatic cancers (including ones from a previously unknown primary).

The sponsor's counts of these are 82 for prasugrel and 78 for clopidogrel. Based on 11718 subject-years of exposure, this is a rate of about 13.7 new events per 1000 subject-years. The sponsor's counts for all events (including previously diagnosed) was 87 for prasugrel and 78 for clopidogrel, for an overall rate of about 14.5/1000 subject-years.

Dr. Marciniak's assessment of non-benign neoplasms in TRILOGY excluded non-melanoma skin cancers and brain tumors, included recurrent cancers, and included some events for which the adjudicators thought there was inadequate information to confirm, but Dr. Marciniak did. He calculates, apparently based on about 108 events, the HR=0.96 (95%CI 0.68-1.36). He cites several reasons for residual concern.

(1) *By Dr. Marciniak's accounting, the rate of reporting was lower in TRILOGY (9 per 1000 subject years) than in TRITON (13 per 1000 subject-years).* Dr. Marciniak asserts that the difference between studies is statistically significant (p7). However, if you count all cancer, the rates are 14.5 per 1000 subject-years in TRILOGY and 14.4 per 1000 subject-years in TRITON[1].

(2) *Rates were higher in some geographic regions and in some quantiles of trial time than in others.* Well, of course this is true of any subsetting of the data. Dr. Marciniak makes no attempt to justify the particular strategies he selected (or even if others with less discrepancy were also performed). He provides no analysis to show that the subsets are any less consistent than would be expected on the basis of chance.

(3) *The hazard ratio was higher in some regions than in others.* The same considerations apply here as in (2).

(4) *Neither TRITON nor TRILOGY was large enough to resolve the safety concern.* Of course, it is true that more data would narrow the overall confidence limits. A decision was made at the time of the initial approval to follow up a retrospective observation in TRITON with a prospective assessment in TRILOGY. Dr. Marciniak now questions which result to believe, clearly favoring the more ominous of the two.

Dr. Marciniak recommends, and Dr. Hicks concurs, that because of the cited defects in the TRlLOGY cancer data, they should be excluded from the label. I do not agree that the TRILOGY data are less reliable than the data from TRITON. In fact, if you count all new cancers, as was pre-specified, there is no discrepancy.

In addition, Dr. Marciniak calls for, and Dr. Hicks concurs in, a comprehensive review of bleeding and cancer in antiplatelet and anticoagulant trials. I do not see that the data with prasugrel lead to further review, but I agree to meet for further discussion.

I agree that the following PMR has been satisfied: 95-2 Cancer data from TRILOGY.

I agree that the following PMC has been satisfied: 95-6 CYP450 genotyping in TRILOGY.

[1] *N=106 on prasugrel and n=81 on clopidogrel, observed over 13,005 subject-years.*

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

/s/

NORMAN L STOCKBRIDGE
10/15/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-307/S008

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader and Clinical/Statistical Review

Date	September 17, 2013 **(September 9, 2013 ERRATA)**
From	Karen A. Hicks, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 22,307 / S008
Applicant	Eli Lilly and Company
Date of Submission	December 14, 2012
PDUFA Goal Date	October 17, 2013
Proprietary Name / Established (USAN) names	Effient® (prasugrel hydrochloride) Tablets
Dosage forms / Strength	5 mg, 10 mg
Proposed Indication(s)	None
Recommended:	*Approval*

These ERRATA are for the Cross-Discipline Team Leader and Clinical/Statistical Review dated September 9, 2013.

1. **Table 35 should be changed FROM**

Table 1. Bleeding Events by Formulation

Population	Prasugrel			Clopidogrel			Total			HR (95% CI)	P-value
	N	n	%	N	n	%	N	n	%		
Non-CABG-Related TIMI Major, Minor, or Minimal Bleeding, New Formulation											
Age < 75 years	2064	336	16.3	3590	369	10.3	5654	705	12.5	1.84 (1.58, 2.14)	<0.0001
Age ≥ 75 years	557	69	12.4	1027	130	12.7	1584	199	12.6	1.24 (0.92, 1.67)	0.17
All	2621	405	15.5	46167	498	10.8	7238	903	12.5	1.70 (1.48, 1.94)	<0.0001
Non-CABG-Related TIMI Major, Minor, or Minimal Bleeding, Old Formulation											
Age < 75 years	299	56	18.7	3589	368	10.3	3888	424	10.9	3.62 (2.71, 4.82)	<0.0001
Age ≥ 75 years	135	30	22.2	1027	130	12.7	1162	160	13.8	3.58 (2.38, 5.40)	<0.0001
All	434	86	19.8	4616	498	10.8	5050	584	11.6	3.58 (2.83, 4.53)	<0.0001
Non-CABG-Related TIMI Major or Minor Bleeding, New Formulation											
Age < 75 years	2064	34	1.7	3590	46	1.3	5654	80	1.4	1.63 (1.03, 2.57)	0.03
Age ≥ 75 years	557	9	1.6	1027	31	3.0	1584	40	2.5	0.84 (0.39, 1.82)	0.64
All	2621	43	1.6	4617	77	1.7	7238	120	1.7	1.35 (0.92, 1.99)	0.12
Non-CABG-Related TIMI Major or Minor Bleeding, Old Formulation											
Age < 75 years	299	11	3.7	3590	46	1.3	3889	57	1.5	7.0 (3.51, 13.89)	<0.0001
Age ≥ 75 years	135	4	3.0	1027	31	3.0	1162	35	3.0	2.72 (0.93, 8.02)	0.0620
All	434	15	3.5	4617	77	1.7	5051	92	1.8	4.83 (2.71, 8.62)	<0.0001
Non-CABG-Related TIMI Major Bleeding, New Formulation											
Age < 75 years	2064	17	0.8	3590	30	0.8	5654	47	0.8	1.32 (0.72, 2.44)	0.37
Age ≥ 75 years	557	8	1.4	1027	18	1.8	1584	26	1.6	1.18 (0.5, 2.80)	0.71
All	2621	25	1.0	4617	48	1.0	7238	73	1.0	1.28 (0.77, 2.10)	0.35
Non-CABG-Related TIMI Major Bleeding, Old Formulation											
Age < 75 years	299	6	2.0	3590	30	0.8	3889	36	0.9	6.90 (2.76, 17.25)	<0.0001
Age ≥ 75 years	135	2	1.5	1027	18	1.8	1162	20	1.7	2.45 (0.55, 10.92)	0.22
All	434	8	1.8	4617	48	1.0	5051	56	1.1	4.74 (2.17, 10.32)	<0.0001
Non-CABG-Related TIMI Minor Bleeding, New Formulation											
Age < 75 years	2064	17	0.8	3590	17	0.5	5654	34	0.6	2.08 (1.04, 4.15)	0.03
Age ≥ 75 years	557	1	0.2	1027	14	1.4	1584	15	1.0	1.44 (0.78, 2.64)	0.15
All	2621	18	0.7	4617	31	0.7	7238	49	0.7	1.46 (0.79, 2.68)	0.23

Population	Prasugrel			Clopidogrel			Total			HR (95% CI)	P-value
	N	n	%	N	n	%	N	n	%		
Non-CABG-Related TIMI Minor Bleeding, Old Formulation											
Age < 75 years	299	6	2.0	3590	17	0.5	3889	23	0.6	8.35 (3.16, 22.08)	<0.0001
Age ≥ 75 years	135	2	1.4	1027	14	1.4	1162	16	1.4	3.10 (0.64, 15.0)	0.15
All	434	8	1.8	4617	31	0.7	5051	39	0.8	5.61 (2.46, 12.79)	<0.0001
Analyses by Ququan Liu, M.D., M.S.											

TO:

Table 2. Bleeding Events by Formulation

Population	Prasugrel			Clopidogrel			Total			HR (95% CI)	P-value
	N	n	%	N	n	%	N	n	%		
Non-CABG-Related TIMI Major, Minor, or Minimal Bleeding, New Formulation											
Age < 75 years	2064	336	16.3	3590	369	10.3	5654	705	12.5	1.84 (1.58, 2.14)	<0.0001
Age ≥ 75 years	557	69	12.4	1027	130	12.7	1584	199	12.6	1.24 (0.92, 1.67)	0.17
All	2621	405	15.5	4617	499	10.8	7238	904	12.5	1.70 (1.48, 1.94)	<0.0001
Non-CABG-Related TIMI Major, Minor, or Minimal Bleeding, Old Formulation											
Age < 75 years	299	56	18.7	3590	369	10.3	3889	425	10.9	3.62 (2.71, 4.82)	<0.0001
Age ≥ 75 years	135	30	22.2	1027	130	12.7	1162	160	13.8	3.58 (2.38, 5.40)	<0.0001
All	434	86	19.8	4617	499	10.8	5051	585	11.6	3.58 (2.83, 4.53)	<0.0001
Non-CABG-Related TIMI Major or Minor Bleeding, New Formulation											
Age < 75 years	2064	34	1.7	3590	46	1.3	5654	80	1.4	1.63 (1.03, 2.57)	0.03
Age ≥ 75 years	557	9	1.6	1027	31	3.0	1584	40	2.5	0.84 (0.39, 1.82)	0.64
All	2621	43	1.6	4617	77	1.7	7238	120	1.7	1.35 (0.92, 1.99)	0.12
Non-CABG-Related TIMI Major or Minor Bleeding, Old Formulation											
Age < 75 years	299	11	3.7	3590	46	1.3	3889	57	1.5	7.0 (3.51, 13.89)	<0.0001
Age ≥ 75 years	135	4	3.0	1027	31	3.0	1162	35	3.0	2.72 (0.93, 8.02)	0.0620
All	434	15	3.5	4617	77	1.7	5051	92	1.8	4.83 (2.71, 8.62)	<0.0001
Non-CABG-Related TIMI Major Bleeding, New Formulation											
Age < 75 years	2064	17	0.8	3590	30	0.8	5654	47	0.8	1.32 (0.72, 2.44)	0.37
Age ≥ 75 years	557	8	1.4	1027	18	1.8	1584	26	1.6	1.18 (0.5, 2.80)	0.71
All	2621	25	1.0	4617	48	1.0	7238	73	1.0	1.28 (0.77, 2.10)	0.35
Non-CABG-Related TIMI Major Bleeding, Old Formulation											
Age < 75 years	299	6	2.0	3590	30	0.8	3889	36	0.9	6.90 (2.76, 17.25)	<0.0001
Age ≥ 75 years	135	2	1.5	1027	18	1.8	1162	20	1.7	2.45 (0.55, 10.92)	0.22
All	434	8	1.8	4617	48	1.0	5051	56	1.1	4.74 (2.17, 10.32)	<0.0001

Population	Prasugrel			Clopidogrel			Total			HR (95% CI)	P-value
	N	n	%	N	n	%	N	n	%		
Non-CABG-Related TIMI Minor Bleeding, New Formulation											
Age < 75 years	2064	17	0.8	3590	17	0.5	5654	34	0.6	2.08 (1.04, 4.15)	0.03
Age ≥ 75 years	557	1	0.2	1027	14	1.4	1584	15	1.0	1.44 (0.78, 2.64)	0.15
All	2621	18	0.7	4617	31	0.7	7238	49	0.7	1.46 (0.79, 2.68)	0.23
Non-CABG-Related TIMI Minor Bleeding, Old Formulation											
Age < 75 years	299	6	2.0	3590	17	0.5	3889	23	0.6	8.35 (3.16, 22.08)	<0.0001
Age ≥ 75 years	135	2	1.4	1027	14	1.4	1162	16	1.4	3.10 (0.64, 15.0)	0.15
All	434	8	1.8	4617	31	0.7	5051	39	0.8	5.61 (2.46, 12.79)	<0.0001
Analyses by Ququan Liu, M.D., M.S.											

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

/s/

KAREN A HICKS
09/17/2013

Cross-Discipline Team Leader and Clinical/Statistical Review

Date	September 9, 2013
From	Karen A. Hicks, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 22,307 / S008
Applicant	Eli Lilly and Company
Date of Submission	December 14, 2012
PDUFA Goal Date	October 17, 2013
Proprietary Name / Established (USAN) names	Effient® (prasugrel hydrochloride) Tablets
Dosage forms / Strength	5 mg, 10 mg
Proposed Indication(s)	None
Recommended:	*Approval*

This CDTL review is based on my review of the submission as well as the primary reviews from the following Effient team members:

- Martina Sahre, Ph.D. (Clinical Pharmacology review dated August 19, 2013)
- Hobart Rogers, Pharm.D., Ph.D. (Pharmacogenomics review dated August 19, 2013)
- Thomas A. Marciniak, M.D. (Clinical, Cancer Review dated August 22, 2013)
- Karen A. Hicks, M.D. and Ququan Liu, M.D., M.S. (Combined Clinical/Statistical review included within the body of the CDTL Review)

Summary and Conclusions:

On December 14, 2012, Eli Lilly and Company submitted a supplemental New Drug Application (sNDA) proposing revisions to the Effient Prescribing Information based on the results of the TRILOGY ACS study and four pharmacokinetic/pharmacodynamic studies. The sNDA also contained final reports for a Postmarketing Requirement and a Postmarketing Commitment. Based on our review of the submitted data, we agree that Study TADI supports current labeling to "consider lowering the maintenance dose to 5 mg in patients < 60 kg."

(b) (4)

The applicant has fulfilled Postmarketing Requirement #2 and Postmarketing Commitment #6 as follows:

- 95-2 You will gather baseline cancer history and cancer adverse event data from the ongoing trial TRILOGY, a 10,300-subject trial being conducted in patients with acute coronary syndrome who are being managed medically (without coronary revascularization). The final report on cancers in this trial is to be submitted to IND 63,449.

- 95-6 You commit to the collection of samples at baseline for genotyping CYP450 enzymes in TRILOGY subjects, to allow a comparison of effectiveness and bleeding in prasugrel and clopidogrel subgroups by metabolizer status. These data will be submitted with the final study report of TRILOGY. The periodic reports will include the fraction of subjects who consented to genetic testing.

Table of Contents

Table of Tables

Table of Figures

1. Introduction

This sNDA proposes revisions to Effient® (prasugrel) Prescribing Information (PI) based on the results of TRILOGY, an unsuccessful trial of prasugrel versus clopidogrel in acute coronary syndrome (ACS) patients who are medically managed, and four pharmacokinetic/pharmacodynamic studies.

The applicant is not seeking any new indications (b) (4) In addition, the applicant proposes to update Effient Prescribing Information with language guiding prasugrel therapy in clopidogrel-treated subjects, herein referred to as "switching."

Per the sponsor, the revisions provide (i) data to support the current 5 mg maintenance dose for patients weighing < 60 kg (b) (4) (iii) additional pharmacodynamic data in clopidogrel-treated subjects administered prasugrel, and (iv) additional malignancy analyses from the TRILOGY study.

This submission also contains final reports for Postmarketing Requirement #2 (95-2) and Postmarketing Commitment #6 (95-6) which are described in the November 30, 2012 approval letter for Supplement S007 as follows:

- 95-2 You will gather baseline cancer history and cancer adverse event data from the ongoing trial TRILOGY, a 10,300-subject trial being conducted in patients with acute coronary syndrome who are being managed medically (without coronary revascularization). The final report on cancers in this trial is to be submitted to IND 63,449.

- 95-6 You commit to the collection of samples at baseline for genotyping CYP450 enzymes in TRILOGY subjects, to allow a comparison of effectiveness and bleeding in prasugrel and clopidogrel subgroups by metabolizer status. These data will be submitted with the final study report of TRILOGY. The periodic reports will include the fraction of subjects who consented to genetic testing.

2. Background

2.1. Currently Available Treatments for Proposed Indications

Effient (prasugrel), a $P2Y_{12}$ inhibitor and new molecular entity, was approved on July 10, 2009 and is indicated for the reduction of thrombotic cardiovascular events (including stent thrombosis) in ACS patients (UA/NSTEMI or ST-elevation MI (STEMI)) who are to be managed with percutaneous coronary intervention (PCI).

To date, the Division of Cardiovascular and Renal Products has approved (4) $P2Y_{12}$ inhibitors, as summarized in Table 1. Only plavix and ticagrelor have indications for the treatment of medically-managed ACS patients.

Table 1. Prescribing Information for FDA-Approved $P2Y_{12}$ Inhibitors

Application	Drug Product	Approval Date	Indication
NDA 19,979	Ticlid (ticlopidine hydrochloride)	10/31/1991	Ticlid is a platelet aggregation inhibitor indicated • To reduce the risk of thrombotic stroke (fatal or nonfatal) in patients who have experienced stroke precursors, and in patients who have had a completed thrombotic stroke. Because TICLID is associated with a risk of life-threatening blood dyscrasias including thrombotic thrombocytopenic purpura (TTP), neutropenia/agranulocytosis and aplastic anemia (see BOXED WARNING and WARNINGS), TICLID should be reserved for patients who are intolerant or allergic to aspirin therapy or who have failed aspirin therapy • As adjunctive therapy with aspirin to reduce the incidence of subacute stent thrombosis in patients undergoing successful coronary stent implantation
NDA 20,839	Plavix (clopidogrel bisulfate)	11/17/1997	Plavix is a $P2Y_{12}$ platelet inhibitor indicated for: • Acute coronary syndrome o For patients with non-ST-segment elevation ACS [unstable angina (UA)/non-ST-elevation myocardial infarction (NSTEMI)] including patients who are to be managed medically and those who are to be managed with coronary revascularization, Plavix has been shown to decrease the rate of a combined endpoint of cardiovascular death, myocardial infarction (MI), or stroke as well as the rate of a combined endpoint of cardiovascular death, MI, stroke, or refractory ischemia o For patients with ST-elevation myocardial infarction (STEMI), Plavix has been shown to reduce the rate of death from any cause and the rate of a combined endpoint of death, re-infarction, or stroke. The benefit for patients who undergo primary PCI is unknown • Recent myocardial infarction, recent stroke, or established peripheral arterial disease. Plavix has been shown to reduce the combined endpoint of new ischemic stroke (fatal or not), new MI (fatal or not), and other vascular death
NDA 22,307	Effient (prasugrel)	7/10/2009	Effient is a $P2Y_{12}$ platelet inhibitor indicated for the reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with acute coronary syndrome who are to be managed with percutaneous coronary intervention (PCI) as follows: • Patients with unstable angina, or, non-ST-elevation myocardial infarction (NSTEMI) • Patients with ST-elevation myocardial infarction (STEMI) when managed with either primary or delayed PCI Effient has been shown to reduce the rate of a combined endpoint of cardiovascular death, nonfatal myocardial infarction (MI), or nonfatal stroke compared to clopidogrel. The difference between treatments was driven predominantly by MI, with no difference on strokes and little difference on CV death.

Application	Drug Product	Approval Date	Indication
NDA 22,433	Brilinta® (ticagrelor)	July 20, 2011	Brilinta is a $P2Y_{12}$ platelet inhibitor indicated to reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS) (unstable angina, non-ST-elevation myocardial infarction, or ST elevation myocardial infarction). BRILINTA has been shown to reduce the rate of a combined endpoint of cardiovascular death, myocardial infarction, or stroke compared to clopidogrel. The difference between treatments was driven by CV death and MI with no difference in stroke. In patients treated with PCI, it also reduces the rate of stent thrombosis.

2.2. Effient Prescribing Information

The current prescribing information has a box warning for bleeding risk as follows:

> "in patients ≥ 75 years of age, Effient is generally not recommended because of the increased risk of fatal and intracranial bleeding and uncertain benefit, except in high-risk patients (diabetes or prior MI), where its effect appears to be greater and its use may be considered."

The prescribing information also states that Effient is to be administered as a 60-mg oral loading dose followed by a 10-mg oral maintenance dose once daily. A 5-mg maintenance dose can be considered for patients weighing < 60 kg. Under Section 2, Dosage and Administration, the prescribing information states:

> "Dosing in Low Weight Patients
>
> "Compared to patients weighing ≥ 60 kg, patients weighing < 60 kg have an increased exposure to the active metabolite of prasugrel and an increased risk of bleeding on a 10 mg once daily maintenance dose. Consider lowering the maintenance dose to 5 mg in patients < 60 kg. The effectiveness and safety of the 5 mg dose have not been prospectively studied."

2.2. Other Relevant Background Information

On September 13, 2007, the applicant requested a Special Protocol Assessment (SPA) for Study H7T-MC-TABY ("A Comparison of Prasugrel and Clopidogrel in Acute Coronary Syndrome (ACS) Subjects with Unstable Angina/Non-ST-Elevation Myocardial Infarction (UA/NSTEMI) Who are Medically Managed—The TRILOGY ACS Study") ("TABY").

On October 19, 2007, the Division responded to the SPA questions.

On January 16, 2008, the applicant submitted Protocol Amendment (a) and on May 7, 2009, the applicant submitted Protocol Amendment (b).

3. Submission Quality and Integrity

The quality of the submission is acceptable. The electronic submission and SAS datasets can be found at the following links:

\\CDSESUB1\EVSPROD\NDA22307\0173

\\CDSESUB1\EVSPROD\NDA22307\0185

\\CDSESUB1\EVSPROD\NDA22307\0200

4. Protocols, Statistical Analysis Plans, and Amendments

4.1. Protocol

This review was based on the original protocol for Study H7T-MC-TABY dated August 28, 2007 and submitted to IND 63,449 with the SPA request on September 13, 2007 (SDN 590, Sequence 0478), Amendment (a) submitted on January 16, 2008 (SDN 630, Sequence 0515) and subsequently dated February 6, 2008, and Amendment (b) dated May 5, 2009 and submitted on May 7, 2009 (SDN 680, Sequence 0564).

This review was also based on Protocol Sample Banking Addendum H7T-MC-TABY(1) dated August 30, 2007 for sites not participating in the IPA Substudy and on Protocol Sample Banking Addendum H7T-MC-TABY(2) dated August 30, 2007 for sites participating in the IPA Substudy.

For Amendment (a), the applicant proposed the following changes to the study protocol:

- Stratify by age < 75 or ≥ 75 with at least 2000 ≥ 75 to be enrolled; the primary analysis will be in subjects < 75; then all subjects; ≥ 75 analyses are considered exploratory
- Lower maintenance dose to 5 mg (from 10 mg) in patients ≥ 75 or < 60 kg
- Lower the loading dose to 30 mg (from 60 mg) for patients needing a loading dose
- Reduce required symptom duration from "at least 20 minutes" to "at least 10 minutes"
- Reduce the high-risk features from five to three (age ≥ 60, prior MI retained; diabetes added; heart failure, elevated creatinine, prior peripheral vascular disease (PVD) or cerebrovascular disease eliminated)
- Add exclusions for history of gastrointestinal (GI) or internal bleeding and current dialysis
- Increase temporary discontinuation prior to surgery from 5 to 7 days
- Redefine onset of index event as time of "first medical contact for evaluation of UA/NSTEMI symptoms: including EMS responders
- Update text to be consistent with current literature, including updated definition of stent thrombosis based on ARC definitions

For Amendment (b), the applicant proposed the following changes to the study protocol:

- Extend clopidogrel treatment from "within 24 hours" to "within 72 hours" after index event
- Extend loading dose from "within 24 hours" to "within 72 hours" after index event
- Reduce angiographic criteria from "at least 1 native coronary stenosis > 50%" to exclude insignificant disease defined as "the absence of at least one stenosis in any native coronary artery visually estimated to be ≥ 30%"
- Add "prior coronary revascularization at least 30 days before the onset of the index ACS event" to the enrichment criteria of 1) age ≥ 60 years; 2) Prior MI; and 3) Diabetes Mellitus
- Reduce required ischemic symptom duration from 10 to 5 minutes
- Increase enrollment window from 7 to 10 days of index event
- Relax bleeding exclusion criteria to allow the investigator's opinion of whether a bleeding event would have a low likelihood of recurrence
- Simplify secondary endpoint testing to a simple hierarchy
- Increase DMC meetings to every six months
- Change stopping guideline for bleeding from an absolute difference in rates to the hazard ratio (> 2.0 with $p < 0.001$)
- Add stent thrombosis as a secondary objective
- Provide for dedicated malignancy data collection
- Add a 30-month treatment limit

All of the applicant's proposed changes were acceptable to the Division except that the Division noted that some of the proposed changes, especially in Amendment (b), allowed the TRILOGY study design to deviate further from prior clopidogrel study designs. In particular, the applicant's proposed change to extend clopidogrel treatment from "within 24 hours of index UA/NSTEMI event" to "within 24 to 72 hours after index event" and to extend loading dose from "within 24 hours of index UA/NSTEMI event" to "within 24 to 72 hours after index event" would make it difficult to compare the results of TRILOGY to the corresponding clopidogrel trial, CURE. In CURE, patients were randomized only if they presented within 24 hours of symptom onset.

The Division advised the applicant that TRILOGY could support the proposed indication (i.e., "prasugrel is indicated for the reduction of atherothrombotic events (CV death, MI, or stroke) in subjects with unstable angina/non-ST-segment elevation myocardial infarction who are managed without acute coronary revascularization") as a superiority trial provided that variations in its conduct (timing of first clopidogrel dose) did not deviate significantly from the clopidogrel trials.

(b) (4)

The Division suggested adding a third analysis with conservation of alpha, in patients ≥ 75 years of age only.

4.2. Statistical Analysis Plan

This review was based on the original statistical analysis plan and one amendment. Version #1 of the Statistical Analysis Plan (SAP) for Study H7T-MC-TABY (TRILOGY) (dated August 27, 2009) was submitted on August 28, 2009 (SDN 699, Sequence 0585). Version #2 (Final SAP) (dated May 7, 2012) was submitted on May 23, 2012 (SDN 960, Sequence 0836).

The primary endpoint was the composite of CV death, MI, or stroke in patients < 75 years of age. A stratified two-sided log-rank test was used for the primary endpoint analysis.

Primary analyses were to be carried out in a hierarchical fashion:

subjects < 75 years of age
↓
all subjects
↓
subjects ≥ 75 years of age

Efficacy endpoint analyses were conducted using the intent-to-treat population (all randomized subjects). Safety endpoint analyses were conducted using the treated population (i.e., subjects who received at least one dose of study drug, either a loading dose or maintenance dose). See Appendix 1 for further details.

5. CMC/Device

There are no outstanding quality issues.

6. Nonclinical Pharmacology/Toxicology

There are no outstanding nonclinical issues.

7. Clinical Pharmacology/Biopharmaceutics

The primary review by Dr. Sahre is an abbreviated review, as the clinical pharmacology of this drug product has been described previously by Drs. Elena Mishina (6/27/2008) and Sudharshan Hariharan (3/20/2010).

7.1. Mechanism of Action and Pharmacokinetic Characteristics

Prasugrel is available as a hydrochloride salt and is a prodrug which is metabolized *in vivo* to the active metabolite (R-138727). R-138727 covalently and irreversibly binds to the $P2Y_{12}$ ADP receptor on the platelet, inhibiting platelet aggregation for the lifespan of the platelet (6-9 days).

Prasugrel is converted rapidly and almost completely into its active metabolite. Per the review by Dr. Sahre, "the first stage is an ester hydrolysis by human carbboxylesterases 1 and 2, which occurs

mostly in the intestines. Thereafter, the drug is oxidized by cytochrome P450 enzymes to the active metabolite." Active metabolite peak concentrations are achieved within 30 minutes. The terminal half-life for the active metabolite is approximately 7.4 hours.

Prasugrel is eliminated primarily in urine (68%) and to a lesser degree in feces (27%). With respect to the active metabolite, body weight is a covariate. Therefore, as body weight decreases, exposure to the active metabolite increases.

A high-fat meal decreases peak concentrations of the active metabolite by approximately 50% and decreases Tmax but does not significantly affect AUC.

Prasugrel is most soluble at lower pH. Therefore, drugs that elevate gastric pH decrease the solubility of this compound. In comparative bioavailability studies, following coadministration with a proton pump inhibitor (i.e., lansoprazole), Cmax decreased by approximately 30% but AUC remained within bioequivalence limits.

7.2. Findings from Clinical Pharmacology Review

This submission contained four clinical pharmacology studies, summarized in Table 2, and one clinical trial (TRILOGY ACS), discussed elsewhere in Section 9.

Table 2. Clinical Pharmacology Studies

Study	Title
H7T-MC-TADI	A Pharmacokinetic and Pharmacodynamic Comparison of Prasugrel and Clopidogrel in Low Body Weight versus Higher Body Weight Aspirin-Treated Subjects with Stable Coronary Artery Disease.
H7T-MC-TACY	A Pharmacokinetic and Pharmacodynamic Comparison of Prasugrel and Clopidogrel in Very Elderly versus Non-Elderly Aspirin-Treated Subjects with Stable Coronary Artery Disease
H7T-MC-TABM	A Pharmacodynamic Comparison of Prasugrel (LY640315) versus Clopidogrel in Subjects with Acute Coronary Syndrome Who Are Receiving Clopidogrel S.W.A.P. SWitching Anti Platelet Study
H7T-CR-TAEH	TRansferring from ClopIdogrel Loading Dose to Prasugrel Loading Dose in Acute Coronary Syndrome PatiEnTs: TRIPLET

The current label specifies a 60-mg loading dose of Effient followed by a once-daily maintenance dose of 10 mg. (b) (4) A recommendation to lower the maintenance dose to 5 mg for patients weighing < 60 kg is already in the label. This submission also includes proposed language to guide prasugrel therapy in clopidogrel-treated ACS subjects when switching from clopidogrel to prasugrel therapy in the loading dose and maintenance dose settings.

The four clinical pharmacology studies sought to address the following issues:

- Study TADI in patients with stable coronary artery disease was conducted to assess the changes in exposure and platelet aggregation measures following dose adjustment for lower weight patients (< 60 kg) receiving 5-mg versus heavier patients (≥ 60 kg) receiving a 10-mg prasugrel maintenance dose;

- Study TACY was conducted to assess the response of platelet aggregation measures after dose adjustment for elderly patients ≥ 75 years of age receiving 5-mg versus younger patients (45 ≤ Age < 65 years) receiving 10-mg;

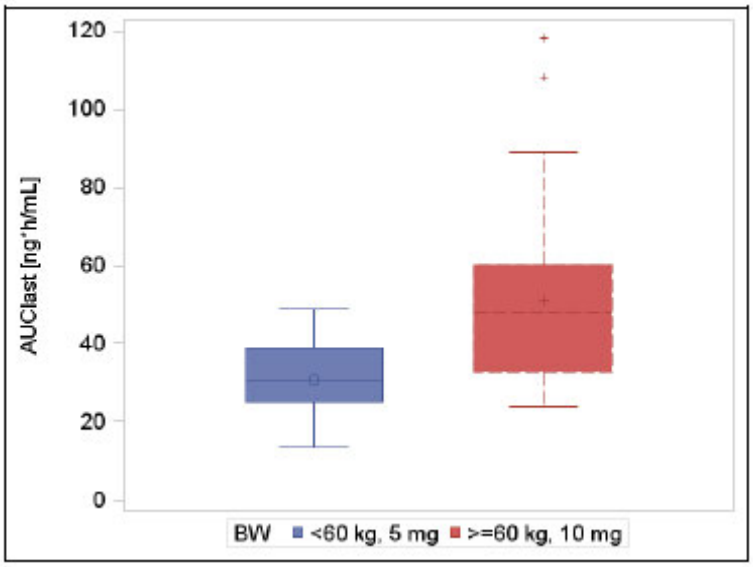
- Study TABM was conducted in patients having an ACS event within the past year to compare platelet aggregation markers after switching patients from a maintenance dose of clopidogrel 75-mg to a dose of prasugrel 10-mg with or without a prasugrel loading dose of 60-mg; and

- Study TAEH was conducted in ACS patients who were to undergo PCI to evaluate the effect of a prasugrel loading dose (30-mg or 60-mg) in addition to a clopidogrel loading dose (600-mg) on $P2Y_{12}$ Reaction Units (PRU) and percent inhibition of platelet aggregation using VerifyNow®.

Weight

In Study TADI, the applicant demonstrated that a dose of 5-mg of prasugrel in patients weighing < 60 kg reduced AUC by 38%, compared to patients weighing ≥ 60 kg and receiving 10-mg of prasugrel. Further, most patients in the low weight groups were shifted to the lower quartiles of exposure seen in the high body weight group, as shown in Figure 1.

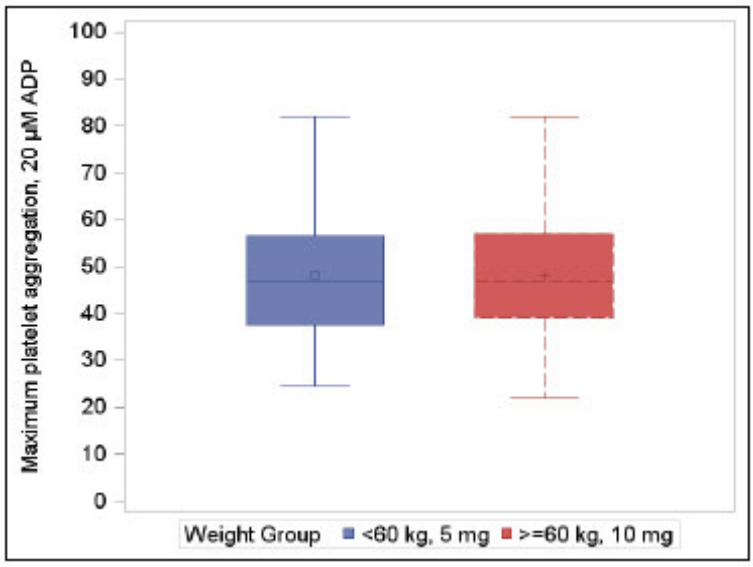
Figure 1. AUC_{last} in Patients Weighing < 60 kg is Similar to Lower Quartiles of Exposure in Patients Weighing ≥ 60 kg



(Review by Martina Sahre, Ph.D. dated August 19, 2013, Figure 4, page 9 of 59. Source: CSR H7T-MC-TADI, analysis dataset pgx_pk.xpt)

Maximum platelet aggregation (MPA) to 20 µM ADP was measured at steady state prior to dosing. MPA in patients ≥ 60 kg (receiving prasugrel 10-mg) and < 60 kg (receiving prasugrel 5-mg) was similar, as demonstrated in Figure 2.

Figure 2. Distribution of MPA is Similar Between Patients Receiving 5 mg (< 60 kg) and Those Receiving 10 mg (≥ 60 kg)



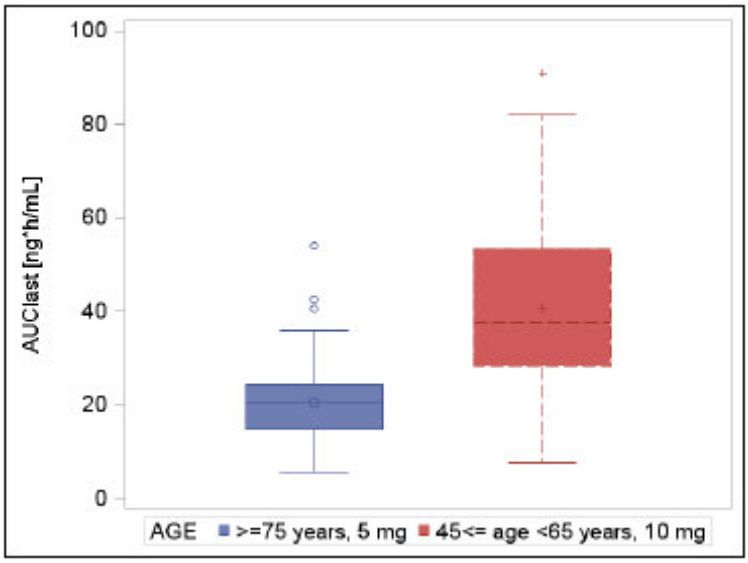
(Review by Martina Sahre, Ph.D. dated August 19, 2013, Figure 5, page 9 of 59. Source: CSR H7T-MC-TADI, analysis dataset lta.xpt)

Per Dr. Sahre, these data support current labeling and no revisions are needed. I agree with her assessment.

Age

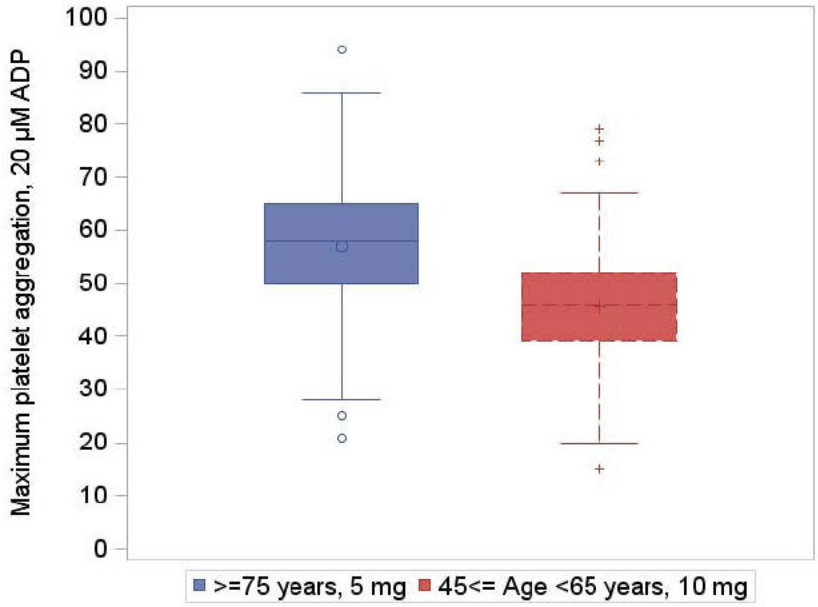
In Study TACY, the applicant evaluated platelet aggregation after decreasing the prasugrel dose in elderly patients (≥ 75 years of age) from 10-mg to 5-mg and compared these results to younger patients (45 - < 65 years of age) receiving a 10-mg maintenance dose. As demonstrated in Figure 3, decreasing the dose from 10-mg to 5-mg in patients ≥ 75 years of age reduced AUC by 49% and significantly increased MPA to 20 µM ADP by 9.4% (Figure 4).

Figure 3. Mean AUC_{last} is Reduced by 49% when Dose is 5 mg (≥ 75 years) vs. 10 mg (45 to 64 years)



(Review by Martina Sahre, Ph.D. dated August 19, 2013, Figure 6, page 10 of 59. Source: CSR H7T-MC-TACY, analysis dataset pgx_pk.xpt)

Figure 4. MPA is Higher in Patients Older than 75 Years Taking 5 mg Prasugrel Compared to Patients 45 to 64 Years Taking 10 mg Prasugrel



(Review by Martina Sahre, Ph.D. dated August 19, 2013, Figure 7, page 11 of 59. Source: CSR H7T-MC-TADI, analysis dataset lta.xpt)

(b) (4)

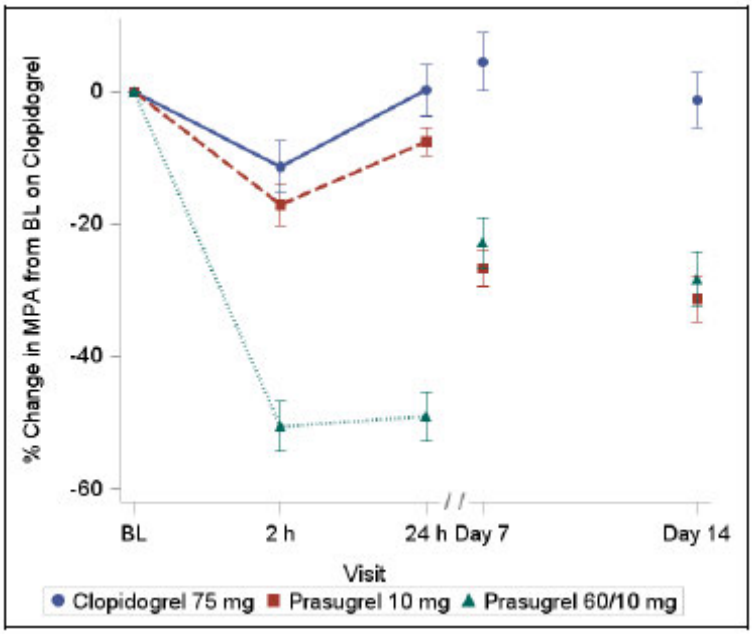
(b) (4)

I agree with her assessment. See also Sections 9.15.2., 9.15.3., and 9.15.4. for a further discussion of benefit and risk in patients ≥ 75 years of age.

Switching from a Clopidogrel Maintenance Dose to a Prasugrel Maintenance Dose

Study TABM addressed switching patients with an ACS event in the past year from clopidogrel (75-mg) to prasugrel by using either a 10-mg maintenance dose (MD) only or a 60-mg loading dose (LD) followed by a 10-mg MD. At 2 hours, MPA, as measured by light transmission aggregometry and VerifyNow™, was significantly lower for those patients who had received the prasugrel 60-mg LD followed by the 10-mg MD, compared to those who received the 10-mg MD only. One week following the switch, both prasugrel arms (60-mg LD followed by 10-mg MD versus 10-mg maintenance dose only) had a similar MPA that was significantly lower than that seen with clopidogrel 75-mg, as shown in Figure 5.

Figure 5. Percent Change in MPA from Baseline on Clopidogrel 75 mg



(Review by Martina Sahre, Ph.D. dated August 19, 2013, Figure 8, page 13 of 59. Source: CSR H7T-MC-TABM, analysis dataset labs.xpt)

Therefore, a patient with an ACS event in the past year may be switched from clopidogrel 75-mg daily to prasugrel 10-mg daily without a loading dose. Compared to clopidogrel, MPA with prasugrel 10-mg MD would be significantly decreased at 1 week, compared to clopidogrel 75-mg daily.

Effect of a Prasugrel Loading Dose following a Clopidogrel Loading Dose

Study TAEH studied three loading dose strategies in ACS patients undergoing PCI: 1) placebo plus prasugrel 60-mg LD/10-mg MD; 2) clopidogrel 600-mg LD plus prasugrel 60-mg LD/10-mg MD; and 3) clopidogrel 600-mg LD plus prasugrel 30-mg MD/10-mg MD. Accumetrics VerifyNow™ $P2Y_{12}$ Reaction Units (PRU) were measured at 6 hours following dosing. There were no statistically significant differences between these groups in platelet aggregation at 6 hours. However, VerifyNow™ may not be able to discriminate between treatments after LDs, rendering these results uninterpretable.

7.3. Postmarketing Commitment #6 (95-6): Pharmacogenomics Substudy

Dr. Rogers' review discusses the findings of the Pharmacogenomics (PG) substudy.

7.3.1. TRILOGY Pharmacogenomics Substudy

A total of 5736 subjects (62% of the study population) were included in this substudy. Approximately 97% of DNA samples were collected at baseline. The primary endpoint event rate in the PG substudy was similar to that seen for the ITT population for the overall study.

Per Dr. Rogers, "no significant CYP2C19 genotype by treatment interactions were observed for efficacy (composite of CV death, MI, or stroke) or safety (Non-CABG-Related TIMI Major or Minor Bleeding). Reduced metabolizers (RMs) tended to have a higher event rate on prasugrel, but such an effect was not observed for clopidogrel. Additionally, when broken down into 4 genotype groups, again no significant differences were observed." These results are displayed in Table 3 and Table 4.

Table 3. Primary Efficacy Composite Endpoint (CV death, MI, or Stroke) – CEC Adjudicated by CYP2C19-Predicted Phenotype Genetic ITT Subjects < 75 Years of Age

	2-Level	4-Level	Prasugrel			Clopidogrel			Hazard Ratio	
Subset	Phenotype	Phenotype	n	N	%	n	N	%	(95% CI)	P-Value
Overall ITT		N/A	364	3662	**10.1**	397	4351	**11.0**	**0.92 (0.79 – 1.01)**	0.21
PG Substudy			202	2037	**9.9**	226	2057	**10.9**	**0.97 (0.85 – 1.10)**	0.24
	EM		139	1500	**9.3**	164	1480	**11.1**	**0.84 (0.67-1.05)**	0.14
		UM	58	642	9.0	66	682	9.7	0.95 (0.66-1.35)	0.75
		EM	81	858	9.4	98	798	12.3	0.77 (0.57-1.03)	0.08
	RM		63	537	**11.7**	62	577	**10.8**	**1.08 (0.76-1.53)**	0.68
		IM	47	439	10.7	47	467	10.1	1.05 (0.70-1.58)	0.81
		PM	16	98	16.3	15	110	13.6	1.16 (0.58-2.36)	0.64

EM: extensive metabolizer; IM: intermediate metabolizer; PM: poor metabolizer; RM: reduced metabolizer; UM: Ultrarapid metabolizer

(Review by Hobart Rogers, Pharm.D., Ph.D., dated August 19, 2013, Table 4, page 55)

Table 4. Non-CABG-Related TIMI Major/Minor Bleeding Events While at Risk - CEC Adjudicated by CYP2C19-Predicted Phenotype Genetic Treated Set TABY PGx

	Predicted		Prasugrel			Clopidogrel			Hazard Ratio	
Subset	Phenotype	Genotype	n	N	%	n	N	%	(95% CI)	P-Value
Overall ITT		N/A	70		**2.0**	46		**1.3**	**1.54 (1.06-2.23)**	0.02
PG Substudy										
	EM		32	1497	**2.1**	25	1477	**1.7**		0.34
		UM	11	641	1.7	14	679	2.1	0.84 (0.38-1.86)	0.76
		EM	21	856	2.5	11	798	1.4	1.82(0.88-3.78)	0.11
	RM		9	533	**1.7**	6	575	**1**		0.35
		IM	9	435	2.1	6	465	1.3	1.59 (0.57-4.47)	0.36
		PM	0	98	0	0	110	0		

EM: extensive metabolizer; IM: intermediate metabolizer; PM: poor metabolizer; RM: reduced metabolizer; UM: Ultrarapid metabolizer

(Review by Hobart Rogers, Pharm.D., Ph.D., dated August 19, 2013, Table 5, page 55)

Lastly, the applicant utilized data from Stratum 3 to evaluate subjects who were switched from clopidogrel to prasugrel after randomization. Stratum 3 subjects received commercial clopidogrel prior

to the index event, were thought to be at steady state at the time of the onset of the index event, and were maintained on commercial clopidogrel until randomization. Dr. Rogers' analyses demonstrated that there were significant reductions in PRU in both extensive and reduced metabolizers.

7.3.2. TRITON Pharmacogenomics Substudy

The TRITON-TIMI 38 (TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel) trial, was a 13,608-patient, multicenter, international, randomized, double-blind, parallel-group study comparing Effient to a regimen of clopidogrel, each added to aspirin and other standard therapy, in patients with ACS (UA, NSTEMI, or STEMI) who were to be managed with PCI.

A total of 2534 subjects (1254 prasugrel and 1280 clopidogrel) were included in the TRITON Pharmacogenomics Substudy (18.6% of the ITT population). This substudy had a number of limitations. First, numerous subjects were consented following randomization, suggesting that the substudy represented merely "a convenience sample." Second, the substudy population was slightly younger with less severe medical history than the overall study, and a higher percentage of clopidogrel subjects had metabolic syndrome. Third, the primary efficacy endpoint results in the substudy participants were inconsistent with the results seen in the overall ITT population. As a result, there was concern about whether the genetic sample in the substudy was representative of the overall ITT population in TRITON.

In contrast, most TRILOGY subjects were consented (and baseline samples were obtained) prior to randomization. In addition, the primary efficacy results in the TRILOGY substudy were consistent with the overall ITT results.

The Clinical Endpoints Committee (CEC)-adjudicated primary endpoint (CV death, MI, stroke) results from the TRITON pharmacogenomics substudy are displayed in Table 5 and are compared to the ITT results for the overall study (Table 6). None of the populations in the substudy demonstrated significant treatment effects with prasugrel, in contrast to the ITT findings.

Table 5. Number and Percentage of Subjects having Genetics Information and Reaching the Composite Primary Endpoint from Randomization through Study End – CEC Adjudicated (TRITON)

Subject population	Prasugrel			Clopidogrel			Total			Cox Proportional HR (95% CI)	Gehan-Wilcoxon p-value
	N	n	%	N	n	%	N	n	%		
UA/NSTEMI	880	76	8.64	914	83	9.08	1794	159	8.86	0.95 (0.69, 1.29)	0.6943
STEMI	374	35	9.36	366	32	8.74	740	67	9.05	1.08 (0.67, 1.74)	0.7689
All ACS	1254	111	8.85	1280	115	8.98	2534	226	8.92	0.98 (0.76, 1.28)	0.8711

(Review by Ququan Liu, M.D., M.S., dated 5/2/2008, Table 5, page 16)

Table 6. Number and Percentage of Subjects Reaching the Composite Primary Endpoint of CV Death, Nonfatal MI, or Nonfatal Stroke - CEC Adjudicated (ITT) (TRITON)

Subject population	Prasugrel			Clopidogrel			Total			Cox Proportional HR (95% CI)	Gehan-Wilcoxon p-value
	N	n	%	N	n	%	N	n	%		
UA/NSTEMI	5044	469	9.30	5030	565	11.23	10074	1034	10.26	0.820 (0.726, 0.927)	0.002
STEMI	1769	174	9.84	1765	216	12.24	3534	390	11.04	0.793 (0.649, 0.968)	0.019
All ACS	6813	643	9.44	6795	781	11.49	13608	1424	10.46	0.812 (0.732, 0.902)	<0.001

(Review by Ququan Liu, M.D., M.S., dated 5/2/2008, Table 6, page 16)

When evaluating extensive metabolizers, prasugrel subjects in the UA/NSTEMI group had a 30% increased occurrence of the primary endpoint, compared to clopidogrel, as shown in Table 7.

Table 7. Number and Percentage of Subjects Reaching the Composite Primary Endpoint from Randomization through Study End - CEC Adjudicated (All Randomized Subjects wtih Extensive Metabolizer Functional Group (EM))

Subject population	Prasugrel			Clopidogrel			Total			Cox Proportional HR (95% CI)	Gehan-Wilcoxon p-value	Log-Rank p-value
	N	n	%	N	n	%	N	n	%			
UA/NSTEMI	596	58	9.73	623	47	7.54	1219	105	8.61	1.30 (0.88, 1.91)	0.2126	0.1847
STEMI	243	18	7.41	253	22	8.70	496	40	8.06	0.844 (0.453, 1.574)	0.5782	0.5930
All ACS	839	76	9.06	876	69	7.88	1715	145	8.45	1.15 (0.83, 1.59)	0.4525	0.3979

(Review by Ququan Liu, M.D., M.S., dated 5/2/2008, Table 7, page 16)

However, when evaluating reduced metabolizers (RMs), prasugrel subjects in the UA/NSTEMI group had a 50% decreased occurrence of the primary endpoint, compared to clopidogrel, as shown in **Error! Reference source not found.**. These results suggested that the TRITON Trial resulted in a favorable outcome for prasugrel patients because numerous clopidogrel patients were reduced metabolizers.

Table 8. Number and Percentage of Subjects Reaching the Composite Primary Endpoint from Randomization through Study End – CEC Adjudicated (All Randomized Subjects with Reduced Metabolizer Function Group (RM))

Subject population	Prasugrel			Clopidogrel			Total			Cox Proportional HR (95% CI)	Gehan-Wilcoxon p-value	Log-Rank p-value
	N	n	%	N	n	%	N	n	%			
UA/NSTEMI	284	18	6.34	291	36	12.37	575	54	9.39	0.50 (0.28, 0.88)	0.0176	0.0139
STEMI	131	17	12.98	113	10	8.85	244	27	11.07	1.52 (0.69, 3.31)	0.2822	0.2923
All ACS	415	35	8.43	404	46	11.39	819	81	9.89	0.74 (0.47, 1.14)	0.1948	0.1675

(Review by Ququan Liu, M.D., M.S., dated 5/2/2008, Table 8, page 18)

Prasugrel STEMI RMs had a 52% increased risk of the primary endpoint in TRITON, compared to clopidogrel. Although there were a small number of events in the STEMI subgroup, this increased hazard ratio was an unexpected finding, given that the CYP2C19 genotype was not thought to influence the disposition of prasugrel.

Dr. Liu concluded that the genetic sample in TRITON was not representative of the ITT population. In isolation, the disparate results in TRITON were difficult to explain.

7.3.3. Pharmacogenomics Substudy Cross-Trial Comparisons (TRILOGY versus TRITON)

In TRILOGY, the primary efficacy endpoint results by CYP2C19 genotype status in UA/NSTEMI patients < 75 years of age demonstrated a higher event rate in prasugrel RMs, compared to clopidogrel RMs, as shown in Table 9. In addition, the event rate in clopidogrel RMs was lower than the event rate in clopidogrel EMs.

In isolation, these findings from TRILOGY may be difficult to interpret. However, if we consider the disparate findings from TRITON with respect to the STEMI RMs, we now have two studies that demonstrate increased event rates in the prasugrel treatment group, compared to clopidogrel. Is this play of chance or do these data suggest there may be prasugrel reduced metabolizers? I suggest that there may be prasugrel RMs and that we have yet to determine the mechanism by which this phenomenon is operative.

Table 9. Primary Efficacy End Point (CV Death, MI, or Stroke) by CYP2C19 Genotype Status Patients < 75 Years

	EM (Non-carriers)		RM (Carriers)		HR (95% CI)	EM vs. RM P-value	P-value*
	Rate (%)	n/N	Rate (%)	n/N			
Prasugrel	9.27	139/1500	**11.73**	65/537	0.80 (0.59, 1.08)	0.16	0.24
Clopidogrel	11.08	164/1480	**10.75**	62/577	1.02 (0.76, 1.37)	0.91	
	Prasugrel vs. Clopidogrel HR (95% CI) 0.84 (0.67, 1.05) P = 0.14		Prasugrel vs. Clopidogrel HR (95% CI) 1.1 (0.76, 1.53) P = 0.68				
Applicant, Top-Line Results, Slide 50, August 8, 2012.							

8. Clinical Microbiology

There are no outstanding clinical microbiology issues.

9. Clinical/Statistical- Efficacy

9.1. TRILOGY Study Design and Objectives

Study H7T-MC-TABY (TRILOGY ACS) was a Phase 3, multicenter, randomized, parallel-group, double-blind, double-dummy, active-controlled study in patients with recent (within 10 days) UA/NSTEMI (index event) who were to be medically managed. The study population was stratified according to age (< 75 years of age / ≥ 75 years of age).

Patient eligibility for this study was determined by the timing of the medical management decision and by commercial clopidogrel status at the time of randomization.

The primary objective of TRILOGY was to determine if prasugrel and aspirin was superior to clopidogrel and aspirin in the treatment of medically managed subjects enrolled within 10 days of the UA/NSTEMI index event.

The TRILOGY study design is displayed in Figure 6. Subjects were randomized within 10 days of the onset of the UA/NSTEMI index event, once the decision for a medical management strategy was made with reasonable certainty (i.e., coronary revascularization was not planned for the index event). The clinical decision for medical management could have been based on results of coronary angiography performed within 10 days of the onset of the index event, results of prior coronary diagnostic evaluation, and/or other subject clinical characteristics such as any comorbidities that would have precluded revascularization; however, the medical management decision was left to the discretion of the investigator.

If subjects were within 10 days of the index event and were either clopidogrel naïve or not at steady state, subjects were in Stratum 1 and were randomized in a 1:1 fashion via interactive voice response system (IVRS) to either Clopidogrel 300-mg loading dose (LD) + 75-mg qd + low-dose aspirin **OR** Prasugrel 30-mg LD plus 5/10-mg MD + low-dose aspirin. In TRILOGY, subjects ≥ 75 years of age or weighing < 60 kg received a prasugrel maintenance dose of 5-mg. All other subjects in TRILOGY received a prasugrel maintenance dose of 10-mg.

Note that in TRITON, the prasugrel LD was 60-mg, not 30-mg, and the maintenance dose was 10-mg daily (not 5-mg in subjects ≥ 75 years of age or weighing < 60 kg).

If subjects were within 10 days of the index event and had already been given a LD of clopidogrel within 72 hours of the index event followed by daily maintenance doses of clopidogrel according to the applicant's definition of standard of care, subjects were in Stratum 2. Stratum 2 subjects were randomized in a 1:1 fashion to either clopidogrel 75-mg qd + low-dose aspirin **OR** prasugrel 5/10 mg + low-dose aspirin.

If subjects were > 10 days from the index event but had received clopidogrel according to the standard of care within 72 hours of the index event and achieved steady state, subjects were in Stratum 3. In Stratum 3, subjects were randomized in a 1:1 fashion to either clopidogrel 75 mg qd + low-dose aspirin **OR** prasugrel 5/10 mg qd + low-dose aspirin.

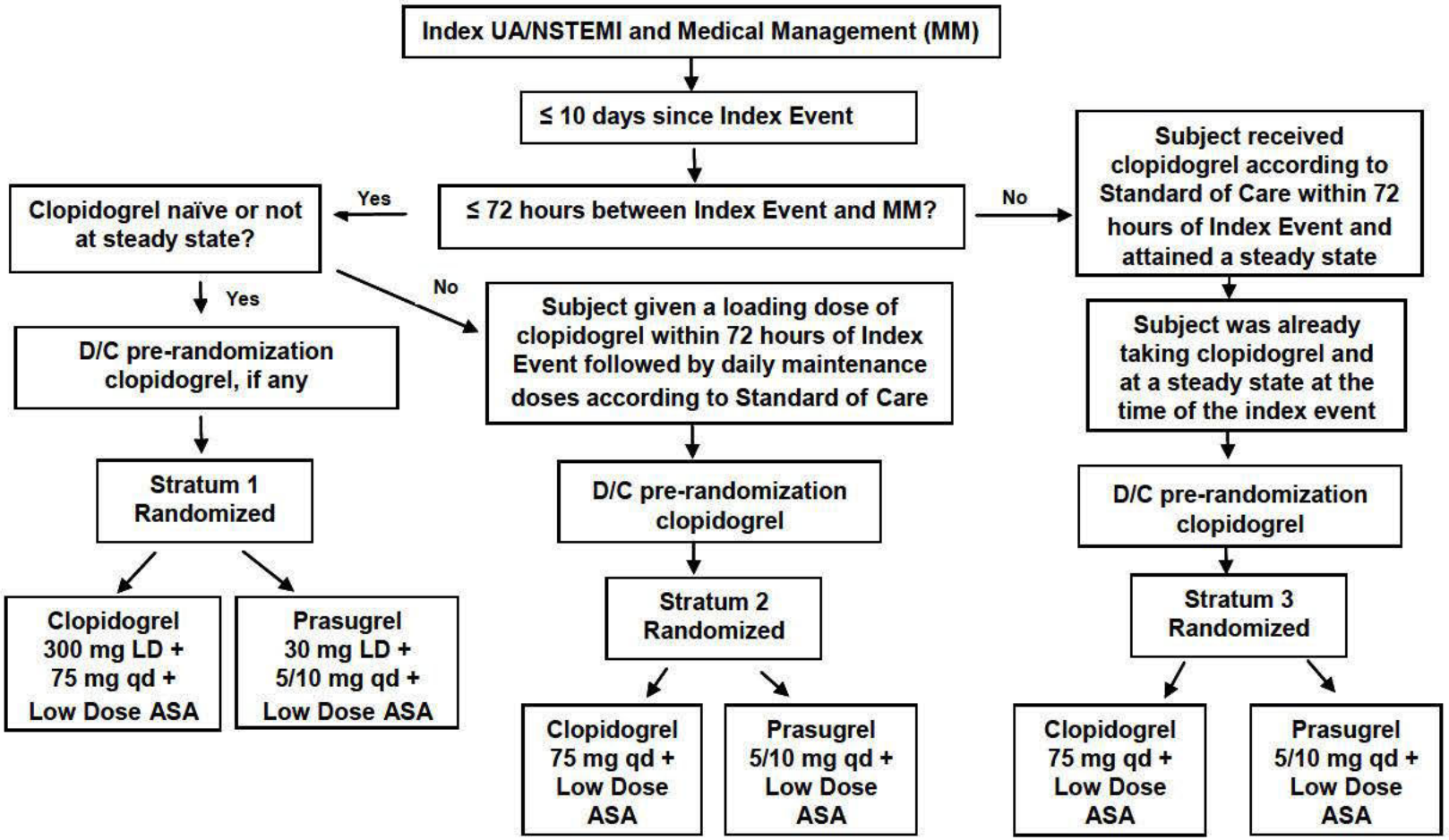
The applicant defined "Standard of Care" as the following:

- Subjects receiving commercial clopidogrel loading dose (LD) within 72 hours after the index event followed by daily clopidogrel 75-mg maintenance dose (MD)
- Subjects receiving commercial clopidogrel MD for ≥ 5 days prior to the Index Event and daily until randomization
- Subjects ≥ 75 years of age or < 60 kg of body weight received the 5-mg MD of prasugrel

All subjects were to be treated with adjunctive aspirin (open-label and commercially available), not to exceed 162-mg, in addition to the study drug for the duration of the study. Low-dose aspirin was "strongly recommended" and was defined as a daily concomitant aspirin dose between 75- and 100-mg. The dose could be increased to a maximum of 325-mg in patients undergoing PCI during follow-up for a period of time, as determined by the investigator and based on the subject's individual clinical circumstances.

A subject was considered "at risk" during the period from the administration of the first dose of study drug through 7 days after permanent study drug discontinuation, or the subject's discontinuation visit, whichever was earlier.

Figure 6. TRILOGY Study Design



ASA: Aspirin; MM: Medical Management; NSTEMI: Non-ST-elevation myocardial infarction; UA: unstable angina.
Low-dose aspirin: between 75 and 100 mg.

9.2. Treatments

After initial stratification by age, subjects were randomized and stratified as shown in Table 10.

Table 10. Dosage & Timing of Study Drug by Commercial Clopidogrel Status at Randomization

Medically Managed UA/NSTEMI Subjects		
Commercial Clopidogrel Status at Time of Randomization	**Randomized Treatment**	**Timing of First Dose of Study Drug**
Stratum 1 (None) Either clopidogrel-naïve or not at steady state[a] on commercial clopidogrel, with a decision for medical management and randomization within 72 hours following the onset of the index event.	**LD/MD:** Clopidogrel 300-mg LD followed by 75-mg once-daily MD or prasugrel 30-mg LD followed by 5/10-mg once-daily MD[b] (each administered on a background of low-dose aspirin)	First dose of study drug was to be given as soon as possible after randomization and no later than 72 hours following the onset of the index event.
Stratum 2 (Initiated) Commercial clopidogrel LD of at least 300-mg administered within 72 hours following the onset of the UA/NSTEMI index event with administration of daily MD thereafter.	**MD Only:** Clopidogrel 75-mg once-daily MD or prasugrel 5/10-mg once-daily[b] (each administered on a background of low-dose aspirin)	First dose of study drug was to be given no later than 24 hours after the last dose of commercial clopidogrel.
Stratum 3 (Ongoing) Commercial clopidogrel treatment prior to the index event and subject deemed to be at steady state at the time of the onset of the index event; and MD maintained up until time of randomization.		
LD: loading dose; MD: maintenance dose. **[a]Subjects defined as clopidogrel-naïve or not at steady state were subjects who: (i) had not received clopidogrel prior to the index event or have received a commercial clopidogrel MD for < 5 consecutive days immediately prior to the index event, AND (ii) had NOT received a commercial clopidogrel LD within 72 hours following the onset of the index event.** **[b]Subjects ≥ 75 years of age or < 60 kg of body weight received the 5-mg MD.** **Clinical Study Report, Table TABY.9.1, page 71.**		

9.3. Inclusion and Exclusion Criteria

Key inclusion criteria were

- UA/NSTEMI index event within 10 days prior to randomization
- No planned PCI or coronary artery bypass graft surgery (CABG) for index event
- ≥ 1 high-risk feature at index event
  - Age ≥ 60 years
  - Prior MI
  - Diabetes mellitus
  - Coronary revascularization (either PCI or CABG) at least 30 days before the onset of the index event

For TRILOGY, recent UA/NSTEMI was defined as follows:

- NSTEMI was defined as a history of chest discomfort or anginal-equivalent symptoms of ≥ 5 minutes duration at rest within 24 hours prior to the index event, with no evidence of persistent ST-segment elevation. Subjects were also required to have a CK-MB or troponin T or I greater than the upper limit of normal (ULN) defined by the local laboratory assay. If CK-MB or troponin were not available, total CK ≥ 2 times ULN was acceptable.

- UA was defined as a history of chest discomfort or anginal-equivalent symptoms of ≥ 5 minutes duration at rest within 24 hours prior to the index event, with ST-segment depression > 1 mm in at least two or more ECG leads without elevation of CK-MB, troponin T, or troponin I.

Key exclusion criteria were

- STEMI
- Fibrinolytic therapy (for index event)
- PCI/CABG within the previous 30 days or planned PCI/CABG for index event
- Cardiogenic shock, refractory ventricular arrhythmias, or NYHA Class IV heart failure within the previous 24 hours
- History of ischemic or hemorrhagic stroke
- Intracranial neoplasm, AV malformation, or aneurysm
- History of any TIA symptoms
- Decision for medical management ≥ 72 hours after the onset of the index event without commercial clopidogrel treatment within 72 hours following the onset of the index event
- Contraindications for antiplatelet therapy
- History of bleeding diathesis
- Platelet count < 100,000 or Hgb < 10 gm/dL
- Hemodialysis/Peritoneal dialysis
- Concomitant NSAID or COX2 inhibitor use (> 2 weeks of daily treatment)

9.4. Study Sites/Investigators

Investigators enrolled subjects at 970 study centers in 52 countries. Each country was assigned to one of 8 regions as shown in Table 11.

Table 11. Study Regions

Regions	Countries
Central/Eastern Europe	Bulgaria, Croatia, Czech Republic, Hungary, Lithuania, Poland, Romania, Russia, Serbia, Slovakia, Ukraine
Western Europe/Scandinavia	Augstria, Belgium, Denmark, Finland, France, Germany, Portugal, Italy, Ireland, Netherlands, Spain, Sweden, Switzerland, UK
Latin America	Argentina, Brazil, Chile, Columbia, Costa Rica, Mexico, Panama, Peru
East Asia	China, Malaysia, Philippines, Singapore, South Korea, Taiwan, Thailand
Indian Subcontinent	India
North America	US/Puerto Rico, Canada
Mediterranean Basin	Tunisia, Israel, Egypt, Malta, Turkey, Greece
Rest of World	Australia, New Zealand, South Africa
Clinical Study Report, page 101.	

Four sites in India (Sites 25062, 25356, 25359, and 25065), summarized in Table 12, were discontinued as a result of non-compliance with Good Clinical Practice (GCP) requirements (record falsification).

Table 12. Excluded Indian Sites

Principle Investigators	Name of Site	Site #
Dr. Ashok Deshpande	Niramaya Medical Foundation and Research Center, Baramati	62
Dr. Aniruddha Dharmadhikari	Shree Saibaba Heart Institute, Nashik	65
Dr. Harshwardan Mardikar	Spanadan Heart Institute, Nagpur	356
Dr. Mukand Kumble	Omega Hospital, Mangalore	359

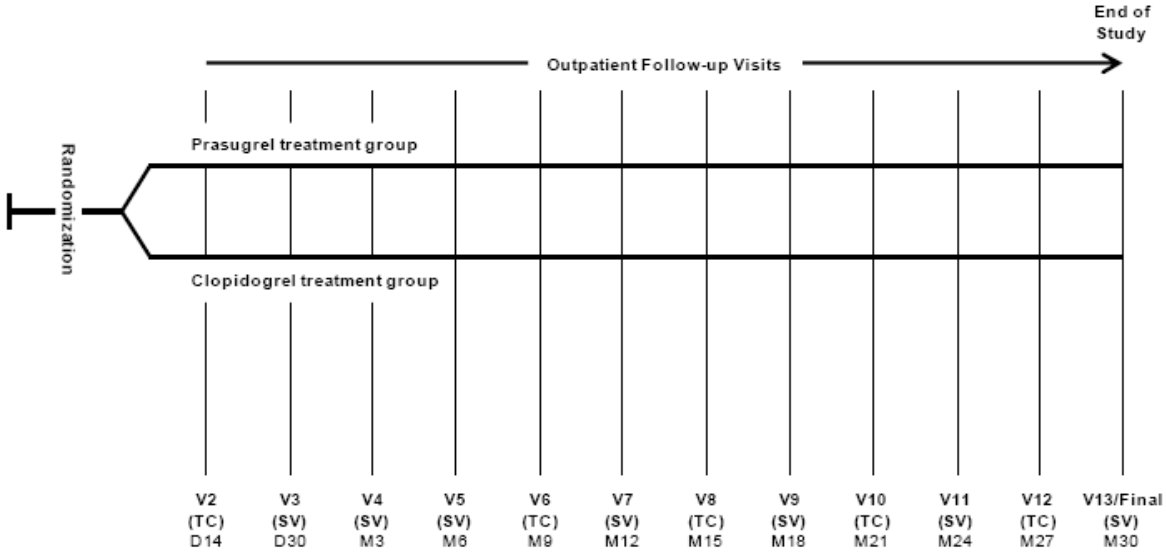
9.5. Study Duration/Dates

TRILOGY was conducted from June 27, 2008 through March 30, 2012. The first and last patient were randomized on June 27, 2008 and September 11, 2011, respectively. The final patient contact occurred on May 22, 2012. The last date vital status was obtained on any patient was May 23, 2012. The database was locked on June 3, 2012. The trial duration was 1425 days, or 3.9 years.

9.6. Study Visit Schedule and Procedures

There were a total of 13 study visits over a course of 30 months, as shown in Figure 7.

Figure 7. Study Visit Schedule (Protocol H7T-MC-TABY)



Abbreviations: SV = site visit; TC = telephone contact.
Visit windows are for Visits 2 and 3, ±3 days; Visit 4, ±7 days; Visits 5 up to Final Visit, ±14 days.

(Protocol H7T-MC-TABY (b) dated May 5, 2009, Figure TABY.2., page 27)

9.7. Endpoints

9.7.1. Primary Efficacy Endpoint

The primary efficacy endpoint was the time to the first occurrence of the composite of CV death, MI, or stroke.

All primary efficacy endpoint events were to be adjudicated by the Clinical Endpoints Committee (CEC).

9.7.2. Secondary Efficacy Endpoints

Secondary efficacy endpoints were the time to the first occurrence of:

- The composite endpoint of CV death and MI
- The composite endpoint of CV death, MI, stroke, or rehospitalization for recurrent unstable angina (UA)
- The composite endpoint of all-cause death, MI, or stroke
- Stent thrombosis

In addition, the components of the primary and secondary composite endpoints were to be analyzed individually in a similar fashion to the primary and secondary composite endpoint (time to first occurrence): CV death, all-cause death, MI, stroke, rehospitalization for recurrent UA, and any coronary revascularization.

All secondary endpoint events were to be adjudicated by the CEC.

9.7.3. Safety Endpoints

Safety endpoints included

1. Non-coronary artery bypass graft (non-CABG)-related TIMI major bleeding
2. Non-coronary artery bypass graft (Non-CABG)-related TIMI life-threatening bleeding (a subset of the Thrombolysis in Myocardial Infarction [TIMI] major bleeding)
3. Non-CABG-related TIMI minor bleeding
4. Non-CABG-related TIMI minimal bleeding
5. Non-CABG-related Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) severe or life-threatening bleeding
6. Non-CABG-related GUSTO moderate bleeding
7. Non-CABG-related GUSTO mild bleeding
8. Fatal bleeding or intracranial hemorrhage (ICH)
9. CABG-related bleeding

9.8. Definitions

9.8.1. Efficacy Endpoints

1) **<u>Cardiovascular Death</u> (CV death):** Cardiovascular death due to documented cardiovascular cause. Additionally, death not clearly attributable to noncardiovascular causes will be considered CV death.

2) **<u>Myocardial Infarction</u> (MI):** The definition of MI is adapted from the universal definition of MI (Thygesen et. Al. 2007) and is dependent on the clinical timing of the event in relation to presenting syndrome and cardiovascular procedures. A subject who experiences any one of the following after randomization will qualify as having had an MI:

- Elevation or re-elevation of the ST segment AND either ischemic chest pain ≥ 20 minutes in duration, or hemodynamic decompensation.
- CK-MB fraction or troponin > ULN AND either ischemic chest pain (or anginal equivalent) ≥ 20 minutes in duration, or hemodynamic decompensation.
- CK-MB fraction or troponin > ULN, AND either ischemic chest pain (or anginal equivalent) ≥ 20 minutes in duration, or ST-segment deviation ≥ 1 mm in one or more leads. If at the onset of the suspected event, the ischemic biomarker was still elevated as a result of the index event, then there must be demonstration of a falling biomarker level prior to the onset of the suspected event, and the subsequent peak of the ischemic biomarker must be 1.5 times the value prior to the onset of the suspected event. These criteria do not need to be met if the ischemic biomarker is not elevated prior to the onset of the suspected event.
- CK-MB > 3 times ULN on at least 1 sample within 24 hours following PCI (for subjects requiring emergent, urgent, or elective PCI at any time after randomization)
- CK-MB > 5 times ULN on at least 1 sample within 24 hours following CABG (for subjects requiring emergent, urgent, or elective CABG surgery at any time after randomization)
- New Q waves ≥ 0.04 seconds or pathology distinct from that of the index event and thought to be new since randomization

In order to detect periprocedural MI in subjects undergoing PCI or CABG during the course of the study, it is recommended that 4 blood samples for CK-MB be drawn: 1 prior to the procedure and

3 within the first 24 hours after PCI/CABG. The second sample should be drawn at least 6 hours after PCI. The third sample should be at least 6 hours later (6 to 8 hours recommended), and the fourth sample should be drawn at least 6 hours after the third sample (6 to 8 hours recommended).

In the rare circumstances where CK-MB testing is not available, a troponin > 3 times ULN on at least 1 sample within 24 hours following PCI (for subjects requiring emergent, urgent, or elective PCI at any time after randomization) or a troponin > 5 times ULN on at least 1 sample within 24 hours following CABG (for subjects requiring emergent, urgent, or elective CABG surgery at any time after randomization) may be used to define and adjudicate a periprocedural MI in place of CK-MB levels.

3) **Stroke:** the rapid onset of new, persistent neurologic deficit lasting more than 24 hours. In the case of clinical diagnosis of stroke, computed tomography (CT) or magnetic resonance imaging (MRI) is strongly recommended, but not required. Computed tomography or MRI scans will be considered by the CEC to support the clinical impression. Available supplemental information from head CT or MRI scans will assist in the determination if there is a demonstrable lesion compatible with an acute stroke. Furthermore, all strokes will be classified as either "ischemic" or "hemorrhagic" based on imaging data, if available, or "uncertain cause" if imaging data are not available.

4) **Rehospitalization for Recurrent Unstable Angina:** Rehospitalization for recurrent UA includes chest discomfort or anginal-equivalent symptoms of ≥ 5 minutes duration at rest and at least one of the following:

- ST-segment depression > 1 mm in at least two or more ECG leads without elevation of CK-MB, troponin T, or troponin I.
- Performance of an unplanned coronary revascularization procedure (PCI or CABG)

Rehospitalization includes admission to any inpatient unit. Emergency room visits or chest pain unit evaluations lasting for < 24 hours are not considered to be rehospitalizaiton. If recurrent UA results in prolongation of a hospitalization initiated for other reasons, it will be considered as a rehospitalization for recurrent UA.

5) **Stent Thrombosis:** Stent thrombosis will be defined based on the Academic Research Consortium definitions (Mauri et. al., 2007):

- **Definite Stent Thrombosis:** A definite stent thrombosis is considered to have occurred by either angiographic or pathological confirmation.
    - **Angiographic confirmation** of stent thrombosis is defined by the presence of an intracoronary thrombus that originates in the stent or in the 5 mm proximal or distal to the stent and presence of at least 1 of the following criteria within a 48 hour time window.
        - Acute onset of ischemic symptoms at rest
        - New ischemic electrocardiographic (ECG) changes that suggest acute ischemia
        - Typical rise and fall in cardiac biomarkers

      The intracoronary thrombus will be further characterized as being non-occlusive or occlusive as follows:

        - Non-occlusive thrombus: intracoronary thrombus is defined as a (spheric, ovoid, or irregular) non-calcified filling defect or lucency surrounded by contrast material (on 3 sides within a coronary stenosis) seen in multiple projections, or persistence of contrast material within the lumen, or a visible embolization or intraluminal material downstream.

- Occlusive thrombus: TIMI 0 or TIMI 1 intrastent or proximal to stent up to the most adjacent proximal side branch or main branch (if originates from the side branch)

  The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered a confirmed stent thrombosis (silent occlusion).

- **Pathological confirmation** of stent thrombosis
  - Evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy.

- **Probable Stent Thrombosis:** Clinical definition of probable stent thrombosis is considered to have occurred after intracoronary stenting in the following cases:

  - Any unexplained death within the first 30 days
  - Irrespective of the time after the index procedure, any MI that is related to documented ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause

- **Possible Stent Thrombosis:** Clinical definition of possible stent thrombosis is considered to have occurred with any unexplained death from 30 days after intracoronary stenting until end of study follow-up.

9.8.2. Bleeding Events

1) **Non-CABG-related TIMI major bleeding** is an intracranial hemorrhage (ICH) **OR** any clinically overt bleeding (including bleeding evident on imaging studies) associated with a fall in hemoglobin (Hgb) of ≥ 5 gm/dL from baseline (accounting for the effect of transfusions on change in Hgb, defined as 1 unit packed red blood cells [RBCs] = 1 gm/dL Hgb = 3% hematocrit [Hct]).

2) **Non-CABG-related TIMI life-threatening bleeding** is any non-CABG-related TIMI major bleeding that is fatal, leads to hypotension that requires treatment with intravenous vasopressor agents, OR requires surgical intervention for ongoing bleeding, **OR** necessitates the transfusion of 4 or more units of blood (whole blood or packed RBCs) over a 48-hour period, **OR** any symptomatic ICH.

3) **Non-CABG-related TIMI minor bleeding** is any clinically overt bleeding (including bleeding evident on imaging studies) associated with a fall in Hgb of ≥ 3 gm/dL, but < 5 gm/dL from baseline (accounting for the effect of transfusions on change in Hgb, defined as 1 unit packed RBCs = 1 gm/dL Hgb = 3% Hct).

4) **Non-CABG-related TIMI minimal bleeding** is any clinically overt bleeding (including bleeding evident on imaging studies) associated with a fall in Hgb of < 3 gm/dL from baseline (accounting for the effect of transfusions on change in Hgb, defined as 1 unit packed RBCs = 1 gm/dL Hgb = 3% Hct).

5) **Non-CABG related GUSTO severe or life-threatening bleeding** is any ICH **OR** any bleeding event resulting in substantial hemodynamic compromise requiring treatment.

6) **Non-CABG-related GUSTO moderate bleeding** is any bleeding event resulting in the need for transfusion that is not considered a GUSTO severe or life-threatening bleed.

7) **Non-CABG-related GUSTO mild bleeding** is any other bleeding event that does not require transfusion or cause hemodynamic compromise.

9.9. Demographics

Baseline characteristics for all randomized subjects < 75 years of age are displayed in Table 13. These characteristics were balanced except for

- Coronary revascularization (PCI or CABG) (37.9% clopidogrel vs. 35.4% prasugrel)
- History of atrial fibrillation ablation (3.6% clopidogrel vs. 0% prasugrel)
- History of contrast induced nephropathy (1.2% clopidogrel vs. 6.8% prasugrel)
- Prior CABG (16.3% clopidogrel vs. 14.6% prasugrel)

Most subjects were Caucasian and were from Central/Eastern Europe. Approximately 36% of subjects were female. With respect to clopidogrel status at randomization, most subjects were in Stratum 2.

Table 13. Baseline Characteristics (All Randomized Subjects < 75 years old)

Randomized Subjects < 75 years	Prasugrel (N = 3620)	Clopidogrel (N = 3623)	Total (N = 7243)
Age (mean ± SD)	61.4 ± 8.55	61.5 ± 8.38	61.5 ± 8.46
Sex (female) (n, %)	1309 (36.2%)	1290 (35.6%)	2599 (35.9%)
Ethnicity (N)	3620	3622	7242
Caucasian	2362 (65.3%)	2374 (65.5%)	4736 (65.4%)
African	87 (2.4%)	72 (2.0%)	159 (2.2)
Hispanic	321 (8.9%)	346 (9.6%)	667 (9.2%)
Asian	821 (22.7%)	800 (22.1%)	1621 (22.4%)
Other	29 (0.8%)	30 (0.8%)	59 (0.8%)
Geographic Region (N)	3620	3623	7243
North America	488 (13.5%)	507 (14.0%)	995 (13.7%)
United States	430 (11.9%)	446 (12.3%)	876 (12.1%)
Central/Eastern Europe	1229 (34.0%)	1200 (33.1%)	2429 (33.5%)
Western Europe/Scandinavia	317 (8.8%)	313 (8.6%)	630 (8.7%)
Latin America	472 (13.0%)	496 (17.7%)	968 (13.4%)
Mediterranean Basin	259 (7.2%)	268 (7.4%)	527 (7.3%)
East Asia	292 (8.1%)	279 (7.7%)	571 (7.9%)
Indian Subcontinent	513 (14.2%)	508 (14.0%)	1021 (14.1%)
Rest of World	50 (1.4%)	52 (1.4%)	102 (1.4%)
Weight (N)	3618	3621	7239
< 60 kg	474 (13.1%)	465 (12.8%)	939 (13.0%)
Clopidogrel Status			
N	3620	3623	7243
None (LD given)	152 (4.2%)	168 (4.6%)	320 (4.4%)
Initiated (initiated for index event)	2507 (69.3%)	2477 (68.4%)	4984 (68.8%)
Ongoing (at steady state)	961 (26.6%)	978 (27.0%)	1939 (26.8%)
Coronary Revascularization (PCI or CABG) (N)	3611	3604	7215
Yes	1279 (35.4%)	1365 (37.9%)	2644 (36.7%)
Peripheral Arterial Disease (N)	3559	3570	7129
Yes	213 (6.0%)	259 (7.3%)	472 (6.6%)
History of Atrial Fibrillation Ablation (N)	208	220	428
Yes	0	8 (3.6%)	8 (1.9%)
History of Contrast Induced Nephropathy (N)	176	162	338
Yes	12 (6.8%)	2 (1.2%)	14 (4.1%)

Randomized Subjects < 75 years	Prasugrel (N = 3620)	Clopidogrel (N = 3623)	Total (N = 7243)
Prior MI (N)	3591	3600	7191
Yes	1556 (43.3%)	1612 (44.8%)	3168 (44.1%)
Prior PCI	3607	3604	7211
Yes	973 (27.0%)	1049 (29.1%)	2022 (28.0%)
Prior Coronary Stent	3594	3602	7196
Yes	857 (23.9%)	912 (25.3%)	1769 (24.6%)
Prior CABG (N)	3615	3613	7228
Yes	527 (14.6%)	588 (16.3%)	1115 (15.4%)
Diabetes Mellitus (N)	3614	3611	7225
Yes	1393 (38.5%)	1418 (39.3%)	2811 (38.9%)
Creatinine Clearance using Cockcroft-Gault Formula (ml/min) (N)	3458	3486	6944
< 60	750 (21.7%)	761 (21.8%)	1511 (21.8%)
< 30	49 (1.4%)	56 (1.6%)	105 (1.5%)
30-60	701 (20.3%)	705 (20.2%)	1406 (20.3%)
≥ 60	2708 (78.3%)	2725 (78.2%)	5433 (78.2%)
Prior TIA (N)	3601	3606	7207
Yes	3(<0.01%)	9 (0.3%)	12 (0.2%)
Prior Ischemic Stroke (N)	3608	3611	7219
Yes	13 (0.4%)	18 (0.5%)	31 (0.4%)
CABG (coronary artery bypass graft) surgery; MI: myocardial infarction; PCI: percutaneous coronary intervention. Percentages may not add up to 100% due to rounding.			

Baseline characteristics for all randomized subjects ≥ 75 years of age are summarized in Table 14. These characteristics were balanced except for

- Family history of coronary artery disease (27.3% clopidogrel vs. 22.9% prasugrel)
- Hyperlipidemia (57.9% clopidogrel vs. 61.9% prasugrel)
- Peripheral arterial disease (9.0% clopidogrel vs. 11.6% prasugrel)
- Chronic renal insufficiency (13.2% clopidogrel vs. 16.2% prasugrel)

Most subjects were Caucasian and were from Central/Eastern Europe. Approximately 50% of subjects were women.

Table 14. Baseline Characteristics (All Randomized Subjects ≥ 75 years old)

Randomized Subjects ≥ 75 years	Prasugrel (N = 1043)	Clopidogrel (N = 1040)	Total (N = 2083)
Age (mean ± SD)	80.3 ± 4.3	80.3 ± 4.4	80.3 ± 4.3
Sex (female) (n, %)	520 (49.9%)	531 (51.1%)	1051 (50.5%)
Ethnicity (N)	1043	1040	2083
Caucasian	767 (73.5%)	773 (74.3%)	1540 (73.9%)
African	14 (1.3%)	12 (1.2%)	26 (1.3%)
Hispanic	109 (10.5%)	86 (8.3%)	195 (9.4%)
Asian	147 (14.1%)	164 (15.8%)	311 (14.9%)
Other	6 (0.6%)	5 (0.5%)	11 (0.5%)
Geographic Region (N)	1043	1040	2083
North America	147 (14.1%)	129 (12.4%)	276 (13.3%)
United States	133 (12.8%)	116 (11.2%)	249 (12.0%)
Central/Eastern Europe	317 (30.4%)	344 (33.1%)	661 (31.7%)
Western	183 (17.6%)	181 (17.4%)	364 (17.5%)

Randomized Subjects ≥ 75 years	Prasugrel (N = 1043)	Clopidogrel (N = 1040)	Total (N = 2083)
Europe/Scandinavia			
Latin America	163 (15.6%)	145 (13.9%)	308 (14.8%)
Mediterranean Basin	70 (6.7%)	61 (5.9%)	131 (6.3%)
East Asia	87 (8.3%)	94 (9.0%)	181 (8.7%)
Indian Subcontinent	56 (5.4%)	64 (6.2%)	120 (5.8%)
Rest of World	20 (1.9%)	22 (2.1%)	42 (2.0%)
Weight (N)	1042	1038	2080
< 60 kg	233 (22.4%)	229 (22.1%)	462 (22.2%)
Clopidogrel Status			
N	1042	1040	2082
None (LD given)	43 (4.1%)	35 (3.4%)	78 (3.8%)
Initiated (initiated for index event)	753 (72.3%)	776 (74.6%)	1529 (73.4%)
Ongoing (at steady state)	246 (23.6%)	229 (22.0%)	475 (22.8%)
Coronary Revascularization (PCI or CABG)(N)	1033	1033	2066
Yes	330 (32.0%)	299 (29.0%)	629 (30.5%)
Peripheral Arterial Disease (N)	1022	1004	2026
Yes	118 (11.6%)	90 (9.0%)	208 (10.3%)
History of Atrial Fibrillation Ablation (N)	139	143	282
Yes	1 (0.7%)	2 (1.4%)	3 (1.1%)
History of Contrast Induced Nephropathy (N)	166	135	301
Yes	7 (4.2%)	6 (4.4%)	13 (4.3%)
Prior MI (N)	1029	1026	2055
Yes	426 (41.4%)	393 (38.3%)	819 (39.9%)
Prior PCI (N)	1033	1026	2059
Yes	214 (20.7%)	189 (18.4%)	403 (19.6%)
Prior Coronary Stent (N)	1024	1019	2043
Yes	179 (17.5%)	153 (15.0%)	332 (16.3%)
Prior CABG (N)	1036	1039	2075
Yes	179 (17.3%)	160 (15.4%)	339 (16.3%)
Diabetes Mellitus (N)	1041	1040	2081
Yes	363 (34.9%)	365 (35.1%)	728 (35.0%)
Family History of Coronary Artery Disease (N)	870	843	1713
Yes	199 (22.9%)	230 (27.3%)	429 (25.0%)
Hyperlipidemia (N)	999	992	1991
Yes	618 (61.9%)	574 (57.9%)	1192 (60.0%)
Chronic Renal Insufficiency (N)	1024	1027	2051
Yes	166 (16.2%)	135 (13.2%)	301 (14.7%)
Creatinine Clearance using Cockcroft-Gault Formula (ml/min) (N)	1002	1007	2009
< 60	723 (72.2%)	688 (68.3%)	1411 (70.2%)
< 30	113 (11.3%)	121 (12.0%)	234 (11.7%)
30-60	610 (60.9%)	567 (56.3%)	1177 (58.6%)
≥ 60	279 (27.8%)	319 (31.7%)	598 (29.8%)
Prior TIA (N)	1036	1030	2066
Yes	5 (0.5%)	6 (0.6%)	11 (0.5%)
Prior Ischemic Stroke (N)	1036	1032	2068
Yes	6 (0.6%)	10 (1.0%)	16 (0.8%)

CABG (coronary artery bypass graft) surgery; MI: myocardial infarction; PCI: percutaneous coronary intervention. Percentages may not add up to 100% due to rounding.

9.10. Time from Index Event to Randomization and to First Dose of Study Drug

Overall, the median time from medical contact to first dose of study drug was approximately 5 days.

The median time from symptom onset to first dose of study drug was generally longer in patients ≥ 75 years of age, compared to patients < 75 years of age except for Stratum 1 in subjects ≥ 75 years of age. The median time from medical contact to first dose of study drug and the median time from symptom onset to first dose of study drug are summarized in Table 15.

In subjects < 75 years of age, the median time from symptom onset to first dose of study drug in Stratum 1 was 31.8 hours (prasugrel) versus 40.3 hours (clopidogrel); in Stratum 2 was 122 hours (prasugrel) versus 121.3 hours (clopidogrel); and in Stratum 3 was 94.6 hours (prasugrel) versus 100.5 hours (clopidogrel).

In subjects ≥ 75 years of age, the median time from symptom onset to first dose of study drug in Stratum 1 was 37.1 hours (prasugrel) versus 28.2 hours (clopidogrel); in Stratum 2 was 131 hours (prasugrel) versus 134 hours (clopidogrel); and in Stratum 3 was 122 hours (prasugrel) versus 115.1 hours (clopidogrel).

Table 15. Timing of Study Drug Treatment Across Strata

Strata	Time from Medical Contact to First Dose of Study Drug				Time from Symptom Onset to First Dose of Study Drug			
	Prasugrel		Clopidogrel		Prasugrel		Clopidogrel	
	N	Median Hours	N	Median Hours	N	Median Hours	N	Median Hours
< 75 years								
Overall	3587	102.3[a]	3590	102.6[a]	3589	112.4[a]	3588	111.7[a]
Stratum 1	148	26.2[b]	168	33.6[b]	151	31.8[b]	168	40.3[b]
Stratum 2	2487	114.9[c]	2450	114.0[c]	2487	122.0[c]	2449	121.3[c]
Stratum 3	952	88.8[c]	972	94.8[c]	951	94.6[c]	971	100.5[c]
≥ 75 years								
Overall	1033	118.5[a]	1027	118.0[a]	1033	124.0[a]	1027	125.3[a]
Stratum 1	43	26.2[b]	33	25.0[b]	43	37.1[b]	33	28.2[b]
Stratum 2	745	123.8[c]	767	123.4[c]	745	131.0[c]	767	134.0[c]
Stratum 3	245	116.6[c]	227	109.2[c]	245	122.0[c]	227	115.1[c]
All								
Overall	4620	108.0[a]	4617	108.4[a]	4622	116.0[a]	4615	115.8[a]
Stratum 1	191	26.2[b]	201	28.2[b]	194	32.5[b]	201	36.5[b]
Stratum 2	3232	117.1[c]	3217	116.3[c]	3232	123.3[c]	3216	123.6[c]
Stratum 3	1197	94.4[c]	1199	96.9[c]	1196	101.0[c]	1198	103.5[c]

[a]First dose of study drug was either loading dose or maintenance dose, depending on strata
[b]Loading dose of study drug
[c]Maintenance dose of study drug

9.11. Subject Disposition

A summary of Subject Cohorts is displayed in Table 16, and Subject Disposition and Treatment Status at the End of Study is shown in Table 16. Subject disposition is summarized in Figures 8 through 10.

Table 16. Summary of Subject Cohorts

	< 75 Years n (%)*	**≥ 75 Years n (%)***	**All Subjects n (%)***
All Randomized Subjects	7243 (77.7%)	2083 (22.3%)	9326 (100.0%)
All Treated Subjects	7180 (77.7%)	2060 (22.3%)	9240 (100.0%)
n=number of subjects in cohort. ***Percentage of all randomized subjects represented by n.**			

A total of 9,446 subjects were enrolled in TRILOGY and 9,326 subjects were randomized, including 4663 subjects in the prasugrel treatment group and 4663 subjects in the clopidogrel treatment group. A total of 8,753 subjects (93.9%) completed the trial, including 4378 subjects (93.9%) in the prasugrel treatment group and 4375 subjects (93.8%) in the clopidogrel treatment group.

A total of 120 subjects from 4 Indian sites were excluded from the efficacy and safety analyses due to site GCP issues, including 113 subjects < 75 years of age and 7 subjects ≥ 75 years of age.

Of the 7356 enrolled subjects < 75 years of age, 7243 subjects (3620 prasugrel, 3623 clopidogrel) were included in the analyses. Of the 7243 randomized subjects < 75 years of age, 6838 subjects (94.4%) completed the study. At study completion, 79.5% of subjects were on study drug and 14.9% were not.

Of the 2090 enrolled subjects ≥ 75 years of age, 2083 subjects (1043 prasugrel, 1040 clopidogrel) were included in the analyses. Of the 2083 randomized subjects ≥ 75 years of age, 1915 subjects (91.9%) completed the study. At study completion, 69.2% of subjects were on study drug and 22.7% were not. There was a significant difference between treatment groups with respect to the percentage of subjects on study drug at trial completion (76.2% prasugrel versus 78.2% clopidogrel; p = 0.028) and with respect to the percentage of subjects not on study drug at trial completion (17.7% prasugrel versus 15.7% clopidogrel; p = 0.011).

In total, 573 subjects (6.1%) did not complete the study, as summarized in Table 17. A total of 559 subjects did not complete the study due to “subject decision,” including 517 subjects (5.5%) due to “withdrawal of participation” and 19 subjects (0.2%) due to “revocation of consent.”

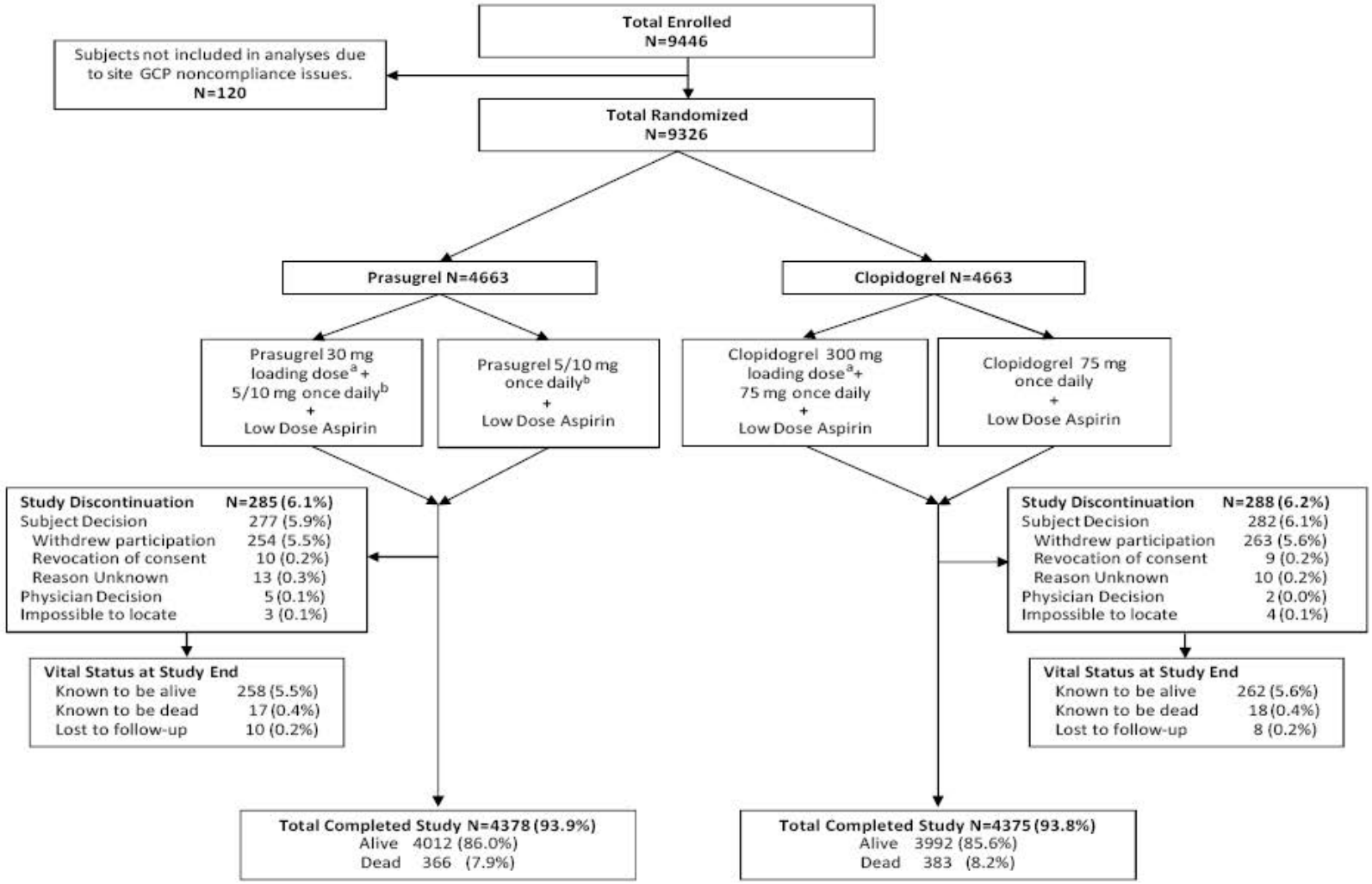
A total of 405 subjects (5.6%) < 75 years of age and 168 subjects (8.1%) ≥ 75 years of age did not complete the trial.

Table 17. Subject Disposition and Treatment Status at End of Study (All Randomized Subjects)

Disposition	Prasugrel n (%)	Clopidogrel n (%)	Total n (%)
Number of Randomized Subjects	4663	4663	9326
Number of Treated Subjects	4623 (88.1%)	4617 (99.0%)	9240 (99.1%)
Study Completed	**4378 (93.9%)**	**4375 (93.8%)**	**8753 (93.9%)**
On Study Drug at Time of Completion	3555 (76.2%)	3644 (78.2%)	7199 (77.2%)
Alive	3315 (71.1%)	3385 (72.6%)	6700 (71.8%)
Dead	240 (5.2%)	259 (5.6%)	499 (5.4%)
Off Study Drug at Time of Completion	823 (17.7%)	731 (15.7%)	1554 (16.7%)
Alive	697 (15.0%)	607 (13.0%)	1304 (14.0%)
Dead	126 (2.7%)	124 (2.7%)	250 (2.7%)
Study Not Completed	**285 (6.1%)**	**288 (6.2%)**	**573 (6.1%)**
On Study Drug at Time of Discontinuation	139 (3.0%)	144 (3.1%)	283 (3.0%)
Study Drug Discontinuation Before Study Discontinuation	146 (3.1%)	144 (3.1%)	290 (3.1%)
Reasons for Study Discontinuation			
Subject Decision	277 (5.9%)	282 (6.1%)	559 (6.0%)
Withdrawal Participation	254 (5.5%)	263 (5.6%)	517 (5.5%)
Revocation of Consent	10 (0.2%)	9 (0.2%)	19 (0.2%)
Not Delineated	13 (0.3%)	10 (0.2%)	23 (0.3%)
Sponsor Decision	0	0	0
Physician Decision	5 (0.1%)	2 (0.04%)	7 (0.08%)
Impossible to locate and establish contact with patient	3 (0.1%)	4 (0.09%)	7 (0.08%)

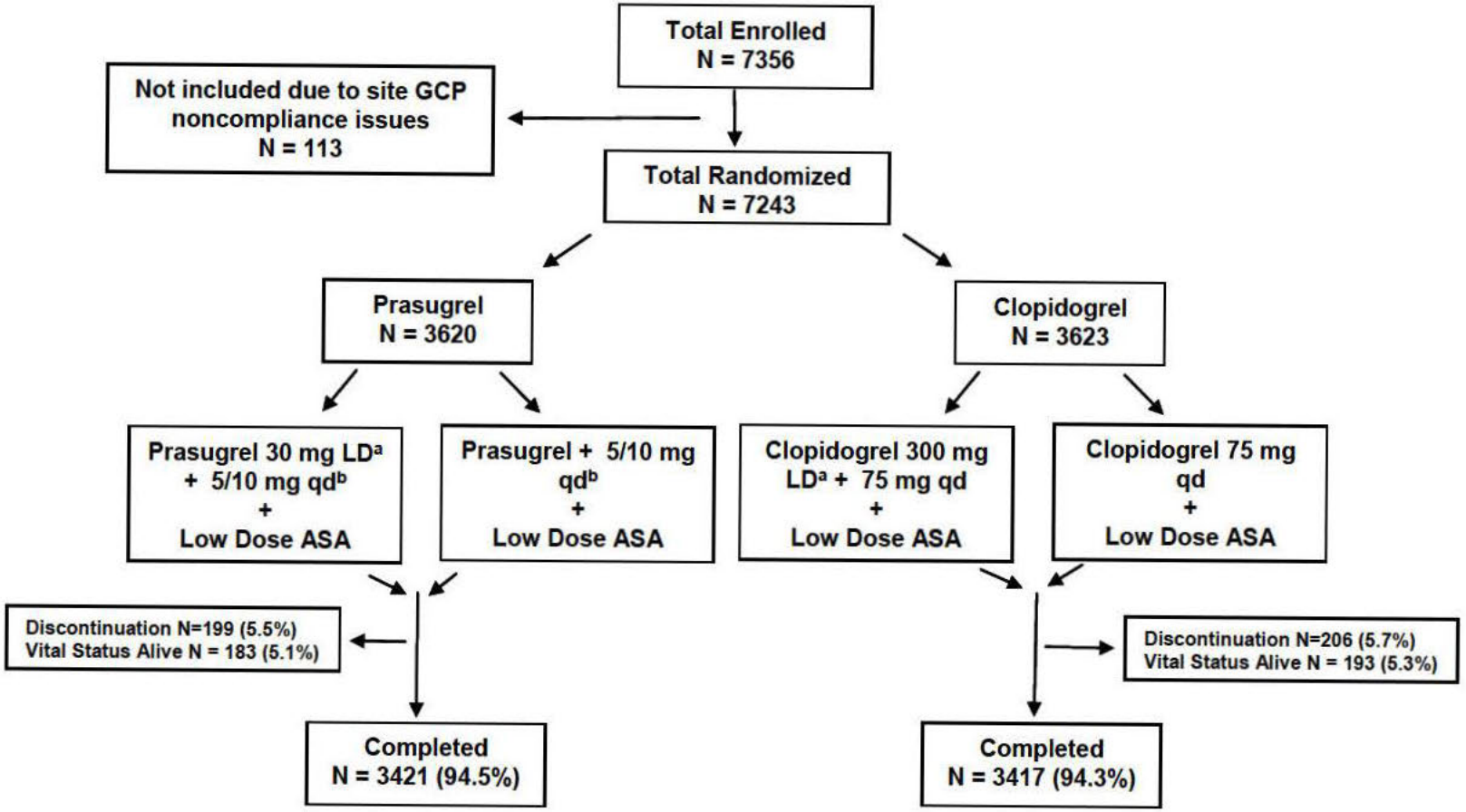
n=number of subjects;
% is percentage of randomized subjects
On study drug is defined as study drug discontinuation within 7 days of study completion or discontinuation.

Figure 8. Subject Disposition for All Randomized Subjects in TRILOGY



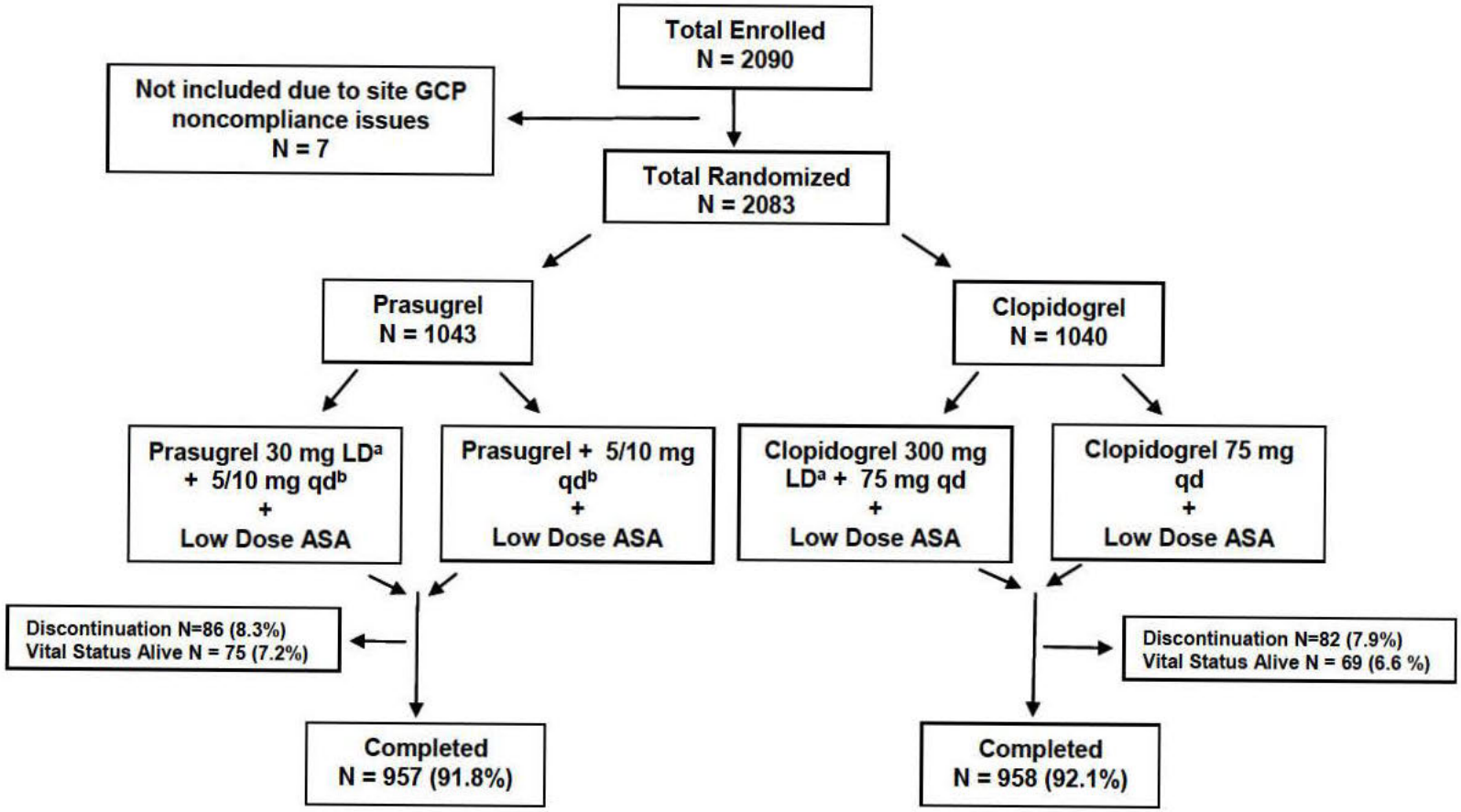
[a]Subjects defined as clopidogrel-naïve or not at steady state assigned to LD of prasugrel or clopidogrel
[b]Subjects < 75 years with body weight < 60 kg (N = 474 [13.1%]) received 5-mg maintenance dose

Figure 9. Subject Disposition (< 75 years)



[a]Subjects defined as clopidogrel-naïve or not at steady state assigned to LD of prasugrel or clopidogrel
[b]Subjects < 75 years with body weight < 60 kg (N = 474 [13.1%]) received 5-mg maintenance dose

Figure 10. Subject Disposition (≥ 75 years)



[a]Subjects defined as clopidogrel-naïve or not at steady state assigned to LD of prasugrel or clopidogrel
[b]Subjects ≥ 75 years of age (N=1043 [100%]) received the 5-mg maintenance dose

9.12. Analysis of Primary Endpoint and its Components

Compared to clopidogrel, prasugrel did not significantly reduce the occurrence of the composite endpoint of CV death, MI, or stroke in patients < 75 years of age, in all patients, or in patients ≥ 75 years of age, as shown in Table 18.

Dr. Liu conducted a sensitivity analysis for the primary endpoint, including the four Indian sites (25062, 25065, 25356, and 25359), and the results were similar. See Appendix 2 for this sensitivity analysis and for other primary endpoint analyses.

Table 18. Primary Efficacy Endpoint (CV Death, MI, or Stroke) (CEC-Adjudicated)

Population	Prasugrel			Clopidogrel			Total			HR (95% CI)	P-value
	N	n	%	N	n	%	N	n	%		
Age < 75 years	3620	364	10.1	3623	397	11.0	7243	761	10.5	0.92 (0.79, 1.06)	0.21
Age ≥ 75 years	1043	257	24.6	1040	251	24.1	2083	508	24.4	1.03 (0.87, 1.23)	0.73
All	4663	621	13.3	4663	648	13.9	9326	1269	13.6	0.96 (0.86, 1.07)	0.45
Analysis by Ququan Liu, M.D., M.S.											

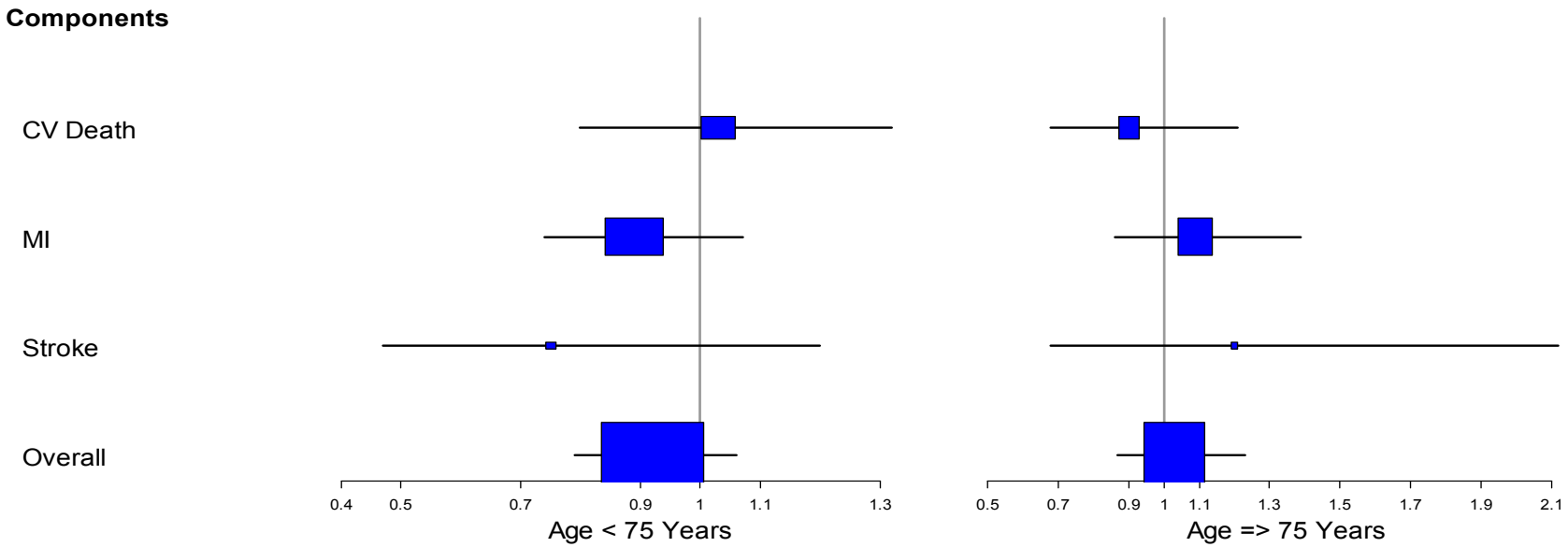
With respect to first events, prasugrel did not significantly reduce the risk of the occurrence of the individual components of the primary endpoint, compared to clopidogrel, regardless of age.

Table 19. Components of Primary Endpoint (1st Events)

Population	Prasugrel			Clopidogrel			Total			HR (95% CI)	P-value
	N	n	%	N	n	%	N	n	%		
CV Death											
Age < 75 years	3620	122	3.4	3623	188	5.2	7243	240	3.3	1.03 (0.80, 1.32)	0.87
Age ≥ 75 years	1043	88	8.4	1040	98	9.4	2083	186	8.9	0.90 (0.68, 1.21)	0.51
All	4663	210	4.5	4663	216	4.6	9326	426	4.6	0.98 (0.81, 1.18)	0.76
MI											
Age < 75 years	3620	211	5.8	3623	238	6.6	7243	449	6.2	0.89 (0.74, 1.07)	0.20
Age ≥ 75 years	1043	143	13.7	1040	131	12.6	2083	274	13.2	1.09 (0.86, 1.39)	0.44
All	4663	354	7.6	4663	369	7.9	9326	723	7.8	0.96 (0.83, 1.11)	0.57
Stroke											
Age < 75 years	3620	31	0.9	3623	41	1.1	7243	72	1.0	0.75 (0.47, 1.20)	0.23
Age ≥ 75 years	1043	26	2.5	1040	22	2.1	2083	48	2.3	1.20 (0.68, 2.12)	0.55
All	4663	57	1.2	4663	63	1.4	9326	120	1.3	0.91 (0.63, 1.30)	0.58
Analysis by Ququan Liu, M.D., M.S.											

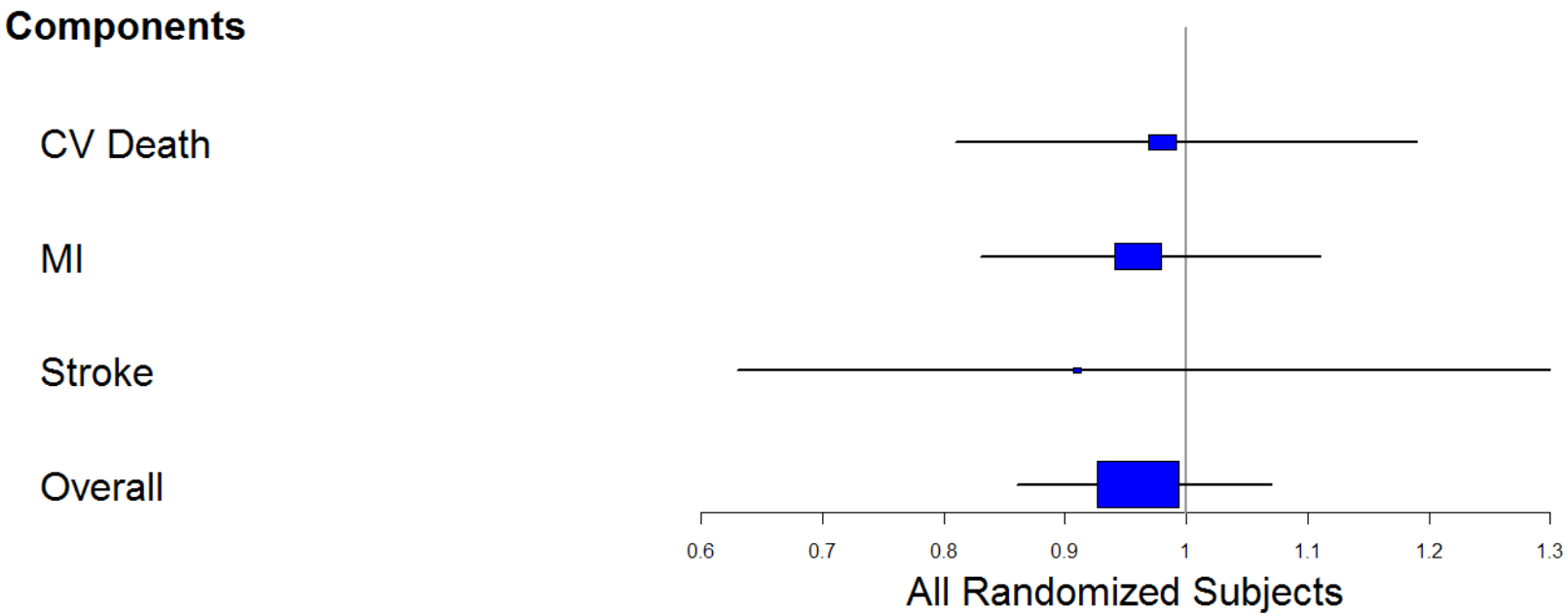
Graphical representations of the components of the primary endpoint for first events by age are presented in Figure 11 and in Figure 12.

Figure 11. Components of Primary Endpoint (1st Events) (By Age Group)



(Ququan Liu, M.D., M.S., Division of Biometrics I, FDA)

Figure 12. Components of Primary Endpoint (1st Events) (All Randomized Subjects)



(Ququan Liu, M.D., M.S., Division of Biometrics I, FDA)

9.12.1. Analysis of Primary Endpoint by Sex

With respect to the primary endpoint, there were no sex-related treatment differences noted in TRILOGY, as shown in Table 20.

Table 20. Primary Efficacy Endpoint (CV Death, MI, or Stroke) by Sex (CEC-Adjudicated)

Population	Prasugrel			Clopidogrel			Total			HR (95% CI)	P-value
	N	n	%	N	n	%	N	n	%		
Sex											
Female	1829	251	13.7	1821	250	13.7	3650	501	13.7	1.00 (0.84, 1.10)	0.96
Male	2834	370	13.1	2842	398	14.0	5676	768	13.5	0.94 (0.81, 1.08)	0.32
Analysis by Ququan Liu, M.D., M.S.											

9.12.2. Analysis of Primary Endpoint by Ethnicity

By ethnicity, there was no significant difference in the occurrence of the composite primary endpoint according to treatment group, as shown in Table 21.

Table 21. Primary Efficacy Endpoint (CV Death, MI, or Stroke) by Ethnicity (CEC-Adjudicated)

Population	Prasugrel			Clopidogrel			Total			HR (95% CI)	P-value
	N	n	%	N	n	%	N	n	%		
Ethnicity											
Not Hispanic or Latino	4233	550	13.0	4230	590	14.0	8463	1140	13.5	0.94 (0.84, 1.06)	0.29
Hispanic or Latino	430	71	16.5	432	58	13.4	862	129	15.0	1.20 (0.85, 1.70)	0.33
Analysis by Ququan Liu, M.D., M.S.											

9.12.3. Analysis of Primary Endpoint by Age and Body Weight

There were no significant differences in the occurrence of the primary endpoint by age and body weight, as shown in Table 22.

Table 22. Primary Efficacy Endpoint (CV Death, MI, or Stroke) by Age and Body Weight (CEC-Adjudicated)

Population	Prasugrel			Clopidogrel			Total			HR (95% CI)	P-value
	N	n	%	N	n	%	N	n	%		
Age < 75 years	**3620**	**364**	**10.1**	**3623**	**397**	**11.0**	**7243**	**761**	**10.5**	**0.92 (0.79, 1.06)**	**0.21**
< 60 kg	476	59	12.4	467	63	13.5	943	122	12.9	0.91 (0.64, 1.29)	0.60
≥ 60 kg	3144	305	9.7	3156	334	10.6	6300	639	10.1	0.92 (0.78, 1.07)	0.26
Age ≥ 75 years	**1043**	**257**	**24.6**	**1040**	**251**	**24.1**	**2083**	**508**	**24.4**	**1.03 (0.87, 1.23)**	**0.73**
< 60 kg	234	56	23.9	231	63	27.3	465	119	25.6	0.94 (0.65, 1.34)	0.72
≥ 60 kg	809	201	24.9	809	188	23.2	1618	389	24.0	1.06 (0.87, 1.29)	0.57
All	**4663**	**621**	**13.3**	**4663**	**648**	**13.9**	**9326**	**1269**	**13.6**	**0.96 (0.86, 1.07)**	**0.45**
Analysis by Ququan Liu, M.D., M.S.											

9.12.4. Primary Endpoint by Formulation

TRILOGY was conducted from June 27, 2008 through March 30, 2012. In TRILOGY, both the old and new formulations of prasugrel were used. The new formulation was introduced between February 4, 2010 and December 26, 2010 and had virtually no salt to base conversion, compared to the drug product used in TRITON.

Although the exact amount of salt to base conversion observed in TRITON was unknown, 5 to 87% of prasugrel salt could have been converted to free base during storage as a result of a reaction between the hydrochloride (HCl) salt and the excipient, croscarmellose sodium. The salt to base conversion was relevant because the relative bioavailability of the prasugrel salt was greater than the base and absorption of the salt was optimal in an acidic environment. Drugs which elevated gastric pH, such as lansoprazole (a proton pump inhibitor) decreased the Cmax of the prasugrel active metabolite up to 30% but did not change significantly the metabolite's AUC and Tmax.

The primary endpoint results by formulation were difficult to interpret, given the small number of patients who received the old formulation of prasugrel, as shown in Table 23. At first glance, only the new formulation appeared to be effective.

However, results by enrollment time (i.e., first-half versus second-half of the trial), shown in Table 24, provided some insight for the disparity in the results by formulation.

Enrollment time appeared to contribute to the differences in the results by formulation, as the event rates for both prasugrel and clopidogrel in the first-half of the trial (prasugrel: 28 per 100 PEY versus clopidogrel: 30 per 100 PEY) were higher than in the second half of the trial (prasugrel: 1.9 per 100 PEY versus clopidogrel: 2.2 per 100 PEY).[1]

Table 23. Primary Endpoint by Formulation

Population	Prasugrel			Clopidogrel			Total			HR (95% CI)	P-value
	N	n	%	N	n	%	N	n	%		
Age < 75 years											
New Formulation	2080	149	7.2	3623	397	11.0	5703	546	9.6	0.79 (0.65, 0.95)	0.01
Old Formulation	308	91	29.6	3623	397	11.0	3931	488	12.4	3.18 (2.53, 4.0)	<0.0001
Both	1227	124	10.1	3623	397	11.0	4850	521	10.7	0.69 (0.56, 0.84)	0.0002
Age ≥ 75 years											
New Formulation	563	116	20.6	1040	251	24.1	1603	367	22.9	1.12 (0.89, 1.40)	0.35
Old Formulation	138	63	45.7	1040	251	24.1	1177	314	26.7	2.31 (1.75, 3.04)	<0.0001
Both	341	78	22.9	1040	251	24.1	1381	329	23.8	0.65 (0.50, 0.84)	0.0009
All											
New Formulation	2643	265	10.0	4663	648	13.9	7306	913	12.5	0.91 (0.78, 1.05)	0.17
Old Formulation	446	154	34.5	4663	648	13.9	5109	802	15.7	2.76 (2.31, 3.29)	<0.0001
Both	1563	202	12.9	4663	648	13.9	6231	850	13.6	0.67 (0.57, 0.79)	<0.0001
Analysis by Ququan Liu, M.D., M.S.											

[1]Analyses by Ququan Liu, M.D., M.S.; PEY = person exposure year.

9.12.5. Primary Endpoint by Enrollment Time

Event rates in the prasugrel and clopidogrel treatment groups were approximately 5-fold higher in the first half of the trial, compared to the second half of the trial, as demonstrated in Table 24.

Table 24. Primary Endpoint by Enrollment Time

Population	Prasugrel			Clopidogrel			Total			HR (95% CI)	P-value
	N	n	%	N	n	%	N	n	%		
First Half of Trial (< 509 days)	2465	534	21.7	2466	549	22.3	4931	1083	22.0	0.97 (0.86, 1.09)	0.55
Second Half of Trial (≥ 509 days)	2198	87	4.0	2197	99	4.5	4395	186	4.2	0.89 (0.67, 1.19)	0.40
Analysis by Ququan Liu, M.D., M.S.											

9.12.6. Primary Endpoint by Commercial Clopidogrel Status at Randomization

There were no significant differences in the primary endpoint by treatment, age, and clopidogrel status at randomization, as demonstrated in Table 25.

Table 25. Primary Endpoint by Commercial Clopidogrel Status at Randomization

Population	Prasugrel			Clopidogrel			Total			HR (95% CI)	P-value
	N	n	%	N	n	%	N	n	%		
Age < 75 years											
Stratum 1	152	17	11.2	168	16	9.5	320	33	10.3	1.11 (0.55, 2.21)	0.77
Stratum 2	2507	242	9.7	2477	262	10.6	4984	504	10.1	0.91 (0.76, 1.08)	0.27
Stratum 3	961	105	10.9	978	119	12.2	1939	224	11.6	0.90 (0.69, 1.17)	0.44
Age ≥ 75 years											
Stratum 1	43	10	23.3	35	9	25.7	78	19	24.4	0.89 (0.36, 2.20)	0.80
Stratum 2	753	169	22.4	776	167	21.5	1529	336	22.0	1.04 (0.84, 1.29)	0.71
Stratum 3	246	78	31.7	229	75	32.8	475	153	32.2	1.03 (0.75, 1.41)	0.87
All											
Stratum 1	195	27	13.9	203	25	12.3	398	52	13.1	1.11 (0.65, 1.91)	0.70
Stratum 2	3260	411	12.6	3253	429	13.2	6513	840	12.9	0.95 (0.83, 1.09)	0.46
Stratum 3	1207	183	15.2	1207	194	16.1	2414	377	15.6	0.96 (0.78, 1.17)	0.67
Analysis by Ququan Liu, M.D., M.S.											

9.12.7. Primary Endpoint by Concomitant Use of Esomeprazole/Omeprazole

Between treatment groups, there were no significant differences in the primary endpoint based on concomitant use of esomeprazole/omeprazole, as shown in Table 26.

Table 26. Primary Endpoint (Esomeprazole/Omeprazole Concomitant Use)

Population	Prasugrel			Clopidogrel			Total			HR (95% CI)	P-value
	N	n	%	N	n	%	N	n	%		
Primary Efficacy Endpoint (Concomitant use of Esomeprazole/Omeprazole)											
Age < 75 years	119	15	12.6	133	17	12.8	252	32	12.7	1.01 (0.50, 2.03)	0.98
Age ≥ 75 years	58	18	31.0	56	15	26.8	114	33	29.0	1.47 (0.72, 2.97)	0.36
All	177	33	18.6	189	32	16.9	366	65	17.8	1.19 (0.73, 1.94)	0.51
Primary Efficacy Endpoint (No Concomitant use of Esomeprazole/Omeprazole)											
Age < 75 years	3501	349	10.0	3490	380	10.9	6991	729	10.4	0.91 (0.79, 1.05)	0.20
Age ≥ 75 years	985	239	24.3	984	236	24.0	1969	475	24.1	1.01 (0.85, 1.20)	0.88
All	4486	588	13.1	4474	616	13.8	8960	1204	13.4	0.95 (0.85, 1.07)	0.37
Analysis by Ququan Liu, M.D., M.S.											

9.13. All-Cause Mortality

By treatment group and age, there was no significant difference in all-cause mortality, as shown in Table 27.

Table 27. All-Cause Mortality

Population	Prasugrel			Clopidogrel			Total			HR (95% CI)	P-value
	N	n	%	N	n	%	N	n	%		
Age < 75 years	3620	208	5.8	3623	218	6.0	7243	426	5.9	0.96 (0.79, 1.16)	0.63
Age ≥ 75 years	1043	178	17.1	1040	191	18.4	2083	369	17.7	0.93 (0.76, 1.15)	0.51
All	4663	386	8.3	4663	409	8.8	9326	795	8.5	0.94 (0.82, 1.09)	0.42
Analysis by Ququan Liu, M.D., M.S.											

9.14. Analysis of Secondary Endpoints

Secondary endpoint results are summarized in Table 28. There were no significant reductions in the occurrence of these endpoints with prasugrel, compared to clopidogrel. In TRILOGY, there were few events of stent thrombosis.

Table 28. Secondary Endpoint Results (TRILOGY)

Population	Prasugrel			Clopidogrel			Total			HR (95% CI)	P-value
	N	n	%	N	n	%	N	n	%		
CV Death and MI											
Age < 75 years	3620	348	9.6	3623	370	10.2	7243	718	9.9	0.94 (0.81, 1.09)	0.39
Age ≥ 75 years	1043	235	22.5	1040	236	22.7	2083	471	22.6	1.0 (0.83, 1.20)	1.0
All	4663	583	12.5	4663	606	13.0	9326	1189	12.8	0.96 (0.86, 1.08)	0.51
CV Death, MI, Stroke, or Rehospitalization for Recurrent Unstable Angina											
Age < 75 years	3620	439	12.1	3623	465	12.8	7243	904	12.5	0.94 (0.83, 1.07)	0.35
Age ≥ 75 years	1043	274	26.3	1040	267	25.7	2083	541	26.0	1.03 (0.87, 1.22)	0.72
All	4663	713	15.3	4663	732	15.7	9326	1445	15.5	0.97 (0.88, 1.08)	0.61
All-Cause Death, MI, or Stroke											
Age < 75 years	3620	399	11.0	3623	429	11.8	7243	828	11.4	0.92 (0.79, 1.06)	0.27
Age ≥ 75 years	1043	282	27.0	1040	279	26.8	2083	561	26.9	1.03 (0.87, 1.23)	0.83
All	4663	681	14.6	4663	708	15.2	9326	1389	14.9	0.96 (0.86, 1.07)	0.47
ARC Definite or Probable Stent Thrombosis (Any Stent)											
Age < 75 years	3620	6	0.2	3623	8	0.2	7243	14	0.2	0.76 (0.26, 2.20)	0.61
Age ≥ 75 years	1043	0	-	1040	2	0.2	2083	2	0.1	-	-
All	4663	6	0.1	4663	10	0.2	9326	16	0.2	0.61 (0.14, 2.67)	0.32
Analysis by Ququan Liu, M.D., M.S.											

9.15. TRITON versus TRILOGY Cross-Trial Comparisons

9.15.1. TRITON Primary Endpoint Results by Age

In TRITON, prasugrel significantly decreased the risk of CV death, nonfatal MI, and nonfatal stroke in the UA/NSTEMI, STEMI, and All ACS populations, compared to clopidogrel, in patients < 75 years of age, as shown in Table 29.

Table 29. Primary Endpoint (CV Death, MI, Stroke) by Age (TRITON)

	UA/NSTEMI			STEMI			All ACS		
	Prasugrel (N=5044)	Clopidogrel (N=5030)	HR 95% CI P-value	Prasugrel (N=1769)	Clopidogrel (N=1765)	HR 95% CI P-value	Prasugrel (N=6813)	Clopidogrel (N=6795)	HR 95% CI P-value
< 75 years									
N	4328	4344	0.78	1584	1543	0.80	5912	5887	0.78
n	356	454	0.68, 0.90	143	173	0.64, 0.99	499	627	0.70, 0.88
%	8.2	10.5	0.0006	9.0	11.2	0.0370	8.4	10.7	<0.0001
≥ 75 years									
N	716	686	0.97	185	222	0.85	901	908	0.94
n	113	111	0.75, 1.26	31	43	0.54, 1.35	144	154	0.75, 1.18
%	15.8	16.2	0.85	16.8	19.4	0.45	16.0	17.0	0.53
Analysis by Ququan Liu, M.D., M.S., Division of Biometrics I, FDA									

9.15.2. TRITON versus TRILOGY Comparison: Primary Endpoint Results by Age

Cross-trial comparisons can be fraught with hazard. Although different ACS populations were studied in TRITON (UA/NSTEMI and STEMI ACS patients treated with PCI) and in TRILOGY (UA/NSTEMI patients treated medically), such comparisons can provide us with some information about event rates and through extrapolation, may assist us in evaluating effectiveness.

In TRITON and TRILOGY, the primary endpoint event rates were higher in patients ≥ 75 years of age, regardless of treatment group, as shown in Table 30. Further, TRILOGY event rates in patients ≥ 75 years of age were much higher than the event rates seen in TRITON.

In TRITON, prasugrel had a large impact on reducing primary endpoint results in patients < 75 years of age within the first three to five days.

In TRILOGY, drug product was initiated approximately 5 days after the index event. This delayed initiation of prasugrel affected the drug product's ability to affect early events, especially in patients < 75 years of age. As a result, TRILOGY was an unsuccessful trial.

Table 30. Primary Endpoint Results by Age (TRITON versus TRILOGY)

Population	Prasugrel			Clopidogrel			Total			HR (95% CI)	P-value
	N	n	%	N	n	%	N	n	%		
TRITON: Primary Endpoint (CV death, nonfatal MI, nonfatal stroke) by Age (All ACS Population)											
Age < 75 years	5912	499	8.4	5887	627	10.7	11799	1126	9.5	0.78 (0.70, 0.88)	< 0.0001
Age ≥ 75 years	901	144	16.0	908	154	17.0	1809	298	16.5	0.94 (0.75, 1.18)	0.5329
TRILOGY: Primary Endpoint (CV death, nonfatal MI, nonfatal stroke) by Age											
Age < 75 years	3620	364	10.1	3623	397	11.0	7243	761	10.5	0.92 (0.79, 1.06)	0.2101
Age ≥ 75 years	1043	257	24.6	1040	251	24.1	2083	508	24.4	1.03 (0.87, 1.23)	0.7313
All	4663	621	13.3	4663	648	13.9	9326	1269	13.6	0.96 (0.86, 1.07)	0.4513
Analysis by Ququan Liu, M.D., M.S.											

9.15.3. TRITON versus TRILOGY Comparison: Patients ≥ 75 years of Age with a History of Diabetes Mellitus or Prior MI

In the prescribing information for Effient, the box warning states that "in patients ≥ 75 years of age, Effient is generally not recommended because of the increased risk of fatal and intracranial bleeding and uncertain benefit, except in high-risk patients (diabetes or prior MI)." These recommendations are based on the TRITON data presented in Table 31 and in Table 32. Patients ≥ 75 years of age with a history of diabetes mellitus or prior MI had favorable point estimates for the primary endpoint ($p < 0.05$ in patients with a prior history of diabetes mellitus) when treated with prasugrel 10-mg daily. These point estimates were not favorable in patients ≥ 75 years of age with no prior history of diabetes mellitus or MI.

In TRILOGY, prasugrel patients ≥ 75 years of age with a prior MI still had a favorable point estimate, although it was not as favorable as what was seen in TRITON, but the upper limit of the 95% CI suggested there could be as much as a 17% increase in the occurrence of the primary endpoint (TRITON: HR 0.72 (95% CI 0.47, 1.09) versus TRILOGY: HR 0.91 (95% CI 0.71, 1.17)). In prasugrel patients ≥ 75 years of age with a history of diabetes, the favorable point estimate was no longer present (TRITON: HR 0.64 (95% CI 0.42, 0.97) versus TRILOGY: HR 1.03 (95% CI 0.79, 1.33)).

Therefore, in patients ≥ 75 years of age with a history of diabetes mellitus or a prior MI, it is critical that Effient is administered at a dose that is know to be effective in reducing the risk of CV death, nonfatal MI, and nonfatal stroke. (b) (4)

(b) (4)

9.15.4. TRITON versus TRILOGY Comparison: Fatal and Intracranial Bleeding

As shown in Table 33, patients ≥ 75 years of age with a history of diabetes mellitus have higher rates of Non-CABG-related fatal bleeding and intracranial hemorrhage (ICH) when receiving a 10-mg prasugrel maintenance dose (TRITON) than when receiving a 5-mg prasugrel maintenance dose (TRILOGY). There are insufficient data to compare fatal bleeding and ICH from TRITON patients ≥ 75 years of age with a prior MI to similar TRILOGY patients.

9.16. Other Analyses

Please see Appendices 2-5 for additional statistical analyses.

Table 31. TRITON versus TRILOGY (Prior MI--Yes/No)

Population	Prasugrel			Clopidogrel			Total			HR (95% CI)	P-value
	N	n	%	N	n	%	N	n	%		
TRITON: Primary Endpoint / Prior MI											
Age < 75 years	1006	123	12.23	996	153	15.36	2002	276	13.79	0.78 (0.62, 0.99)	0.0390
Age ≥ 75 years	220	38	17.27	212	48	22.64	432	86	19.91	0.72 (0.47, 1.09)	0.1192
All	1226	161	13.13	1208	201	16.64	2434	362	14.87	0.77 (0.62, 0.94)	0.0118
TRITON: Primary Endpoint / No Prior MI											
Age < 75 years	4906	376	7.66	4891	474	9.69	9797	850	8.68	0.78 (0.68, 0.90)	0.0004
Age ≥ 75 years	681	106	15.57	696	106	15.23	1377	212	15.40	1.05 (0.80, 1.37)	0.7963
All	5587	482	8.63	5587	580	10.38	11174	1062	9.50	0.83 (0.73, 0.93)	0.0017
TRILOGY: Primary Endpoint / Prior MI											
Age < 75 years	1556	188	12.08	1612	213	13.21	3168	401	12.66	0.90 (0.74, 1.10)	0.2940
Age ≥ 75 years	426	130	30.52	393	131	33.33	819	261	31.87	0.91 (0.71, 1.17)	0.3956
All	1982	318	16.04	2005	344	17.16	3987	662	16.60	0.91 (0.78, 1.06)	0.1770
TRILOGY: Primary Endpoint / No Prior MI											
Age < 75 years	2035	174	8.55	1988	180	9.05	4023	354	8.80	0.95 (0.77, 1.17)	0.5881
Age ≥ 75 years	603	126	20.90	633	144	22.75	1236	240	19.42	1.19 (0.92, 1.54)	0.8332
All	2638	300	11.37	2621	294	11.22	5259	594	11.30	1.02 (0.87, 1.20)	0.6599
Analysis by Ququan Liu, M.D., M.S.											

Table 32. TRITON versus TRILOGY (Prior Diabetes Mellitus—Yes/No)

Population	Prasugrel			Clopidogrel			Total			HR (95% CI)	P-value
	N	n	%	N	n	%	N	n	%		
TRITON: Primary Endpoint / History of DM											
Age < 75 years	1327	143	10.78	1336	197	14.75	2663	340	12.77	0.72 (0.58, 0.89)	0.0022
Age ≥ 75 years	249	37	14.86	234	51	21.79	483	88	18.22	0.64 (0.42, 0.97)	0.0368
All	1576	180	11.42	1570	248	15.80	3146	428	13.60	0.71 (0.58, 0.85)	0.0003
TRITON: Primary Endpoint / No History of DM											
Age < 75 years	4985	356	7.14	4551	430	9.45	9036	786	8.70	0.82 (0.71, 0.94)	0.0043
Age ≥ 75 years	652	107	16.41	674	103	15.28	1326	210	15.84	1.09 (0.83, 1.43)	0.5588
All	5237	463	8.84	5225	533	10.20	10462	996	9.52	0.86 (0.76, 0.98)	0.0184
TRILOGY: Primary Endpoint / History of DM											
Age < 75 years	1393	182	13.07	1418	209	14.74	2811	391	13.91	0.90 (0.74, 1.10)	0.2820
Age ≥ 75 years	363	115	31.68	365	112	30.68	728	227	31.81	1.03 (0.79, 1.33)	0.8639
All	1756	297	16.91	1783	321	18.00	3539	618	17.46	0.95 (0.81, 1.11)	0.4518
TRILOGY: Primary Endpoint / No History of DM											
Age < 75 years	2221	181	8.15	2193	187	8.53	4414	368	8.34	0.94 (0.77, 1.16)	0.5836
Age ≥ 75 years	678	142	20.94	675	139	20.59	1353	281	20.77	1.03 (0.82, 1.30)	0.7620
All	2899	323	11.14	2868	326	11.37	5767	649	11.25	0.98 (0.84, 1.14)	0.8307
Analysis by Ququan Liu, M.D., M.S.											

Table 33. TRITON versus TRILOGY (Fatal Bleeding and Intracranial Hemorrhage in Patients ≥ 75 years with a History of DM or Prior MI)

Population	Prasugrel			Clopidogrel			Total			HR (95% CI)	P-value
	N	n	%	N	n	%	N	n	%		
TRITON: Non-CABG-Related Fatal Bleeding / Prior MI											
Age < 75 years	998	3	0.30	980	0	-	1978	3	0.15	-	0.0868
Age ≥ 75 years	218	4	1.83	208	0	-	426	4	0.94	-	0.0559
All	1216	7	0.58	1188	0	-	2404	7	0.29	-	0.0093
TRILOGY: Non-CABG-Related Fatal Bleeding / Prior MI											
Age < 75 years	1542	2	0.13	1599	1	0.06	3141	3	0.10	2.08 (0.19, 22.99)	0.5378
Age ≥ 75 years	423	2	0.47	389	2	0.51	812	4	0.49	0.94 (0.13, 6.70)	0.9804
All	1965	4	0.20	1988	3	0.15	3953	7	0.18	1.30 (0.29, 5.79)	0.7000
TRITON: Non-CABG-Related Fatal Bleeding / History of DM											
Age < 75 years	1308	5	0.38	1322	2	0.15	2630	7	0.27	2.54 (0.49, 13.07)	0.2486
Age ≥ 75 years	247	2	0.81	231	1	0.43	478	3	0.63	1.81 (0.16, 20.17)	0.6315
All	1555	7	0.45	1553	3	0.19	3108	10	0.32	2.36 (0.61, 9.11)	0.2044
TRILOGY: Non-CABG-Related Fatal Bleeding / History of DM											
Age < 75 years	1378	1	0.07	1405	1	0.07	2783	2	0.07	1.07 (0.07, 17.11)	0.9611
Age ≥ 75 years	360	1	0.28	362	1	0.28	722	2	0.28	1.08 (0.07, 17.40)	0.8136
All	1738	2	0.12	1767	2	0.11	3505	4	0.11	1.06 (0.15, 7.49)	0.8413
Analysis by Ququan Liu, M.D., M.S.											

Population	Prasugrel			Clopidogrel			Total			HR (95% CI)	P-value
	N	n	%	N	n	%	N	n	%		
TRITON: Non-CABG-Related ICH / Prior MI											
Age < 75 years	998	3	0.30	980	0	-	1978	3	0.15	-	0.0868
Age ≥ 75 years	218	4	1.83	208	0	-	426	4	0.94	-	0.0559
All	1216	7	0.58	1188	0	-	2404	7	0.29	-	0.0093
TRILOGY: Non-CABG-Related ICH / Prior MI											
Age < 75 years	1542	6	0.39	1599	5	0.31	3141	11	0.35	1.25 (0.38, 4.10)	0.7134
Age ≥ 75 years	423	3	0.71	389	4	1.03	812	7	0.86	0.69 (0.16, 3.09)	0.6195
All	1965	9	0.46	1988	9	0.45	3953	18	0.45	0.99 (0.32, 2.49)	0.9678
TRITON: Non-CABG-Related ICH / History of DM											
Age < 75 years	1308	3	0.23	1322	7	0.53	2630	10	0.38	1.44 (0.11, 1.69)	0.2170
Age ≥ 75 years	247	2	0.81	231	1	0.43	478	3	0.63	1.53 (0.14, 16.89)	0.6312
All	1555	5	0.32	1553	8	0.52	3108	13	0.42	0.62 (0.20, 1.90)	0.4106
TRILOGY: Non-CABG-Related ICH / History of DM											
Age < 75 years	1378	2	0.15	1405	6	0.43	2783	8	0.29	0.36 (0.07, 1.80)	0.2013
Age ≥ 75 years	360	1	0.28	362	3	0.83	722	4	0.55	0.37 (0.04, 3.52)	0.3485
All	1738	3	0.17	1767	9	0.51	3505	12	0.34	0.35 (0.10, 1.31)	0.1022
Analysis by Ququan Liu, M.D., M.S.											

10. Safety

In TRILOGY, median exposure was 443 days in all randomized subjects, with no significant difference between treatment groups. Subjects < 75 years of age had a median duration of treatment of 453 days, compared to 364 days for subjects ≥ 75 years of age. Approximately 21% of subjects (1905 subjects) were on study drug for at least 24 months.

A total of 86 subjects (40 prasugrel subjects; 46 clopidogrel subjects) were randomized but did not receive study drug.

There are no new safety issues in this NDA. The safety update discussed discontinuation of the ACCOAST study due to increased risk of early TIMI Major or Minor bleeding following administration of prasugrel prior to PCI. The applicant plans to submit a labeling supplement to address the bleeding risks.

10.1. Safety Endpoints

Results for bleeding-related safety endpoints are shown in Table 34.

In subjects < 75 years of age, prasugrel significantly increased

- Non-CABG-related TIMI Major, Minor, or Minimal Bleeding
- Non-CABG-related TIMI Major or Minor Bleeding
- Non-CABG-related TIMI Minor Bleeding

Compared to clopidogrel.

In all TRILOGY subjects, prasugrel significantly increased

- Non-CABG-Related TIMI Major, Minor, or Minimal Bleeding
- Non-CABG-Related GUSTO Severe or Life-Threatening or Moderate Bleeding
- Non-CABG-Related GUSTO Severe or Life-Threatening, Moderate, or Mild Bleeding

compared to clopidogrel.

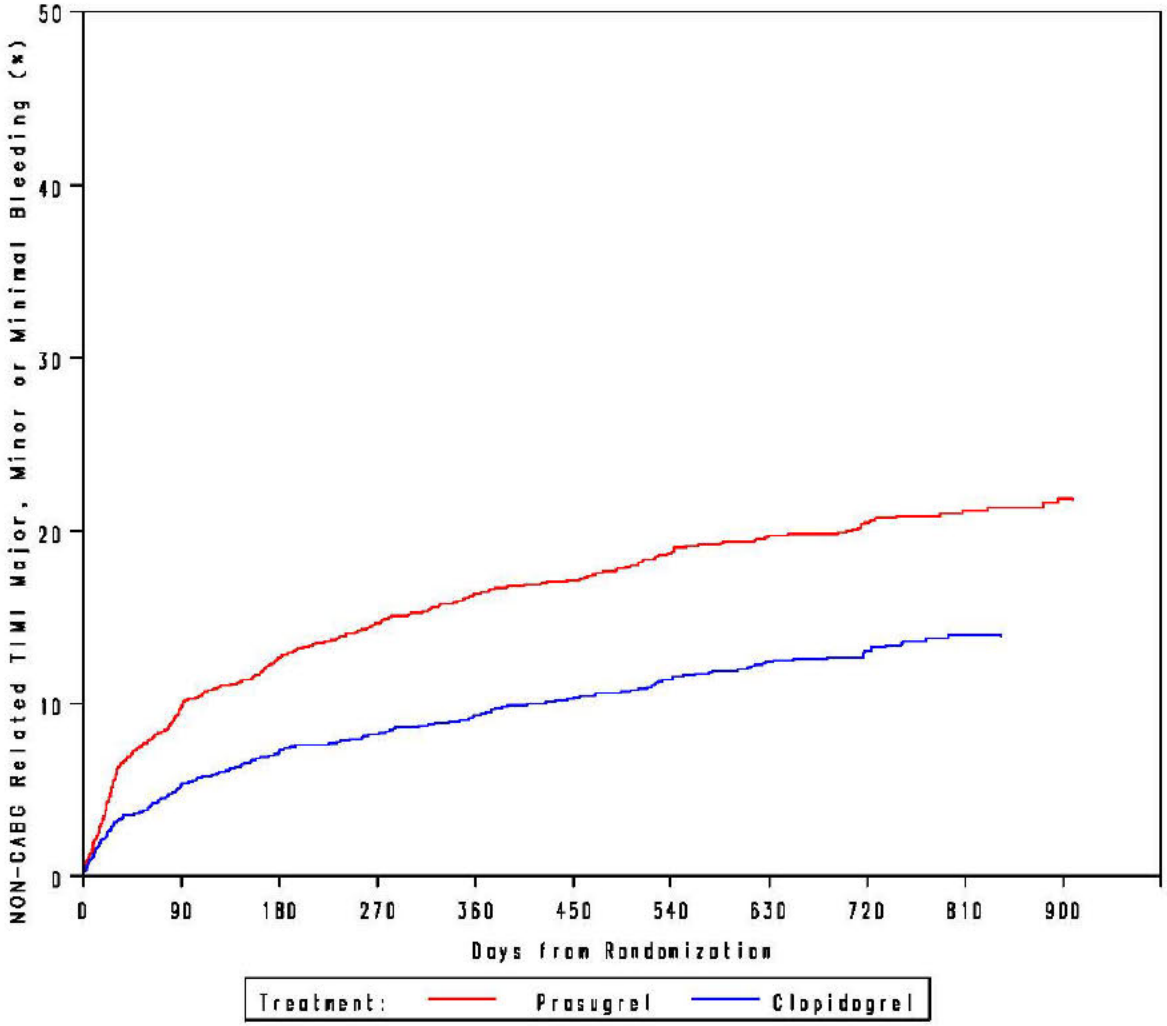
Kaplan-Meier Curves for Non-CABG-Related TIMI Major, Minor, or Minimal Bleeding for Subjects < 75 years of age, Subjects ≥ 75 years of age, and All Randomized Subjects are presented in Figure 13, Figure 14, and Figure 15. Much of this bleeding occurred within the first 90 days, but bleeding curves continued to separate throughout the remainder of the trial.

Table 34. Bleeding Events (TRILOGY)

Population	Prasugrel			Clopidogrel			Total			HR (95% CI)	P-value
	N	n	%	N	n	%	N	n	%		
Non-CABG-Related TIMI Major Bleeding											
Age < 75 years	3590	39	1.1	3590	30	0.8	7180	69	1.0	1.31 (0.81, 2.11)	0.27
Age ≥ 75 years	1033	19	1.8	1027	18	1.8	2060	37	1.8	1.09 (0.57, 2.08)	0.79
All	4623	58	1.3	4617	48	1.0	9240	106	1.2	1.23 (0.84, 1.81)	0.29
Non-CABG-Related TIMI Life-Threatening Bleeding											
Age < 75 years	3590	16	0.5	3590	17	0.2	7180	33	0.5	0.95 (0.48, 1.88)	0.88
Age ≥ 75 years	1033	9	0.9	1027	10	1.0	2060	19	0.9	0.94 (0.38, 2.31)	0.90
All	4623	25	0.5	4617	27	0.6	9240	52	0.6	0.95 (0.55, 1.63)	0.85
Non-CABG-Related Fatal Bleeding											
Age < 75 years	3590	4	0.1	3590	4	0.1	7180	8	0.1	1.01 (0.25, 4.09)	0.99
Age ≥ 75 years	1033	3	0.3	1027	5	0.5	2060	8	0.4	0.62 (0.15, 2.58)	0.55
All	4623	7	0.2	4617	9	0.2	9240	16	0.2	0.80 (0.30, 2.14)	0.68
Non-CABG-Related Symptomatic Intracranial Hemorrhage											
Age < 75 years	3590	4	0.1	3590	11	0.3	7180	15	0.2	0.37 (0.12, 1.16)	0.08
Age ≥ 75 years	1033	5	0.5	1027	5	0.5	2060	10	0.5	1.07 (0.31, 3.69)	0.92
All	4623	9	0.2	4617	16	0.4	9240	25	0.3	0.58 (0.26, 1.31)	0.19
Non-CABG-Related Fatal Intracranial Hemorrhage											
Age < 75 years	3590	2	<0.1	3590	3	<0.1	7180	5	0.1	0.67 (0.11, 4.04)	0.66
Age ≥ 75 years	1033	2	0.2	1027	1	<0.1	2060	3	0.2	2.07 (0.19, 22.91)	0.54
All	4623	4	<0.1	4617	4	< 0.1	9240	8	<0.1	1.02 (0.26, 4.09)	0.98
Non-CABG-Related TIMI Minor Bleeding											
Age < 75 years	3590	32	0.9	3590	17	0.5	7180	49	0.7	1.91 (1.06, 3.44)	0.03
Age ≥ 75 years	1033	9	0.9	1027	14	1.4	2060	23	1.1	0.65 (0.28, 1.51)	0.65
All	4623	41	0.9	4617	31	0.7	9240	72	0.8	1.34 (0.84, 2.14)	0.11
Non-CABG-Related TIMI Major or Minor Bleeding											
Age < 75 years	3590	70	2.0	3590	46	1.3	7180	116	1.6	1.54 (1.06, 2.23)	0.02
Age ≥ 75 years	1033	27	2.6	1027	31	3.0	2060	58	2.8	0.90 (0.54, 1.50)	0.65
All	4623	97	2.1	4617	77	1.7	9240	174	1.9	2.00 (1.46, 2.75)	0.11

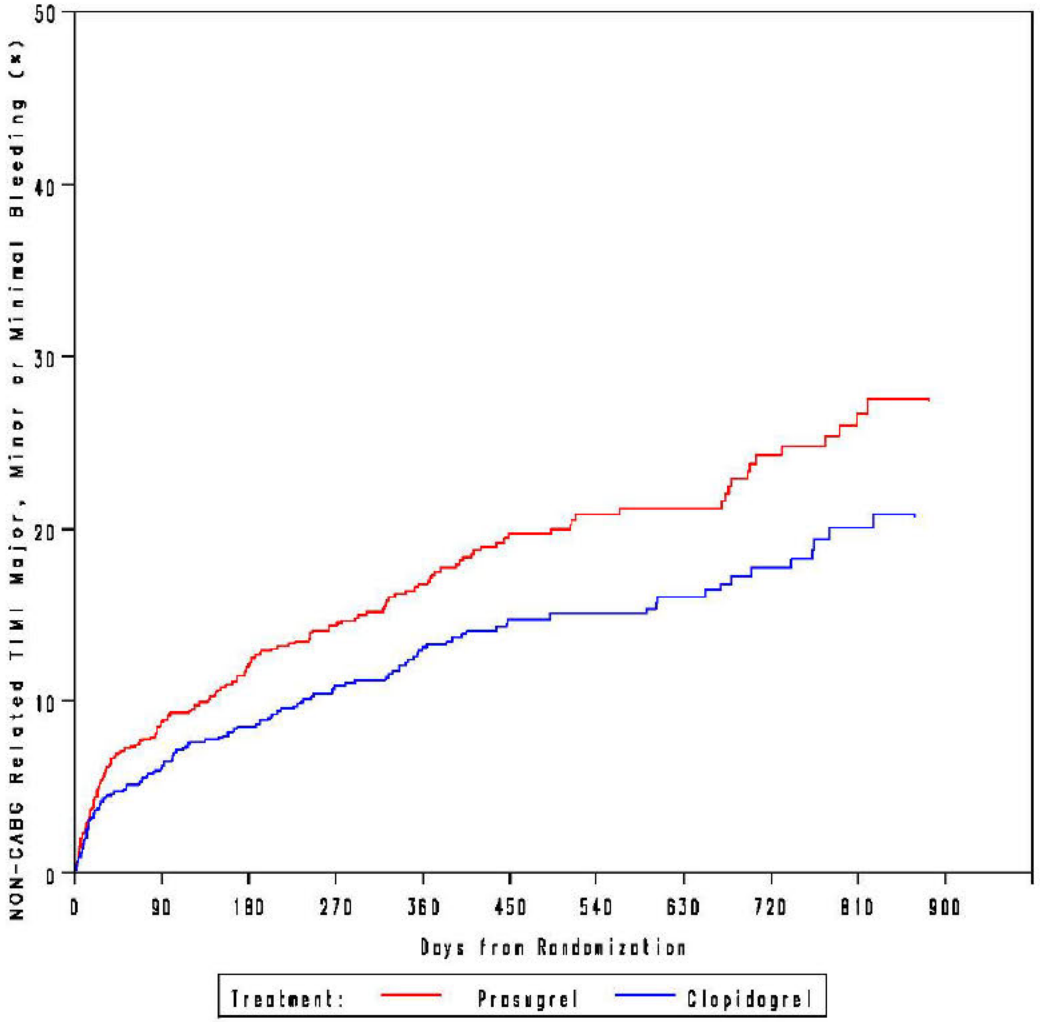
Population	Prasugrel			Clopidogrel			Total			HR (95% CI)	P-value
	N	n	%	N	n	%	N	n	%		
Non-CABG-Related TIMI Major, Minor, or Minimal Bleeding											
Age < 75 years	3590	607	16.9	3590	369	10.3	7180	976	13.6	1.71 (1.50, 1.95)	< 0.0001
Age ≥ 75 years	1033	173	16.8	1027	130	12.7	2060	303	14.7	1.39 (1.10, 1.74)	0.0045
All	4623	780	16.9	4617	499	10.8	9240	1279	13.8	1.63 (1.46, 1.82)	< 0.0001
Non-CABG-Related GUSTO Severe or Life-Threatening Bleeding											
Age < 75 years	3590	38	1.2	3590	28	0.8	7180	66	0.9	1.37 (0.84, 2.24)	0.20
Age ≥ 75 years	1033	18	1.7	1027	18	1.8	2060	36	1.8	1.03 (0.54, 1.98)	0.93
All	4623	56	1.2	4617	46	1.0	9240	102	1.1	1.24 (0.84, 1.84)	0.28
Non-CABG-Related GUSTO Severe or Life-Threatening or Moderate Bleeding											
Age < 75 years	3590	71	2.0	3590	44	1.2	7180	115	1.6	1.64 (1.12, 2.38)	0.01
Age ≥ 75 years	1033	42	4.1	1027	37	3.6	2060	79	3.8	1.16 (0.74, 1.80)	0.55
All	4623	113	2.4	4617	81	1.8	9240	194	2.1	1.42 (1.07, 1.89)	0.02
Non-CABG-Related GUSTO Severe or Life-Threatening, Moderate, or Mild Bleeding											
Age < 75 years	3590	620	17.3	3590	379	10.6	7180	999	13.9	1.70 (1.50, 1.94)	< 0.0001
Age ≥ 75 years	1033	179	17.3	1027	131	12.8	2060	310	15.1	1.42 (1.14, 1.78)	0.0021
All	4623	799	17.3	4617	510	11.1	9240	1309	14.2	1.63 (1.46, 1.82)	< 0.0001
CABG-Related TIMI Major Bleeding											
Age < 75 years	85	4	4.7	84	4	4.8	106	8	4.7	1.01 (0.18, 5.63)	1.00
Age ≥ 75 years	21	2	9.5	12	0	-	33	2	6.1	-	0.52
All	106	6	5.7	96	4	4.2	202	10	5.0	0.72 (0.15. 3.17)	0.75
CABG-Related Bleeding: TIMI Major or Minor											
Age < 75 years	85	4	4.7	84	4	4.8	106	8	4.7	1.01 (0.18, 5.63)	1.00
Age ≥ 75 years	21	2	9.5	12	1	8.3	33	3	9.1	0.86 (0.01, 18.51)	1.00
All	106	6	5.7	96	5	5.2	202	11	5.5	0.92 (0.21, 3.74)	1.00
Analyses by Ququan Liu, M.D., M.S.											

Figure 13. Kaplan-Meier Estimates of CEC-Adjudicated Non-CABG-Related TIMI Major, Minor, or Minimal Bleeding (Subjects < 75 Years)



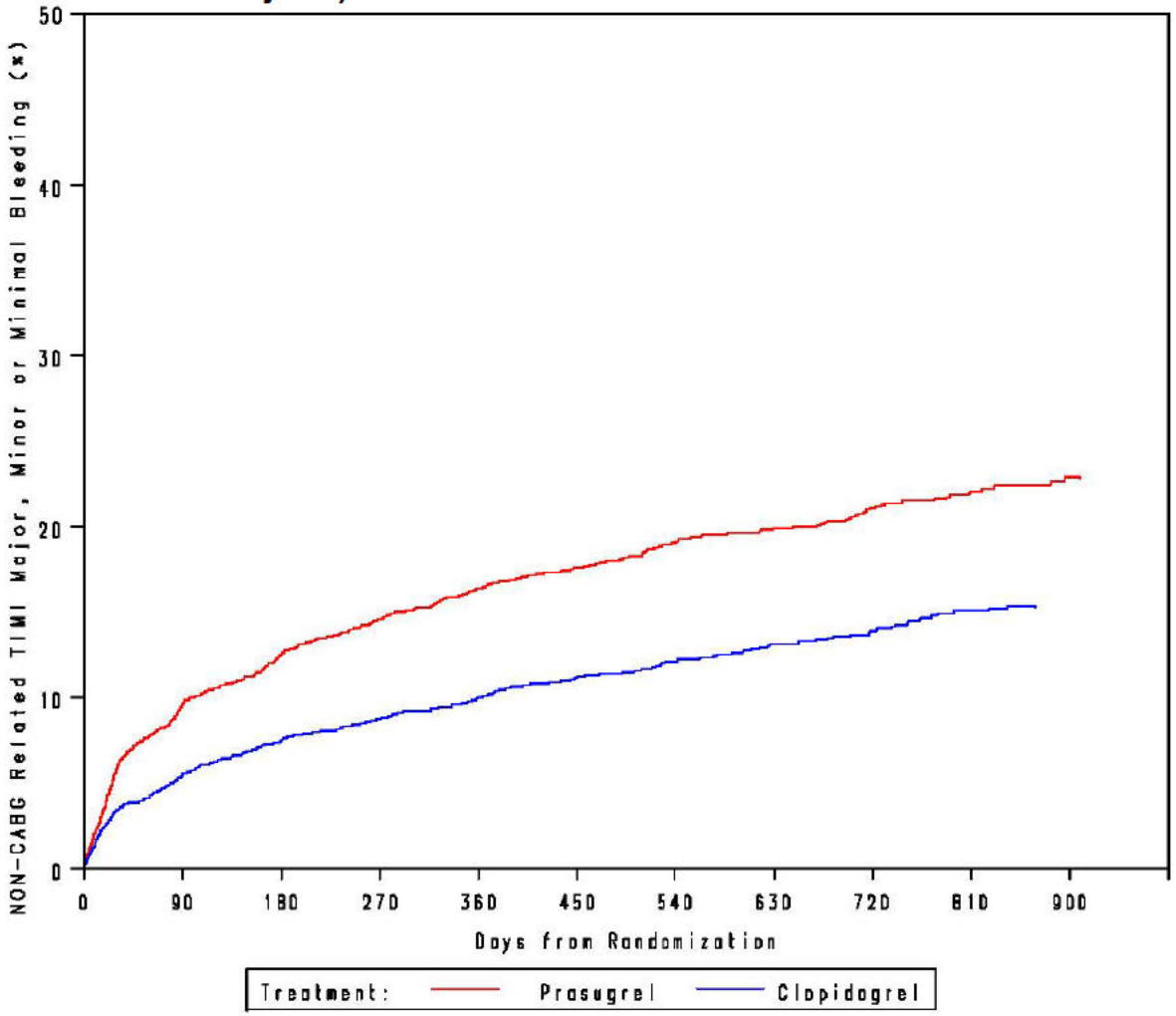
(Analysis by Ququan Liu, M.D., M.S.)

Figure 14. Kaplan-Meier Estimates of CEC-Adjudicated Non-CABG-Related TIMI Major, Minor, or Minimal Bleeding (Subjects ≥ 75 Years)



(Analysis by Ququan Liu, M.D., M.S.)

Figure 15. Kaplan-Meier Estimates of CEC-Adjudicated Non-CABG-Related TIMI Major, Minor, or Minimal Bleeding (All Randomized Subjects)



(Analysis by Ququan Liu, M.D., M.S.)

10.2. Bleeding by Formulation

Most patients in TRILOGY received the new formulation, as shown in Table 35. Since few patients received the old formulation, confidence intervals for these analyses are generally wide. That said, the old formulation had a hazard ratio of about 3.6 compared to placebo with respect to the occurrence of Non-CABG-related TIMI Major, Minor, or Minimal bleeding. The new formulation had a hazard ratio of 1.2 to 1.8 compared to placebo (age ≥ 75 years and age < 75 years, respectively) with respect to the occurrence of Non-CABG-related TIMI Major, Minor, or Minimal bleeding.

The bleeding risk with the new formulation was driven by an increase in TIMI Minor bleeding events in subjects < 75 years of age.

Overall, bleeding risk appeared to be greatest with the old formulation, which was an unexpected finding since the new formulation is more bioavailable and should cause more bleeding. Given the small number of patients who received the old formulation, I think the discrepant results are somewhat difficult to interpret.

Table 35. Bleeding Events by Formulation

Population	Prasugrel			Clopidogrel			Total			HR (95% CI)	P-value
	N	n	%	N	n	%	N	n	%		
Non-CABG-Related TIMI Major, Minor, or Minimal Bleeding, New Formulation											
Age < 75 years	2064	336	16.3	3590	369	10.3	5654	705	12.5	1.84 (1.58, 2.14)	<0.0001
Age ≥ 75 years	557	69	12.4	1027	130	12.7	1584	199	12.6	1.24 (0.92, 1.67)	0.17
All	2621	405	15.5	46167	498	10.8	7238	903	12.5	1.70 (1.48, 1.94)	<0.0001
Non-CABG-Related TIMI Major, Minor, or Minimal Bleeding, Old Formulation											
Age < 75 years	299	56	18.7	3589	368	10.3	3888	424	10.9	3.62 (2.71, 4.82)	<0.0001
Age ≥ 75 years	135	30	22.2	1027	130	12.7	1162	160	13.8	3.58 (2.38, 5.40)	<0.0001
All	434	86	19.8	4616	498	10.8	5050	584	11.6	3.58 (2.83, 4.53)	<0.0001
Non-CABG-Related TIMI Major or Minor Bleeding, New Formulation											
Age < 75 years	2064	34	1.7	3590	46	1.3	5654	80	1.4	1.63 (1.03, 2.57)	0.03
Age ≥ 75 years	557	9	1.6	1027	31	3.0	1584	40	2.5	0.84 (0.39, 1.82)	0.64
All	2621	43	1.6	4617	77	1.7	7238	120	1.7	1.35 (0.92, 1.99)	0.12
Non-CABG-Related TIMI Major or Minor Bleeding, Old Formulation											
Age < 75 years	299	11	3.7	3590	46	1.3	3889	57	1.5	7.0 (3.51, 13.89)	<0.0001
Age ≥ 75 years	135	4	3.0	1027	31	3.0	1162	35	3.0	2.72 (0.93, 8.02)	0.0620
All	434	15	3.5	4617	77	1.7	5051	92	1.8	4.83 (2.71, 8.62)	<0.0001

Population	Prasugrel			Clopidogrel			Total			HR (95% CI)	P-value
	N	n	%	N	n	%	N	n	%		
Non-CABG-Related TIMI Major Bleeding, New Formulation											
Age < 75 years	2064	17	0.8	3590	30	0.8	5654	47	0.8	1.32 (0.72, 2.44)	0.37
Age ≥ 75 years	557	8	1.4	1027	18	1.8	1584	26	1.6	1.18 (0.5, 2.80)	0.71
All	2621	25	1.0	4617	48	1.0	7238	73	1.0	1.28 (0.77, 2.10)	0.35
Non-CABG-Related TIMI Major Bleeding, Old Formulation											
Age < 75 years	299	6	2.0	3590	30	0.8	3889	36	0.9	6.90 (2.76, 17.25)	<0.0001
Age ≥ 75 years	135	2	1.5	1027	18	1.8	1162	20	1.7	2.45 (0.55, 10.92)	0.22
All	434	8	1.8	4617	48	1.0	5051	56	1.1	4.74 (2.17, 10.32)	<0.0001
Non-CABG-Related TIMI Minor Bleeding, New Formulation											
Age < 75 years	2064	17	0.8	3590	17	0.5	5654	34	0.6	2.08 (1.04, 4.15)	0.03
Age ≥ 75 years	557	1	0.2	1027	14	1.4	1584	15	1.0	1.44 (0.78, 2.64)	0.15
All	2621	18	0.7	4617	31	0.7	7238	49	0.7	1.46 (0.79, 2.68)	0.23
Non-CABG-Related TIMI Minor Bleeding, Old Formulation											
Age < 75 years	299	6	2.0	3590	17	0.5	3889	23	0.6	8.35 (3.16, 22.08)	<0.0001
Age ≥ 75 years	135	2	1.4	1027	14	1.4	1162	16	1.4	3.10 (0.64, 15.0)	0.15
All	434	8	1.8	4617	31	0.7	5051	39	0.8	5.61 (2.46, 12.79)	<0.0001
Analyses by Ququan Liu, M.D., M.S.											

10.3. Bleeding by Commercial Clopidogrel Status at Randomization

In subjects < 75 years of age, Non-CABG-Related TIMI Major, Minor, or Minimal Bleeding was significantly increased in all Strata, as shown in Table 36. These results appeared to be driven by the Non-CABG-Related TIMI Minor Bleeding in Stratum 2 in which study drug was initiated. See Appendix 4 for these analyses.

Further, in patients ≥ 75, Non-CABG-Related TIMI Major, Minor, or Minimal bleeding was significantly increased in Stratum 2. See Appendix 4 for these analyses.

Table 36. Bleeding by Commercial Clopidogrel Status at Randomization (None, Initiated, Ongoing)

Population	Prasugrel			Clopidogrel			Total			HR (95% CI)	P-value
	N	n	%	N	n	%	N	n	%		
Non-CABG-Related TIMI Major, Minor, or Minimal Bleeding											
Age < 75 years											
Stratum 1	151	29	19.21	168	13	7.74	319	42	13.17	2.74 (1.42, 5.26)	0.0017
Stratum 2	2487	441	17.73	2449	265	10.82	4936	706	14.30	1.70 (1.46, 1.98)	<0.0001
Stratum 3	952	137	14.39	972	90	9.26	1924	227	11.80	1.63 (1.25, 2.12)	0.0003
Age ≥ 75 years											
Stratum 1	43	11	25.58	33	7	21.21	76	18	23.68	1.15 (0.45, 2.97)	0.7714
Stratum 2	745	130	17.45	767	101	13.17	1512	231	15.28	1.39 (1.08, 1.81)	0.0119
Stratum 3	245	32	13.06	227	22	9.69	472	54	11.44	1.43 (0.83, 2.46)	0.1967
All											
Stratum 1	194	40	20.62	201	20	9.95	395	60	15.19	2.24 (1.31, 3.83)	0.0025
Stratum 2	3232	571	17.67	3216	366	11.38	6448	937	14.53	1.62 (1.42, 1.84)	< 0.0001
Stratum 3	1197	169	14.12	1199	112	9.34	2396	281	11.73	1.58 (1.25, 2.01)	0.0001
Analysis by Ququan Liu, M.D., M.S.											

10.4. Cancer Postmarketing Requirement #2

Dr. Marciniak conducted the primary review of cancer in TRILOGY, and he also conducted a review of cancer in TRITON as well as in other antiplatelet and anticoagulant outcome trials. His primary review of cancer in TRILOGY stands on its own merit as a Cross-Discipline Team Leader Review and requires few additional comments from me.

In TRITON, Dr. Marciniak demonstrated that there was a significant increase in solid cancer events in the prasugrel treatment arm, compared to clopidogrel ($p = 0.0013$ by log rank test). The solid cancer rate curves separated at about 4 months and continued to separate over the subsequent 16 months of follow-up. Survival after the first solid cancer event in TRITON was approximately 70% in both treatment arms. In TRITON, bleeding was more common in the prasugrel treatment arm, compared to clopidogrel. Since it was unclear if these observations were causally-related, the result of increased detection due to bleeding, or were random occurrences, the applicant was required to collect cancer data in TRILOGY.

In TRILOGY, Dr. Marciniak found that solid cancer rates were low (0.92 per 100 person exposure year (PEY), compared to 1.28 per 100 PEY in TRITON) and were not increased with prasugrel, compared to clopidogrel. He also noted that in TRILOGY, cancers appeared to be underreported in Asian and Eastern European sites. Further, solid cancer results "were unfavorable for prasugrel in patients enrolled in the first half of the trial (RR about 1.07), becoming favorable in patients enrolled in the second half (RR about 0.7)." Dr. Marciniak noted a similar finding in US patients randomized to prasugrel (RR about 1.7 in first-half of trial versus RR about 0.51 in second-half of the trial), compared to clopidogrel.

In summary, as submitted, TRILOGY did not show increased solid cancer rates with prasugrel. However, Dr. Marciniak trusts the TRITON rather than the TRILOGY results because TRITON is "more consistent with the increased solid cancer rates with increased bleeding [seen] in the recent anticoagulant trials and because TRILOGY has evidence for underreporting from Asia and Eastern Europe and a suspicious reversal of the increased cancer rates in the second half of the trial." For these reasons, he recommends that TRILOGY cancer results are not included in the prescribing information. Further, he recommends that the FDA conduct a "rigorous analysis of bleeding and cancer in all antiplatelet and anticoagulant outcome trials" to determine whether solid cancer promotion "is a peculiar effect of prasugrel, a class effect of $P2Y_{12}$ platelet inhibitors, a class effect of all platelet inhibitors, or an effect of all drugs that increase bleeding." I concur.

11. Advisory Committee Meeting

There was no Advisory Committee Meeting for this application.

12. Pediatrics

This application triggered PREA as a (b) (4)

The PeRC agreed with the Division's recommendation to grant a full waiver in pediatric patients because studies would be impossible or highly impractical, given the limited number of children with the condition to study.

13. Other Relevant Regulatory Issues

13.1. Financial Disclosures

TRILOGY is the only trial providing efficacy data in this submission and is an unsuccessful trial. The applicant identified 25 investigators with a financial interest who contributed a total of 142 subjects (1.5%) to this 9,326 subject trial conducted in 52 countries at 970 sites. Given the size of this study, their participation is not thought to have influenced the outcome of this trial in any meaningful way.

13.2. Compliance with Good Clinical Practice

TRILOGY was conducted in compliance with good clinical practices.

13.3. DSI Audits

No DSI audits were requested or conducted for this application.

14. Labeling

The review team revised the applicant's proposed changes to the prescribing information, and these revisions are currently under review by Dr. Norman L. Stockbridge, Division Director.

The applicant proposed key changes to the following sections of the prescribing information, as highlighted in red:

- Under Highlights (Dosage and Administration): Continue at 10 mg once daily with or without food. Consider 5 mg once daily for patients < 60 kg (b) (4)

(b) (4)

(b) (4)

CDTL Comments: See above comments.

(b) (4)

Other changes made by the review team to the label include

- **removal of the p-values listed in Table 1 (Section 6, 6.1) and Table 7 (Section 14) of the current prescribing information because these are subgroup analyses and there were no adjustments for multiplicity.**

15. Recommendations/Risk Benefit Assessment

15.1. Summary of Key Findings

1. In TRILOGY,

   a. prasugrel and aspirin were **not** superior to clopidogrel and aspirin in reducing the first occurrence of CV death, MI, or stroke in medically managed subjects enrolled within 10 days of the UA/NSTEMI index event. Subgroup analyses for the primary efficacy endpoint by sex, ethnicity, weight, geographical regions, inclusion of 4 Indian sites, and concomitant use of esomeprazole/omeprazole did not reveal any significant differences in treatment effect.

   b. with respect to Non-CABG-related bleeding,

      - prasugrel subjects < 75 years of age had a significant increase in
        1) TIMI Major, Minor, or Minimal Bleeding;
        2) TIMI Major or Minor bleeding; and
        3) TIMI Minor bleeding,

        compared to clopidogrel.

      - all prasugrel subjects had a significant increase in
        1) TIMI Major, Minor, or Minimal bleeding;
        2) GUSTO Severe or Life-Threatening or Moderate Bleeding; or
        3) GUSTO Severe or Life-Threatening, Moderate, or Mild Bleeding,

        compared to clopidogrel.

   c. with respect to CABG-related bleeding, there was no significant difference in TIMI Major or in TIMI Major or Minor bleeding events between treatment groups

2. Compared to TRITON (10-mg prasugrel MD), TRILOGY subjects age ≥ 75 years (with a history of diabetes mellitus or prior MI) on 5-mg prasugrel MD had a lower rate of Non-CABG-related fatal bleeding and ICH but reduced effectiveness.

3. Weight

As body weight decreases, prasugrel exposure increases. Patients with stable coronary artery disease and body weight ≤ 60 kg (receiving prasugrel 5-mg) had a 38% reduction in AUC_{last}, compared to patients with body weight > 60 kg (receiving prasugrel 10-mg). Further, AUC_{last} in patients weighing < 60 kg (and receiving prasugrel 5-mg) was similar to lower quartiles of exposure in patients weighing ≥ 60 kg (and receiving prasugrel 10-mg). This reduction was expected and was predicted from simulations.

The applicant proposed a reduction of dose from 10-mg to 5-mg in patients weighing < 60 kg; this recommendation is currently in the label and no revisions are needed.

4. Age

Compared to patients ≤ 75 years receiving 10-mg prasugrel, exposure in older patients (> 75 years) receiving 5-mg prasugrel was approximately half. Maximum platelet aggregation in older patients (> 75 years, 5 mg) was increased by about 9.4% compared to younger patients (≤ 75 years, 10 mg) and was statistically significant.

The relationship between pharmacodynamic markers and clinical outcome has not been established.

(b) (4)

5. Switching from a Clopidogrel Maintenance Dose to a Prasugrel Maintenance Dose

a. In patients with an ACS event in the past year, switching from a maintenance dose of clopidogrel 75-mg directly (i.e., next dose) to prasugrel 10-mg, with or without a prasugrel loading dose (60-mg), resulted in a significantly lower MPA at 7 days, as measured by light transmission aggregometry and VerifyNow™, compared to clopidogrel 75-mg. Further, at 2 hours, MPA was significantly lower for those patients who had received the prasugrel 60-mg LD followed by the 10-mg MD, compared to those who received the prasugrel 10-mg MD only.

   Therefore, a patient with an ACS event in the past year may be switched from clopidogrel 75-mg daily to prasugrel 10-mg daily without a loading dose. Compared to clopidogrel, MPA with prasugrel 10-mg MD would be significantly decreased at 1 week, compared to clopidogrel 75-mg.

b. In TRILOGY, Stratum 3 data for subjects < 75 years were used to inform switching from clopidogrel 75-mg to either prasugrel 5-mg or prasugrel 10-mg. Stratum 3 subjects received commercial clopidogrel prior to the index event, were thought to be at steady state at the time of the onset of the index event, and were maintained on commercial clopidogrel until randomization. At 30 days, in CYP2C19 EMs and RMs, there was a significant reduction from baseline in LS mean $P2Y_{12}$ reaction units (PRU). Similar results were observed for subjects ≥ 75 years of age.

In summary, patients at steady state may be switched from clopidogrel 75-mg to prasugrel (5-mg or 10-mg) without a loading dose.

6. Switching From Clopidogrel Loading Dose to Prasugrel Loading Dose in ACS Patients Undergoing PCI

   Study TAEH studied three loading dose strategies in ACS patients undergoing PCI: 1) placebo plus prasugrel 60-mg LD/10-mg MD; 2) clopidogrel 600-mg LD plus prasugrel 60-mg LD/10-mg MD; and 3) clopidogrel 600-mg LD plus prasugrel 30-mg MD/10-mg MD. Accumetrics VerifyNow™ $P2Y_{12}$ Reaction Units (PRU) were measured at 6 hours following dosing. There were no statistically significant differences between these groups in platelet aggregation at 6 hours. However, VerifyNow™ may not be able to discriminate between treatments after LDs, rendering these comparisons uninterpretable.

7. Postmarketing Requirements and Postmarketing Commitments

   a. The applicant has fulfilled Postmarketing Requirement #2 as follows:

      "95-2 You will gather baseline cancer history and cancer adverse event data from the ongoing trial TRILOGY, a 10,300-subject trial being conducted in patients with acute coronary syndrome who are being managed medically (without coronary revascularization). The final report on cancers in this trial is to be submitted to IND 63,449."

      - As submitted, TRILOGY did not show increased solid cancer rates with prasugrel, compared to clopidogrel. However, given the underreporting from Asia and Eastern Europe and a suspicious reversal of the increased cancer rates with prasugrel in the second half of the trial, Dr. Marciniak thinks TRITON is more consistent with the increased solid cancer rates with increased bleeding seen in recent anticoagulant trials. Therefore, we recommend that TRILOGY cancer results are not included in the prescribing information.

      - Dr. Marciniak recommends that the FDA conduct a "rigorous anlaysis of bleeding and cancer in all antiplatelet and anticoagulant outcome trials" to determine whether solid cancer promotion "is a peculiar effect of prasugrel, a class effect of P2Y12 platelet inhibitors, a class effect of all platelet inhibitors, or an effect of all drugs that increase bleeding."

   b. The applicant has fulfilled Postmarketing Commitment #6 as follows:

      "95-6 You commit to the collection of samples at baseline for genotyping CYP450 enzymes in TRILOGY subjects, to allow a comparison of effectiveness and bleeding in prasugrel and clopidogrel subgroups by metabolizer status. These data will be submitted with the final study report of TRILOGY. The periodic reports will include the fraction of subjects who consented to genetic testing."

      - In the TRILOGY Pharmacogenomics Substudy

        - The primary efficacy endpoint results (CV death, MI, stroke) in the substudy were consistent with the results from the overall study

        - CYP2C19 genotype was not significantly associated with either the efficacy (CV death, MI, stroke) or safety (TIMI Major or Minor Bleeding) of clopidogrel or prasugrel. In contrast to much of the published literature, no associations were established between CYP2C19 genotype and clopidogrel. These results may be related to the fact that patients were not invasively managed with PCI.

- There was a significant difference in PRU when switching from clopidogrel 75-mg to either prasugrel 5- or 10-mg at 30 days regardless of CYP2C19 genotype; this finding is consistent with current knowledge that prasugrel is a more potent inhibitor of platelet reactivity compared to clopidogrel.

- The pharmacogenomics data from TRITON and TRILOGY comprise the largest database from randomized prospective clinical trials that is currently available to the Agency. Considering the totality of information, these data suggest there may be prasugrel reduced metabolizers (higher primary endpoint event rate in prasugrel RMs than in clopidogrel RMs in TRILOGY and higher primary endpoint event rate in prasugrel STEMI RMs versus clopidogrel STEMI RMs in TRITON).

  The mechanism and pathways by which reduced metabolizers are possible with prasugrel have yet to be elucidated.

8. Outstanding Issues related to the Use of Prasugrel for the Approved Indication

- The data contained in this application do not inform us about the bleeding risk of the new formulation (prasugrel 60-mg loading dose) in ACS patients to be managed with PCI.

15.2. Recommended Regulatory Action

The review team recommends approval of this sNDA pending incorporation of our proposed labeling changes.

Based on our review of the submitted data, we

- agree that Study TADI supports current labeling to "consider lowering the maintenance dose to 5 mg in patients < 60 kg."

- We recommend conducting further analyses of bleeding and cancer in antiplatelet and anticoagulant outcome trials to determine whether solid cancer promotion "is a peculiar effect of prasugrel, a class effect of $P2Y_{12}$ platelet inhibitors, a class effect of all platelet inhibitors, or an effect of all durgs that increase bleeding."

- agree with incorporating language into prescribing information with respect to switching from clopidogrel to prasugrel ("Discontinuing clopidogrel 75-mg and initiating a prasugrel 10-mg maintenance dose with or without a prasugrel 60-mg loading dose resulted in a 14% decrease in MPA by Day 7. This decrease in MPA was not greater than that typically produced by a 10-mg maintenance dose of prasugrel alone.")

The applicant has fulfilled Postmarketing Requirement #2 (95-2) and Postmarketing Commitment #6 (95-6) as stated below:

- 95-2 You will gather baseline cancer history and cancer adverse event data from the ongoing trial TRILOGY, a 10,300-subject trial being conducted in patients with acute coronary syndrome who are being managed medically (without coronary revascularization). The final report on cancers in this trial is to be submitted to IND 63,449.

- 95-6 You commit to the collection of samples at baseline for genotyping CYP450 enzymes in TRILOGY subjects, to allow a comparison of effectiveness and bleeding in prasugrel and clopidogrel subgroups by metabolizer status. These data will be submitted with the final study report of TRILOGY. The periodic reports will include the fraction of subjects who consented to genetic testing.

15.3. Risk/Benefit Assessment

When used in the indicated population, ACS patients who are to be managed with PCI as follows:

- Patients with unstable angina or non-ST-elevation myocardial infarction (NSTEMI)
- Patients with ST-elevation myocardial infarction (STEMI) when managed with either primary or delayed PCI

the benefits of prasugrel therapy outweigh the risks.

15.4. Recommendation for Postmarketing Risk Evaluation and Management Strategies

N/A.

15.5. Recommendation for other Postmarketing Requirements and Commitments

N/A.

15.6. Recommended Comments to Applicant

None.

16. Appendix 1: Additional Protocol and Amendment Information (TRILOGY)

Protocol and Amendments for Study H7T-MC-TABY ("A Comparison of Prasugrel and Clopidogrel in Acute Coronary Syndrome (ACS) Subjects with Unstable Angina/Non-ST-Elevation Myocardial Infarction (UA/NSTEMI) Who are Medically Managed—The TRILOGY ACS Study") ("TABY").

This review was based on the original protocol (dated August 28, 2007) submitted to IND 63,449 with the SPA on September 13, 2007 (SDN 590), Protocol Amendment (a) (dated February 6, 2008) submitted on January 16, 2008 (SDN 630), and Protocol Amendment (b) (dated May 5, 2009) submitted on May 7, 2009 (SDN 680).

Objectives

Primary Objective
The primary objective of this study was to test the hypothesis that prasugrel and aspirin were superior to clopidogrel and aspirin in the treatment of medically managed subjects enrolled within 10 days of the unstable angina/non-ST-segment elevation myocardial infarction (UA/NSTEMI) index event. Superiority was assessed by the reduction in the risk of the composite endpoint of first occurrence of cardiovascular (CV) death, myocardial infarction (MI), or stroke throughout the study.

The primary analysis was conducted in a hierarchical manner, with evaluation of the primary endpoint performed first in medically managed UA/NSTEMI subjects < age 75 years. Conditional on successfully establishing superiority in the primary analysis, the same composite endpoint would be evaluated in the entire population.

Secondary Objectives
The following secondary endpoints were analyzed in both the population of medically managed UA/NSTEMI subjects age < 75 years and the entire medically managed UA/NSTEMI population (subjects < age 75 years and subjects ≥ 75 years).

Efficacy Objectives
The secondary efficacy objectives were to compare the prasugrel and clopidogrel groups with respect to:

- The risk of the composite endpoint of first occurrence of CV death and MI
- The risk of the composite endpoint of first occurrence of CV death, MI, stroke, or rehospitalization for recurrent UA
- The risk of the composite endpoint of first occurrence of all-cause death, MI, or stroke
- Stent thrombosis

Safety Objectives
In subjects receiving prasurgrel or clopidogrel, the safety objectives were to evaluate the incidence of:
- Non-coronary artery bypass graft (non-CABG)-related life-threatening bleeding (a subset of the Thrombolysis in Myocardial Infarction [TIMI] major bleeding)
- Non-CABG-related TIMI major bleeding
- Non-CABG-related TIMI major or minor bleeding
- Non-CABG-related TIMI major, minor, or minimal bleeding
- Non-CABG-related Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) severe or life-threatening bleeding
- Non-CABG-related GUSTO severe or life-threatening bleeding or moderate bleeding
- Non-CABG-related GUSTO severe or life-threatening, moderate, or mild bleeding

- Fatal bleeding or intracranial hemorrhage (ICH)
- CABG-related bleeding

AND

- To evaluate the overall safety and tolerability (based on vital signs, laboratory values, non-benign neoplasms, the occurrence of treatment-emergent adverse events including adverse events meeting the regulatory definition of a serious adverse event, and those events leading to permanent discontinuation of study drug) in subjects receiving prasugrel or clopidogrel

Substudy Objectives

Two substudies were performed in Study TABY. The first substudy investigated pharmacodynamic response (platelet function), genetic variants related to drug metabolism, and biomarker of inflammation and hemodynamic stress. The second substudy investigated health outcomes. Both cohorts (population < 75 years of age and the population ≥ 75 years of age) were eligible for participation in the substudies.

- **Platelet Function Substudy**

  a. Pharmacodynamic Objectives: Platelet aggregation was measured by the Accumetrics VerifyNow® $P2Y_{12}$ and aspirin assays. The key function objectives were:

     - To demonstrate a lower risk of the composite endpoint of CV death, MI, or stroke in subjects with greater attenuation of platelet aggregation, irrespective of baseline treatment
     - To compare the prasugrel and clopidogrel groups with respect to degree of platelet aggregation
     - To compare the prasugrel and clopidogrel groups with respect to intra- and inter-subject variability in platelet aggregation during maintenance dosing
     - To assess the incidence of bleeding events by degree of platelet aggregation

  b. Genomic Objectives: Genomic substudy objectives were:

     - To assess the interaction between treatment groups and the presence of genetic variation in drug metabolizing enzymes and transporters on platelet function
     - To assess the interaction between treatment group and the presence of genetic variation in drug metabolism enzymes and transporters on clinical efficacy and/or safety outcomes.

  c. Other Objectives: Other substudy objectives were:

     - To assess the effect of the prasugrel and clopidogrel groups on biomarkers of inflammation (high-sensitivity C-reactive protein [hsCRP]) and hemodynamic stress (N-terminal prohormone brain natriuretic peptide [NT-proBNP] or brain natriuretic peptide [BNP]).

- Health Outcome Substudy Objectives: Health outcome objectives were:

  - To compare the prasugrel and clopidogrel treatment arms with respect to:

    a. Major healthcare resource use, cumulative medical costs, and incremental cost effectiveness
    b. Health-related quality of life

  - To examine healthcare costs and resource use as a function of both treatment assignment and degree of platelet aggregation

Other Objectives
Other prespecified and exploratory analyses were conducted, as specified in the statistical analysis plan (SAP), to include repeating the primary and all secondary analyses in the age ≥ 75 years population

Study Duration
TRILOGY was to continue until

- An estimated 688 subjects < 75 years of age experienced an adjudicated event of the composite triple endpoint of CV death, MI, or stroke.
- All subjects < 75 years of age had either completed at least 6 months of follow-up (completion of Visit 5 per study schedule) or discontinued before 6 months of follow-up
- At least 2000 subjects ≥ 75 years of age were randomized into the study, with the last subject having either completed at least 3 months of follow-up (completion of Visit 4 per study schedule) or discontinued before 3 months of follow-up)

The study population of approximately 10,300 subjects was to be enrolled at an estimated 800 sites globally (7800 subjects < 75 years of age and a maximum enrollment of 2500 subjects ≥ 75 years of age). A Study Operations Committee (SOC) was to monitor the proportion of subjects meeting the primary endpoint per blinded review. If this event rate was different than what was expected, the SOC could recommend modifying the number of subjects randomized.

Subjects were to remain on study drug for a maximum of 30 months or until study completion, whichever was earlier. A rolling close out over a 3-month period was planned.

Inclusion Criteria (Protocol Amendment (b))
Prior to study entry, study participants signed the informed consent per local rules and regulations. Subjects were eligible for study entry if they were of legal age (at least 18 years old) and competent mental condition to provide written informed consent and meet all of the following criteria:

1. Have had a UA/NSTEMI index event within 10 days (240 hours) prior to randomization (based on the disease diagnostic criteria)

   Disease Diagnostic Criteria: Definition of UA/NSTEMI
   For the purposes of this study, recent UA/NSTEMI will be defined as follows:

   - NSTEMI is defined as a history of chest discomfort or anginal-equivalent symptoms of ≥ 5 minutes duration at rest within 24 hours prior to the index event, with no evidence of persistent ST-segment elevation. Subjects must also have a CK-MB or troponin T or I greater than the upper limit of normal (ULN) defined by the local laboratory assay. If CK-MB or troponin are not available, total CK ≥ 2 times ULN is acceptable.

   - UA is defined as a history of chest discomfort or anginal-equivalent symptoms of ≥ 5 minutes duration at rest within 24 hours prior to the index event, with ST-segment depression > 1 mm in at least two or more ECG leads without elevation of CK-MB, troponin T, or troponin I.

   The onset for the index event will be the first medical contact for evaluation of UA/NSTEMI symptoms. First medical contact is defined as the date and time of first contact with medical personnel for the index event including Emergency Medical Systems (EMS) responders for pre-hospital evaluation. Emergency Room personnel for the initial hospital evaluation, or other medical personnel for other locations of first evaluation. If the subject was already hospitalizaed at the time of the UA/NSTEMI sysmptoms, the onset of the index event will be the date and time when the subject is initially evaluated fro UA/NSTEMI (that is, when ECG or biomarker for myocardial damage are first obtained), provided that the subject meets all other inclusion and exclusion criteria.

2. Have had a medical management strategy decision made with reasonable certainty; that is, neither PCI nor CABG is planned for treatment of the index event

    - For subjects whose medical management decision and randomization occurs no later than 72 hours following onset of the index event, prior clopidogrel treatment is not a consideration for eligibility
    - For subjects with a medical management decision who are randomized beyond 72 hours of onset of the index event, clopidogrel must be administered according to standard of care practice for ACS patients no later than 72 hours following the onset of the index event.

3. Have had at least 1 of the following 4 high-risk features at the time of the UA/NSTEMI event:

    - Age ≥ 60 years
    - Prior MI evidenced by pre-existing Q waves, or demonstration of infarciton on imaging studies, or prior documentation of elevated cardiac markers
    - Diabetes Mellitus—defined by concomitant treatment with an oral hypoglycemic agent and/or insulin
    - Coronary revascularization (either PcI or CABG) at least 30 days before the onset of the index ACS event

4. Deleted (replaced with new Exclusion Criterion [39])

Exclusion Criteria
Subjects may not be entered into the study if they meet any of the following criteria:

Cardiovascular Exclusion Criteria
5. Decision for medical management > 72 hours after the onset of the index event without commercial clopidogrel treatment within 72 hours following the onset of the index event (Note: commercial clopidogrel treatment must continue daily thereafter until randomization)
6. Planned PCI or CABG as treatment for the index ACS event—either during the index hospitalization or thereafter
7. PCI or CABG performed within the previous 30 days
8. STEMI as the index event
9. Cardiogenic shock within the previous 24 hours (defined as a systolic blood pressure < 90 mm Hg associated with clinical evidence of end-organ hypoperfusion, or hypotension requiring vasopressors to maintain systolic blood pressure over 90 mm Hg and associated with clinical evidence of end-organ hypoperfusion)
10. Refractory ventricular arrhythmias within the previous 24 hours
11. Symptoms of New York Heart Association (NYHA) Class IV congestive heart failure (CHF) within the previous 24 hours

Note: See also Exclusion Criterion [39]

Exclusion Criteria Related to Bleeding (Protocol Amendment (b))
12. Contraindicated for antiplatelet therapy
13. Received fibrinolytic therapy as initial treatment for the index event
14. Any history of bleeding diathesis
15. Clinical findings associated, in the judgment of the investigator, with an unacceptabley high risk of bleeding

16. Any of the following:
    - History of ischemic or hemorrhagic stroke
    - Intracranial neoplasm, arteriovenous malformation, or aneurysm
    - History of any TIA symptoms
17. International Normalized Ratio (INR) > 1.5, if test is performed
18. Platelet count of < 100,000/mm^3
19. Anemia (hemoglobin [Hgb] < 10 gm/dL
20. Deleted; combined with [21]
21. History of spontaneous gastrointestinal or non-gastrointestinal internal bleeding requiring in-hospital treatment, unless the event has been definitively treated an, in the investigator's opinion, has a low likelihood of recurrence
22. Currently receiving hemodialysis or peritoneal dialysis

    Note: For criteria dependent on laboratory values (i.e., criteria 17-19), the values obtained closest to randomization should be used to determine eligibility

Prior/Concomitant Therapy Exclusion Criteria

23. History of intolerance or allergy to aspirin or approved thienopyridines (ticlopidine or clopidogrel)
24. Treated with ticlopidine within 5 days of randomization
25. Receiving prasugrel treatment at the time of screening
26. Receiving oral anticoagulants at the time of screening or are anticipated to require oral anticoagulants therapy during the course of the study
27. Receiving daily treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) or cyclooxygenase-2 (COX2) inhibitors that cannot be discontinued or are anticipated to require > 2 weeks of daily treatment with NSAIDs or COX2 inhibitors during the study

General Exclusion Criteria

28. Unwilling to provide or not sufficiently mentally competent to provide written informed consent
29. Study site personnel directly affiliated with the study or are immediate family of study site personnel directly affiliated with the study. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
30. Employed by Eli Lilly and Compeny, Ube Industries Limited, Daiichi Sankyo Pharma In, the academic research organization (ARO), or the contract research organization (CRO) (that is, employees, temporary contract workers, or designees responsible for the conduct of the study). Immediate family of Lilly employees may participate in Lilly-sponsored clinical studies, but are not permitted to participate at a Lilly facility. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
31. Previously completed or withdrawn from this study or any other study investigating prasugrel
32. Received treatment within the last 30 days with a drug or device that has not received regulatory approval for any indication at the time of study entry or are presently enrolled in another interventional drug or device study.
33. Females who are known to be pregnant, who have given birth within the past 90 days, or who are breastfeeding.
34. Females of childbearing potential (that is, females who are not surgically or chemically sterilized and who are between menarch and 1-year post menopause) and do not agree to use a reliable method of birth control during the study.
35. Concomitant medical illness (for example, terminal malignancy) that, in the opinion of the investigator, is associated with reduced survival over the expected treatment period.
36. Known severe hepatic dysfunction (that is, with cirrhosis or portal hypertension)
37. Conditions associated with poor treatment compliance, including alcoholism, mental illness, or durg dependence
38. Unable to cooperate with protocol requirements and follow-up procedures

Additional Cardiovascular Exclusion Criterion added in Amendment (b):

39. Insignificant coronary disease identified during coronary angiography performed for the index ACS event (defined as the absence of at least one stenosis in any native coronary artery visually estimated to be ≥ 30%)

    Note: This criterion does not apply to subjects with prior percutaneous coronary intervention or prior coronary artery bypass grafting.

    Note: Coronary angiography is not mandated per protocol.

Standard of Care for Commercial Clopidogrel Use in UA/NSTEMI Subjects

Standard of care for commercial clopidogrel use in UA/NSTEMI subjects in TRILOGY is defined as:

- For clopidogrel-naïve subjects, treatment initiation with a clopidogrel loading dose of at least 300 mg within 72 hours following the onset of the index event followed by once-daily 75-mg maintenance dose until randomization

- For subjects on commercial clopidogrel treatment prior to the index event, continue the once-daily 75-mg maintenance dose until randomization

Statistical and Analytical Plans

The primary endpoint was the composite of CV death, MI, or stroke. Time from randomization to the first occurrence of the primary endpoint (CV death, MI, or stroke, whichever occurred first) was to be compared between treatment groups using a stratified two-sided log-rank test where the subject category was defined (See Table 10).

Primary analyses were to be carried out in a hierarchical manner. First, treatment groups would be compared within the < 75 year old subjects using the methodology described above. Conditional on successfully establishing superiority of prasugrel over clopidogrel in the < 75 year old subjects, treatment groups would be compared on all subjects using a stratified two-sided log rank test with two stratification variables: subject category as in Table 10 and age (< 75 or ≥ 75).

The three secondary composite endpoints, stent thrombosis, and individual event endpoints (all-cause death; CV death; MI (fatal and nonfatal); stroke (fatal and nonfatal); rehospitalization for recurrent UA; and any coronary revascularization) were to be tested at $\alpha = 0.05$ (two-sided) in patients < 75 years of age using the same methodology as the primary outcome. Similar analyses were to be conducted in subjects ≥ 75 years of age.

All efficacy analyses would be conducted in the intent-to-treat (ITT) population (all randomized subjects). All safety analyses would be conducted in the treated population (subjects who received at least 1 dose of study drug, either a loading dose or maintenance dose).

Interim analyses were to be conducted by the Data Monitoring Committee (DMC**)** every 6 months, starting March 28, 2009. Study termination was to be considered only for a strong likelihood of excessive life-threatening bleeding or deaths in the prasugrel group compared with the clopidogrel group.

Determination of Sample Size

Sample size calculations were conducted to achieve 90% power for those subjects < 75 years of age. To detect a 22% relative risk reduction with prasugrel versus clopidogrel, using a two-sided test at $\alpha = 0.05$, a total of 688 subjects experiencing an event of the composite primary endpoint was required, considering the following assumptions:

- 8% clopidogrel event rate for the primary endpoint the first year followed by 4% event rate the second year
- 5% annual drop-out rate (i.e., lost to follow-up or revoked consent)
- Minimum follow-up of 6 months on all subjects < 75 years old

Therefore, approximately 7800 subjects < 75 years of age had to be randomized to obtain the required number of events over a projected accrual period of approximately 24 months with a maximum follow-up period of up to 30 months. This would result in an approximate 18-month median follow-up time.

Since this study was event-driven, the actual number of subjects enrolled could vary, according to observed event rates. Therefore, enrollment would continue until the sponsor projected that 688 events would occur. The projected number of events was based on the observed event rate (pooled over both treatment groups since treatment assignment was still blinded) and the recruitment rate.

Enrollment of subjects ≥ 75 years of age would continue until at least 2000 subjects were randomized.

Study Schedule

See Table 37 for full details.

Table 37. Study Schedule for Study H7T-MC-TABY (TRILOGY ACS)

Procedure	Screen	Visit 1 Day 1[a]	Visit 2 Telephone Contact Day 14 (±3 days)	Visit 3 Day 30 (±3 days)	Visit 4 Month 3 (±7 days)	Visit 5 Month 6 (±14 days)	Visits 6, 8, 10, 12 Telephone Contacts Months 9, 15, 21, and 27 (±14 days)	Visits 7, 9, 11 Months 12, 18, and 24 (±14 days)	Early Disc. From Study Drug[b]	Visit 13 / Final Visit Month 30 / Disc. From Study
Screening, review all available data (medical history, physical exam, ECG, pre-existing conditions, Creatinine, Troponin I/T or CK-MB) to determine eligibility for study	•									
Informed consent (prior to study procedures)		•								
Randomization through IVRS		•								
Directed physical exam[o]		•		•	•	•		•	•	•
Vital signs		•		•	•	•		•	•	•
ECG		•		•		•		•[m]	•	•

Procedure	Screen	Visit 1 Day 1[a]	Visit 2 Telephone Contact Day 14 (±3 days)	Visit 3 Day 30 (±3 days)	Visit 4 Month 3 (±7 days)	Visit 5 Month 6 (±14 days)	Visits 6, 8, 10, 12 Telephone Contacts Months 9, 15, 21, and 27 (±14 days)	Visits 7, 9, 11 Months 12, 18, and 24 (±14 days)	Early Disc. From Study Drug[b]	Visit 13 / Final Visit Month 30 / Disc. From Study
Concomitant medications recorded (including aspirin dose)[c]		•	•	•	•	•	•	•	•	•
Adverse events recorded		•	•	•	•	•	•	•	•	•
Study Drug										
First dose[d]		•								
Study drug MD dispensed [e]		•		•	•	•		•		
Study drug reconciled (MD)				•	•	•		•	•	•
Central Laboratory Measures										
Hematology and chemistry labs		•		•		•		•	•	•
HbA_{1c} (diabetics only) [n]		•								
Local Laboratory Measures										
Urine or serum pregnancy [f]		•								

Procedure	Screen	Visit 1 Day 1[a]	Visit 2 Telephone Contact Day 14 (±3 days)	Visit 3 Day 30 (±3 days)	Visit 4 Month 3 (±7 days)	Visit 5 Month 6 (±14 days)	Visits 6, 8, 10, 12 Telephone Contacts Months 9, 15, 21, and 27 (±14 days)	Visits 7, 9, 11 Months 12, 18, and 24 (±14 days)	Early Disc. From Study Drug[b]	Visit 13 / Final Visit Month 30 / Disc. From Study
Platelet Function Substudy										
Predose Accumetrics VerifyNow® $P2Y_{12}$ assay [g]		•[h]								
Postdose Accumetrics VerifyNow $P2Y_{12}$ assay [g]		•[h]		•[i]	•[i]	•[i]		•[i]	•[i]	•[i]
Accumetrics VerifyNow® Aspirin assay		•[j]		•						
Biomarker measurements [k]		•		•		•			•[k]	•[k]
Genotyping for drug metabolism enzymes and transporters		•								
Health Outcomes Substudy										
EQ-5D questionnaire [l]		•			•			• (Visit 7 only)	•	•

Abbreviations: CK-MB = creatine kinase-MB fraction; Disc. = Discontinuation; ECG = electrocardiogram; IVRS = interactive voice response system; LD = loading dose; MD = maintenance dose; No. = number; NP = nurse practitioner; PA = physician's assistant; V = visit.

[a] Visit 1 is to occur within 10 days of the onset of the index event.

[b] Subjects prematurely discontinued from the study drug will have early discontinuation visit procedures performed upon withdrawal.

[c] Subjects will supply their own daily aspirin therapy with the dose determined at the investigator's discretion. The recommended dose after discharge from the index hospitalization is 75 to 100 mg.

[d] At Visit 1, subjects who are considered clopidogrel-naïve (have not received clopidogrel prior to the index event) or who are deemed to not be at steady state (that is, subjects who have received a maintenance dose of clopidogrel for <5 consecutive days immediately prior to the index event AND who have not received a commercial clopidogrel loading dose within 72 hours following the onset of the index event with administration of daily maintenance dose thereafter) will be randomized to either a clopidogrel 300-mg loading dose followed by 75-mg once-daily maintenance dose or prasugrel 30-mg loading dose followed by a 10-mg once-daily maintenance dose. Subjects ≥75 years of age or <60 kg body weigh at the time of randomization and who are randomized to prasugrel will receive prasugrel 30-mg LD followed by 5-mg once daily maintenance dose. The first dose should be given as soon as possible after randomization and up to 72 hours following the onset of the index event. Subjects who have received a commercial clopidogrel loading dose within 72 hours following the onset of the index event and daily maintenance doses thereafter or who have received ≥5 consecutive days of commercial clopidogrel immediately prior to the index event will be randomized to either clopidogrel 75-mg once-daily maintenance dose or prasugrel 10-mg once-daily maintenance dose. Subjects ≥75 years of age or <60 kg body weight at time of randomization and who are randomized to prasugrel will receive a 5-mg once daily maintenance dose. The first dose of study drug for these subjects should be administered as soon as possible after randomization and up to 24 hours following the previous dose of commercial clopidogrel.

[e] After the first dose of study drug, subsequent doses should be administered once daily and may be taken with or without food. For subjects participating in the platelet function substudy, the MD should be taken at least 2 hours prior to the planned outpatient visit.

[f] A urine or serum pregnancy test will be performed locally for women of childbearing potential, and must be performed (with results reviewed) prior to randomization.

[g] An additional platelet function measurement should be collected if a subject experiences an efficacy endpoint event or a bleeding event during the index hospitalization or at any time.

[h] At Visit 1, the platelet function measurement should be obtained both prior to study drug and at 120 ± 10 minutes following administration of study drug.

[i] The platelet function measurement should be obtained no less than 2 hours following administration of the daily MD.

[j] At Visit 1, the VerifyNow® Aspirin assay should be obtained only prior to administration of the LD.

[k] Biomarker measurements include hs-CRP and NT-proBNP (or BNP). At the early discontinuation from study drug visit or at the final discontinuation visit, biomarkers will be collected only if the subject discontinues from the study prior to Month 6.

[l] Quality of life will be measured in all subjects using the EQ-5D (except at a small minority of sites where an appropriate translation of the questionnaire is unavailable), with additional selected measures in a subgroup of subjects. Quality-of-life surveys will be collected at baseline, 3 months, 12 months, and end of study.

[m] Electrocardiograms not performed at Visit 9.

- Hb A_{1c}. will be performed only on patients who are diabetic at baseline.
- The directed physical exam must be performed by a physician, physician's assistant (PA), or nurse practitioner (NP).

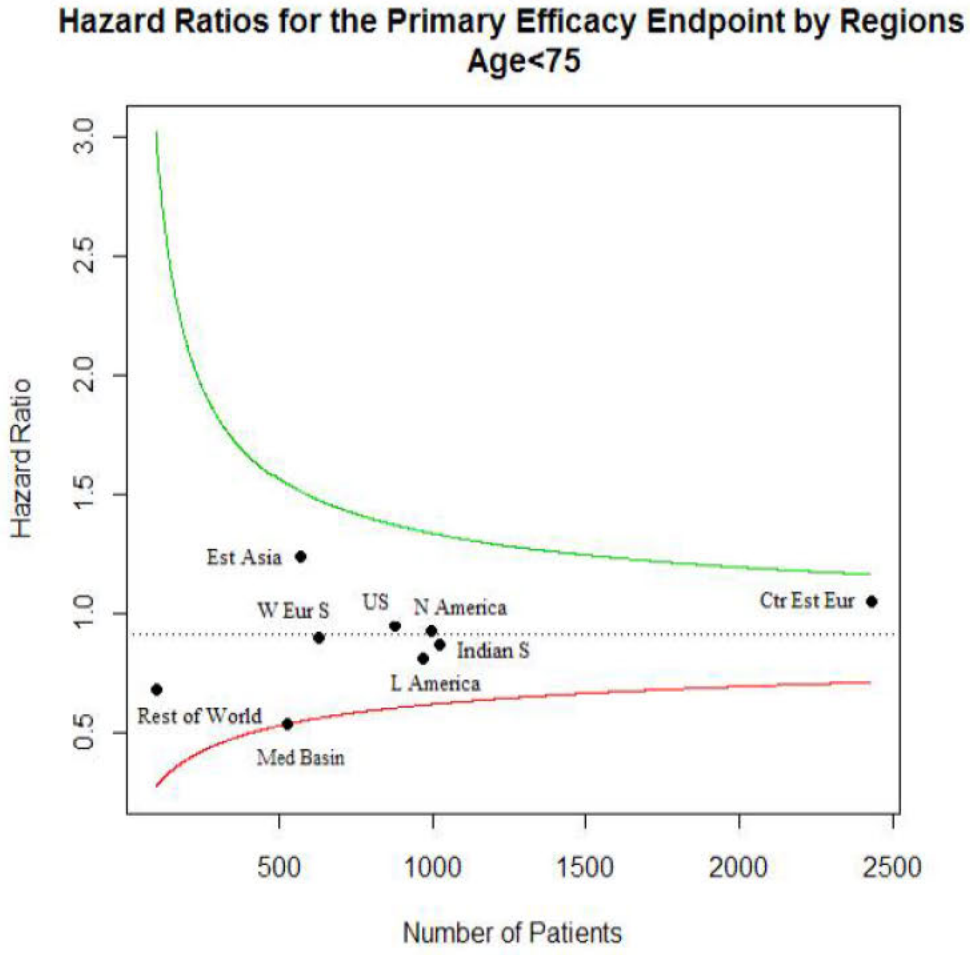
(Protocol Amendment (b), pages 84-87)

17. Appendix 2: Additional Primary Efficacy Endpoint Analyses (TRILOGY)

Population	Prasugrel			Clopidogrel			Total			HR (95% CI)	P-value
	N	n	%	N	n	%	N	n	%		
Primary Efficacy Endpoint (PPI Use at Randomization)											
Age < 75 years	830	90	10.8	836	125	15.0	1666	215	12.9	0.70 (0.53, 0.92)	0.0093
Age ≥ 75 years	348	87	25.0	330	98	29.7	678	185	27.3	0.81 (0.61, 1.08)	0.17
All	1178	117	9.9	1166	223	19.1	2344	400	17.1	0.75 (0.62, 0.91)	0.0045
Primary Efficacy Endpoint (No PPI Use at Randomization)											
Age < 75 years	2790	274	9.8	2787	272	9.8	5577	546	9.8	1.01 (0.86. 1.20)	0.86
Age ≥ 75 years	695	170	24.5	710	153	21.6	1405	323	23.0	1.18 (0.95, 1.47)	0.13
All	3485	444	12.7	3497	425	12.2	6982	869	12.5	1.07 (0.94, 1.22)	0.29
Analysis by Ququan Liu, M.D., M.S.											

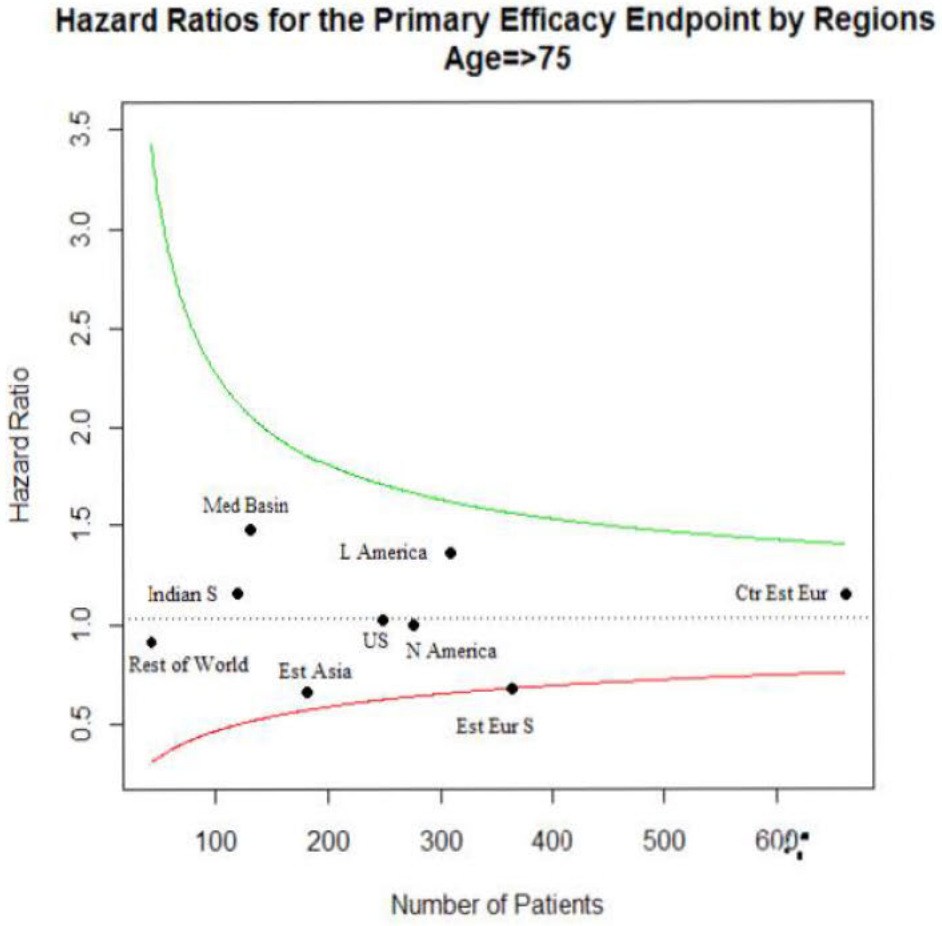
Population	Prasugrel			Clopidogrel			Total			HR (95% CI)	P-value
	N	n	%	N	n	%	N	n	%		
FDA Sensitivity Analysis: Primary Efficacy Endpoint, Including 4 Indian Sites											
Age < 75 years	3676	371	10.1	3680	405	11.0	7356	776	10.6	0.92 (0.79, 1.05)	0.21
Age ≥ 75 years	1048	257	24.5	1042	253	24.8	2090	510	24.4	1.02 (0.86, 1.21)	0.83
All	4724	628	13.3	4723	658	13.9	9447	1286	13.6	0.96 (0.86, 1.07)	0.40
Includes 4 Indian Sites (25062, 25065, 25356, and 25359) (n = 120) **Analysis by Ququan Liu, M.D., M.S.**											

Figure 16. Hazard Ratios for the Primary Efficacy Endpoint by Regions (Age < 75)



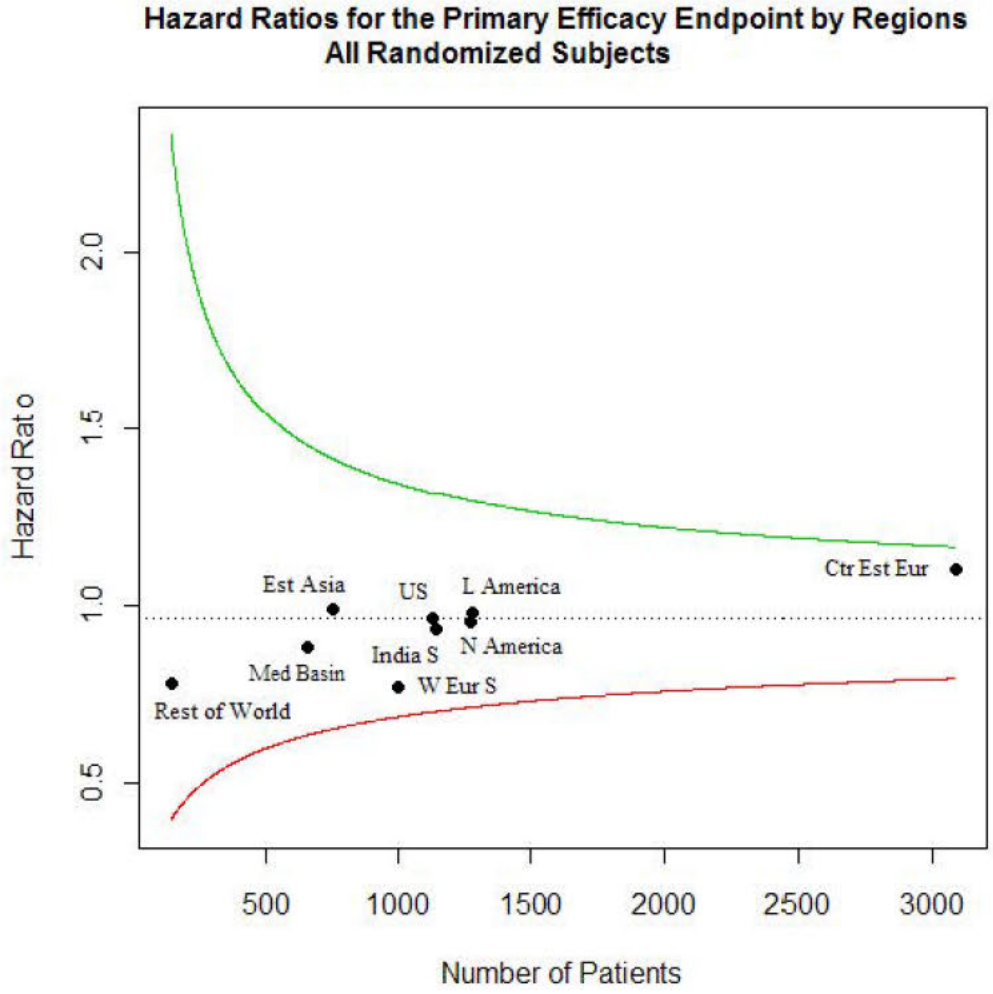
(Ququan Liu, M.D., M.S., Division of Biometrics I, FDA)

Figure 17. Hazard Ratios for the Primary Efficacy Endpoint by Regions (Age ≥ 75)



(Ququan Liu, M.D., M.S., Division of Biometrics I, FDA)

Figure 18. Hazard Ratios for the Primary Efficacy Endpoint by Regions, All Randomized Subjects



(Ququan Liu, M.D., M.S., Division of Biometrics I, FDA)

18. Appendix 3: Analyses in Asians (TRILOGY)

Population	Prasugrel			Clopidogrel			Total			HR (95% CI)	P-value
	N	n	%	N	n	%	N	n	%		
Primary Efficacy Endpoint, Asian (East Asian & West Asian)											
Age < 75 years	821	85	10.4	800	81	10.1	1621	166	10.2	1.05 (0.77, 1.42)	0.77
Age ≥ 75 years	147	27	18.4	164	41	0.25	311	68	21.9	0.78 (0.48, 1.27)	0.38
All	968	112	11.6	964	122	12.7	1932	234	12.1	0.97 (0.75, 1.25)	0.83
Non-CABG-Related TIMI Major, Minor, or Minimal Bleeding, Asian											
Age < 75 years	814	60	7.4	795	36	4.5	1609	96	6.0	1.68 (1.11, 2.54)	0.02
Age ≥ 75 years	147	12	8.2	162	14	8.6	309	26	8.4	1.06 (0.49, 2.31)	1.00
All	961	72	7.5	957	50	5.2	1918	122	6.4	1.52 (1.06, 2.18)	0.03
Non-CABG-Related TIMI Major ICH Bleeding Event, Asian											
Age < 75 years	814	1	0.1	795	3	0.4	1609	4	0.3	0.31 (0.03, 2.95)	0.28
Age ≥ 75 years	147	0	-	162	1	0.6	309	1	0.3	-	-
All	961	1	0.1	957	4	0.4	1918	5	0.3	0.25 (0.03, 2.21)	0.17
Non-CABG-Related TIMI Major Fatal ICH Bleeding Event, Asian											
Age < 75 years	814	9	-	795	1	0.13	1609	1	0.06	-	-
Age ≥ 75 years	147	9	-	162	0	-	309	0	-	-	-
All	961	9	-	957	1	0.10	1918	1	0.05	-	-

Subjects ≥ 75 years of age or < 60 kg of body weight received the 5-mg prasugrel maintenance dose. Others received the 10-mg prasugrel maintenance dose.

Analysis by Ququan Liu, M.D., M.S.

19. Appendix 4: Additional Bleeding Analyses (TRILOGY)

	Prasugrel n	Prasugrel N	Prasugrel %	Clopidogrel n	Clopidogrel N	Clopidogrel %	Total n	Total N	Total %	HR (95% CI)	P-value
Non-CABG-Related TIMI Life-Threatening Bleeding by Body Weight											
< 60 kg	703	5	0.71	692	5	0.72	1395	10	0.72	0.93 (0.27, 3.21)	0.8981
≥ 60 kg	3920	20	0.51	3925	22	0.56	7845	42	0.54	0.92 (0.50, 1.69)	0.8036
Non-CABG-Related TIMI Major or Minor Bleeding by Body Weight											
< 60 kg	703	10	1.42	692	15	2.17	1395	25	1.79	0.65 (0.29, 1.45)	0.2906
≥ 60 kg	3920	87	2.22	3925	62	1.58	7845	149	1.90	1.43 (1.03, 1.98)	0.0324
Non-CABG-Related TIMI Fatal Bleeding by Body Weight											
< 60 kg	703	1	0.14	692	2	0.29	1395	3	0.22	0.45 (0.04, 5.00)	0.5002
≥ 60 kg	3920	6	0.15	3925	7	0.18	7845	13	0.17	0.89 (0.30, 2.63)	0.8267
Subjects ≥ 75 years of age or < 60 kg of body weight received the 5-mg prasugrel maintenance dose. Others received the 10-mg prasugrel maintenance dose.											
Analyses by Ququan Liu, M.D., M.S.											

Population	Prasugrel N	Prasugrel n	Prasugrel %	Clopidogrel N	Clopidogrel n	Clopidogrel %	Total N	Total n	Total %	HR (95% CI)	P-value
Non-CABG-Related TIMI Life-Threatening Bleeding Requiring Inotropes											
Age < 75 years	3590	1		3590	1		7180	2		-	-
Age ≥ 75 years	1033	0		1027	1		2060	1		-	-
All	4623	1		4617	2		9240	3		-	-
Non-CABG-Related TIMI Life-Threatening Bleeding Requiring Surgical Intervention											
Age < 75 years	3590	3	<0.1	3590	1	<0.1	7180	4	<0.1	3.03 (0.32, 29.12)	0.31
Age ≥ 75 years	1033	2		1027	0		2060	2		-	
All	4623	5	0.1	4617	1	<0.1	9240	6	<0.1	2.00 (0.36, 10.90)	0.10
Non-CABG-Related TIMI Life-Threatening Bleeding Requiring Transfusion											
Age < 75 years	3590	10	0.3	3590	2	<0.1	7180	12	0.2	4.96 (1.09, 22.65)	0.02
Age ≥ 75 years	1033	4	0.4	1027	3	0.3	2060	7	0.3	1.36 (0.31, 6.09)	0.69
All	4623	14	0.3	4617	5	0.1	9240	19	0.2	2.85 (1.03, 7.91)	0.04
Analyses by Ququan Liu, M.D., M.S.											

Population	Prasugrel			Clopidogrel			Total			HR (95% CI)	P-value
	N	n	%	N	n	%	N	n	%		
Non-CABG-Related TIMI Major, Minor, or Minimal Bleeding by Commercial Clopidogrel Status at Randomization (None, Initiated, Ongoing)											
Age < 75 years											
Stratum 1	151	29	19.2	168	13	7.7	319	42	13.2	2.74 (1.42, 5.26)	0.0017
Stratum 2	2487	441	17.7	2449	265	10.8	4936	706	14.3	1.70 (1.46, 1.98)	<0.0001
Stratum 3	952	137	14.4	972	90	9.3	1924	227	11.8	1.63 (1.25, 2.12)	0.0003
Age ≥ 75 years											
Stratum 1	43	11	25.6	33	7	21.2	76	18	23.7	1.15 (0.45, 2.97)	0.7714
Stratum 2	745	130	17.5	767	101	13.2	1512	231	15.3	1.39 (1.08, 1.81)	0.0119
Stratum 3	245	32	13.1	227	22	9.7	472	54	11.4	1.43 (0.83, 2.46)	0.1967
All											
Stratum 1	194	40	20.6	201	20	10.0	395	60	15.2	2.24 (1.31, 3.83)	0.0025
Stratum 2	3232	571	17.7	3216	366	11.4	6448	937	14.5	1.62 (1.42, 1.84)	< 0.0001
Stratum 3	1197	169	14.1	1199	112	9.3	2396	281	11.7	1.58 (1.25, 2.01)	0.0001
Non-CABG-Related TIMI Major or Minor Bleeding by Commercial Clopidogrel Status at Randomization											
Age < 75 years											
Stratum 1	151	1	0.7	168	1	0.6	319	2	0.6	1.13 (0.07, 18.04)	0.93
Stratum 2	2487	53	2.1	2449	30	1.2	4936	83	1.7	1.76 (1.13, 2.76)	0.01
Stratum 3	952	16	1.7	972	15	1.5	1924	31	1.6	1.11 (0.55, 2.25)	0.77
Age ≥ 75 years											
Stratum 1	43	1	2.3	33	1	3.0	76	2	2.6	0.72 (0.05, 11.45)	0.81
Stratum 2	745	20	2.7	767	25	3.3	1512	45	3.0	0.84 (0.47, 1.51)	0.55
Stratum 3	245	6	2.5	227	5	2.2	472	11	2.3	1.18 (0.36, 3.86)	0.79
All											
Stratum 1	194	2	1.0	201	2	1.0	395	4	1.0	1.04 (0.15, 7.41)	0.97
Stratum 2	3232	73	2.3	3216	55	1.7	6448	128	2.0	1.34 (0.94, 1.90)	0.10
Stratum 3	1197	22	1.8	1199	20	1.7	2396	42	1.8	1.13 (0.62, 2.07)	0.70

Population	Prasugrel			Clopidogrel			Total			HR (95% CI)	P-value
	N	n	%	N	n	%	N	n	%		
Non-CABG-Related TIMI Major Bleeding by Commercial Clopidogrel Status at Randomization											
Age < 75 years											
Stratum 1	151	0	-	168	0	-	319	0	-	-	
Stratum 2	2487	33	1.3	2449	21	0.9	4936	54	1.1	1.57 (0.91, 2.71)	0.10
Stratum 3	952	6	0.6	972	9	0.9	1924	15	0.8	0.70 (0.25, 1.95)	0.49
Age ≥ 75 years											
Stratum 1	43	1	2.3	33	0	-	76	1	1.3	-	-
Stratum 2	745	12	1.6	767	15	2.0	1512	27	1.8	0.85 (0.40, 1.81)	0.67
Stratum 3	245	6	2.5	227	3	1.3	472	9	1.9	2.02 (0.50, 8.09)	0.31
All											
Stratum 1	194	1	0.5	201	0	-	395	1	0.3	-	-
Stratum 2	3232	45	1.4	3216	36	1.1	6448	81	1.3	1.26 (0.81, 1.96)	0.30
Stratum 3	1197	12	1.0	1199	12	1.0	2396	24	1.0	1.03 (0.46, 2.29)	0.95
Non-CABG-Related TIMI Minor Bleeding by Commercial Clopidogrel Status at Randomization											
Age < 75 years											
Stratum 1	151	1	0.7	168	1	0.6	319	2	0.6	1.13 (0.07, 18.04)	0.93
Stratum 2	2487	21	0.8	2449	9	0.4	4936	30	0.6	2.32 (1.06, 5.06)	0.03
Stratum 3	952	10	1.1	972	7	0.7	1924	17	0.9	1.49 (0.57, 3.91)	0.42
Age ≥ 75 years											
Stratum 1	43	0	-	33	1	3.0	76	1	1.3	-	-
Stratum 2	745	8	1.1	767	10	1.3	1512	18	1.2	0.82 (0.32, 2.08)	0.68
Stratum 3	245	1	0.4	227	3	1.3	472	4	0.9	0.33 (0.04, 3.21)	0.32
All											
Stratum 1	194	1	0.5	201	2	1.0	395	3	0.8	0.52 (0.05, 5.75)	0.59
Stratum 2	3232	29	0.9	3216	19	0.6	6448	48	0.7	1.53 (0.86, 2.74)	0.14
Stratum 3	1197	11	0.9	1199	10	0.8	2396	21	0.9	1.13 (0.48, 2.65)	0.79
Analysis by Ququan Liu, M.D., M.S.											

20. Appendix 5: Additional Analyses by Sex, Age, and Weight (TRILOGY)

	Prasugrel n N %	Clopidogrel n N %	Total n N %	HR (95% CI)	P-value
Non-CABG Related TIMI Major Bleeding, Female					
Age<75 yrs	8 1298 0.62	7 1278 0.55	15 2576 0.58	1.14 (0.42, 3.16)	0.8012
Age≥75 yrs	6 516 1.16	9 525 1.71	15 1041 1.44	0.70 (0.25, 1.96)	0.4781
All	14 1814 0.77	16 1803 0.89	30 3617 0.83	0.90 (0.44, 1.84)	0.7464
Non-CABG Related TIMI Major Bleeding, Male					
Age<75 yrs	31 2292 1.35	23 2312 1.00	54 4604 1.17	1.37 (0.80, 2.35)	0.2494
Age≥75 yrs	13 517 2.52	9 502 1.79	22 1019 2.16	1.49 (0.64, 3.48)	0.3683
All	44 2809 1.57	32 2814 1.14	76 5623 1.35	1.4 (0.89, 2.21)	0.1457
Non-CABG Related TIMI Major Life-Threatening Bleeding, Female					
Age<75 yrs	3 1298 0.23	3 1278 0.23	6 2576 0.23	1.01 (0.20, 5.0)	0.9913
Age≥75 yrs	4 516 0.78	5 525 0.95	9 1041 0.87	0.83 (0.22, 3.08)	0.7542
All	7 1814 0.39	8 1803 0.44	15 3617 0.41	0.89 (0.32, 2.47)	0.8031
Non-CABG Related TIMI Major Life-Threatening Bleeding, Male					
Age<75 yrs	13 2292 0.57	14 2312 0.61	27 4604 0.59	0.94 (0.44, 2.0)	0.8757
Age≥75 yrs	5 517 0.97	5 502 1.00	10 1019 0.98	1.0 (0.29, 3.49)	0.9913
All	18 2809 0.64	19 2814 0.68	37 5623 0.66	0.96 (0.51, 1.83)	0.8982
Non-CABG Related TIMI Major Fatal Bleeding, Female					
Age<75 yrs	1 1298 0.08	0 1278 -	1 2576 0.04	-	-
Age≥75 yrs	1 516 0.19	2 525 0.38	3 1041 0.29	0.49 (0.04, 5.38)	0.5478
All	2 1814 0.11	2 1803 0.11	4 3617 0.11	1.01 (0.14, 7.16)	0.9992
Non-CABG Related TIMI Major Fatal Bleeding, Male					
Age<75 yrs	3 2292 0.13	4 2312 0.17	7 4604 0.15	0.77 (0.17, 3.42)	0.7288
Age≥75 yrs	2 517 0.39	3 502 0.60	5 1019 0.49	0.66 (0.11, 3.93)	0.6372
All	5 2809 0.18	7 2814 0.25	12 5623 0.21	0.73 (0.23, 2.29)	0.5836

	Prasugrel n N %	Clopidogrel n N %	Total n N %	HR (95% CI)	P-value
Non-CABG Related TIMI Major ICH Bleeding, Female					
Age<75 yrs	1 1298 0.77	4 1278 0.31	5 2576 0.19	0.26 (0.03, 2.29)	0.1806
Age≥75 yrs	2 516 0.39	5 525 0.95	7 1041 0.67	0.43 (0.08, 2.22)	0.2906
All	3 1814 0.17	9 1803 0.50	12 3617 0.33	0.35 (0.09, 1.29)	0.10
Non-CABG Related TIMI Major ICH Bleeding, Male					
Age<75 yrs	7 2292 0.31	8 2312 0.35	15 4604 0.33	0.89 (0.32, 2.46)	0.8210
Age≥75 yrs	4 517 0.77	2 502 0.40	6 1019 0.59	2.10 (0.39, 11.5)	0.3838
All	11 2809 0.39	10 2814 0.36	21 5623 0.37	1.12 (0.48, 2.65)	0.7842
Non-CABG Related TIMI Major Fatal ICH Bleeding, Female					
Age<75 yrs	1 1298 0.08	0 1278 -	1 2576 0.04	-	-
Age≥75 yrs	0 516 -	1 525 0.19	1 1041 0.10	-	-
All	1 1814 0.06	1 1803 0.06	2 3617 0.06	1.01 (0.06, 16.16)	0.9991
Non-CABG Related TIMI Major Fatal ICH Bleeding, Male					
Age<75 yrs	1 2292 0.04	3 2312 0.13	4 4604 0.09	0.34 (0.04, 3.25)	0.3238
Age≥75 yrs	2 515 0.39	0 502 -	2 1019 0.20	-	-
All	3 2809 0.11	3 2814 0.11	6 5623 0.11	1.0 (0.2, 5.0)	0.9996
Non-CABG Related TIMI Major or Minor Bleeding, Female					
Age<75 yrs	16 1298 1.23	9 1278 0.70	25 2576 0.97	1.80 (0.79, 4.07)	0.1556
Age≥75 yrs	13 516 2.52	13 525 2.48	26 1041 2.50	1.01 (0.47, 2.19)	0.9963
All	29 1814 1.60	22 1803 1.22	51 3617 1.41	1.33 (0.77, 2.32)	0.3181
Non-CABG Related TIMI Major or Minor Bleeding, Male					
Age<75 yrs	54 2292 2.36	37 2312 1.60	91 4604 1.98	1.49 (0.98, 2.26)	0.0614
Age≥75 yrs	14 517 2.71	18 502 3.59	32 1019 3.14	0.80 (0.40, 1.61)	0.5035
All	68 2809 2.42	55 2814 1.95	123 5623 2.19	1.26 (0.88, 1.80)	0.2047
Non-CABG Related TIMI Major, Minor, or Minimal Bleeding, Female					
Age<75 yrs	270 1298 20.80	145 1278 11.35	415 2576 16.11	1.94 (1.59, 2.38)	<.0001
Age≥75 yrs	91 516 17.64	64 525 12.19	155 1041 14.89	1.48 (1.08, 2.05)	0.0158
All	361 1814 19.90	209 1803 11.59	570 3617 15.76	1.82 (1.53, 2.15)	<.0001

	Prasugrel n	N	%	Clopidogrel n	N	%	Total n	N	%	HR (95% CI)	P-value
Non-CABG Related TIMI Major, Minor, or Minimal Bleeding, Male											
Age<75 yrs	337	2292	14.70	224	2312	9.69	561	4604	12.19	0.56 (1.32, 1.85)	<.0001
Age≥75 yrs	82	517	15.86	66	502	13.15	148	1019	14.52	1.28 (0.93, 1.77)	0.1386
All	419	2809	14.92	290	2814	10.31	709	5623	12.61	1.50 (1.29, 1.74)	<.0001
Non-CABG Related TIMI Major Bleeding, Female											
<60 kg	4	444	0.90	5	438	1.14	9	882	1.02	0.81 (0.22, 3.02)	0.7356
≥60 kg	10	1370	0.73	11	1365	0.81	21	2735	0.77	0.92 (0.39, 2.17)	0.8574
Non-CABG Related TIMI Major Bleeding, Male											
<60 kg	4	259	1.54	4	254	1.57	8	513	1.56	0.94 (0.24, 3.78)	0.9512
≥60 kg	40	2550	1.57	28	2560	1.09	68	5110	1.33	1.46 (0.90, 2.37)	0.1264
Non-CABG Related TIMI Major Life-Threatening Bleeding, Female											
<60 kg	2	444	0.45	3	438	0.68	5	882	0.57	0.67 (0.11, 4.02)	0.6295
≥60 kg	5	1370	0.36	5	1365	0.37	10	2735	0.37	0.99 (0.29, 3.41)	0.9842
Non-CABG Related TIMI Major Life-Threatening Bleeding, Male											
<60 kg	3	259	1.16	2	254	0.79	5	513	0.98	1.36 (0.23, 8.18)	0.6737
≥60 kg	15	2550	0.59	15	2560	0.59	32	5110	0.63	0.90 (0.45, 1.80)	0.7560
Non-CABG Related TIMI Major Fatal Bleeding, Female											
<60 kg	0	444	-	1	438	0.23	1	882	0.11	-	-
≥60 kg	2	1370	0.15	1	1365	0.07	3	2735	0.11	1.94 (0.18, 21.45)	0.5609
Non-CABG Related TIMI Major Fatal Bleeding, Male											
<60 kg	1	259	0.39	1	254	0.39	2	513	0.39	0.95 (0.06, 15.23)	0.9855
≥60 kg	4	2550	0.16	6	2560	0.23	10	5110	0.20	0.68 (0.19, 2.41)	0.5393
Non-CABG Related TIMI Major ICH Bleeding, Female											
<60 kg	1	444	0.23	3	438	0.68	4	882	0.45	0.34 (0.04, 3.32)	0.3075
≥60 kg	2	1370	0.15	6	1365	0.44	8	2735	0.29	0.34 (0.07, 1.68)	0.1612
Non-CABG Related TIMI Major ICH Bleeding, Male											
<60 kg	1	259	0.39	1	254	0.39	2	513	0.38	0.44 (0.04, 4.89)	0.5563
≥60 kg	10	2550	0.39	8	2560	0.31	18	5110	0.66	1.28 (0.51, 3.24)	0.6071
Non-CABG Related TIMI Major ICH Fatal Bleeding, Female											
<60 kg	0	444	-	0	438	-	0	882	-	-	-
≥60 kg	1	1370	0.07	1	1365	0.07	2	2735	0.07	0.96 (0.06, 15.33)	0.9961

	Prasugrel n N %	Clopidogrel n N %	Total n N %	HR (95% CI)	P-value
Non-CABG Related TIMI Major ICH Fatal Bleeding, Male					
<60 kg	0 259 -	1 254 0.39	1 513 0.19	-	-
≥60 kg	3 2550 0.12	2 2560 0.08	5 5110 0.10	1.52 (0.25, 9.07)	0.6504
Non-CABG Related TIMI Major or Minor Bleeding, Female					
<60 kg	5 444 1.13	8 438 1.83	13 882 1.48	0.63 (0.21, 1.93)	0.3945
≥60 kg	24 1370 1.75	14 1365 1.03	38 2735 1.39	1.74 (0.90, 3.35)	0.0977
Non-CABG Related TIMI Major or Minor Bleeding, Male					
<60 kg	5 259 1.93	7 254 2.76	12 513 2.34	0.66 (0.21, 2.07)	0.4714
≥60 kg	63 2550 2.47	48 2560 1.88	111 5110 2.17	1.34 (0.92, 1.96)	0.1266
Non-CABG Related TIMI Major, Minor, or Minimal Bleeding, Female					
<60 kg	72 444 16.22	48 438 10.96	120 882 13.61	1.57 (1.09, 2.26)	0.0251
≥60 kg	289 1370 21.10	161 1365 11.80	450 2735 16.45	1.90 (1.57, 2.30)	<.0001
Non-CABG Related TIMI Major, Minor, or Minimal Bleeding, Male					
<60 kg	17 259 6.56	16 254 6.30	33 513 6.43	1.05 (0.53, 2.07)	0.9170
≥60 kg	402 2550 15.76	274 2560 10.70	676 5110 13.23	1.53 (1.31, 1.78)	<.0001

Subjects ≥ 75 years of age or < 60 kg of body weight received the 5-mg prasugrel maintenance dose. Others received the 10-mg prasugrel maintenance dose.

Analyses by Ququan Liu, M.D., M.S.

	Prasugrel n N %	Clopidogrel n N %	Total n N %	HR (95% CI)	P-value*
Non-CABG Related TIMI Major, Minor, or Minimal Bleeding, Age<75 yrs					
Male	337 2292 14.70	224 2312 9.69	561 4604 12.19	0.72 (0.63, 0.81)	<.0001
Female	270 1298 20.80	145 1278 11.35	415 2576 16.11		
Non-CABG Related TIMI Major, Minor, or Minimal Bleeding, Age≥75 yrs					
Male	82 517 15.86	66 502 13.15	148 1019 14.52	0.98 (0.78, 1.23)	0.8809
Female	91 516 17.64	64 525 11.35	155 1041 14.89		
Non-CABG Related TIMI Major, Minor,or Minimal Bleeding, All Ages					
Male	419 2809 14.91	290 2814 10.31	709 5623 12.01	0.76 (0.68, 0.85)	<.0001
Female	361 1814 19.90	209 1803 11.59	570 3617 15.76		
Non-CABG Related TIMI Major, Minor, or Minimal Bleeding, <60 kg					
Male	17 259 6.56	16 254 6.30	33 513 6.43	0.43 (0.29, 0.63)	<.0001
Female	72 444 16.21	48 438 10.96	120 882 13.61		
Non-CABG Related TIMI Major, Minor, or Minimal Bleeding, ≥60 kg					
Male	402 2550 15.76	274 2560 10.70	676 5110 13.23	0.77 (0.68, 0.87)	<.0001
Female	289 1370 21.09	161 1365 11.80	450 2735 16.45		

***p-value for heterogeneity (for sex-related treatment effects) Cox model (treatment, sex)**

	Prasugrel			Clopidogrel			Total			P-value*
	n	N	%	n	N	%	n	N	%	
Non-CABG Related TIMI Major, Minor, or Minimal Bleeding, Age<75 yrs										
Male	337	2292	14.70	224	2312	9.69	561	4604	12.19	0.0973
Female	270	1298	20.80	145	1278	11.35	415	2576	16.11	
Non-CABG Related TIMI Major, Minor, or Minimal Bleeding, Age≥75 yrs										
Male	82	517	15.86	66	502	13.15	148	1019	14.52	0.5268
Female	91	516	17.64	64	525	11.35	155	1041	14.89	
Non-CABG Related TIMI Major, Minor,or Minimal Bleeding, All Ages										
Male	419	2809	14.91	290	2814	10.31	709	5623	12.01	0.0945
Female	361	1814	19.90	209	1803	11.59	570	3617	15.76	
Non-CABG Related TIMI Major, Minor, or Minimal Bleeding, <60 kg										
Male	17	259	6.56	16	254	6.30	33	513	6.43	0.3280
Female	72	444	16.21	48	438	10.96	120	882	13.61	
Non-CABG Related TIMI Major, Minor, or Minimal Bleeding, ≥60 kg										
Male	402	2550	15.76	274	2560	10.70	676	5110	13.23	0.0836
Female	289	1370	21.09	161	1365	11.80	450	2735	16.45	
***p-value for interaction of "treatment by sex" Cox model**										

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

/s/

KAREN A HICKS
09/09/2013

ALIZA M THOMPSON
09/10/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-307/S008

MEDICAL REVIEW(S)

CLINICAL REVIEW UPDATED

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: September 19, 2013

Reviewer: Thomas A. Marciniak, M.D.
Medical Team Leader

NDA: 22-307 S008

Drug: prasugrel (Effient®)

Subject: Cancer in TRILOGY

Summary and Recommendation
This review is an update to my review dated August 22, 2013. It updates that review for statistical significance of some of the results as suggested by the Division Director. It also clarifies a reference to the PLATO trial. This review completely replaces the prior one. I have not changed my conclusions or my recommendations.

TRILOGY is an outcomes trial of prasugrel vs. clopidogrel in patients with acute coronary syndromes managed medically. It also addresses a post-marketing requirement (PMR) to "gather baseline cancer history and cancer adverse event data" from it. The reason for the PMR was an apparent increase in solid cancer rates with prasugrel in the TRITON trial. The TRILOGY data as submitted do not show increased solid cancer rates with prasugrel. However, I trust the TRITON rather than the TRILOGY results because TRITON is more consistent with the increased solid cancer rates with increased bleeding in the recent anticoagulant trials and because TRILOGY has evidence for underreporting from Asia and Eastern Europe and a suspicious reversal of the increased cancer rates in the second half of the trial. Also, TRILOGY has unfavorable results in the US.

I recommend the following:

- We do not include the TRILOGY cancer results in labeling.
- We proceed with a rigorous analysis of bleeding and cancer in all antiplatelet and anticoagulant outcome trials.

Background

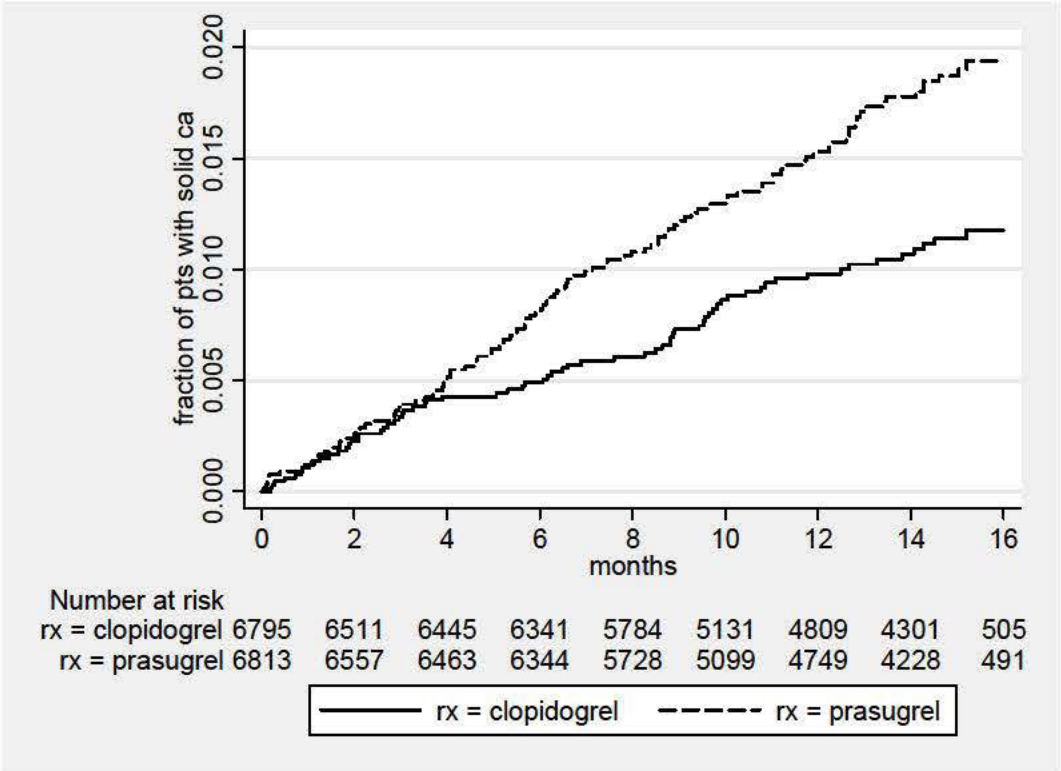
Cancer in TRILOGY is not just about TRILOGY and not just about prasugrel. The index study for an association between bleeding and cancer was prasugrel TRITON. However, other drugs that cause bleeding also produce higher cancer rates. I discuss all of the data that I have analyzed relevant to these associations below.

Cancer in TRITON

I raised the issue of whether a drug that affects bleeding might also affect cancer rates in my review of prasugrel, a platelet inhibitor, for its original indication based on the TRITON trial. The details of the data and my discussion are available in the Medical Reviews, Parts 18 to 23, available at http://www.accessdata.fda.gov/ drugsatfda_docs/nda/2009/022307s000TOC.cfm. I also discussed TRITON in a review on bleeding and cancer filed for the apixaban approval and available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202155Orig1s000MedR.pdf. I repeat the findings from prasugrel TRITON below because of the relevance to TRILOGY and for ease of reference.

I analyzed solid cancer rates in the large TRITON outcomes trial of prasugrel vs. clopidogrel in acute coronary syndromes (Wiviott, Braunwald et al. 2007) because my interpretation of the prasugrel 24-month mouse carcinogenicity study was that prasugrel may be a tumor promoter for a wide variety of solid cancers. To my surprise the solid cancer event rates by arm in TRITON showed the strikingly different incidence curves shown in Figure 1.

Figure 1: Times to First Solid Cancer* Events in the Prasugrel TRITON Study

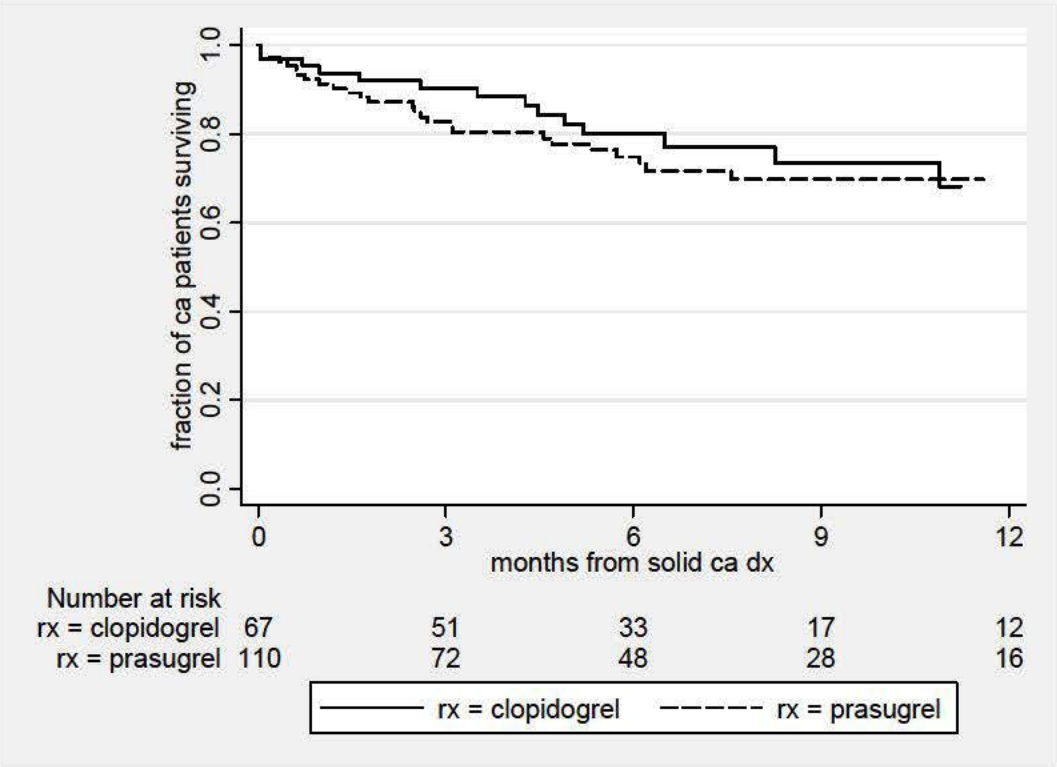


*excluding non-melanoma skin and brain; p = 0.0013 by log rank test

The solid cancer event rates begin to diverge at about 4 months and continue to diverge throughout 16-months of follow-up. The hazard ratio estimated by Cox regression is about 1.6 (95% CI 1.2-2.2). The absolute risk difference at 16 months is about 0.8%. While Figure 1 includes recurrent cancers as well as new cancers, the results limited to new solid cancers (excluding non-melanoma skin and brain) are similar although of lower statistical significance (p = 0.024).

Experiencing a solid cancer event was similarly deadly in both arms as shown in Figure 2.

Figure 2: Survival after First Solid Cancer* Events in the Prasugrel TRITON Study



*excluding non-melanoma skin and brain; p >0.5 by log rank test

Survival at 9 months is only about 70%. If anything survival was slightly worse for prasugrel patients with solid cancer events despite their greater numbers. There does not appear to be a lead-time bias or early detection bias that would lead to the appearance of lengthened survival after diagnosis.

Bleeding was more common in the prasugrel arm in TRITON. The prasugrel:clopidogrel hazard ratio for non-CABG-related TIMI major bleeding was 1.3 (95% CI 1.03-1.7) and for TIMI life-threatening bleeding was 1.5 (95% CI 1.08-2.1).

Variations on these findings were presented and discussed at a meeting of the Cardiovascular and Renal Drugs Advisory Committee on February 3, 2009. The variations presented by the sponsor

were misleading and inaccurate: While I had prospectively excluded non-melanoma skin cancers based on the mouse carcinogenicity study results and because non-melanoma skin cancers are much less serious than other solid tumors and likely not to be reported completely, the sponsor included some skin cancers. The sponsor's presentations were misleading and inaccurate because they did not count skin cancers that they had miscoded to the MedDRA procedure system-organ class. The omitted skin cancers were predominantly in the prasugrel arm. I describe the details of the miscounts and the correct results in my prasugrel review referenced above.

Cancer with Anticoagulant Drugs

The prasugrel TRITON cancer results alone do not help us understand whether solid cancer promotion is a peculiar effect of prasugrel, a class effect of $P2Y_{12}$ platelet inhibitors, a class effect of all platelet inhibitors, or an effect of all drugs that increase bleeding. While my preliminary analyses of older clopidogrel studies did not confirm a similar effect, I analyzed the FDA submissions for new, potent platelet inhibitors and for new anticoagulants. My preliminary analyses of the trials of new anticoagulants showed reasonably consistent results: Whatever arm has more bleeding has more solid cancer events and the solid cancers are deadly.

I had developed a rigorous methodology for ascertaining cancer events in CV outcome trials for a meta-analysis of angiotensin receptor blockers and cancer. FDA staff can access the review plan with the details of the methodology for this latter meta-analysis under Tracked Safety Issue 935 in a DARRTS communication filed August 31, 2012. Using this rigorous methodology I ascertained cancer events in the APPRAISE-2 and ARISTOTLE trials of apixaban. I presented the cancer findings for both trials in some detail in a review filed for the apixaban approval and available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202155Orig1s000MedR.pdf. I summarize the major findings below.

The apixaban trial cancer results are very illuminating because the bleeding rates are reversed in its two large CV outcome trials: In APPRAISE-2, a placebo-controlled trial in recent ACS patients in which apixaban was added to standard antiplatelet therapy, there was much more major bleeding in the apixaban arm and the trial was terminated early. In ARISTOTLE, an active-controlled trial in atrial fibrillation patients against warfarin, there was more major bleeding in the warfarin arm. The cancer results parallel the bleeding results, with more solid cancers in the apixaban arm in APPRAISE-2 and more solid cancers in the warfarin arm in ARISTOTLE. I provide more details in my apixaban review referenced above, but I've summarized the comparisons of the two trials in Table 1.

Table 1: Bleeding and Cancer in the Apixaban Trials

	APPRAISE-2	ARISTOTLE
population	acute coronary syndromes	atrial fibrillation
concomitant antiplatelet therapy	yes	no
control	placebo	warfarin
N	7,392	18,201
median age, y	67	70
male, %	68%	65%
median follow-up, y	0.66	1.8
TIMI major bleeding HR (95% CI)*	2.6 (1.5-4.5)	0.57 (0.46-0.7)

solid cancer HR (95% CI)*	2.3 (1.2-4.3)	0.85 (0.7-1.0)

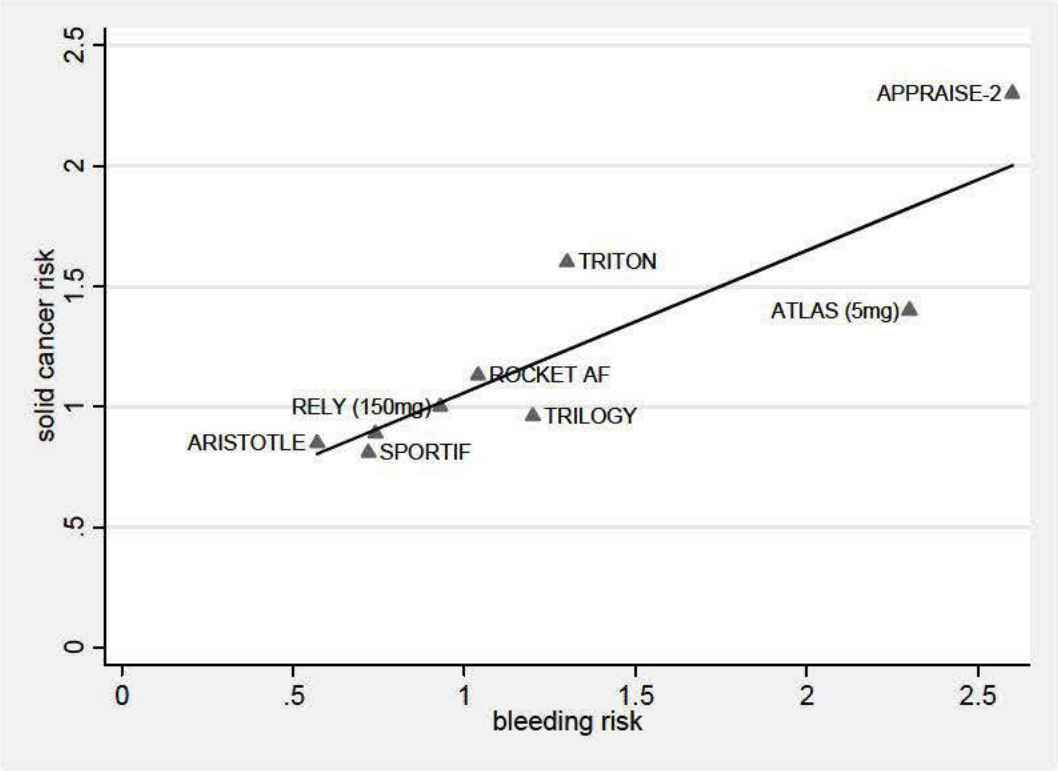
*HR (95% CI) = hazard ratio apixaban:control (95% confidence interval)

The correspondence between bleeding rates and cancer rates in the apixaban trials is striking. The one hazard ratio that is not highly statistically significant is the one for solid cancers in ARISTOTLE ($p = 0.058$). The solid cancers were deadly, although equally deadly in the apixaban and control arms: about 40% dead at 9 months following the cancer event in APPRAISE-2 and 28% at one year in ARISTOTLE.

ARISTOTLE has another relevant similarity to TRILOGY: ARISTOTLE, like TRILOGY, had substantial enrollment in Asia. In ARISTOTLE about 16% of the trial patients were Asian (2,922) while in TRILOGY 21% were Asian (2,016). In ARISTOTLE solid cancer rates were lower in Asia (1.3 per 100 PEY) than in the US, Canada, and Western Europe (about 2.08-2.21 per 100 PEY) and were similar to rates in Eastern Europe and Latin America. The Asian:US rate ratio in ARISTOTLE is consistent with the ratios of rates reported in international cancer statistics, i.e., rates in some Asian countries are 2 to 3 fold lower than in Western countries. (Jemal, Bray et al. 2011) While the solid cancer rates were lower in ARISTOTLE, the slightly lower risk of solid cancer with apixaban compared to warfarin was identical in the Asian patients to that in the whole study and bleeding rates, i.e., higher with warfarin, were similar in Asian patients to those in the whole study. I describe the relevance of these comparisons under Cancers in TRILOGY below.

I have done similar preliminary analyses of solid cancer rates in all new anticoagulant trials. I show a scatterplot of solid cancer risk vs. bleeding risk for the new anticoagulant trials and the prasugrel trials in Figure 3.

Figure 3: Risk of Solid Cancer vs. Bleeding Risk in Anticoagulant and Prasugrel Trials



(line is fitted linear regression line)

There does appear to be a positive correlation between solid cancer risk and bleeding risk. While Figure 3 does not show the additional details, in general the solid cancer incidence curves take several months to diverge and then continue to diverge for the duration of the studies. The survival following the cancer events is similar in the drug and control arms. Both of these facts suggest that the effect is not a simple early detection bias of bleeding leading to earlier diagnosis. More data should help to resolve the question of whether the increased cancer rates are solely the results of earlier detection.

The prasugrel studies are inconsistent with each other and appear to be outliers in opposite directions on Figure 3. TRITON perhaps is a high outlier for solid cancer risk while TRILOGY perhaps is a low outlier. I discuss below under Cancers and TRILOGY and Completeness of Follow-up in TRILOGY findings that are relevant to the question of whether TRILOGY is the outlier.

Cancer in TRILOGY

The sponsor's summary of the overall results for cancers is reassuring: "Overall, the total of all new non-benign neoplasms is balanced when comparing the prasugrel and clopidogrel groups (82/4554 [1.80%] versus 78/4551 [1.71%]; HR=1.045 [0.767, 1.425]; p=0.786) (Table TABY.12.37). Figure TABY.12.27 shows the occurrence of all new, nonbenign neoplasms over the course of the study among treated subjects without a baseline history of malignancy or with curative treatment prior to randomization (primary neoplasm analysis population). The curves were similar, and prasugrel cases did not occur earlier than clopidogrel cases. Most neoplasms

were diagnosed after the first month of the study (prasugrel, n=81 [99%]; clopidogrel, n=74 [95%]) (Table TABY.14.165)."

I checked the ascertainment and adjudication of malignancies as reported in the case report forms and datasets submitted and did not identify any major problems with either. However, I have in my prior analyses, e.g., for TRITON and the apixaban studies, uniformly handled some cases differently than the sponsor's adjudications: Some cancers are reported with limited information, e.g., "subject's spouse was contacted (after many previous attempts to contact the subject). it was reported that the subject died on 07 aug 2011, reason of death - lung cancer. no other information . . ." The sponsor adjudicated such cases as not confirmed. I have classified these cases as malignancies.

My primary analysis does differ from the sponsor: The sponsor counted new "non-benign neoplasms" (all malignancies including non-melanoma skin cancers, brain tumors, and hematologic malignancies) in its primary analysis. For TRITON I had pre-specified analyzing solid cancers excluding non-melanoma skin cancers and brain tumors. (See my TRITON review referenced above.) I have consistently analyzed solid cancers and, at least for my primary analyses, counted both new malignancies and recurrent ones, i.e., treatment emergent malignancy events. Regardless, in terms of cancer risks, my results for solid cancer events are actually slightly more favorable for prasugrel than the sponsor's results for new "non-benign neoplasms": my estimated HR is 0.96 (95% CI 0.68-1.36, p = 0.82.)

Hence the TRILOGY results as submitted do not suggest an increased solid cancer risk with prasugrel and are inconsistent with the TRITON results. Which results should we trust? The sponsor would argue that we should trust TRILOGY because TRILOGY was prospectively designed to capture malignancies. We skeptics would point out that in TRILOGY, as opposed to TRITON, the sponsor therefore knew in advance what to obscure. After the extensive deliberations on cancer cases and documentation for TRITON they also knew what documentation to submit. Because Lilly has already shown a willingness to misrepresent cancer findings as they demonstrated at the TRITON advisory committee meeting, I am skeptical of the new, favorable results. However, while skepticism is not enough to reject the TRILOGY findings, there are several lines of evidence suggesting that TRILOGY has problems regarding cancer ascertainment:

- **Solid cancer rates were low in TRILOGY**. In TRILOGY the solid cancer event rate was about 0.92 per 100 PEY.[1] In TRITON the solid cancer event rate was about 1.28 per 100 PEY. If cancer ascertainment was prospectively defined in TRILOGY while dependent upon adverse event reporting in TRITON, why is the TRILOGY rate lower? Cross comparisons of trials are hazardous because of different patient populations. However, one major cancer risk factor, age, suggests that cancer rates should be higher in TRILOGY, i.e., median age was higher in TRILOGY (66) than TRITON (61). The difference in rates is statistically significant if the rates are adjusted by age (p = 0.012 by Cox regression) or age and sex (p = 0.034).

[1] PEY = person exposure year. In TRILOGY I calculated person exposure year as the time from randomization to the first of death, earliest study end date (1jan12), or 985 days. I used this same ITT period for counting cancers.

Dr. Stockbridge claims that "Better screening at baseline would be expected to reduce the cancers observed during TRILOGY." However, prior to the trial start we recommended to the sponsor incorporating cancer screening into TRILOGY once subjects had been randomized, stabilized, and discharged from their index ACS event. The sponsor rejected the screening, stating that "The Sponsor does not believe that study-mandated cancer screening is either feasible or likely to improve assessment of the between-arm difference in cancer outcome." The TRILOGY protocol did not require any specific cancer screening nor did it exclude patients with a history of cancer.

We likely can not sort out the impacts of all risk factors that could explain the differing rates but there are anomalous results that suggest that there was underreporting of cancers in TRILOGY. I discuss them next.

- **Asian and Eastern European sites appear to have underreported cancers in TRILOGY.** About 21% of randomized patients were from Asia in TRILOGY while none were from Asia (excluding Israel) in TRITON. Reported solid cancer rates in Asian patients in TRILOGY were very low, about 0.15 per 100 PEY, or more than 10-fold lower than in the US (1.7) and Western Europe (2.0). As I noted above, cancer rates in Asia as reported in international statistics are 2 to 3 fold lower in Asia than in the Western world. As I also noted above, cancer rates in Asia in ARISTOTLE were about half of Western rates but significantly higher than in TRILOGY ($p<0.001$ by Cox regression.) Ten-fold lower suggests underreporting.

  About 35% of randomized patients were from Eastern Europe in TRILOGY while 24% were from Eastern Europe in TRITON. Reported solid cancer rates in Eastern European patients in TRILOGY were low, about 0.68 per 100 PEY compared to 1.14 in TRITON and 1.17 in ARISTOTLE ($p = 0.001$ by Cox regression.) Hence there also appears to be underreporting of solid cancers from Eastern Europe in TRILOGY.

  Whether there is some underreporting of cancers in other or all regions is impossible to determine because we can only detect substantial underreporting as is likely in Asia and possible in Eastern Europe. However, there is some evidence for underreporting overall as I discuss next.

- **Cancer results were only favorable in the second half of the trial.** The solid cancer results were unfavorable for prasugrel in patients enrolled in the first half of the trial (RR about 1.07) becoming favorable in patients enrolled in the second half (RR about 0.7) as shown in Table 2.

  Table 2: Solid Cancer Rates for Patients Enrolled by Half in TRILOGY

	half 1		half 2	
	rate*	RR†	rate*	RR†
clopidogrel	0.93		0.99	
prasugrel	0.99	1.07	0.69	0.70

*rate per 100 PEY; †RR = relative risk prasugrel:clopidogrel

The interaction between treatment and trial half for the solid cancer rates as reported by the sponsor is statistically significant (p = 0.033 by Cox regression). The rates above are also consistent by quarter: clopidogrel is favorable in quarters 1 and 2 patients and prasugrel in quarters 3 and 4 patients. The anomalous rate appears to be the low prasugrel rate in the second half patients. Two other recent studies have shown this pattern of success predominantly in second half patients: ticagrelor PLATO and rivaroxaban ATLAS. ATLAS showed a somewhat surprising mortality benefits predominantly in second half patients. In PLATO, the results in the US were overall unfavorable for ticagrelor. In the first half they were highly unfavorable for both mortality and the primary endpoint but in the second half they were neutral on mortality and favorable for the primary endpoint. While these results could be the play of chance, the TRILOGY results in US patients below are additionally concerning.

- **Cancer results were not favorable in the US.** The point estimate for the HR of solid cancer in the US is 1.3. The US patients also demonstrate the second half favorable effect as shown in Table 3.

Table 3: Solid Cancer Rates for US Patients Enrolled by Half in TRILOGY

	half 1		half 2	
	rate*	RR†	rate*	RR†
clopidogrel	1.32		1.94	
prasugrel	2.20	1.66	1.00	0.51

*rate per 100 PEY; †RR = relative risk prasugrel:clopidogrel

US patients comprised about 12% of TRILOGY enrollment, so the numbers are small and the confidence intervals for these estimates wide.

Discussion

TRILOGY is inconsistent with TRITON. While TRILOGY shows a completely neutral effect of prasugrel compared to clopidogrel on solid cancer rates despite a moderate increase in bleeding rates with prasugrel, prasugrel in TRITON and the arms with more bleeding in the anticoagulant trials showed higher rates of solid cancer events. I believe TRITON is more consistent with the other studies than TRILOGY. TRILOGY US results are consistent with TRITON.

Another interpretation might be that TRITON and TRILOGY are small studies relative to the sample sizes needed to have reasonable power to detect a relative risk of 1.3-1.6. Their results represent chance variation around the true effect. If one examines Figure 3 and visually averages the TRITON and TRILOGY results, one would place the average effect above the regression line. There does appear to be an association of bleeding and solid cancers, both for the anticoagulants and for prasugrel.

I am not impressed that pre-specification of malignancy as an adverse event of interest produced more accurate cancer ascertainment in TRILOGY. The apparent underreporting in Asia and Eastern Europe suggests that improved ascertainment was not achieved. The results by half are also suspicious. Finally, the quote above regarding the lung cancer death with no other information confirms that TRILOGY did not solve the basic problem with all event

ascertainments: obtaining the desired information. I judge TRITON to be the better of the two studies regarding cancer ascertainment. I do not consider TRILOGY to be an adequate trial because of the apparent underreporting of cancer cases; its cancer results should not be included in labeling.

The issue of the relationship between bleeding and cancer remains incompletely elucidated. One critical question is whether the relationship is the result of early detection based on procedures done to determine the cause of the bleeding or whether tumor promotion is involved. The available data that the incidence curves continue to diverge throughout the observed follow-up and that survival after a cancer event remains poor suggest the latter but we likely do not yet have sufficient data to answer definitively the question of early detection vs. tumor promotion. Both mechanisms could be active. Another critical question is whether the relationship between bleeding and cancer varies quantitatively depending upon the mechanism for increasing bleeding, e.g., platelet inhibition vs. anticoagulation. The prasugrel TRITON results suggest that platelet inhibition may produce more solid cancer increases but the TRITON results could also be chance high variation.

This issue is relevant to the well-being of the millions of patients in the US taking antiplatelet and anticoagulant drugs. The most expeditious way of addressing it short term is with a rigorous analysis of bleeding and cancer in all of the antiplatelet and anticoagulant outcome trials submitted. Completing such a rigorous analysis should be a priority for the Division and for the FDA.

References

Jemal, A., F. Bray, et al. (2011). "Global cancer statistics." CA: A Cancer Journal for Clinicians **61**(2): 69-90.

Roe, M. T., P. W. Armstrong, et al. (2012). "Prasugrel versus clopidogrel for acute coronary syndromes without revascularization." N Engl J Med **367**(14): 1297-309.

Wiviott, S. D., E. Braunwald, et al. (2007). "Prasugrel versus clopidogrel in patients with acute coronary syndromes." N Engl J Med **357**(20): 2001-15.

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

/s/

THOMAS A MARCINIAK
09/19/2013

CLINICAL REVIEW

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: August 22, 2013

Reviewer: Thomas A. Marciniak, M.D.
Medical Team Leader

NDA: 22-307 S008

Drug: prasugrel (Effient®)

Subject: Cancer in TRILOGY

Summary and Recommendation
TRILOGY is an outcomes trial of prasugrel vs. clopidogrel in patients with acute coronary syndromes managed medically. It also addresses a post-marketing requirement (PMR) to "gather baseline cancer history and cancer adverse event data" from it. The reason for the PMR was an apparent increase in solid cancer rates with prasugrel in the TRITON trial. The TRILOGY data as submitted do not show increased solid cancer rates with prasugrel. However, I trust the TRITON rather than the TRILOGY results because TRITON is more consistent with the increased solid cancer rates with increased bleeding in the recent anticoagulant trials and because TRILOGY has evidence for underreporting from Asia and Eastern Europe and a suspicious reversal of the increased cancer rates in the second half of the trial. Also, TRILOGY has unfavorable results in the US.

I recommend the following:

- We do not include the TRILOGY cancer results in labeling.
- We proceed with a rigorous analysis of bleeding and cancer in all antiplatelet and anticoagulant outcome trials.

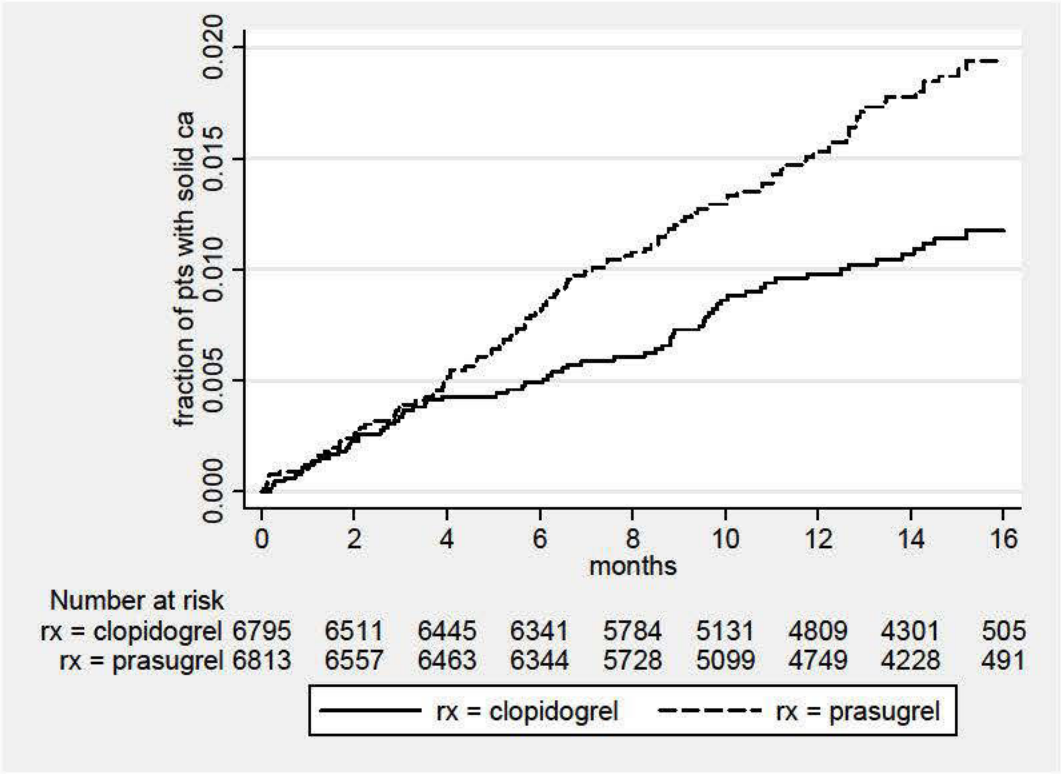
Background
Cancer in TRILOGY is not just about TRILOGY and not just about prasugrel. The index study for an association between bleeding and cancer was prasugrel TRITON. However, other drugs that cause bleeding also produce higher cancer rates. I discuss all of the data that I have analyzed relevant to these associations below.

Cancer in TRITON

I raised the issue of whether a drug that affects bleeding might also affect cancer rates in my review of prasugrel, a platelet inhibitor, for its original indication based on the TRITON trial. The details of the data and my discussion are available in the Medical Reviews, Parts 18 to 23, available at http://www.accessdata.fda.gov/ drugsatfda_docs/nda/2009/022307s000TOC.cfm. I also discussed TRITON in a review on bleeding and cancer filed for the apixaban approval and available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202155Orig1s000MedR.pdf. I repeat the findings from prasugrel TRITON below because of the relevance to TRILOGY and for ease of reference.

I analyzed solid cancer rates in the large TRITON outcomes trial of prasugrel vs. clopidogrel in acute coronary syndromes (Wiviott, Braunwald et al. 2007) because my interpretation of the prasugrel 24-month mouse carcinogenicity study was that prasugrel may be a tumor promoter for a wide variety of solid cancers. To my surprise the solid cancer event rates by arm in TRITON showed the strikingly different incidence curves shown in Figure 1.

Figure 1: Times to First Solid Cancer* Events in the Prasugrel TRITON Study



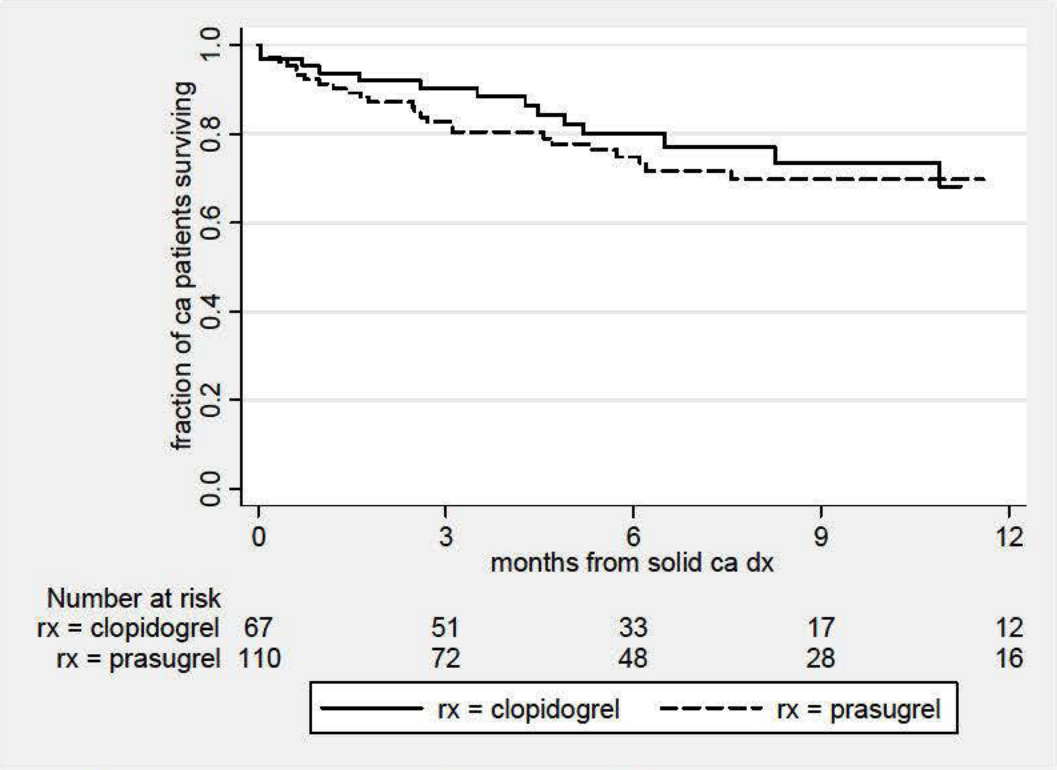
*excluding non-melanoma skin and brain; p = 0.0013 by log rank test

The solid cancer event rates begin to diverge at about 4 months and continue to diverge throughout 16-months of follow-up. The hazard ratio estimated by Cox regression is about 1.6 (95% CI 1.2-2.2). The absolute risk difference at 16 months is about 0.8%. While Figure 1 includes recurrent cancers as well as new cancers, the results limited to new solid cancers

(excluding non-melanoma skin and brain) are similar although of lower statistical significance (p = 0.024).

Experiencing a solid cancer event was similarly deadly in both arms as shown in Figure 2.

Figure 2: Survival after First Solid Cancer* Events in the Prasugrel TRITON Study



*excluding non-melanoma skin and brain; p >0.5 by log rank test

Survival at 9 months is only about 70%. If anything survival was slightly worse for prasugrel patients with solid cancer events despite their greater numbers. There does not appear to be a lead-time bias or early detection bias that would lead to the appearance of lengthened survival after diagnosis.

Bleeding was more common in the prasugrel arm in TRITON. The prasugrel:clopidogrel hazard ratio for non-CABG-related TIMI major bleeding was 1.3 (95% CI 1.03-1.7) and for TIMI life-threatening bleeding was 1.5 (95% CI 1.08-2.1).

Variations on these findings were presented and discussed at a meeting of the Cardiovascular and Renal Drugs Advisory Committee on February 3, 2009. The variations presented by the sponsor were misleading and inaccurate: While I had prospectively excluded non-melanoma skin cancers based on the mouse carcinogenicity study results and because non-melanoma skin cancers are much less serious than other solid tumors and likely not to be reported completely, the sponsor included some skin cancers. The sponsor's presentations were misleading and inaccurate because they did not count skin cancers that they had miscoded to the MedDRA

procedure system-organ class. The omitted skin cancers were predominantly in the prasugrel arm. I describe the details of the miscounts and the correct results in my prasugrel review referenced above.

Cancer with Anticoagulant Drugs

The prasugrel TRITON cancer results alone do not help us understand whether solid cancer promotion is a peculiar effect of prasugrel, a class effect of $P2Y_{12}$ platelet inhibitors, a class effect of all platelet inhibitors, or an effect of all drugs that increase bleeding. While my preliminary analyses of older clopidogrel studies did not confirm a similar effect, I analyzed the FDA submissions for new, potent platelet inhibitors and for new anticoagulants. My preliminary analyses of the trials of new anticoagulants showed reasonably consistent results: Whatever arm has more bleeding has more solid cancer events and the solid cancers are deadly.

I had developed a rigorous methodology for ascertaining cancer events in CV outcome trials for a meta-analysis of angiotensin receptor blockers and cancer. FDA staff can access the review plan with the details of the methodology for this latter meta-analysis under Tracked Safety Issue 935 in a DARRTS communication filed August 31, 2012. Using this rigorous methodology I ascertained cancer events in the APPRAISE-2 and ARISTOTLE trials of apixaban. I presented the cancer findings for both trials in some detail in a review filed for the apixaban approval and available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202155Orig1s000MedR.pdf. I summarize the major findings below.

The apixaban trial cancer results are very illuminating because the bleeding rates are reversed in its two large CV outcome trials: In APPRAISE-2, a placebo-controlled trial in recent ACS patients in which apixaban was added to standard antiplatelet therapy, there was much more major bleeding in the apixaban arm and the trial was terminated early. In ARISTOTLE, an active-controlled trial in atrial fibrillation patients against warfarin, there was more major bleeding in the warfarin arm. The cancer results parallel the bleeding results, with more solid cancers in the apixaban arm in APPRAISE-2 and more solid cancers in the warfarin arm in ARISTOTLE. I provide more details in my apixaban review referenced above, but I've summarized the comparisons of the two trials in Table 1.

Table 1: Bleeding and Cancer in the Apixaban Trials

	APPRAISE-2	ARISTOTLE
population	acute coronary syndromes	atrial fibrillation
concomitant antiplatelet therapy	yes	no
control	placebo	warfarin
N	7,392	18,201
median age, y	67	70
male, %	68%	65%
median follow-up, y	0.66	1.8
TIMI major bleeding HR (95% CI)*	2.6 (1.5-4.5)	0.57 (0.46-0.7)
solid cancer HR (95% CI)*	2.3 (1.2-4.3)	0.85 (0.7-1.0)

*HR (95% CI) = hazard ratio apixaban:control (95% confidence interval)

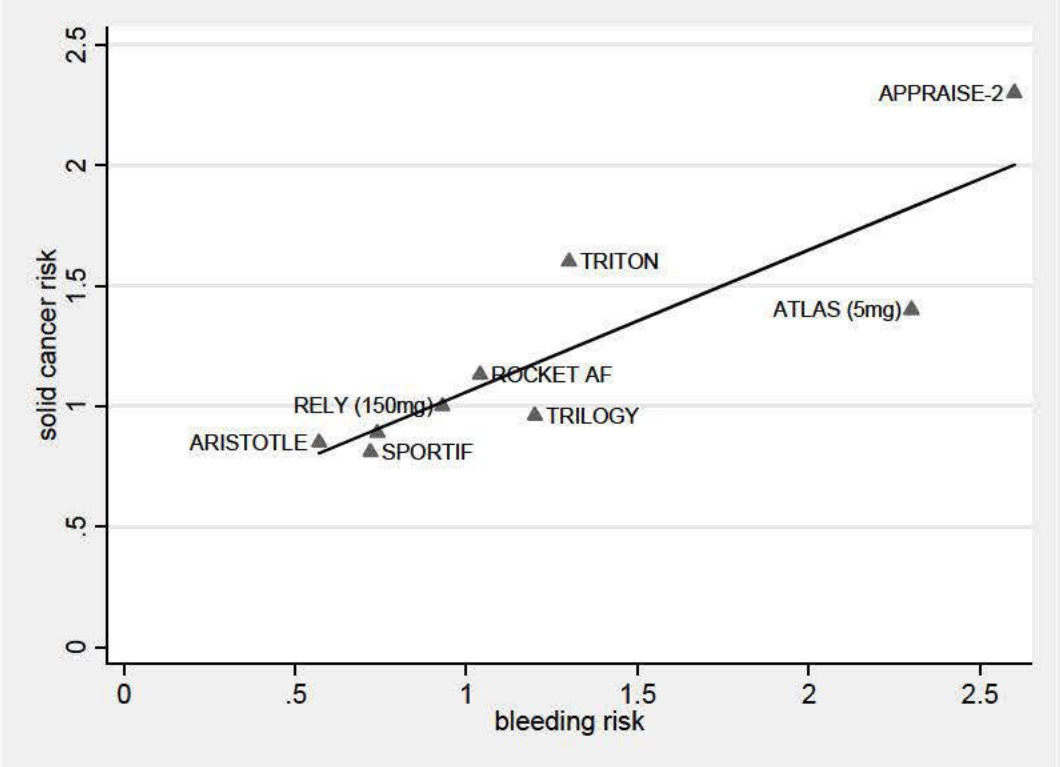
The correspondence between bleeding rates and cancer rates in the apixaban trials is striking. The one hazard ratio that is not highly statistically significant is the one for solid cancers in

ARISTOTLE (p = 0.058). The solid cancers were deadly, although equally deadly in the apixaban and control arms: about 40% dead at 9 months following the cancer event in APPRAISE-2 and 28% at one year in ARISTOTLE.

ARISTOTLE has another relevant similarity to TRILOGY: ARISTOTLE, like TRILOGY, had substantial enrollment in Asia. In ARISTOTLE about 16% of the trial patients were Asian (2,922) while in TRILOGY 21% were Asian (2,016). In ARISTOTLE solid cancer rates were lower in Asia (1.3 per 100 PEY) than in the US, Canada, and Western Europe (about 2.08-2.21 per 100 PEY) and were similar to rates in Eastern Europe and Latin America. The Asian:US rate ratio in ARISTOTLE is consistent with the ratios of rates reported in international cancer statistics, i.e., rates in some Asian countries are 2 to 3 fold lower than in Western countries. (Jemal, Bray et al. 2011) While the solid cancer rates were lower in ARISTOTLE, the slightly lower risk of solid cancer with apixaban compared to warfarin was identical in the Asian patients to that in the whole study and bleeding rates, i.e., higher with warfarin, were similar in Asian patients to those in the whole study. I describe the relevance of these comparisons under Cancers in TRILOGY below.

I have done similar preliminary analyses of solid cancer rates in all new anticoagulant trials. I show a scatterplot of solid cancer risk vs. bleeding risk for the new anticoagulant trials and the prasugrel trials in Figure 3.

Figure 3: Risk of Solid Cancer vs. Bleeding Risk in Anticoagulant and Prasugrel Trials



(line is fitted linear regression line)

There does appear to be a positive correlation between solid cancer risk and bleeding risk. While Figure 3 does not show the additional details, in general the solid cancer incidence curves take several months to diverge and then continue to diverge for the duration of the studies. The survival following the cancer events is similar in the drug and control arms. Both of these facts suggest that the effect is not a simple early detection bias of bleeding leading to earlier diagnosis. More data should help to resolve the question of whether the increased cancer rates are solely the results of earlier detection.

The prasugrel studies are inconsistent with each other and appear to be outliers in opposite directions on Figure 3. TRITON perhaps is a high outlier for solid cancer risk while TRILOGY perhaps is a low outlier. I discuss below under Cancers and TRILOGY and Completeness of Follow-up in TRILOGY findings that are relevant to the question of whether TRILOGY is the outlier.

Cancer in TRILOGY

The sponsor's summary of the overall results for cancers is reassuring: "Overall, the total of all new non-benign neoplasms is balanced when comparing the prasugrel and clopidogrel groups (82/4554 [1.80%] versus 78/4551 [1.71%]; HR=1.045 [0.767, 1.425]; p=0.786) (Table TABY.12.37). Figure TABY.12.27 shows the occurrence of all new, nonbenign neoplasms over the course of the study among treated subjects without a baseline history of malignancy or with curative treatment prior to randomization (primary neoplasm analysis population). The curves were similar, and prasugrel cases did not occur earlier than clopidogrel cases. Most neoplasms were diagnosed after the first month of the study (prasugrel, n=81 [99%]; clopidogrel, n=74 [95%]) (Table TABY.14.165)."

I checked the ascertainment and adjudication of malignancies as reported in the case report forms and datasets submitted and did not identify any major problems with either. However, I have in my prior analyses, e.g., for TRITON and the apixaban studies, uniformly handled some cases differently than the sponsor's adjudications: Some cancers are reported with limited information, e.g., "subject's spouse was contacted (after many previous attempts to contact the subject). it was reported that the subject died on 07 aug 2011, reason of death - lung cancer. no other information . . ." The sponsor adjudicated such cases as not confirmed. I have classified these cases as malignancies.

My primary analysis does differ from the sponsor: The sponsor counted new "non-benign neoplasms" (all malignancies including non-melanoma skin cancers, brain tumors, and hematologic malignancies) in its primary analysis. For TRITON I had pre-specified analyzing solid cancers excluding non-melanoma skin cancers and brain tumors. (See my TRITON review referenced above.) I have consistently analyzed solid cancers and, at least for my primary analyses, counted both new malignancies and recurrent ones, i.e., treatment emergent malignancy events. Regardless, in terms of cancer risks, my results for solid cancer events are actually slightly more favorable for prasugrel than the sponsor's results for new "non-benign neoplasms": my estimated HR is 0.96 (95% CI 0.68-1.36, p = 0.82.)

Hence the TRILOGY results as submitted do not suggest an increased solid cancer risk with prasugrel and are inconsistent with the TRITON results. Which results should we trust? The

sponsor would argue that we should trust TRILOGY because TRILOGY was prospectively designed to capture malignancies. We skeptics would point out that in TRILOGY, as opposed to TRITON, the sponsor therefore knew in advance what to obscure. After the extensive deliberations on cancer cases and documentation for TRITON they also knew what documentation to submit. Because Lilly has already shown a willingness to misrepresent cancer findings as they demonstrated at the TRITON advisory committee meeting, I am skeptical of the new, favorable results. However, while skepticism is not enough to reject the TRILOGY findings, there are several lines of evidence suggesting that TRILOGY has problems regarding cancer ascertainment:

- **Solid cancer rates were low in TRILOGY**. In TRILOGY the solid cancer event rate was about 0.92 per 100 PEY.[1] In TRITON the solid cancer event rate was about 1.28 per 100 PEY. If cancer ascertainment was prospectively defined in TRILOGY while dependent upon adverse event reporting in TRITON, why is the TRILOGY rate lower? Cross comparisons of trials are hazardous because of different patient populations. However, one major cancer risk factor, age, suggests that cancer rates should be higher in TRILOGY, i.e., median age was higher in TRILOGY (66) than TRITON (61). We likely can not sort out the impacts of all risk factors that could explain the differing rates but there are anomalous results that suggest that there was underreporting of cancers in TRILOGY. I discuss them next.

- **Asian and Eastern European sites appear to have underreported cancers in TRILOGY.** About 21% of randomized patients were from Asia in TRILOGY while none were from Asia (excluding Israel) in TRITON. Reported solid cancer rates in Asian patients in TRILOGY were very low, about 0.15 per 100 PEY, or more than 10-fold lower than in the US (1.7) and Western Europe (2.0). As I noted above, cancer rates in Asia as reported in international statistics are 2 to 3 fold lower in Asia than in the Western world. As I also noted above, cancer rates in Asia in ARISTOTLE were about half of Western rates. Ten-fold lower suggests underreporting.

  About 35% of randomized patients were from Eastern Europe in TRILOGY while 24% were from Eastern Europe in TRITON. Reported solid cancer rates in Eastern European patients in TRILOGY were low, about 0.68 per 100 PEY compared to 1.14 in TRITON and 1.17 in ARISTOTLE. Hence there also appears to be underreporting of solid cancers from Eastern Europe in TRILOGY.

  Whether there is some underreporting of cancers in other or all regions is impossible to determine because we can only detect substantial underreporting as is likely in Asia and possible in Eastern Europe. However, there is some evidence for underreporting overall as I discuss next.

- **Cancer results were only favorable in the second half of the trial.** The solid cancer results were unfavorable for prasugrel in patients enrolled in the first half of the trial (RR

[1] PEY = person exposure year. In TRILOGY I calculated person exposure year as the time from randomization to the first of death, earliest study end date (1jan12), or 985 days. I used this same ITT period for counting cancers.

about 1.07) becoming favorable in patients enrolled in the second half (RR about 0.7) as shown in Table 2.

Table 2: Solid Cancer Rates for Patients Enrolled by Half in TRILOGY

	half 1		half 2	
	rate*	RR†	rate*	RR†
clopidogrel	0.93		0.99	
prasugrel	0.99	1.07	0.69	0.70

*rate per 100 PEY; †RR = relative risk prasugrel:clopidogrel

The rates above are also consistent by quarter: clopidogrel is favorable in quarters 1 and 2 patients and prasugrel in quarters 3 and 4 patients. The anomalous rate appears to be the low prasugrel rate in the second half patients. Two other recent studies have shown this pattern of success predominantly in second half patients: ticagrelor PLATO and rivaroxaban ATLAS. Both PLATO and ATLAS showed their somewhat surprising mortality benefits predominantly in second half patients. While these results could be the play of chance, the TRILOGY results in US patients below are additionally concerning.

- **Cancer results were not favorable in the US.** The point estimate for the HR of solid cancer in the US is 1.3. The US patients also demonstrate the second half favorable effect as shown in Table 3.

Table 3: Solid Cancer Rates for US Patients Enrolled by Half in TRILOGY

	half 1		half 2	
	rate*	RR†	rate*	RR†
clopidogrel	1.32		1.94	
prasugrel	2.20	1.66	1.00	0.51

*rate per 100 PEY; †RR = relative risk prasugrel:clopidogrel

US patients comprised about 12% of TRILOGY enrollment, so the numbers are small and the confidence intervals for these estimates wide.

Discussion

TRILOGY is inconsistent with TRITON. While TRILOGY shows a completely neutral effect of prasugrel compared to clopidogrel on solid cancer rates despite a moderate increase in bleeding rates with prasugrel, prasugrel in TRITON and the arms with more bleeding in the anticoagulant trials showed higher rates of solid cancer events. I believe TRITON is more consistent with the other studies than TRILOGY. TRILOGY US results are consistent with TRITON.

Another interpretation might be that TRITON and TRILOGY are small studies relative to the sample sizes needed to have reasonable power to detect a relative risk of 1.3-1.6. Their results represent chance variation around the true effect. If one examines Figure 3 and visually averages the TRITON and TRILOGY results, one would place the average effect above the regression line. There does appear to be an association of bleeding and solid cancers, both for the anticoagulants and for prasugrel.

I am not impressed that pre-specification of malignancy as an adverse event of interest produced more accurate cancer ascertainment in TRILOGY. The apparent underreporting in Asia and Eastern Europe suggests that improved ascertainment was not achieved. The results by half are also suspicious. Finally, the quote above regarding the lung cancer death with no other information confirms that TRILOGY did not solve the basic problem with all event ascertainments: obtaining the desired information. I judge TRITON to be the better of the two studies regarding cancer ascertainment. I do not consider TRILOGY to be an adequate trial because of the apparent underreporting of cancer cases; its cancer results should not be included in labeling.

The issue of the relationship between bleeding and cancer remains incompletely elucidated. One critical question is whether the relationship is the result of early detection based on procedures done to determine the cause of the bleeding or whether tumor promotion is involved. The available data that the incidence curves continue to diverge throughout the observed follow-up and that survival after a cancer event remains poor suggest the latter but we likely do not yet have sufficient data to answer definitively the question of early detection vs. tumor promotion. Both mechanisms could be active. Another critical question is whether the relationship between bleeding and cancer varies quantitatively depending upon the mechanism for increasing bleeding, e.g., platelet inhibition vs. anticoagulation. The prasugrel TRITON results suggest that platelet inhibition may produce more solid cancer increases but the TRITON results could also be chance high variation.

This issue is relevant to the well-being of the millions of patients in the US taking antiplatelet and anticoagulant drugs. The most expeditious way of addressing it short term is with a rigorous analysis of bleeding and cancer in all of the antiplatelet and anticoagulant outcome trials submitted. Completing such a rigorous analysis should be a priority for the Division and for the FDA.

References

Jemal, A., F. Bray, et al. (2011). "Global cancer statistics." CA: A Cancer Journal for Clinicians **61**(2): 69-90.

Roe, M. T., P. W. Armstrong, et al. (2012). "Prasugrel versus clopidogrel for acute coronary syndromes without revascularization." N Engl J Med **367**(14): 1297-309.

Wiviott, S. D., E. Braunwald, et al. (2007). "Prasugrel versus clopidogrel in patients with acute coronary syndromes." N Engl J Med **357**(20): 2001-15.

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

/s/

THOMAS A MARCINIAK
08/22/2013

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: **Applicant:** **Stamp Date:**

NDA 22,307-S8 **Eli Lilly and Company** **CD: 12/14/2012;**

(Seq. 0173; SDN 594) **DR: 12/17/2012**

Drug Name: Effient® (prasugrel) **NDA/BLA Type: 501 (b)(1)**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			Electronic CTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?				
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.,* Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?		X		Per FDA agreement.
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			Located in Module 2.5, Clinical Overview.
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: H7T-MC-TAAH Study Title: ("A Double-Blind-Randomized, Multicenter, Dose-Ranging Trial of CS-747 (LY640315) Compared with Clopidogrel in Subjects Undergoing Percutaneous Coronary Intervention (Joint Utilization of Medications to Block Platelets") Optimally) (JUMBO-TIMI 26) (Date of Report: June 24, 2005)	X			

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Sample Size: 904 Arms: Prasugrel 40/7.5 mg: 199 Prasugrel 60/10 mg: 200 Prasugrel 60/15 mg: 251 Clopidogrel 300/75 mg: 254 Location in submission: This study report is not included in this submission but was included in the previous NDA in which prasugrel was approved.				
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1: H7T-MC-TABY (A Comparison of Prasugrel and Clopidogrel in Acute Coronary Syndrome (ACS) Subjects with Unstable Angina/Non-ST-Elevation Myocardial Infarction (UA/NSTEMI) Who are Medically Managed—The TRILOGY ACS Study Indication: The sponsor is not seeking any new indications because the study failed on its primary endpoint (composite of cardiovascular death, myocardial infarction, or stroke). Pivotal Study #2 Indication:	X			The subject is seeking labeling changes, primarily in (b) (4)
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		X		The sponsor will submit this rationale.
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?				Under Review-- numerous additional analyses were requested. The results of the primary and major secondary analyses were submitted.
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			The sponsor received a waiver for pediatric assessment for ACS previously.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		X		The sponsor will submit this rationale.
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	previously by the Division?				
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___X_____

The sponsor was asked to submit the following information, as previously requested:

1. **DSMB charter, amendments, minutes, results of all interim analyses, and any communications**
   - The sponsor submitted all versions of the DMC charter, the minutes, and the communications. The minutes contain a summary of the interim analyses. However, they do not have on hand the results of the interim analyses. The sponsor is inquiring about the interim analyses with the DMC statistician.

2. **Clinical Events (Adjudication) Committee charter, adjudication instructions, or guidance documents, and minutes**
   - The sponsor provided all charter versions. The sponsor clarified that there were no additional instructions, and no minutes were taken.

3. **Executive Committee charter, even if the charter is an informal one, as well as meeting minutes**
   - The sponsor submitted minutes from a single Executive Committee meeting. No other minutes were taken and no charter was created.

4. **Any communications to sites regarding final follow-up or study closeout**
   - The sponsor provided communications to sites on these topics in the application

The sponsor was also asked to submit the following information to us:

1. **Updated define file for all datasets and resubmission of analysis datasets**

   - On 1/31/2013 (SDN 605, Sequence 185), the sponsor submitted a revised data definition document and resubmitted SAS Analysis Datasets and Blankcrf.pdf. because the information provided in the original submission would have resulted in navigational difficulties.

2. **Define file for the Tables of Significant and Notable Patients (TOSNP) so FDA understands what adverse events are included in each table (specifically primary and secondary efficacy endpoints and major safety endpoints). Currently, there do not appear to be tables for CV death, myocardial infarction, or (all) stroke, although we note there is a TOSNP for death.**

   - Per an email from dated 2/4/2013, the sponsor plans to resubmit Table 3.1 from the "TOSNP Navigational Guide" adding the dataset/variable name information to the TOSNP Detail column of the table for each entry.

   - The sponsor will also submit the tables listed below. Each will contain links to the case report forms (CRFs), including adjudication documents, for each subject listed:
     - Primary endpoint
     - Cardiovascular death
     - Stroke
     - Myocardial Infarction
     - Stent Thrombosis
     - Rehospitalization for recurrent Unstable Angina
     - Non-CABG TIMI Major bleeding (including fatal and life-threatening)
     - Non-CABG TIMI Major or Minor bleeding
     - Non-CABG TIMI Major, Minor, or Minimal bleeding
     - CABG-related TIMI bleeding (all categories)

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

N/A

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

N/A. The issues above were already addressed or are in the process of being addressed.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Karen A. Hicks, M.D.	2/11/2013
Reviewing Medical Officer	Date
Karen A. Hicks, M.D.	2/11/2013
Clinical Team Leader	Date

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

/s/

KAREN A HICKS
02/11/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-307/S008

STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	22-307 / S_0173
Drug Name:	EFFIENT™ (prasugrel hydrochloride) Tablets
Indication(s):	Treatment of subjects with acute coronary syndromes (ACS)
Applicant:	Eli Lilly
Date(s):	Date of Document: December, 14 2012 PDUFA Due Date: October 14, 2013
Review Priority:	Standard
Biometrics Division:	Biometrics I, HFD-710
Statistical Reviewer:	Ququan Liu, M.D., M.S.
Concurring Reviewers:	James Hung, Ph.D.
Medical Division:	Division of Cardio-Renal Drug Products, HFD-110
Clinical Team:	Karen Hicks, M.D, Norman Stockbridge, M.D., Ph.D.
Project Manager:	Alison Blaus
Keywords:	EFFIENT™ , Prasugrel, ACS

Table of Contents

1. EXECUTIVE SUMMARY

This is a negative study in terms of efficacy. The study did not demonstrate that prasugrel is superior to clopidogrel in the reduction of incidence of the primary composite endpoint of cardiovascular (CV) death, myocardial infarction (MI), or stroke in the treatment of medically managed subjects enrolled within 10 days of the unstable angina/non-ST-segment elevation myocardial infarction (UA/NSTEMI) index event. No additional efficacy information will be updated to the current label.

2. INTRODUCTION

2.1 Brief Overview of Clinical Studies

This sNDA includes proposed revisions to the Effient Prescribing Information (Pl) based on the results of the TRILOGY Study (TABY).

Study TABY was designed to complement the TRITON-TIMI 38 study (approved on July 10, 2009) by evaluating the relative efficacy and safety of prasugrel and clopidogrel in a population managed with a different treatment strategy for the acute ACS event. The primary objective of the study was to test the hypothesis that prasugrel and aspirin is superior to clopidogrel and aspirin in the treatment of medically managed subjects enrolled within 10 days of the unstable angina/non-ST-segment elevation myocardial infarction (UA/NSTEMI) index event. Superiority was assessed by the reduction in risk of the composite endpoint of first occurrence of cardiovascular (CV) death, myocardial infarction (MI), or stroke throughout the study.

2.2 Data Sources

The sponsor's SAS datasets were stored in the directory of \\cdsesub1\evsprod\NDA022307\0173\ of the Center's electronic document room.

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The quality of data and analysis of TABY study seems acceptable. Consistent results can be generated from both raw and derived data.

3.2 Evaluation of Efficacy

The analysis results of the primary composite endpoint and secondary endpoints were verified. Comprehensive subgroup analyses requested by the medical reviewer were also conducted.

During the early stage of review, it was decided that a joint clinical/statistical review would be conducted. For details on evaluation of efficacy, please refer to Dr. Hick's CDTL review, section 9.

Conclusion:

The TABY study findings are negative. There is no statistically significant difference between prasugrel and clopidogrel groups in incidence of the primary composite endpoint of cardiovascular (CV) death, myocardial infarction (MI), or stroke. Nor did any of the components of the primary composite endpoint.

3.3 Evaluation of Safety

A comprehensive subgroup analysis of bleeding requested by the medical reviewer was conducted. For details of the analyses and findings, please refer to Dr. Hick's CDTL review, section 10.

4. SUMMARY AND CONCLUSIONS

4.1 Statistical Issues and Collective Evidence

No statistical issue is identified. The efficacy finding is negative and additional findings for safety are identified.

4.2 Conclusions and Recommendations

This is a negative study in terms of efficacy. The study did not demonstrate that prasugrel is superior to clopidogrel in the reduction of incidence of the primary composite endpoint of cardiovascular (CV) death, myocardial infarction (MI), or stroke in the treatment of medically managed subjects enrolled within 10 days of the unstable angina/non-ST-segment elevation myocardial infarction (UA/NSTEMI) index event. No additional efficacy information will be updated to the current label.

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

/s/

QUQUAN LIU
09/09/2013

HSIEN MING J HUNG
09/09/2013

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 22-307/SN0173 Applicant: Eli Lilly Stamp Date: 12/14/2012

Drug Name: Effient® (prasugrel) NDA/BLA Type: Standard

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	x			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	x			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	x			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	x			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? __Yes_____

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	x			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	x			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			x	
Appropriate references for novel statistical methodology (if present) are included.			x	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	x			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	x			

Additional Comments:

Please provide statistical analysis programs for the analyses of primary and secondary endpoints.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Ququan Liu	02/11/2013
Reviewing Statistician	Date
Supervisor/Team Leader	Date

File name: 5_Statistics Filing Checklist for a New NDA_BLA22307

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

/s/

QUQUAN LIU
02/11/2013

HSIEN MING J HUNG
02/11/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-307/S008

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

ADDENDUM TO CLINICAL PHARMACOLOGY REVIEW

Brand Name	Effient
INN Name	Prasugrel
NDA Number and Type	2,307_S008
Applicant	Eli Lilly and Company
Reviewer	Martina Sahre, PhD
Team Leader	Rajanikanth Madabushi, PhD

Reason for Addendum

The clinical pharmacology review archived 8/19/2013 contained errors which may lead to incorrect conclusions. This addendum identifies the errors and provides corrections below:

1. **Location: Section 1.3 "Summary of Clinical Pharmacology of Biopharmaceutical Findings"**
    a. First bullet, last sentence:
    Old: "Maximum platelet aggregation in older patients (>75 years, 5 mg) was reduced by about 9.4% compared to younger patients (≤75 years, 10 mg)."
    Corrected: "Maximum platelet aggregation in older patients (>75 years, 5 mg) was increased by about 9.4% compared to younger patients (≤75 years, 10 mg)."
    b. Second bullet, first sentence:
    Old: "As body weight increases, prasugrel exposure increases."
    Corrected: "As body weight decreases, prasugrel exposure increases."
    c. Second bullet, second sentence:
    Old: "Patients with body weight ≤60 kg have on average a 36% higher exposure than heavier patients (>60 Kg)."
    Corrected: "Patients with body weight ≤60 kg receiving 5 mg prasugrel have on average a 38% lower exposure than patients >60 kg, receiving 10 mg prasugrel."
2. **Location: Section 2.2.4 "What are the PK characteristics of the drug and its major metabolite?"**
    a. Second paragraph, eighth sentence;
    Old: "As body weight increases, exposure increases."
    Corrected: "As body weight decreases, exposure increases."
3. **Location: Section 2.3.1, subheading "Age"**
    a. Third paragraph, last sentence:
    Old: "However, the MPA to 20 μM ADP was reduced by 9.4%, which was statistically significant (Figure 7)."
    Corrected: "However, the MPA to 20 μM ADP was increased by 9.4%, which was statistically significant (Figure 7)."
4. **Location: Individual Study Review for TACY, Conclusions**
    a. Fifth sentence:
    Old: "However, the MPA to 20 μM ADP was reduced as well, with both groups being statistically significantly different."
    Corrected: "However, the MPA to 20 μM ADP was increased as well, with both groups being statistically significantly different.

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

/s/

MARTINA D SAHRE
09/10/2013

RAJANIKANTH MADABUSHI
09/11/2013

GENERAL CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

Brand Name	Effient
INN Name	Prasugrel
NDA Number and Type	22,307_S008
Applicant Name	Eli Lilly and Company
Submission Date	14 December, 2012
EDR Link	\\cdsesub1\evsprod\nda022307\0173
Indication	Reduction of thrombotic cardiovascular events in patients with acute coronary syndrome managed with percutaneous coronary intervention.
Dosage Form & Strengths	5 and 10 mg tablets
OCP Division	OCP/DCP1, Cardiovascular and renal products team
OND Division	ODEI, Division of Cardiovascular and renal products
Reviewers	Martina Sahre, PhD Hobart Rogers, PharmD, PhD (Pharmacogenomics)
Team Leaders	Rajanikanth Madabushi, PhD Mike Pacanowski, PharmD, M.P.H. (Pharmacogenomics)

Table of Contents

List of Tables

List of Figures

List of Abbreviations

ACS	Acute coronary syndrome
ADP	Adenosine diphosphate
AM	Active metabolite
ASA	Acetyl salicylic acid
CAD	Coronary artery disease
LD	Loading dose
LTA	Light transmission aggregometry
MD	Maintenance dose
MI	Myocardial infarction
MM	Medically managed
MPA	Maximum platelet aggregation
NSTEMI	Non ST-elevation myocardial infarction
PCI	Percutaneous coronary intervention
PD	Pharmacogenomics
PK	Pharmacokinetics
PK/PD	Pharmacokinetics/Pharmacodynamics
PRU	VerifyNow® platelet reactivity units
STEMI	ST-elevation myocardial infarction
TABM	Study H7T-MC-TABM
TABY, TRILOGY	Study H7T-MC-TABY
TACY	Study H7T-MC-TACY
TADI	Study H7T-MC-TADI
TAEH	Study H7T-CR-TAEH
TRITON	Study H7T-MC-TAAL
UA	Unstable angina
VASP	Vasodilator associated stimulated phosphoprotein

1 Executive Summary

Eli Lilly and Company is seeking approval for a change in labeling (Supplement S008) for prasugrel hydrochloride, trade name Effient®. The applicant does not propose any changes to the labeled indication for Effient®.

The submission contains four clinical pharmacology studies and one clinical trial (TRILOGY). The clinical pharmacology trials included assessment of the effect of age and body weight on pharmacokinetics and platelet aggregation markers in patients with stable coronary artery disease. Two other trials aimed to assess the effect on platelet aggregation markers when patients were switched from clopidogrel to prasugrel after a loading dose or a maintenance dose. Based on the results of the clinical pharmacology studies, the applicant is proposing labeling changes to (b) (4)

The TRILOGY trial was conducted to assess efficacy in patients with acute coronary syndrome due to unstable angina or non ST-elevation myocardial infarction (NSTEMI), who were only medically managed, i.e. the patients did not undergo revascularization by surgical means. The TRILOGY trial failed to show a statistically significant difference from clopidogrel in the medically managed population.

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the clinical pharmacology information submitted to NDA 22,307_S008. From a clinical pharmacology perspective, the NDA is acceptable pending agreement with the applicant on the labeling changes proposed by this reviewer.

1.2 Identify recommended Phase 4 study commitments if the NDA is judged approvable

None.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

The following are overall observations gained from the review of the clinical pharmacology studies:

- Compared to patients ≤75 years receiving 10 mg prasugrel, the applicant found that the exposure in older patients (>75 years) taking 5 mg was approximately half. This finding is consistent with previously reported findings for prasugrel (NDA 22307). Maximum platelet aggregation in older patients (>75 years, 5 mg) was reduced by about 9.4% compared to younger patients (≤75 years, 10 mg).
- As body weight increases, prasugrel exposure increases. This is consistent with previous reports. Patients with body weight ≤60 kg have on average a 36% higher exposure than heavier patients (>60 Kg). The applicant proposed a reduction of dose to 5 mg in this patient group and the recommendation to reduce the dose is currently in the label.

- Switching from a maintenance dose of clopidogrel 75 mg directly (i.e. next dose) to prasugrel 10 mg with or without an added prasugrel loading dose (LD), resulted in an increased inhibition of platelet aggregation.
- Increased platelet inhibition was observed with prasugrel when switching from clopidogrel regardless of CYP2C19 genotype.
- Administering clopidogrel LD followed by a prasugrel LD vs. a prasugrel LD alone did not result in a statistically significant difference between these groups. However, the marker used for the comparison, VerifyNow $P2Y_{12}$ platelet reactivity units (PRUs), may not be able to discriminate treatments after LDs, rendering the interpretability of the comparison questionable.

2 Question-Based Review

This is an abbreviated review for Effient® (prasugrel hydrochloride). The clinical pharmacology of this drug has been previously reviewed (Elena Mishina, 6/27/2008 and Sudharshan Hariharan, 3/20/2010). This review will focus on the four clinical pharmacology studies submitted in supplement S008 and important clinical pharmacology findings drawn from clinical study TRILOGY.

2.1 General attributes of the drug

2.1.1 Regulatory Background or History

Effient® (prasugrel hydrochloride) is a member of the thienopyridine class of platelet aggregation inhibitors, which are antagonists at the $P2Y_{12}$ ADP receptor. It was developed by Daiichi Sankyo, Inc. and Eli Lilly and Co. In July 2009, Effient® was approved for the use in patients with acute coronary syndrome (ACS) who are to be managed with percutaneous coronary intervention (PCI), which excluded the use in patients who are being managed without revascularization at index hospitalization. The present submission is a supplement and primarily contains one major clinical trial (TRILOGY, aka TABY), which assessed the superiority of prasugrel treatment compared to clopidogrel in patients with unstable angina or non-ST-segment elevation myocardial infarction (UA/NSTEMI) who are to be medically managed, i.e. who will receive pharmaceutical treatment only, for various reasons.

2.1.2 Highlights of the Chemistry and Physicochemical Properties

Prasugrel is available as a hydrochloride salt and itself is a prodrug which is metabolized *in vivo* to the active metabolite (Prasugrel-AM or R-138727) (Figures 1 and 2). The chemistry of prasugrel and its metabolites were reviewed in the original submission.

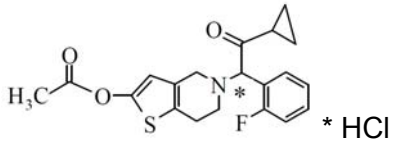


Figure 1. Prasugrel hydrochloride

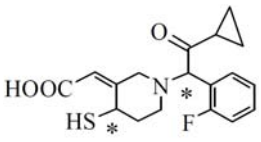


Figure 2. Prasugrel-AM (R-138727)

2.1.3 Mechanism of Action

Prasugrel-AM covalently and irreversibly binds to the $P2Y_{12}$ ADP receptor on the platelet. This binding effectively inhibits platelet aggregation through the ADP pathway for the remainder of the lifespan of the platelet (6-9 days).

2.1.4 What are the proposed dosage and route of administration?

The current label specifies a 60 mg loading dose followed by a once-daily maintenance dose of 10 mg. (b) (4) A recommendation to lower the maintenance dose to 5 mg for patients who weigh less than 60 kg is already in the label. See Section 3 for detailed labeling recommendations by the reviewers.

2.2 General clinical pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The current submission includes two studies assessing the impact on PK and platelet aggregation markers of a 5 mg maintenance dose for patients in specific populations (low body weight, very elderly) compared to a 10 mg dose. Two further studies assess platelet aggregation markers (via LTA, VerifyNow® P2Y12, or VASP) when patients are switched from clopidogrel to prasugrel from either maintenance, or loading dose pretreatment.

The fifth study included is a phase 3 clinical study in patients with UA/NSTEMI who were to be medically managed.

2.2.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology and clinical studies?

The response endpoints selected in the pharmacokinetics/pharmacodynamics (PK/PD) trials mentioned in Section 2.2.1 above are the following:

- Light transmission aggregometry (LTA)
    - maximum platelet aggregation (MPA) to 5 and 20 μM ADP,
    - inhibition of platelet aggregation (IPA) derived from MPA, and
    - residual platelet aggregation (RPA) to 5 and 20 μM ADP;
- VerifyNow® P2Y12 test
    - platelet reactivity units (PRU);
- Vasodilator associated stimulated phosphoprotein (VASP) assay
    - platelet reactivity index (PRI).

The mechanism of action is the reduction of platelet aggregation, and the above listed markers measure this reduction. However, a correlation between inhibition of platelet

aggregation measures and the clinical endpoint (death, non-fatal myocardial infarction (MI), and non-fatal stroke) have not been established to date.

The clinical trial TRILOGY, included in this submission, measured platelet reactivity markers (VerifyNow® P2Y12 PRUs) in a subpopulation (N= 2690, or 28.8% of the total population in TRILOGY).

The primary endpoint in TRILOGY, the clinical Phase 3 study is a composite of cardiovascular (CV) death, non-fatal myocardial infarction (MI), and non-fatal stroke.

2.2.3 Are the active moieties in plasma appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Please refer to Section 2.5.

2.2.4 What are the PK characteristics of the drug and its major metabolite?

The PK characteristics of prasugrel have been previously reviewed (NDA 22307; DARRTS date: 6/27/2008).

Briefly, prasugrel is converted almost completely and quickly into an active metabolite. The first stage is an ester hydrolysis by human carboxylesterases 1 and 2, which occurs mostly in the intestines. Thereafter, the drug is oxidized by cytochrome P450 enzymes to the active metabolite (see Figure 3). The prodrug prasugrel itself is not detected in plasma. Absorption and formation of metabolites is fast and active metabolite peak concentrations are reached within 30 minutes. The terminal half-life for the active metabolite is around 7.4 hours. Prasugrel is predominantly eliminated into urine (68%) and to a lesser degree in feces (27%). Body weight was found to be a covariate for the exposure of the active metabolite. As body weight increases, exposure increases. A high-fat meal does not have an impact on active metabolite AUC, but it reduces peak concentrations and Tmax. Prasugrel is pH dependently soluble, with higher solubility observed at lower pH. Therefore, an interaction with proton-pump inhibitors is expected to decrease solubility of the compound. In comparative BA studies, after coadministration with a proton pump inhibitor, AUC remained within bioequivalence limits and Cmax decreased.

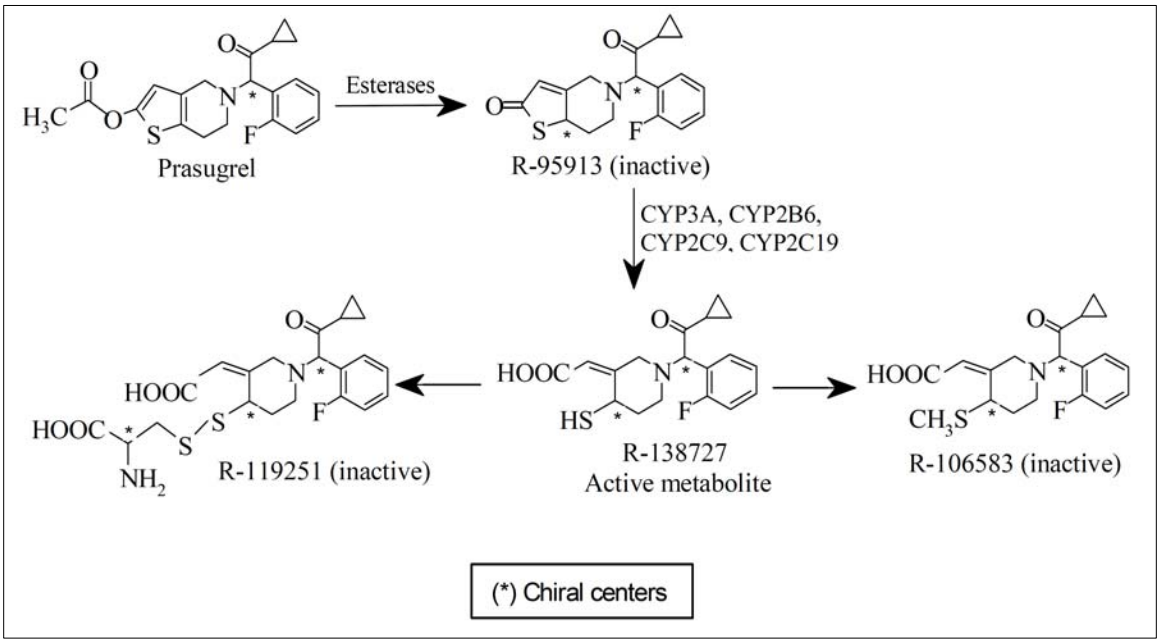


Figure 3. Metabolic pathway of active metabolite formation

[Source: Figure 2.7.2.1 Clinical Pharmacology Summary (Module 2.7.2)]

2.3 Intrinsic Factors

2.3.1 What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

The effects of age, gender, race and weight have been evaluated (NDA 22307; DARRTS date: 6/27/2008).

Body weight

Body weight is a predictor for the exposure. A decrease in body weight from 85 to 60 kg increased the Cmax and AUClast of the active metabolite of prasugrel by an average 49 and 45%, respectively (Source: Clinical pharmacology review, NDA 22307; DARRTS date: 6/27/2008). Based on simulations, a dose reduction to 5 mg in patients weighing less than 60 kg was recommended. The label currently includes a recommendation to "consider lowering the maintenance dose to 5 mg" for patients weighing 60 kg or less.

In the present submission, study TADI (H7T-MC-TADI) was conducted to assess the changes in exposure and platelet aggregation measures after dose adjustment for lower weight patients (<60 kg) receiving 5 mg versus heavier patients (≥60 kg) receiving a 10 mg prasugrel maintenance dose. The study enrolled patients with stable coronary artery disease (CAD).

The applicant found that a dose of 5 mg in lower weight patients resulted in 38% reduction of AUC by 38% and that most patients in the low weight groups were shifted to the lower quartiles of exposure seen in the high body weight group (Figure 4).

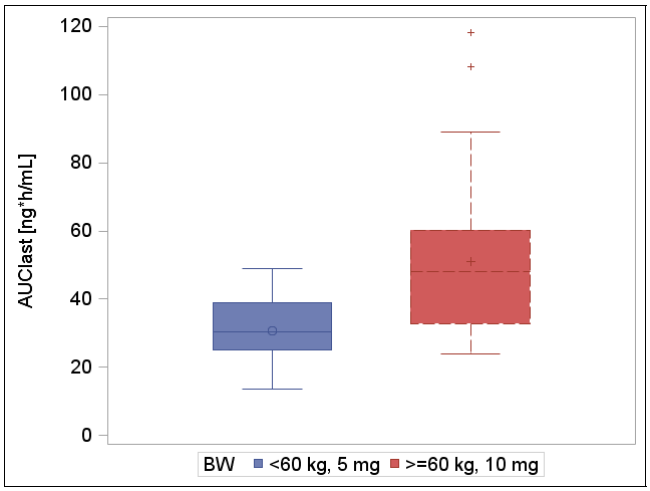


Figure 4. AUClast in patients weighing <60 kg is similar to lower quartiles of exposure in patients weighing ≥60 kg

[Source: CSR H7T-MC-TADI, analysis dataset pgx_pk xpt]

Maximum platelet aggregation to 20 µM ADP was measured pre-dose at steady state. There was no statistically significant difference in MPA between patients ≥60 kg taking 10 mg and those weighing <60 kg taking 5 mg prasugrel (Figure 5).

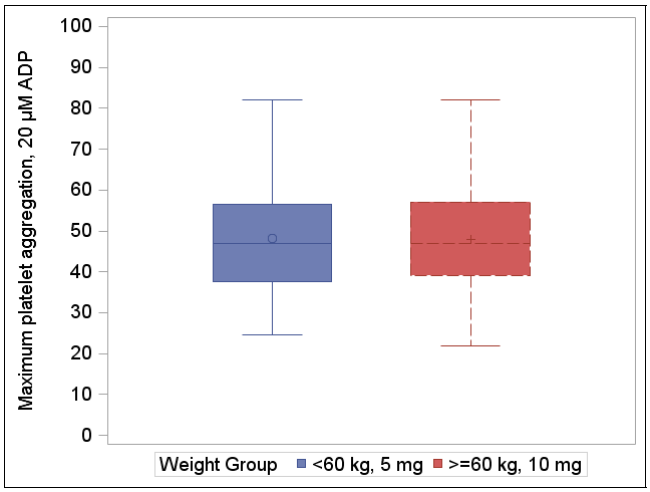


Figure 5. Distribution of MPA is similar between patients receiving 5 mg (<60 kg) and those receiving 10 mg (≥60 kg)

[Source: CSR H7T-MC-TADI, analysis dataset lta xpt]

Since the findings are consistent with that previously reported, no changes to the current label are warranted.

Age

Age does not influence the pharmacokinetics of prasugrel; however, age is an independent predictor of efficacy and safety of prasugrel. In TRITON, patients older than 75 years had a higher risk for thrombotic events (cardiovascular death, non-fatal MI, and

non-fatal stroke) compared to patients younger than 75 years. In addition, these elderly patients showed higher bleeding incidence. Therefore, the original review (NDA# 22,307, 6/27/2008) concluded that a dose reduction to 5 mg might lead to reduced efficacy, thus potentially altering the benefit-risk balance. It should be noted that prasugrel is labeled for the use in patients with a prior MI or a history of diabetes mellitus. In this subset the benefit-risk balance was found to be favorable.

In the present submission, study H7T-MC-TACY (TACY) was conducted to assess the response of platelet aggregation measures after dose adjustment for elderly patients (≥75 years of age) receiving 5 mg versus younger patients (45≤ age <65 years) receiving 10 mg prasugrel maintenance dose.

As expected, decreasing the dose from 10 mg to 5 mg lead to a reduction in AUC by 49% (see Figure 6). However, the MPA to 20 µM ADP was reduced by 9.4%, which was statistically significant (Figure 7).

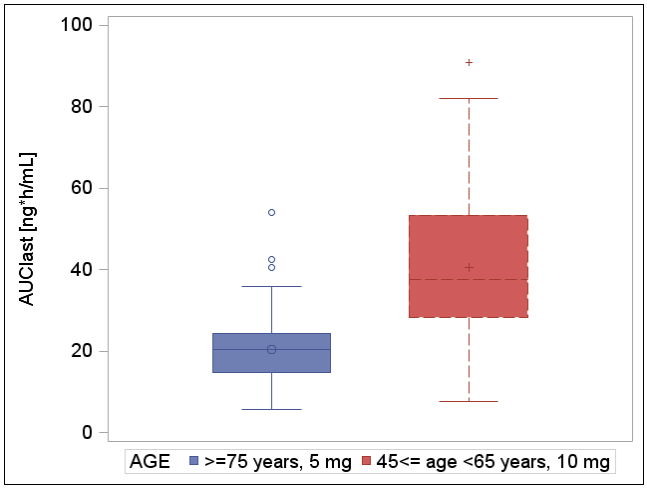


Figure 6. Mean AUClast is reduced by 49% when dose is 5 mg (≥75 years) vs 10 mg (45 to 64 years)

[Source: CSR H7T-MC-TACY, analysis dataset pgx_pk.xpt]

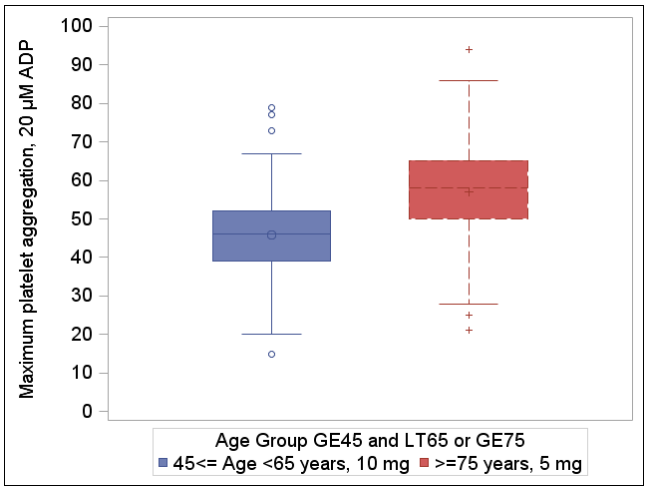


Figure 7. MPA is higher in patients older than 75 years taking 5 mg prasugrel compared to patients 45 to 64 years taking 10 mg prasugrel

[Source: H7T-MC-TACY, analysis dataset lta.xpt]

(b) (4)

(b) (4)

[redacted]

Genomics

The applicant conducted a pharmacogenomic (PG) substudy of the TRILOGY-ACS study. This substudy consisted of 5736 subjects (62% of the overall population) who consented to provide DNA on a voluntary basis. The PG substudy did not identify any associations between CYP2C19 genotype and rates of major cardiovascular events or bleeding in either the clopidogrel- or prasugrel-treated patients. A tendency toward higher event rates was observed among prasugrel-treated reduced metabolizers (RMs), though it is unlikely that CYP2C19 genotype significantly influences the disposition of prasugrel (based on data submitted in the original NDA).

Table 1. Primary Efficacy Composite Endpoint (CV death, MI or Stroke) – CEC Adjudicated by CYP2C19-Predicted Phenotype Genetic ITT Subjects <75 Years of Age

	2-Level	4-Level	Prasugrel			Clopidogrel			Hazard Ratio	
Subset	Phenotype	Phenotype	n	N	%	n	N	%	(95% CI)	P-Value
Overall ITT		N/A	364	3662	**10.1**	397	4351	**11.0**	**0.92 (0.79 – 1.01)**	0.21
PG Substudy			202	2037	**9.9**	226	2057	**10.9**	**0.97 (0.85 – 1.10)**	0.24
	EM		139	1500	**9.3**	164	1480	**11.1**	**0.84 (0.67-1.05)**	0.14
		UM	58	642	9.0	66	682	9.7	0.95 (0.66-1.35)	0.75
		EM	81	858	9.4	98	798	12.3	0.77 (0.57-1.03)	0.08
	RM		63	537	**11.7**	62	577	**10.8**	**1.08 (0.76-1.53)**	0.68
		IM	47	439	10.7	47	467	10.1	1.05 (0.70-1.58)	0.81
		PM	16	98	16.3	15	110	13.6	1.16 (0.58-2.36)	0.64

EM: extensive metabolizer, RM: reduced metabolizer, IM: intermediate metabolizer, UM: ultra-rapid metabolizer, PM: poor metabolizer

2.4 Switching from Clopidogrel to Prasugrel

2.4.1 How does the effect on platelet aggregation markers compare when patients are switched from a maintenance dose of clopidogrel directly to prasugrel?

The applicant conducted a study to compare platelet aggregation markers after switching patients from a maintenance dose of clopidogrel 75 mg to a dose of prasugrel 10 mg in patients with a prior ACS event in the past year. Patients were taking 75 mg clopidogrel for 2 weeks before being assigned to either continue clopidogrel (control), switch directly to prasugrel 10 mg, or to receive a single 60 mg loading dose of prasugrel followed by maintenance doses of 10 mg.

When switching from clopidogrel to prasugrel with a loading dose, platelet aggregation was lower on the first day of switching compared to a direct switch to 10 mg prasugrel. One week after the switch, both prasugrel arms (60 mg, followed by 10 mg MD and 10 mg MD alone) were not statistically significantly different from each other. However, both

prasugrel arms showed significantly lower platelet aggregation compared to clopidogrel 75 mg.

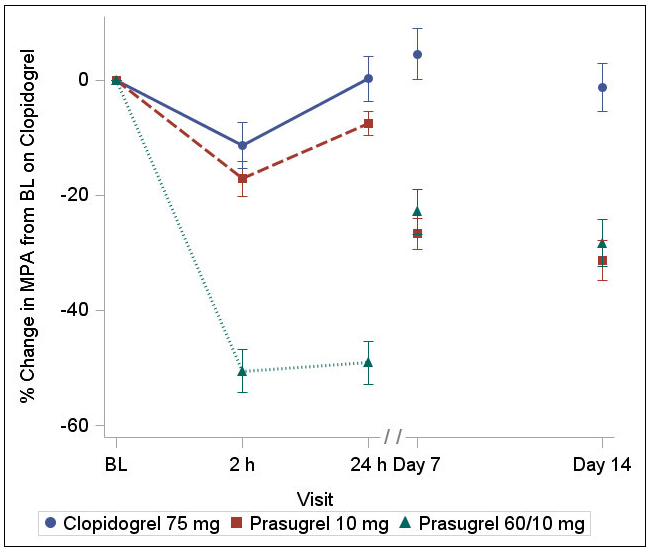


Figure 8. Percent change in MPA from baseline on clopidogrel 75 mg
[Source: H7T-CR-TABM, analysis dataset labs.xpt]

(b) (4)

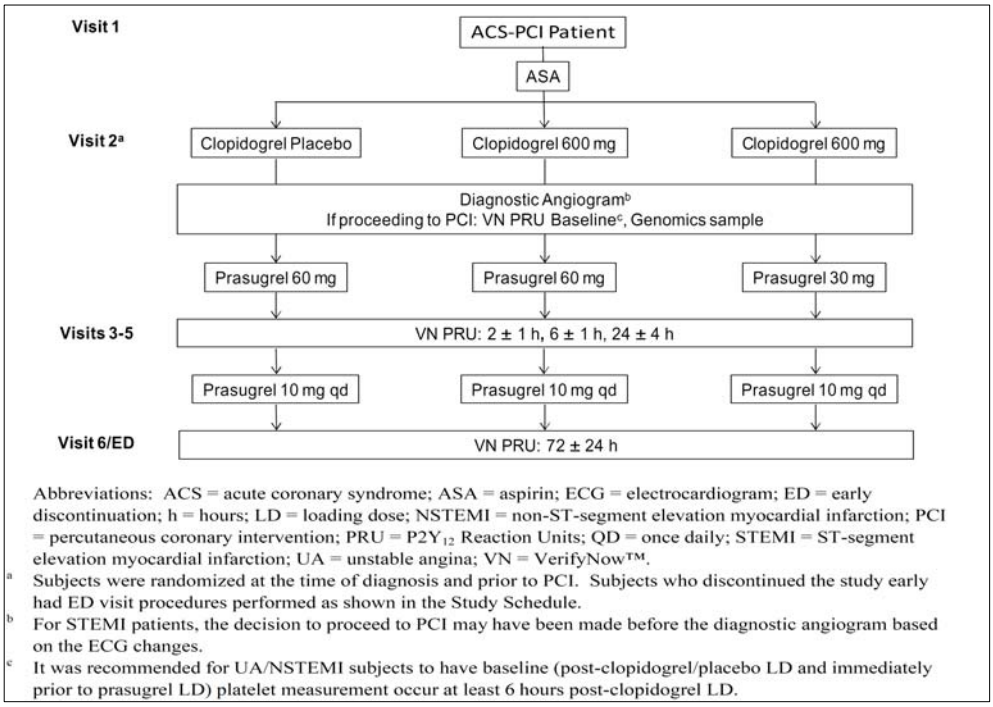
Table 2. Comparison of P2Y12 Reaction Units (PRU) Change from Baseline at Day 30 by CYP2C19 Predicted Phenotype Genetic PD Set for Subjects Switching from Clopidogrel to Prasugrel after Randomization H7T-MC-TABY PGx

Population	Time Points	Statistics	EM	RM	P-value*
Age < 75 Years Old	Day 30	n	106	57	0.0837
		Mean	-114.2	-139.2	
		SD	90.34	82.23	
		Minimum	-348	-330	
		Median	-119.0	-147.0	
		Maximum	285	9	
		P-value**	<0.0001	<0.0001	

[Source: H7T-MC-TABY-PGx page 227]

2.4.2 How does the effect on platelet aggregation markers compare when patients are given a loading dose of prasugrel after a loading dose of clopidogrel?

The applicant studied the effect of a prasugrel loading dose in addition to a clopidogrel loading dose in study H7T-CR-TAEH. For this study, patients with ACS who were to undergo PCI were enrolled into three groups (see Figure 9).



Abbreviations: ACS = acute coronary syndrome; ASA = aspirin; ECG = electrocardiogram; ED = early discontinuation; h = hours; LD = loading dose; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; PRU = $P2Y_{12}$ Reaction Units; QD = once daily; STEMI = ST-segment elevation myocardial infarction; UA = unstable angina; VN = VerifyNow™.

[a] Subjects were randomized at the time of diagnosis and prior to PCI. Subjects who discontinued the study early had ED visit procedures performed as shown in the Study Schedule.

[b] For STEMI patients, the decision to proceed to PCI may have been made before the diagnostic angiogram based on the ECG changes.

[c] It was recommended for UA/NSTEMI subjects to have baseline (post-clopidogrel/placebo LD and immediately prior to prasugrel LD) platelet measurement occur at least 6 hours post-clopidogrel LD.

Figure 9. Schematic of study design and time points
[Source: CSR H7T-CR-TAEH Figure TAEH.5.1.]

The sponsor used the VerifyNow® P2Y12 PRU and percent inhibition as the only PD markers in this study. The data was highly variable, but showed that there was no significant difference between the three treatment groups.

A literature search was done to assess how reliably VerifyNow® P2Y12 PRUs are able to distinguish between treatments. A number of reports pointed out that the PD marker is reliable when platelet aggregation is not maximally inhibited, however, at the minima the test is less well able to distinguish between treatments when compared to LTA–derived measures.[1 2 3] Data from study TABM had two groups receiving maintenance doses of

[1] Jakubowski J et al. "A Comparison of the VerifyNow P2Y12 Point-of-Care Device and Light Transmission Aggregometry to Monitor Platelet Function with Prasugrel and Clopidogrel: An Integrated Analysis" *J Cardiovasc Pharmacol*. 2010;56(1):29-37

[2] Jakubowski J et al. "The use of the VerifyNow P2Y12 point-of-care device to monitor platelet function across a range of P2Y12 inhibition levels following prasugrel and clopidogrel administration." *Thromb Haemost.* 2008;99:409-415

[3] Varenhorst C et al. "Assessment of P2Y12 inhibition with the point-of-care device VerifyNow P2Y12 in patients treated with prasugrel or clopidogrel coadministered with aspirin." *Am Heart J.* 2009;562.e1-562.e9

clopidogrel and prasugel and one group receiving a loading dose of prasugrel. To assess how well VerifyNow® P2Y12 PRUs were able to distinguish between treatments, data from the three groups was taken from the 2 and 24 h measurement time points, where MPA to 20 µM ADP and PRUs were measured. The results from the comparison can be seen in Figure 10. After a loading dose with prasugrel, both MPA and PRUs are comparatively lower than in the two maintenance dose groups and the resolution of PRUs at this lower end of the measurable spectrum is low. Hence, changes below what is observed with prasugrel 60 mg cannot be reliably detected. Thus, study TAEH may not have been able to distinguish between the three treatment groups. (b) (4)

Figure 10. Maximum platelet aggregation vs VerifyNow P2Y12 PRU as observed in study TABM at 2 and 24 h post LD

[Source: CSR H7T-CR-TABM analysis dataset labs.xpt]

Further, in most of the patients, the time difference between the clopidogrel/placebo loading dose and prasugrel loading dose during PCI was less than 6 hrs (median if < 6h group is 1.4 hr). Since the effect of clopidogrel is not fully evolved by the time of administration of the prasugrel loading dose, it is not possible to evaluate the impact of prasugrel on clopidogrel.

2.5 Analytical section

2.5.1 Pharmacokinetics

Prasugrel is a prodrug that is converted by esterases in the intestines to a precursor metabolite R-95913, which is then metabolized by cytochrome P450 enzymes, mainly CYP3A4, to the active metabolite R-138727. Similarly, clopidogrel is also a prodrug is metabolized with an intermediary to the active metabolite. In addition to this, the active

metabolite of prasugrel and clopidogrel are volatile in blood, thus they are derivatized with 2-bromo-3'-methoxyacetophenone (IUPAC: 2-bromo-1-(3-methoxyphenyl)ethanone) and kept on ice to be able to analyze them.

For study H7T-MC- TADI, the analytes that were quantified are the active metabolites for prasugrel and clopidogrel in their derivatized form (R-138727-MP and R-361015-MP) and an inactive metabolite of prasugrel R-106583. Two other prasugrel metabolites were part of the analytical method, but method performance for them did not meet acceptance criteria. In study H7T-MC-TACY, only the prasugrel and clopidogrel active metabolites were quantified. For clopidogrel active metabolite, two different methods were used that differed in the internal standard used.

The characteristics and performance of both assays during the studies are shown in Tables 3 and 4.

2.5.2 Pharmacodynamics

- For the determination of LTA measures, venous blood was collected into citrate tubes.
- For the determination of VerifyNow® P2Y12 measures, citrate blood was collected. If the samples were collected and any of the following exceptions applied, then the sample was not used in the analysis dataset:
    - Timing of blood draws was outside of the protocol allowed window (2 ± 1 h, 6 ± 1 h, 24 ± 4 h, and 75 ± 24 h post prasugrel LD),
    - Co-administration of a GP IIb/IIIa inhibitor within 7 days of blood sample,
    - Samples assayed outside the manufacturer specified window of 10 min to 4 h after sample collection,
    - BASE value of <100, when all other BASE values for the patient were >200,
    - Compliance violations, and
    - Samples that did not result in a PRU value.

The commercial VerifyNow® P2Y12 assay was used for analysis.

Table 3. Analytical method performance for study TADI

	Parameter	R138727-MP (Prasugrel-AM)	R106583 (Prasugrel non-AM)	R361015_MP (Clopidogrel-AM)
Assay	Protocol Number	03088VKJV_LI	04389VDCE_LI	110410PVRLC_EII
	LLOQ and ULOQ	0.5 and 250 ng/mL	1 and 500 ng/mL	0.5 and 250 ng/mL
	Reference standard	R138727, Lot# 7, Potency 90.1%	R106583, lot#8, 97.1% purity	R-361015, lot# R-361015-04, 97.3% purity
	Internal standard	R138727-d4, Lot# 1, Potency 88.7%	R121721, lot# 3, 95.7% purity	cis-Clopidogrel-MP-13C,D3, lot# 6-MAR-75-2
	Specificity	No interference	No interference	No interference
Calibration samples	Calibration range	0.5 to 250 ng/mL	1 to 500 ng/mL	0.5 to 250 ng/mL
	Accuracy (%Bias)	-2.44 to 2.30%	-3.32 to 1.67%	-3.23 to 2.23%
	Precision (%CV)	2.51 to 3.61%	2.33 to 4.42%	2.72 to 3.74%
QC samples	Concentration	1, 125, 200 ng/mL	2.5, 250, 400 ng/mL	1, 125, 200 ng/mL
	Inter run			
	Accuracy (%Bias)	2.80 to 5.36%	-3.44 to -1.16%	-3.37 to 8.60%
	Precision (%CV)	3.59 to 5.06%	2.76 to 4.45%	2.85 to 4.70%
Stability	Freeze-thaw cycles			
	-20° C	3	5	5
	-70°C	3	5	5
	Room temperature	24 h	24 h	24 h

Sources: 110410pvrlc-eii.pdf (clopidogrel-AM), 03088vkjv-li-r6-method-report.pdf (prasugrel-AM(R138727)), 04389vdce_li_r6.pdf (prasugrel-non-AM (R119251, R106583, R95913))

Table 4. Analytical method performance for study TACY

	Parameter	R138727-MP (Prasugrel-AM)	R361015-MP (Clopidogrel-AM)	
Assay	Protocol Number	03088VKJV LI	06145vjjw-eii-r2	110410PVRLC EII
	LLOQ and ULOQ	0.5 and 250 ng/mL	0.5 and 250 ng/mL	0.5 and 250 ng/mL
	Reference standard	R138727, Lot# 7, Potency 90.1%	R361015 (ROX-2324), lot# 1, 88.9% purity	R-361015, lot# R-361015-04, 97.3% purity
	Internal standard	R138727-d4, Lot# 1, Potency 88.7%	R135772, lot# 1, 97.6% purity	cis-Clopidogrel-MP-13C,D3, lot# 6-MAR-75-2
	Specificity	No interference	No interference	No interference
Calibration samples	Calibration range	0.5 to 250 ng/mL weighting: 1/x2	0.5 to 250 ng/mL weighting $1/x^2$	0.5 to 250 ng/mL weighting: 1/x2
	Accuracy (%Bias)	-2.44 to 2.30%	-4.58 to 3.08%	-3.23 to 2.23%
	Precision (%CV)	2.51 to 3.61%	2.38 to 7.75%	2.72 to 3.74%
Quality control samples	Concentration	1, 125, 200 ng/mL	1, 125, 250 ng/mL	1, 125, 200 ng/mL
	Inter run			
	Accuracy (%Bias)	2.80 to 5.36%	-0.19 to 11.10%	-3.37 to 8.60%
	Precision (%CV)	3.59 to 5.06%	0.57 to 7.47%	2.85 to 4.70%
Stability	Freeze-thaw cycles			
	-20° C	3	5	5
	-70°C	3	5	5
	Room temperature	24 h	24 h	24 h

Source: CSR page 781 ff, documents 03088vkjv-li-r6 (prasugrel-AM), 06145vjjw-eii-r2, and 110410vrlc-eii (clopidogrel-AM)

3 Draft Labeling Recommendations

Changes to the proposed label are shown below. Deleted text will be shown in red, strikethrough format, added text will be blue and underlined.

(b) (4)

2 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

4 Appendices

4.1 Clinical pharmacology and biopharmaceutics individual study review

4.1.1 H7T-MC-TABM

Clinical Pharmacology Review
Intrinsic Factor Study

Study	H7T-MC-TABM
Title	"A pharmacokinetic comparison of prasugrel (LY640315) versus clopidogrel in subjects with acute coronary syndrome who are receiving clopidogrel" S.W.A.P. - SWitching Anti Platelet Study
Study Period	December 9, 2008 to December 16, 2009
Sponsor	Eli Lilly, Inc.
Phase	2
EDR Link	\\cdsesub1\evsprod\NDA022307\0173\m5\53-clin-stud-rep\534-rep-human-pd-stud\5342-patient-pd-stud-rep\h7t-mc-tabm\tabm-04-body.pdf
Rationale	Prior to study TABM differences in efficacy in patients switching from a clopidogrel maintenance dose (75 mg) to a prasugrel maintenance dose (10 mg) had not been evaluated. This study was designed to elucidate the difference in mean maximum platelet aggregation (MPA) when patients are switched from a maintenance dose of clopidogrel to prasugrel.

Study Design

Randomized, multi-center, double-blind, double-dummy, multiple dose, active control, 3-arm parallel

Treatments

A. Placebo LD followed by prasugrel 10 mg MD for 13–15 days
B. Placebo LD followed by clopidogrel 75 mg MD for 13–15 days
C. Prasugrel 60 mg LD followed by prasugrel 10 mg MD for 13-15 days

Patient Population

Patients who had had a qualifying ACS event between 30 to 330 days before study entry and who had been taking aspirin and clopidogrel 75 mg daily were eligible to enroll.

Pharmacokinetics

Not collected.

Pharmacodynamics

Pharmacodynamic samples were collected separately (different collection tubes) for assessment of MPA and VerifyNow P2Y12 analysis. The samples were collected at the following time points:

- Visit 1 (study entry)
- Visit 2 (baseline MPA prior to LD/MD and 2±0.5 h post dose)

- Visit 3 (24±2 h, prior to MD)
- Visit 4 (8±1 days, prior to MD)
- Visit 5 (14±1 days, no MD on that day)

The protocol required at least a 5 day duration between visits 4 and 5.

Analytical Methods

Pharmacodynamics

Measurement of platelet aggregation using the light transition aggregometry method was done with platelet-rich plasma in response to 5 and 20 μM ADP. The resulting parameters were maximum and residual platelet aggregation (MPA and RPA). RPA is the percent aggregation measured 6 minutes after addition of 5 and 20 μM ADP.
The response to study drug was also measured using the VerifyNow device. This device computes the P2Y12 reaction units, a BASE value and the device-reported % inhibition of platelet aggregation. The BASE value represents the rate and extent of platelet aggregation in response to Thrombin receptor activating peptide (TRAP) and gives the baseline platelet aggregation independent of the P2Y12 pathway. As such, the BASE value serves as an internal standard. The PRU value is based on the rate and extent of platelet aggregation in response to ADP. Finally, the percent inhibition of platelet aggregation is calculated as Inhibition[%]=(1-PRU/BASE)*100 and represents the proportion of reduction from BASE due to P2Y12 inhibition.
A tertiary measure for the extent of platelet aggregation was VASP phosphorylation, which was measured in a whole blood flow cytometric assay. The resulting parameter is the platelet reactivity index (PRI), given in percent, which is the ratio of non-phosphorylated VASP to phosphorylated VASP.

Statistical Methods

The statistical analysis used an analysis of covariance (ANCOVA) model with treatment and study site as fixed effects. The latest MPA measurement before randomization was added into the model as a covariate. The difference between clopidogrel and prasugrel LD was part of the assessment of all three treatments, however, the difference in mean MPA after prasugrel LD and MD was not part of the primary endpoint. The analysis was conducted using the data from the PD population (primary). The secondary analysis population data was given by the ITT population.

Results

Study Population

ITT/Safety: All randomized patients exposed to any dose of study drug in the double-blind phase.
PD: All randomized patients having who had blood-draws at 1 week after randomization, took 80% of their doses and were compliant the days before the week 1 blood draw. Patients were considered to have completed the study when they had a week 1 blood sample for MPA.

Table 1. Patient disposition

Treatment	Placebo / P 10 mg	Placebo/ C 75 mg	P 60 mg/ P 10 mg	Total
Entered				159
Randomized	47	48	44	139
Completed	43	46	39	128
Discontinued	4	2	5	11
ITT/Safety	47	48	44	139
Non-compliant at week 1	11	15	13	39
PD	36	33	31	100

[Source: H7T-MC-TABM CSR, page 63 ff.]

Table 2. Patient demographics and vital characteristics (PD population)

Parameter	Placebo / P 10 mg	Placebo/ C 75 mg	P 60 mg/ P 10 mg
Age [Median (range)] [years]	56.89 (41.2-73.4)	56.76 (43.9-69.1)	55.75 (42.2-75.3)
Age <65	30	28	25
≥65 Age ≤75	8	5	6
Male	28	21	21
Female	8	12	10
Race			
White	30	20	26
Black/African American	6	9	4
Asian	0	0	0
Other	0	4	1
Weight [kg]	94.1 (50.9-136.0)	93.2 (57.1-123.2)	90.3 (61.7-140.0)
Current Smoker (Non-Smoker/Smoker)	21/15	26/7	23/8
Qualifying ACE Event (UA/NSTEMI/STEMI)	16/7/13	13/7/13	12/7/12
Clopidogrel at time of qualifying ACS (Yes/No)	8/28	6/27	7/24

[Source: H7T-MC-TABM CSR , page 47 ff.]

Pharmacodynamics

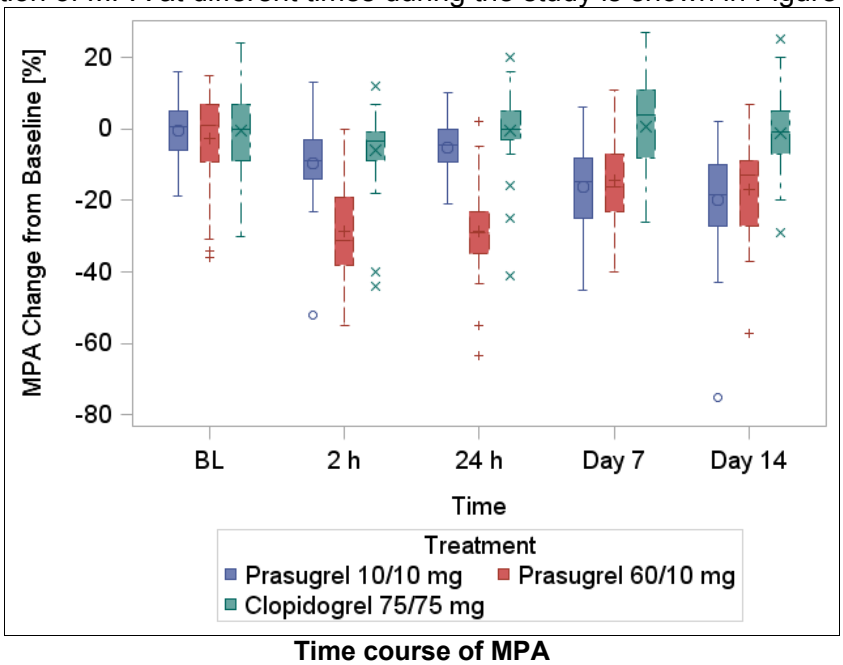
The primary endpoint was the difference in mean MPA (20 μM ADP) after 1 week of study drug treatment in patients receiving placebo LD/prasugrel 10 mg MD compared to those receiving placebo LD/clopidogrel 75 mg. See Table 3 below.

Table 3. MPA to 20 µM ADP – week 1 (PD population)

Parameter		Placebo/ C 75 mg	Placebo / P 10 mg	P 60 mg / P10 mg
MPA to 20 µM ADP	Baseline Mean	53.8 54.5	60.2 43.9	55.4 41.0
	LS Mean (SE)	55.0 (2.09)	41.1 (1.99)	41.0 (2.00)
	LS Mean Difference (CI)		-13.91 (-19.10, -8.73)	-13.98 (-19.26, -8.71)
	p-value		<0.0001	<0.0001

[Source: H7T-MC-TABM CSR page 81]

The distribution of MPA at different times during the study is shown in Figure 1 below.



Time course of MPA

[Source: H7T-MC-TABM, analysis dataset labs.xpt]

Reviewer's Note: When taking a 10 mg prasugrel maintenance dose after discontinuing clopidogrel, maximum platelet aggregation is reduced compared to clopidogrel 75 mg after 1 week of dosing. Adding an additional prasugrel loading dose after discontinuation of clopidogrel decreased MPA after 2.5 hours, however, after 1 week of dosing with 10 mg prasugrel, it made no difference whether a loading dose of 60 mg was given, or whether patients were started on the maintenance dose of prasugrel.

Safety

There were no deaths during the study, however, three subjects who were in the prasugrel arm reported serious adverse events. They were chest pain, in-stent coronary artery restenosis and syncope. All SAEs were considered not study drug-related by the investigator and all occurred in the placebo LD/prasugrel 10 mg MD group.

Conclusions

The sponsor compared three treatment modalities to elucidate the platelet aggregation response when switching patients from a daily clopidogrel 75 mg maintenance dose (MD) to prasugrel 10 mg maintenance dose. The treatments modalities were (1) no loading dose (placebo) followed by clopidogrel 75 mg, (2) no loading (placebo) dose followed by 10 mg prasugrel, and (3) prasugrel 60 mg loading dose (LD) followed by 10 mg prasugrel daily. The comparisons showed that switching from a clopidogrel MD directly to a prasugrel MD lowered platelet activity compared to the clopidogrel 75 mg MD dose, likewise, a prasugrel LD followed by daily maintenance doses lowered the platelet response further after one week of treatment. A comparison of the two prasugrel treatment modalities after one week, showed no statistically significant difference. (b) (4) , based on this study, it seems feasible to switch patients directly from a clopidogrel MD to a prasugrel MD, if further effect increase is desired. An administration of a loading dose of prasugrel does, expectedly, lower MPA during the first day, but no more than a prasugrel LD would when given to thienopyridine naïve patients. Therefore, there does not seem to be much difference whether a patient is reloaded on prasugrel vs. just switching to prasugrel and both modalities seem to be feasible for use.

Recommendations for Labeling

The applicant proposes to add the following language to the label:

(b) (4)

In addition, the following language, which is similar to part of what was studied in TABM, is in the current label:
[…] "Discontinuing clopidogrel 75 mg and initiating prasugrel 10 mg with the next dose resulted in increased inhibition of platelet aggregation but not greater than that typically produced by a 10-mg maintenance dose of prasugrel alone."

(b) (4)

Based on this information we recommend the following changes to the applicant's proposed labeling for TABM:

[…]"Discontinuing clopidogrel 75 mg and initiating a prasugrel 10 mg maintenance dose with or without a loading dose of prasugrel 60 mg results in a 14% decrease of MPA by Day 7 (b) (4) This decrease in MPA is not greater than that typically produced by a 10-mg maintenance dose of prasugrel alone. […] (b) (4)

4.1.2 H7T-CR-TAEH

Clinical Pharmacology Review
Intrinsic Factor Study

Study	H7T-CR-TAEH
Title	"Transferring from clopidogrel loading dose to prasugrel loading dose in acute coronary syndrome patients: TRIPLET"
Study Period	May 17, 2010 to November 14, 2011
Sponsor	Eli Lilly, Inc.
Phase	2
EDR Link	\\cdsesub1\evsprod\NDA022307\0173\m5\53-clin-stud-rep\534-rep-human-pd-stud\5342-patient-pd-stud-rep\h7t-cr-taeh\taeh-04-body.pdf
Reviewer	Martina Sahre, PhD
Team Leader	Rajanikanth Madabushi, PhD
Rationale	Patients with UA/NSTEMI or STEMI are recommended to receive a loading dose of clopidogrel as early as possible. Switching one patient from clopidogrel to prasugrel is not routinely done and there is little available data. A prior study assessing switching patients from a clopidogrel maintenance dose to a prasugrel maintenance dose showed that prasugrel achieved additional platelet inhibition. Thus, this study was designed to show that there is no difference between dose groups when prasugrel is administered as a 60 or 30 mg loading dose to patients who previously received 600 mg clopidogrel or placebo.

Study Design

Randomized, multi-center, double-blind, double-dummy, multiple dose, active control, 3-arm parallel

Treatments

A. Placebo ≤24 h pre-PCI, followed by prasugrel 60 mg during PCI, prasugrel 10 mg maintenance dose (MD)
B. Clopidogrel 600 mg ≤24 h pre-PCI, followed by prasugrel 60 mg during PCI, prasugrel 10 mg (MD)
C. Clopidogrel 600 mg ≤24 h pre-PCI, followed by prasugrel 30 mg during PCI, prasugrel 10 mg (MD)

Patient Population

Patients who presented with STEMI or UA/NSTEMI were eligible to participate if they were scheduled to undergo angiography and subsequent PCI. Patients had to weigh at least 60 kg and be younger than 75 years of age. Prior history of TIA and stroke precluded the participation in the trial.

Pharmacodynamics

The degree of platelet inhibition was measured using P2Y12 reaction units (PRU) and the percent inhibition of the P2Y12 receptor as measured by the VerifyNow® P2Y12 assay.
Samples were collected at the following time points at visit 2 at least 6 h after the clopidogrel loading dose (for UA/NSTEMI), but before prasugrel dose. In patients with

STEMI, this sample was to be taken anytime after the clopidogrel or placebo LD, but before the prasugrel LD. After the prasugrel LD, samples were taken at 2 ± 1, 6 ± 1, 24 ± 4 h. Prasugrel 10 mg MD were administered around 24 ± 4 h after the LD until the last sample was taken at 72 ± 24 hours post LD. The last sample was to be taken about 24 hours after the last dose, i.e. on the last sampling day patients were told to hold the prasugrel dose until the sample was taken. If the dose was forgotten the day before, then patients were asked to take the dose if sampling 24 hours later was possible.

Analytical Methods

Please refer to Section 4.1.1 (Analytical Methods) for information about the assay.

Reviewer's Note: *During the review, it became apparent that the variability of the measures, even with sites reporting problems with the VerifyNow system accounted for, were very high. A literature search was done on reports of limited ability of the VerifyNow system to distinguish between treatments. Three articles were found that compared the VerifyNow system to LTA results (see Footnotes 1 to 3). Both papers were from a clinical site in Uppsala, Sweden and found that at the lower end of LTA-derived IPA to 20 µM ADP, VN PRUs reached levels of zero faster than LTA and thus could not distinguish between lower levels of IPA (see Figure 10). Applied to a comparison between treatments, this might suggest that very high numbers of patients will have to be enrolled in trials assessing VN PRU after loading doses, when platelet aggregation would be expected to be lowest, to be able to distinguish between these very small changes in PRUs. As can be seen from the results, they are highly variable and, at the lowest levels of platelet aggregation, indistinguishable, but the question arises whether that lack of statistical difference is due to a true lack of difference between the groups or due to a lack of the test to distinguish treatments at these low levels of inhibition. Based on the literature reports it may likely be the latter.*

Statistical Methods

The analyses were based on data from the PD and EP populations. The difference in ADP induced platelet aggregation between clopidogrel-naïve and pretreated patients (primary EP) was calculated using repeated measures linear mixed effects model, with all valid PRU values from baseline until 72 hours post prasugrel LD. The model contained treatment, country, visit and treatment*visit as fixed effects and patient and an error term as random effects. The least square means, standard errors and 95% confidence intervals for the difference were to be reported.

Results

Study Population

Table 1. Patient disposition

Treatment	Placebo / P 60 mg	C 600 mg/ P 60 mg	C 600 mg/ P 30 mg	Total
Screened				287
Randomized	110	83	89	282
Completed Study	85	62	62	209
on medication	57	51	50	158
Discontinued study medication	25 52	21 29	27 38	73 119
ITT/Safety	109	79	88	276

PD	52	47	50	149
EP	43	38	45	126

Source: CSR, page 37 ff.

ITT/Safety: All randomized patients exposed to any dose of study drug.
PD: All randomized patients having who received a prasugrel loading dose and had at least one evaluable PD measurement after visit 2.
EP: This population included patients in the PD population who had a valid PD measurement 6 h after prasugrel LD (i.e. at visit 4).

Table 2. Patient demographics

Treatment / Parameter	Placebo / P 60 mg	C 600 mg/ P 60 mg	C 600 mg/ P 30 mg	Total
Age [Median (range)] [years]	58.6 (38.1-75.3)	57.1 (31.2-74.1)	58.5 (34.2-74.1)	58.4 (31.2-75.3)
Age <65	79	62	72	213
Age ≥65	30	17	16	63
Male/Female	78/31	63/16	72/16	213/63
Race (White/Black or African American/Asian/Native Hawaiian or other Pacific Islander/Multi-racial)	83/3/22/1/0	56/2/17/3/1	67/7/14/0/0	206/12/53/4/1
Ethnicity (Hispanic or Latino/Not Hispanic or Latino/Not Applicable)	31/63/15	19/46/14	22/51/15	72/160/44
Weight [kg]	81.7 (60.0-143.0)	84.6 (61.0-145.0)	81.4 (60.0-148.0)	82.4 (60.0-148.0)
Current Smoker (Non-Smoker/Smoker)	24/38	26/22	24/35	74/95

Source: CSR , page 42 ff.

Pharmacodynamics

Results show that six hours after a prasugrel loading dose, PRUs are heterogeneous, as observed from large variances associated with mean PRUs and percent inhibition. While statistically not significant, due to the large standard deviations, this study probably does not have the power to determine that there is, indeed, no difference between the three treatments. The original sample size calculation anticipated a standard deviation of 20 for the mean difference, which is clearly smaller than what was observed in the trial.

Table 3. Inhibition of platelet aggregation measured by PRU and PRI 6 hours post prasugrel LD (PD population)

Parameter		**Placebo / P 60 mg**	**C 600 mg/ P 60 mg**	**C 600 mg/ P 30 mg**
PRU	Mean (SD)	62.7 (105.6)	44.2 (82.17)	57.8 (80.48)
	LS Mean (SE)	57.86 (11.86)	35.61 (12.36)	53.92 (11.74)
	LS Mean Difference (CI)		22.24 (-10.98, 55.47)	3.93 (-28.20, 36.07)

	p-value		0.188	0.809
% Inh.	Mean (SD)	79.1 (32.65)	85.2 (25.62)	78.7 (29.54)
	LS Mean (SE)	79.87 (3.95)	86.77 (4.13)	78.55 (3.93)
	LS Mean Difference (CI)		-6.89 (-18.02, 4.24)	1.33 (-9.44, 12.10)
	p-value		0.223	0.808

Source: CSR page 109

Reviewer Comments:
The time-course of effects on PRU are shown in Figure 2. Based on the results, there does not seem to be any difference between the three treatment arms at baseline contrary to the expectation. Since treatments B & C were to receive clopidogrel 600 mg prior to PCI, the baseline (i.e., pre-prasugrel LD) in these arms would be expected to be lower compared to treatment A.

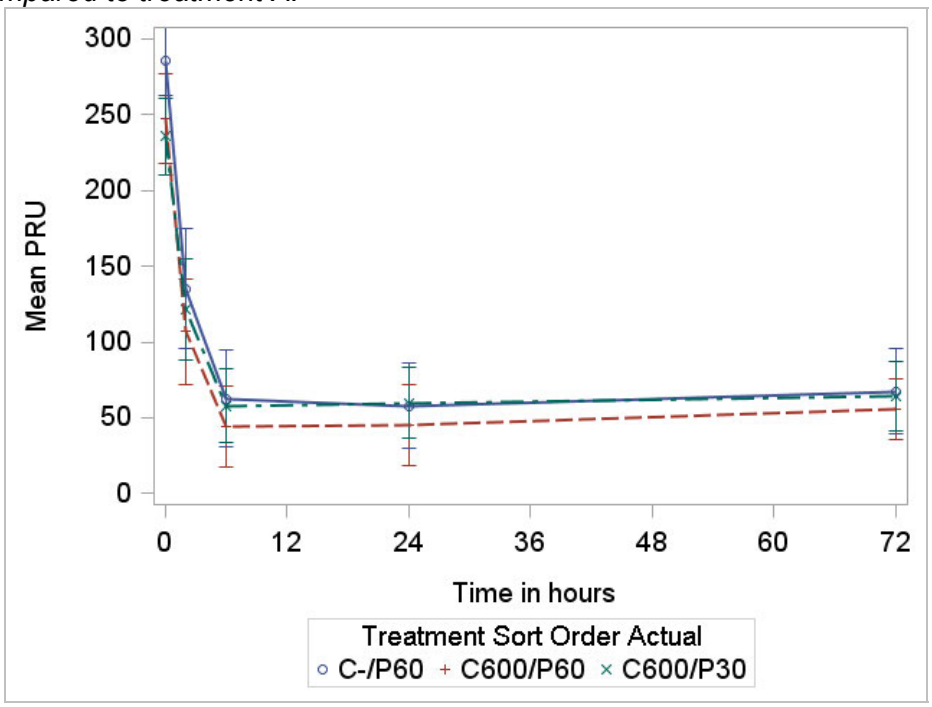


Figure 1. Time course of mean PRU
Source: bmervat.xpt

The reason for the similar baselines across the three treatment arms can be traced to the lack of time difference between the clopidogrel/placebo loading dose and prasugrel loading dose during PCI. Because of this, it becomes difficult to interpret the findings of this study.

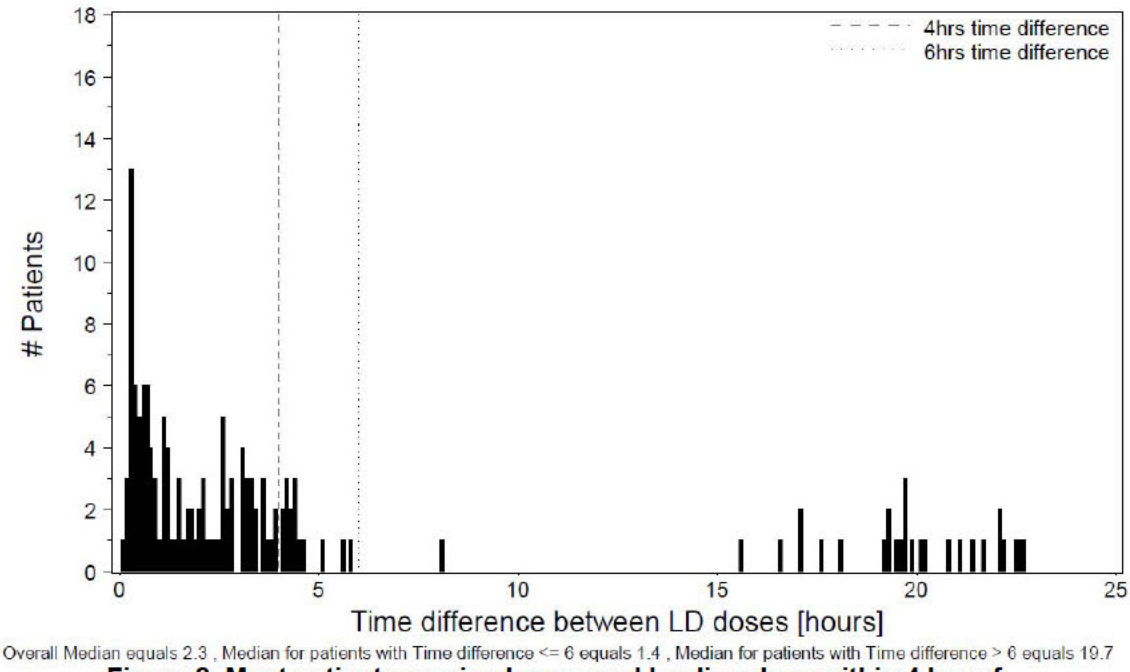


Figure 2. Most patients received prasugrel loading dose within 4 hrs of clopidogrel/placebo loading dose
Source: Figure TAEH.7.17. of the Study Report

Safety

Two female patients, who were randomized to the placebo clopidogrel followed by 60 mg prasugrel LD, died during the study. The cause of death was cardio-respiratory arrest for one patient and ventricular arrhythmia leading to cardiogenic shock for the second patient. Neither instance was considered related to study drug or study procedures by the PI.
There were eleven SAEs recorded during the study, 8 of which occurred in the clopidogrel 600 mg/prasugrel 60 mg group. Most of them were not bleeding events.

Conclusions

Given uncertainties with the ability of the VerifyNow assay to distinguish between treatments and variability being very high, (b) (4) Further, the study does not allow for appropriate comparison of PD effects as most of the patients received loading doses of clopidogrel/placebo and prasugrel within 4 hrs. (b) (4)

Additional Comments

According to the sponsor, patients in India, in particular in site 50, which was the highest and third-highest enrolling site in India and overall, respectively, showed different responses to study treatment compared to other sites and overall. However, the results of the mixed model sensitivity analysis comparing treatments 6 hours after a prasugrel loading dose did not show that conclusions reached from the analysis using all centers would be changed.

4.1.3 H7T-MC-TADI

Clinical Pharmacology Study Review
Intrinsic Factor Study

Study	H7T-MC-TADI
Title	A pharmacokinetic and pharmacodynamic comparison of prasugrel and clopidogrel in low body weight versus higher body weight aspirin-treated subjects with stable coronary artery disease.
Study Period	April 9, 2010 to August 3, 2011
Sponsor	Eli Lilly, Inc
Phase	1b
EDR Link	\\cdsesub1\evsprod\NDA022307\0173\m5\53-clin-stud-rep\534-rep-human-pd-stud\5342-patient-pd-stud-rep\h7t-mc-tadi\tadi-04-body.pdf
Rationale	Patients weighing less than 60 kg have an increased risk of bleeding when taking a 10 mg dose of prasugrel due to higher exposure. This study aimed to establish non-inferiority of prasugrel 5 mg in stable coronary artery disease (CAD) patients weighing less than 60 kg, compared to heavier patients taking a 10 mg dose.

Study Design

Randomized, multi-center, partially-blind, double-dummy, multiple dose, active control, three-period

Treatments

A. Prasugrel 5 mg
B. Prasugrel 10 mg
C. Clopidogrel 75 mg

Table 1. Treatments

Population	Sequence	Period and Treatment		
		1	2	3
		Single-blind*	Double-blind	
<60 kg	1	A	B	C
	2	A	C	B
≥60 kg	1	B	A	C
	2	B	C	A

Source: CSR p. 19; P=Prasugrel, C=Clopidogrel; *Subjects were masked to treatment

Patient Population

Patients were eligible to participate in the trial if they were at least 18 years and less than 75 years old with a history of stable coronary artery disease.

Pharmacokinetics

Pharmacokinetic analyses were done using a non-compartmental model in WinNonlin software. The original statistical analysis plan included using a previously developed

PopPK model to calculate parameter estimates, however the data were too sparse to allow for this. The PK parameters reported are AUClast, Tmax, and Cmax.
Samples for characterization of the concentration-time course of prasugrel and clopidogrel were taken at 0.5, 1, 2, 3, 4 hours post-dose at the following time points:
visit 2 (start of period 1),
visit 3 (end of period 1) after the first administration of period 2 study drug,
visit 4 (end of period 2) after the first administration of period 3 study drug, and
visit 5 (end of period 3) after the last administration of period 3 study drug.
There was no washout period between treatments.
Therefore all subjects with low body weight have one 4-hour concentration profile each for prasugrel 5 mg and, depending on sequence, either two profiles for prasugrel 10 mg or clopidogrel 75 mg. For patients with high body weight, each would have one prasugrel 10 mg profile and either 2 prasugrel 5 mg or 2 clopidogrel 75 mg profiles, depending on sequence of treatment.
Reviewer's note: The CSR states that exact time of dosing was not noted in the eCRF and that it was derived from the 0.5 h blood draw time. For the primary outcome (which is a PD outcome) this should not matter, as this was to be collected prior to the maintenance dose. The results from PK analysis should still be interpretable. The sampling scheme is reasonable.

Pharmacodynamics

Pharmacodynamic parameters included the following:

- maximum platelet aggregation (MPA) to 5 and 20 μM ADP,
- residual platelet aggregation (RPA) to 5 and 20 μM ADP,
- inhibition of platelet aggregation (IPA) to 5 and 20 μM ADP,
- inhibition of residual platelet aggregation (IRPA) to 5 and 20 μM ADP,
- platelet reactivity index (PRI) measured by vasodilator-associated stimulated phosphoprotein (VASP), and
- P2Y12 reaction units (PRU) measured by the VerifyNow® P2Y12 assay.

Light transition aggregometry was used to measure MPA, RPA, IPA, and IRPA.
Samples were collected at the following time points:

- pre-dose during visit 2 (start of period 1),
- visit 3 (end of period 1),
- visit 4 (end of period 2), and
- visit 5 (end of period 3).

Analytical Methods

Pharmacokinetics

Concentrations of clopidogrel (R361015_MP), prasugrel active metabolite (R138727_MP) and an inactive prasugrel metabolite (R106583) were quantified using validated methods. The runs for two other inactive metabolites did not meet acceptance criteria (although the method was validated) and were subsequently not analyzed. All validated assays use LC/MS/MS for quantification. Prasugrel and clopidogrel active metabolites are stabilized by a derivatization with 2-bromo-3'-methoxyacetophenone,

which is added to the sample collection tube prior to collection of a whole blood sample as described in the validation report. Please refer to Table 3 for details pertaining to the performance of the analytical method during sample analysis.

Pharmacodynamics

Light transmission aggregometry

Measurement of platelet aggregation using the light transition aggregometry method was done in platelet-rich plasma in response to 5 and 20 μM ADP. The resulting parameters were maximum and residual platelet aggregation (MPA and RPA). RPA is the percent aggregation measured 6 minutes after addition of 5 and 20 μM ADP.

VerifyNow P2Y12

The response to study drug was also measured using the VerifyNow device. This device computes the P2Y12 reaction units, a BASE value and the device-reported % inhibition of platelet aggregation. The BASE value represents the rate and extent of platelet aggregation in response to Thrombin receptor activating peptide (TRAP) and gives the baseline platelet aggregation independent of the P2Y12 pathway. As such, the BASE value serves as an internal standard. The PRU value is based on the rate and extent of platelet aggregation in response to ADP. Finally, the percent inhibition of platelet aggregation is calculated as Inhibition[%]=(1-PRU/BASE)*100 and represents the proportion of reduction from BASE due to P2Y12 inhibition.

VASP

A tertiary measure for the extent of platelet aggregation was VASP phosphorylation, which was measured in a whole blood flow cytometric assay. The resulting parameter is the platelet reactivity index (PRI), given in percent, which is the ratio of non-phosphorylated VASP to phosphorylated VASP.

Reviewer's note: The methods used by the applicant appear adequate.

Results

Study Population

Table 2. Patient disposition

Treatment/Parameter	BW <60 kg	BW ≥60 kg	Total
Randomized	34	38	72
Primary ITT	33	37	70
Withdrawn/Discontinued post Period 1	1	1	2
Withdrawn/Discontinued post Period 2	1	1	2
Age [years] [Median (range)]	64 (43-74)	64.8 (41-75)	64.6 (41-75)
Male/Female	5/29	26/12	31/41
Race			
White	33	34	67
Black or African American	0	4	4
Asian	1	0	1
Weight [kg]	56.4 (45.0-59.8)	84.7 (62.5-134.1)	71.33 (45.0-134.1)

Source: CSR p. 31 ff. and 34 ff.

Pharmacokinetics

The geometric mean ratio (GMR) comparing the low to the high body weight group was determined for AUClast, where the last time point was taken at 4 hours post-dose. The resulting GMR was 0.62 with 0.53 and 0.72 marking the lower and higher bounds of the 90% CI, respectively.

There were four concentration-time profiles available from most patients, with the treatment in period 3 having two concentration-time profiles.

Table 3. Prasugrel-AM pharmacokinetic parameters (Patients <60kg)

	BW <60 kg			BW ≥60 kg		
Treatment	P 5 mg	P 10 mg		P 5 mg		P 10 mg
Visit	2	3 or 4	5	3 or 4	5	2
N	34	33	17	36	16	38
*Cmax [ng/mL]	31.0 (51)	65.1 (52)	68.6 (56)	19.4 (70)	17.7 (58)	48.5 (60)
**Tmax [h]	0.50 (0.5-1.00)	0.50 (0.5-3.00)	0.50 (0.5-1.00)	0.50 (0.50-2.02)	0.50 (0.50-1.03)	0.50 (0.47-2.00)
*AUClast [ng*h/mL]	28.9 (37)	59.3 (39)	59.3 (44)	19.9 (50)	18.3 (37)	46.7 (44)

***Geometric mean (CV%), ** Median (Min-Max); Source: adapted from CSR page 96**

Table 4. Clopidogrel-AM pharmacokinetic parameters

	Patients <60kg		Patients ≥60 kg	
Treatment	Clopidogrel 75 mg			
Visit	3 or 4	5	3 or 4	5
N	31	15	37	20
*Cmax [ng/mL]	17.8 (58)	21.6 (40)	11.3 (79)	12.2 (64)
**Tmax [h]	0.50 (0.50-2.00)	0.50 (0.50-0.50)	0.50 (0.50-3.00)	0.50 (0.50-2.00)
*AUClast [ng*h/mL]	17.9 (41)	19.4 (32)	12.9 (62)	12.5 (59)

***Geometric mean (CV%), ** Median (Min-Max); Source: adapted from CSR page 96**

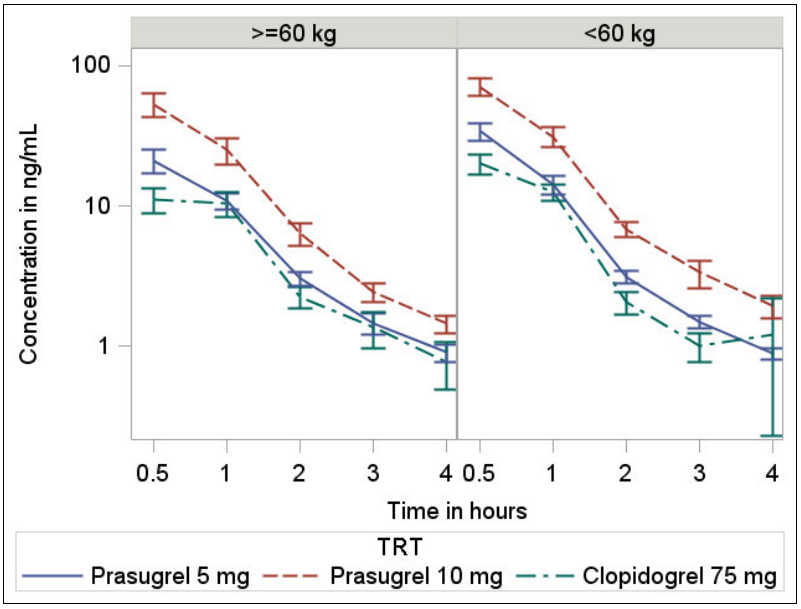


Figure 1. Mean concentration of prasugrel active metabolite by treatment (log-linear scale).
[Source: tadi_wnl_pk_final_24oct2011_mod2_o.xpt]

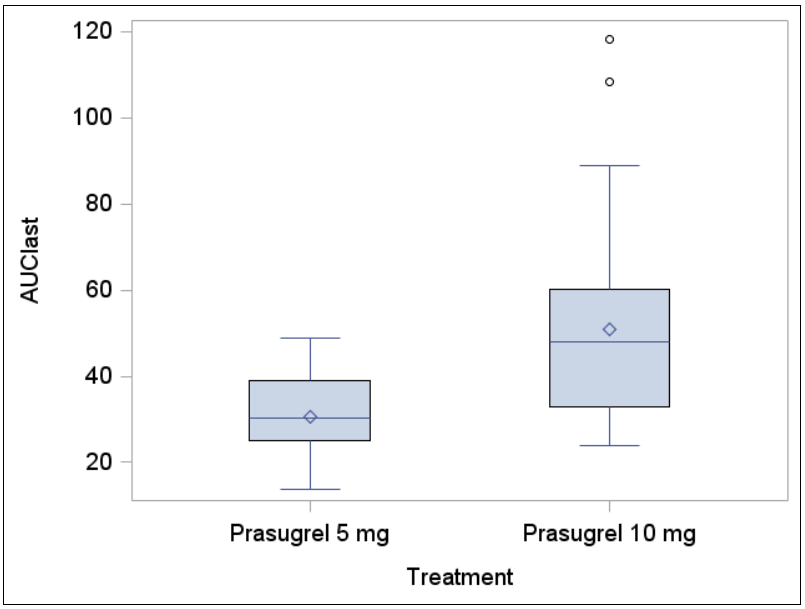


Figure 2. Comparison of AUClast in Period 1
[Source: pgx_pk]

Pharmacodynamics

Non-inferiority of Prasugrel 5 mg in Low Weight Patients

The primary objective of the study was to find that a 5 mg dose in subjects weighing less than 60 kg was non-inferior to a 10 mg dose of prasugrel in patients weighing 60 kg or more. The difference between the median of MPA in low body weight patients and the 75% percentile of MPA in higher body weight patients was computed. The upper 97.5% CI was not to exceed a margin of 15% difference.

The sponsor's analysis found that the difference between the median MPA for patients less than 60 kg and the 75th percentile of MPA for patients heavier than 60 kg was -10.10, with a 95% CI of the difference of -23.40 to 0.20. Therefore the upper 97.5% CI boundary excludes a 15% difference in MPA.

Baseline MPA was similar between patients in the low and high body weight groups (Figure 3). The comparison for non-inferiority was done using period 1 data. This period was the single-blind period (subjects were masked to treatment) designed to compare the two treatments for non-inferiority.

The MPA and the IPA to 20 µM ADP are shown in Figures 4 and 5, respectively and are similar between the two groups. Figure 6 shows the comparison across treatments by body weight group.

Mean PRU for patients in the low weight group was 129.53 compared to 102.09 in the higher weight group. VASP PRI has mean values of 33.54 and 27.79 for the low and high weight groups, respectively. None of the two measures were considered statistically significantly different between the two weight groups.

Reviewer's Note: It is currently not known how to interpret changes in platelet aggregation with regards to clinical endpoints (i.e. death, non-fatal MI or stroke). A difference of -10.10% between median and 75th percentile of MPA for low and high body

weight groups, respectively is difficult to interpret. However, the TRILOGY study adjusted doses for patients weighing less than 60 kg and found that bleeding was not statistically significantly different from clopidogrel.

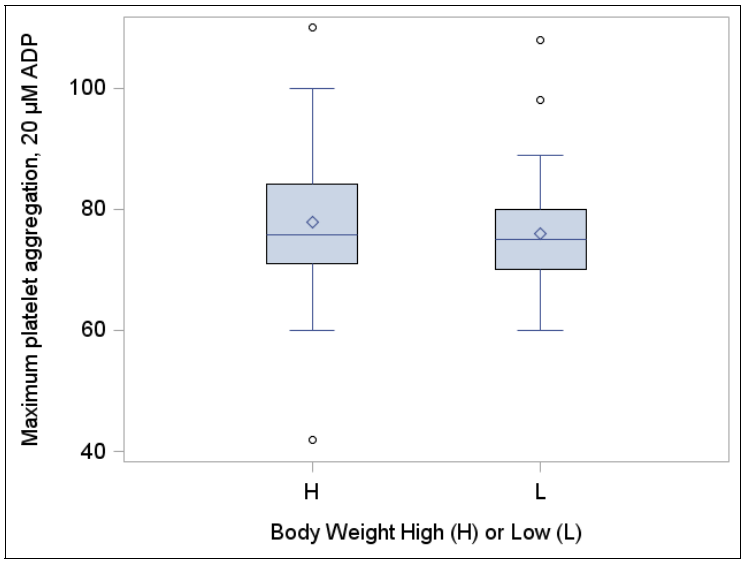


Figure 3. Baseline MPA by weight group
[Source: lta.xpt]

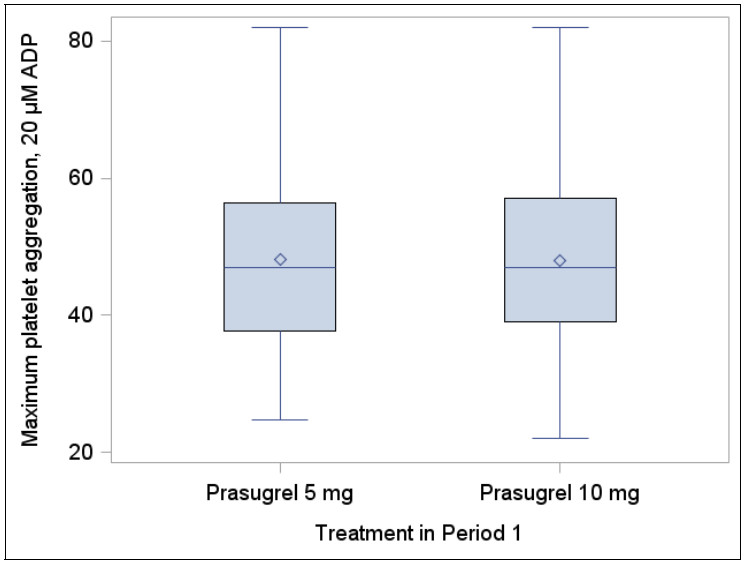


Figure 4. Comparison of MPA to 20 µM ADP at end of period 1
[Source: lta.xpt]

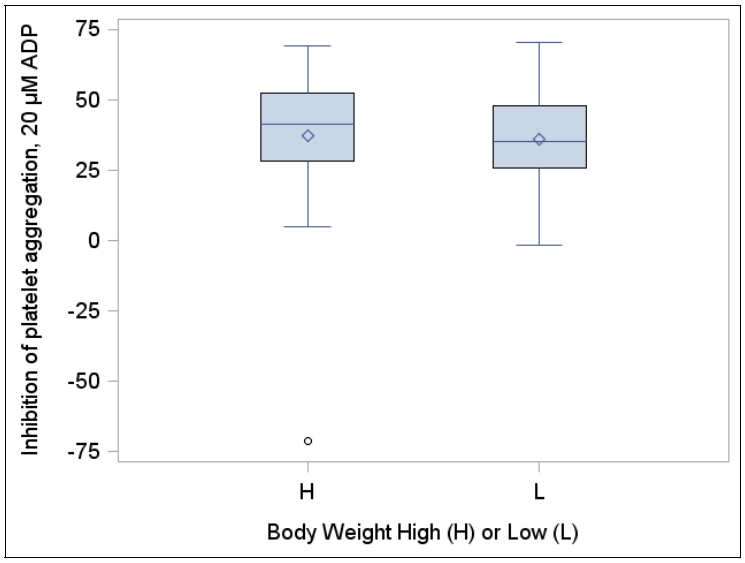


Figure 5. IPA to 20 µM ADP after period 1
[Source: lta.xpt]

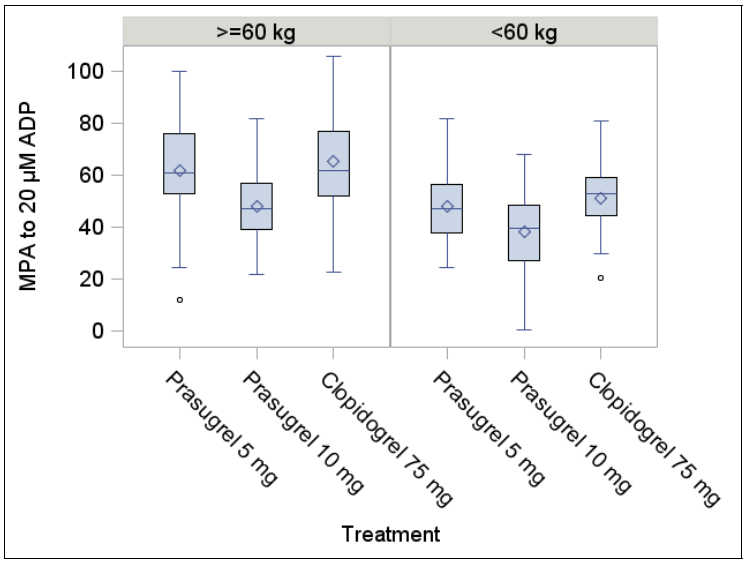


Figure 6. MPA to 20 µM ADP compared between treatments
[Source: lta.xpt]

Safety

Was there any death or serious adverse events? ☒ Yes ☐ No
One subject developed a subarachnoid hemorrhage 17 days after the last intake of study drug (last period study treatment was prasugrel 10 mg) with fatal outcome. This event was ruled not related to study drug or protocol procedures. The narrative is available in the CSR on page 103.

Conclusions

The original review included population PK analyses of available data from three trials TAAD, TABR, and TAAL. In all three trials it was found that systemic exposure increased with decreasing body weight due to decreased clearance. Analysis of bleeding event data showed that patients with a body weight of less than 60 kg were at a higher risk for bleeds than patients weighing more than 60 kg. The label includes a recommendation to decrease the maintenance dose of prasugrel to 5 mg in patients weighing less than 60 kg, noting, however, that the effectiveness of this reduced dose had not been studied prospectively.

The present study was done in patients with stable CAD and showed that AUClast is about 38% lower in lower weight patients who were given 5 mg prasugrel compared to higher weight patients on 10 mg prasugrel. This reduction is expected and had been predicted from simulations. In addition, maximum platelet aggregation in patients weighing less than 60 kg who received 5 mg prasugrel was similar to that of patients weighing more than 60 kg and receiving 10 mg prasugrel. Patients receiving 5 mg prasugrel also did not show lower response than clopidogrel 75 mg. Therefore, the adjustment of dose from 10 to 5 mg prasugrel (maintenance dose) for subjects weighing less than 60 kg seems reasonable.

Recommendations for Labeling

A dose adjustment to 5 mg in patients weighing less than 60 kg is already included in the label and the sponsor does not propose changes to the dose. New information pertains to the population studied in this study.

4.1.4 H7T-MC-TACY

Clinical Pharmacology Review
Intrinsic Factor Study

Study	H7T-MC-TACY
Title	"A pharmacokinetic and pharmacodynamic comparison of prasugrel and clopidogrel in very elderly versus non-elderly aspirin-treated subjects with stable coronary artery disease."
Study Period	March 30, 2010 to October 17, 2011
Sponsor	Eli Lilly, Inc.
Phase	1b
EDR Link	\\cdsesub1\evsprod\NDA022307\0173\m5\53-clin-stud-rep\534-rep-human-pd-stud\5342-patient-pd-stud-rep\h7t-mc-tacy\tacy-04-body.pdf
Rationale	The present study was aiming to elucidate whether the response (MPA to 20 μM ADP) in the very elderly (≥75 years) group receiving 5 mg prasugrel MD was non-inferior compared to younger subjects (45≤ age <65 years) receiving 10 mg prasugrel MD. At the MD of 10 mg, very elderly patients tend to show increased bleeding risk.

Study Design

Randomized, multi-center, partially-blind, double-dummy, multiple dose, active control, three-period

Treatments

A. Prasugrel 5 mg
B. Prasugrel 10 mg
C. Clopidogrel 75 mg

Table 1. Treatment arms

Population	Sequence	Period and Treatment		
		1	2	3
		Single-blind*	Double-blind	
≥75 years	1	A	B	C
	2	A	C	B
45≤ age <65 years	1	B	A	C
	2	B	C	A

[Source: CSR p. 20; P=Prasugrel, C=Clopidogrel]

***Subjects were masked to treatment**

Patient Population

Patients with stable coronary artery disease (CAD) weighing at least 60 kg and being either 75 years and older, or between 45 and 64 years old were eligible to participate in the study.

Pharmacokinetics

Samples for characterization of the concentration-time course of prasugrel and clopidogrel were taken at 0.5, 1, 2, 3, 4 hours post-dose at the following time points:

- visit 2 (start of period 1),
- visit 3 (end of period 1) after the first administration of period 2 study drug,
- visit 4 (end of period 2) after the first administration of period 3 study drug, and
- visit 5 (end of period 3) after the last administration of period 3 study drug.

Pharmacokinetic parameter estimates were derived using non-compartmental analysis in WinNonlin® software. The original statistical analysis plan included using a previously developed popPK model to calculate parameter estimates, however the data were too sparse to allow for this. The PK parameters estimated were AUClast, Cmax and Tmax.

Reviewer's note: Time of dosing was not captured in the source document or the eCRF and the sponsor used the 0.5 hour time point to back-calculate the time of dosing, albeit under the assumption that the PK sample was collected exactly 30 minutes after dosing. There were two samples in two subjects each that had exactly same clock times and their times were adjusted based on observed concentrations. While this is not a very good practice, the impact of this adjustment is likely to be minimal.

Pharmacodynamics

Pharmacodynamic parameters included platelet aggregation as measured by light transmission aggregometry (LTA), platelet reactivity index (PRI) as measured by vasodilator-associated stimulated phosphoprotein (VASP) and the P2Y12 reaction units (PRU) as measured by the VerifyNow® P2Y12 assay.
Samples were collected at the following time points:

- pre-dose during visit 2 (start of period 1),
- visit 3 (end of period 1),
- visit 4 (end of period 2), and
- visit 5 (end of period 3).

Analytical Methods

Pharmacokinetics

The concentrations of clopidogrel (R361015_MP) and prasugrel active metabolite (R138727_MP) were quantified using validated methods. All validated assays use LC/MS/MS for quantification. Prasugrel and clopidogrel active metabolites are stabilized by derivatization with 2-bromo-3'-methoxyacetophenone, which is added to the sample collection tube prior to collection of a whole blood sample. The method for clopidogrel analysis changed with regards to the internal standard used. The older method used an

analog internal standard, while the newer method used an internal standard that was stable-isotope labeled. The sponsor refers to a cross-validation with acceptable results in their bioanalytical reports, however, no actual results were shown in this report. The characteristics and performance of the methods are shown in Table 4.

Reviewer's Note: The analytical methods seem adequate to assess clopidogrel and prasugrel concentrations, based on method validation reports and abbreviated bioanalytical reports submitted by the sponsor.

Pharmacodynamics

Please see review for study TADI in Section 4.1.3 above for further information.

Results

Demographics

A total of 155 patients were randomized and 4 patients discontinued after Period 1, and 4 after Period 2. Patient disposition and demographics are shown in Table 2 below.

	Age ≥75 years	**45≤ Age <65 years**	**Total**
Randomized	73	82	155
Primary ITT	72	79	151
Safety	73	82	155
Withdrawn/Discontinued post Period 1	1	3	4
Withdrawn/Discontinued post Period 2	3	1	4
Age [Median (range)] [years]	78.13 (74.6 to 87.7)	55.62 (44.7 to 65.1)	63.61 (44.7 to 87.7)
Male/Female	54/19	65/17	119/36
Race			
White	69	72	141
Black or African American	4	8	12
Multiple	0	2	2
Weight [kg]	85.35 (60.4 to 112.7)	93.10 (60.2 to 145.0)	89.45 (60.2 to 145.0)

[Source: CSR p. 35 ff., 38 ff.]

Pharmacokinetics

The geometric mean ratio (GMR) comparing the very elderly to the non-elderly group was determined for AUClast, where the last time point was taken at 4 hours post-dose. The resulting GMR was 0.51 with 0.46 and 0.58 marking the lower and higher bounds of the 90% CI, respectively. The sponsor also included weight into the model and GMR for AUClast was 0.46 (90% CI: 0.41 – 0.51).

There were four concentration-time profiles available from most patients, one each for Periods 1 and 2, and a beginning and end of Period 3 profile. PK parameters are summarized in Tables 3 and 4 and Figures 1 and 2.

Table 3. Mean pharmacokinetic parameters for prasugrel

Geometric mean (CV%)						
	Age ≥75 years			**45≤ Age <65 years**		
Dose	5 mg	10 mg		5 mg		10 mg
Visit	2	3 or 4	5	3 or 4	5	2
N	71	69	32	77	37	80
Cmax [ng/mL]	19.4 (65)	40.6 (58)	41.6 (57)	16.1 (77)	16.6 (85)	38.5 (70)
Tmax [h]	0.50 (0.00-3.00)	0.50 (0.50-2.00)	0.50 (0.50-1.00)	0.50 (0.5-3.00)	0.5 (0.5-3.00)	0.50 (0.47-3.00)
AUClast [ng*h/mL]	18.9 (43)	40.1 (35)	43.7 (34)	16.1 (54)	16.1 (54)	36.7 (49)

[Source: CSR page 102]

Table 4. Mean pharmacokinetic parameters for clopidogrel

Geometric mean (CV%)				
	Age ≥75 years		**45≤ Age <65 years**	
Visit	3 or 4	5	3 or 4	5
N	70	33	77	41
Cmax [ng/mL]	11.4 (73)	12.9 (78)	11.6 (77)	11.1 (71)
Tmax [h]	0.50 (0.50-3.00)	0.50 (0.50-1.08)	0.50 (0.50-2.00)	0.50 (0.50-4.00)
AUClast [ng*h/mL]	12.6 (59)	14.0 (68)	12.0 (69)	11.4 (66)

[Source: CSR page 102]

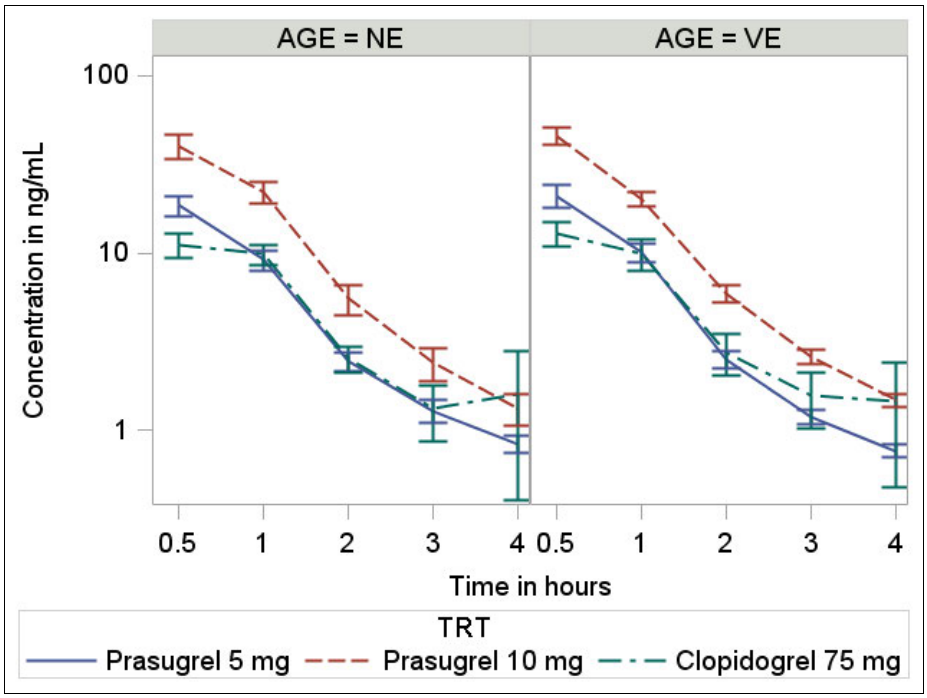


Figure 1. Mean concentrations of active metabolites in plasma (log-linear scale)
NE=non-elderly (45≤ Age <65 years), VE=very elderly (Age ≥75 years)
[Source: tacy_wnl_pk_final_24jan2012_mod2_o.xpt]

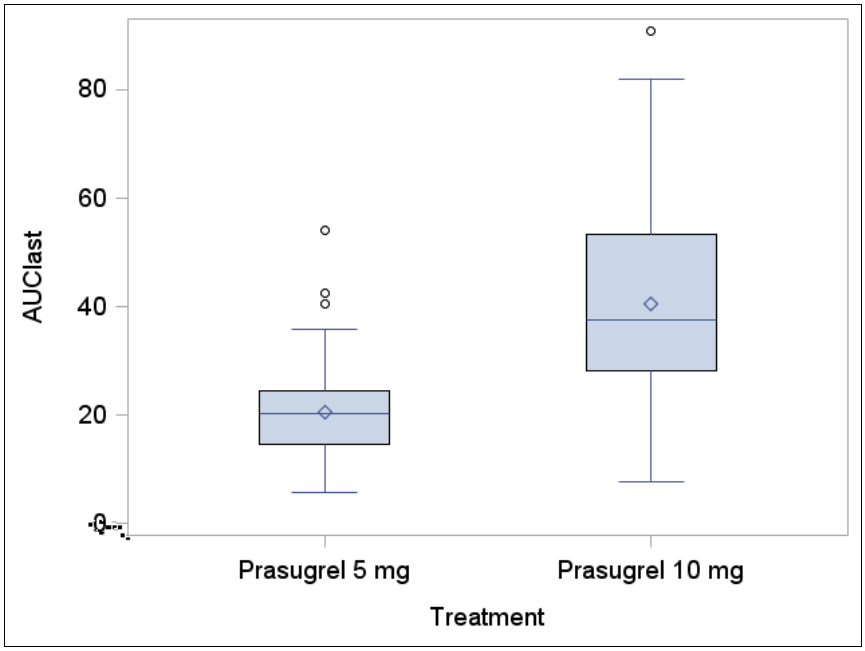


Figure 2. Comparison of AUClast in Period 1
10 mg = 45≤ Age <65 years, 5 mg = Age ≥75 years
[Source: pgx_pk xpt]

Pharmacodynamics

The primary objective of the study was to test whether a 5 mg dose in subjects older than 75 years of age was non-inferior to a 10 mg dose of prasugrel in patients less than 75 years of age. The difference between the median of MPA in patients younger than 75 years and the 75th percentile of MPA in at least 75 year old patients was computed. The upper 97.5% CI was not to exceed a margin of 15% difference.

The sponsor's analysis found that the difference between the median MPA for the younger patients and the 75th percentile of MPA for the older patients was 6.00%, with a 95% CI of the difference of 1.00% to 9.00%. Therefore the upper 97.5% CI boundary excludes a 15% difference in MPA.

Baseline MPA was similar between age groups (Figure 3). Figures 4 and 5 show the maximum platelet aggregation after patients took prasugrel 5 mg or 10 mg for 12 ± 2 days in period 1. This period was the single-blind period (subjects were masked to treatment) designed to compare the two treatments for non-inferiority.

A comparison of the mean MPA between age groups showed that patients 75 years and older, who received 5 mg prasugrel had statistically significantly higher mean MPA values than patients between the ages of 45 and 65 years.

Reviewer's Note: It is currently not known how to interpret changes in platelet aggregation with regards to clinical endpoints (i.e. death, non-fatal MI or stroke). A difference of 9.37% between median and 75th percentile of MPA between younger and elderly age groups, respectively, is difficult to interpret. It is also difficult to interpret whether the comparison to the 75th percentile is useful here, because the somewhat arbitrary no-concern difference of 15% shows that there is no difference between 5 mg in older compared to 10 mg in younger subjects, while the LS mean differences between the two groups show that there is a statistically significant difference between the two groups. It is known that elderly patients tend to bleed easier, but also tend to clot more easily. Any pharmacodynamic rationale may need better understanding of differences in clotting properties between younger and older patients. That said, when comparing MPA between prasugrel 5 mg and clopidogrel 75 mg, prasugrel 5 mg still achieved larger reduction in MPA to 20 µM ADP.

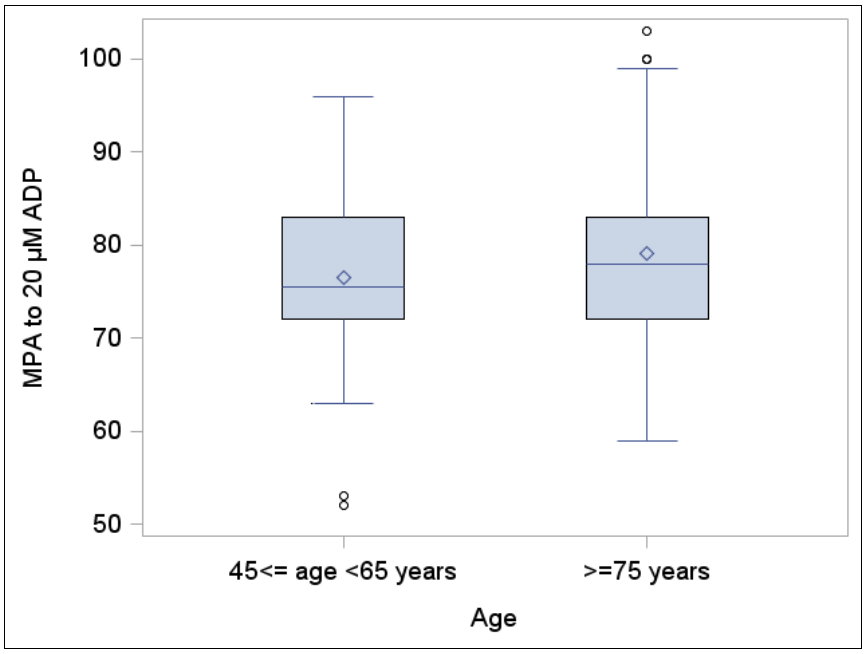


Figure 3. Baseline MPA by weight group
[Source: lta.xpt]

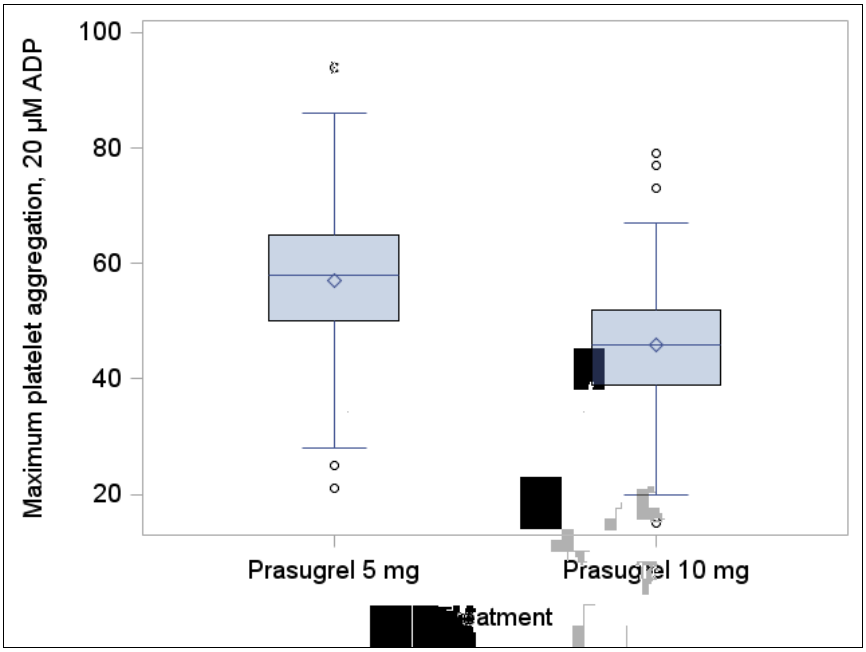


Figure 4. Comparison of MPA to 20 µM ADP at end of period 1
[Source: lta.xpt]

APPEARS THIS WAY ON ORIGINAL

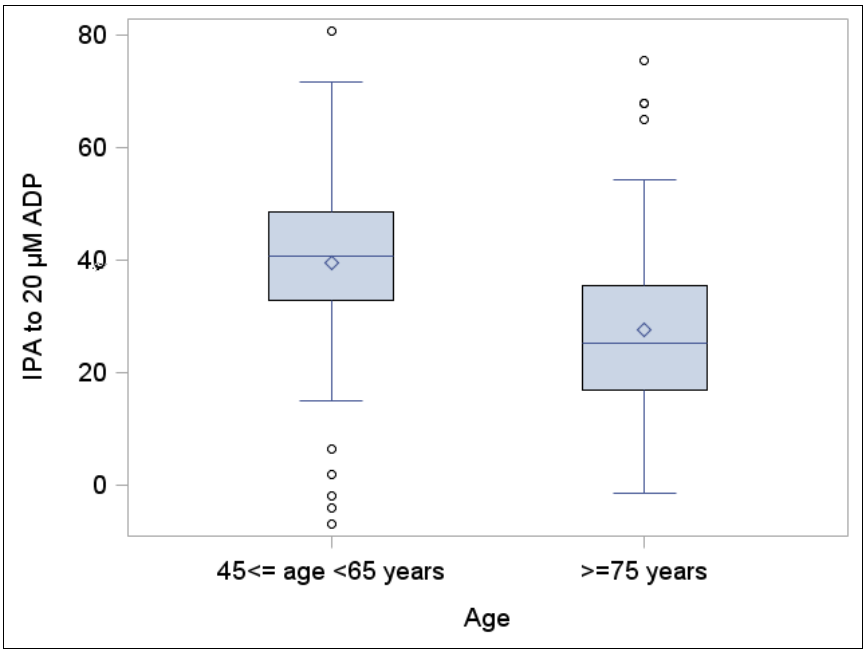


Figure 5. IPA to 20 µM ADP after period 1
[Source: lta.xpt]

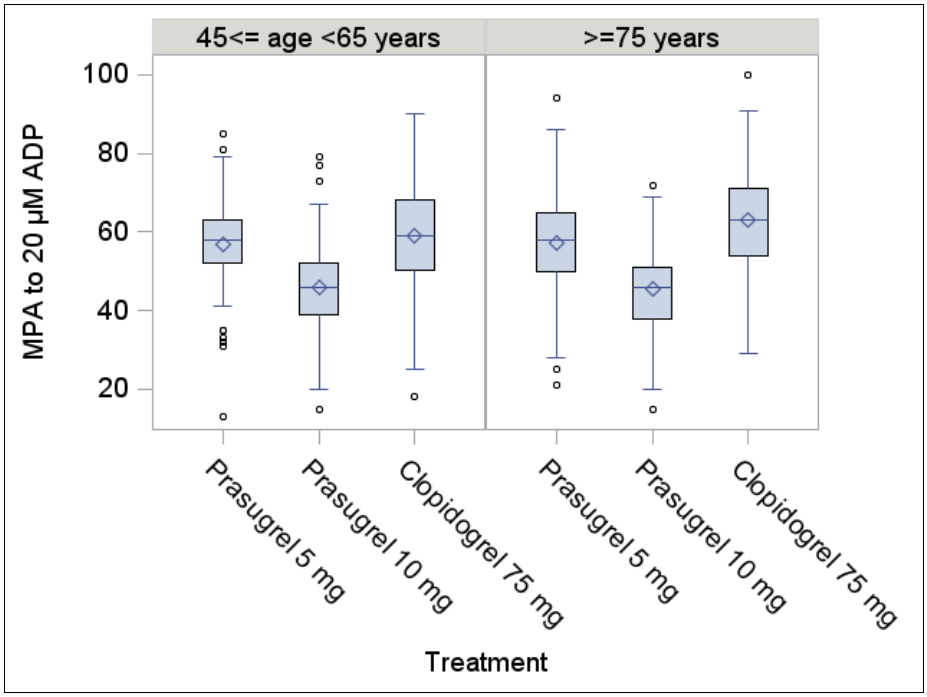


Figure 6. MPA to 20 µM ADP compared between treatments
[Source: lta.xpt]

Mean PRU measured with the VerifyNow® $P2Y_{12}$ system was 175.52 and 85.46 for the elderly versus younger age groups, respectively and VASP PRI means were 44.30 for the elderly patients and 27.74 for the younger patients. In both cases the results were statistically significantly different.

Safety

No serious adverse events or death occurred during the study.

Conclusions

The review of population PK analyses did not seem to support age as a covariate on pharmacokinetics, nevertheless, the sponsor finds that patients 75 years and older show about a 19% higher exposure than younger patients. The present study showed that baseline levels of MPA to 20 μM ADP are similar between the two groups studied (patients 75 and older and patients between 45 and 65 years of age). For patients 75 years and older, the prasugrel dose was lowered to 5 mg (maintenance dose) and the resulting AUClast in the very old patients was reduced to about 50% of the exposure seen in younger patients. This was expected based on the lack of influence of age on prasugrel's exposure. However, the MPA to 20 μM ADP was reduced as well, with both groups being statistically significantly different. Prasugrel 5 mg in patients 75 and older did not seem to show higher MPA to 20 μM ADP compared to 75 mg clopidogrel. This suggests that while halving the dose in patients older than 75 years results in less reduction in MPA than prasugrel 10 mg in younger patients, it may at least yield the same efficacy (in terms of MPA reduction) as clopidogrel. Of note is the fact that it is not possible to assess this change in MPA with regards to the clinical endpoint, as a true relationship between them has not been established.

Recommendations for Labeling

4.2 Pharmacogenomics review

OFFICE OF CLINICAL PHARMACOLOGY
GENOMICS GROUP REVIEW

NDA/BLA Number	022307
Submission Date	12/14/2012
Applicant Name	Eli Lilly and Co.
Generic Name	Prasugrel
Proposed Indication	Treatment of ACS
Primary Reviewer	Hobart Rogers, Pharm.D, Ph.D
Secondary Reviewer	Michael Pacanowski, Pharm.D, M.P.H

EXECUTIVE SUMMARY

Prasugrel is a thienopyridine inhibitor of platelet activation and aggregation mediated by the P2Y12 receptor. The sponsor submitted a supplemental NDA (sNDA) composed of the TRILOGY ACS (TABY) study. This review focuses on the pharmacogenomic (PG) substudy of the TABY study. The TABY PG substudy fulfilled the requirement of the post marketing commitment #6 as part of the approval letter on 07/10/09. The PG substudy did not identify any associations between CYP2C19 genotype and efficacy or safety in either the clopidogrel- or prasugrel-treated arms of TABY. (b) (4)

[redacted]

1 BACKGROUND

Prasugrel is a thienopyridine inhibitor of platelet activation and aggregation mediated by the P2Y12 receptor. Prasugrel was approved by the FDA on 07/10/09 for the treatment of ACS in patients who are managed with Percutaneous Coronary Intervention (PCI). During review of the original NDA, it was observed that within the clopidogrel arm, CYP2C19 poor metabolizers (PMs) had higher event rates compared with extensive metabolizers (EMs), which is consistent with prior studies. However, the opposite effect was observed in prasugrel treated subjects. As such, the Agency issued a post marketing commitment as follows:

You commit to the collection of samples at baseline for genotyping CYP450 enzymes in TRILOGY subjects, to allow a comparison of effectiveness and bleeding in prasugrel and clopidogrel subgroups by metabolizer status. These data will be submitted with the final study report of TRILOGY. The periodic reports will include the fraction of subjects who consented to genetic testing.

In the current submission the sponsor proposes to update the labeling with the findings from the TRILOGY-TIMI 38 ACS study (referred to as TABY hereafter), which

evaluates the efficacy and safety of prasugrel in subjects with ACS who were medically managed.

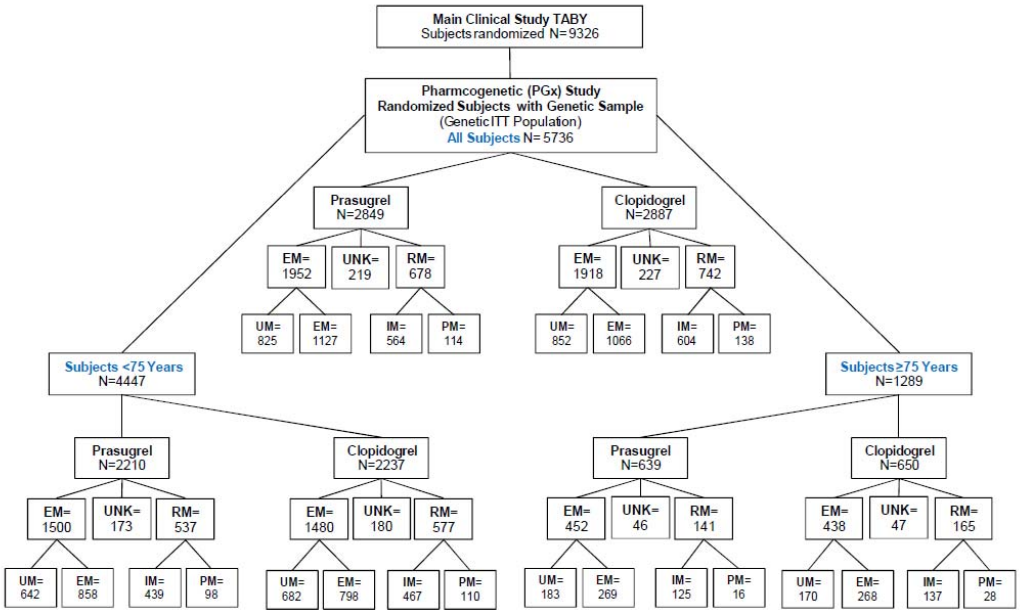
The purpose of this review is to evaluate the sponsor's PG data and subsequent analyses of the TABY study and determine whether relevant pharmacogenomic findings need to be communicated in the labeling.

2 SUBMISSION CONTENT RELATED TO GENOMICS

(b) (4)

(b) (4) The overall TABY study consisted of 9,326 medically managed subjects with UA/STEMI who were randomized 1:1 to receive either prasugrel or clopidogrel. The ITT set consisted of 7,243 subjects who were less than 75 years of age. Of these subjects 5,736 consented for the PG substudy (Figure 1). This represented a 62% sample acquisition.

Figure 1. PG substudy of TABY



The sponsor assessed CYP2C19 genotype status in the PG subset of subjects in the TABY trial. The primary objective was to assess the interaction between treatment groups and the presence of CYP2C19 genetic variation on clinical efficacy in medically

managed ACS subjects <75 years of age (n = 4447) who were enrolled within 10 days of an unstable angina/non-ST-segment elevation myocardial infarction (UA/NSTEMI) index event, as measured by the primary efficacy measure in the TABY (the main study) analysis: a composite endpoint of cardiovascular (CV) death, myocardial infarction (MI), or stroke.

DNA samples were collected at baseline, where possible, from subjects who consented for the voluntary PG study. Subjects were also permitted to enroll in the substudy by providing DNA at any visit, but collection at baseline was encouraged. All DNA samples available from TABY were genotyped utilizing the DMET™ Plus Gene Chip Platform. CYP2C19 phenotype derived from genotype was assigned in both a 2-level and a 4-level manor (Table 1).

Table 1. CYP2C19 2-Level and 4-Level Predicted Phenotypes

2-level Phenotype	4-level Phenotype	Genotype
EM	UM	*1/*17 *17/*17
	EM	*1/*1
RM	IM	*1/*2-*8
	PM	2-*8/2-*8
UNK		2-*8/*17

(source: page 81 PG Substudy Report for the TABY Clinical Study)

The primary analyses were performed on the 2 CYP2C19 genotype-predicted metabolizer groups: EMs and reduced metabolizers (RMs). EMs and RMs are non-carriers and carriers of reduced function CYP2C19 alleles respectively. The primary analysis assessed the treatment by CYP2C19-predicted phenotype interaction effect. Subsequent comparisons were performed to further determine the effects of CYP2C19-predicted phenotype within treatments followed by comparison of treatment effects within genotype groups.

The following endpoints were evaluated using a 2-level and 4-level phenotype assignment 1) composite of CV death, MI or stroke (primary efficacy endpoint), 2) pharmacodynamics (PD) 3) Non-CABG-related TIMI major or minor bleeding.

Moreover, the sponsor conducted additional analysis of a PD substudy of TABY, in which patients who had received clopidogrel prior to the index event were switched to prasugrel 5 or 10 mg. Approximately one third of TABY subjects participated in a PFS substudy, of these 1770 subjects (890 prasugrel, 880 clopidogrel) also provided DNA samples for the PG substudy. The key objective of the genetic PD analysis was to assess the interaction between treatment groups and CYP2C19 genetic variation on platelet reactivity. Platelet aggregation (reactivity) was measured by the Accumetrics VerifyNow® P2Y12 assay, as assessed by P2Y12 reaction units (PRU). Measurements were performed at baseline (prior to first study drug administration), 2 hours post initial

study drug administration, and during the maintenance phase at timepoints including 30 days, 3 months, 6 months and every 6 months throughout study participation.

3 KEY QUESTIONS AND SUMMARY OF FINDINGS

3.1 Did CYP2C19 genotype/phenotype influence the efficacy or safety of clopidogrel and/or prasugrel in the TABY PGx substudy of the TRILOGY ACS study?

No. CYP2C19 genotype was not significantly associated with either the efficacy or safety of clopidogrel or prasugrel. In contrast to much of the published literature, no associations were established between CYP2C19 genotype and clopidogrel. This is potentially related to the fact that patients were not invasively managed with PCI.

3.1.1 Sponsor's Analysis

Baseline demographics were similar between the PG substudy and the overall TABY study comparing the parameters of age, gender, weight, and BMI. The ethnic and geographic distribution of the PG substudy was different, likely because of regional differences in regulations regarding DNA collection (Table 2). All other demographic and clinical characteristics were similar.

Table 2. Demographics and Baseline Characteristics Summary of Genetic Substudy Efficacy Population and Clinical Study Efficacy Population ITT Set; Genetic ITT Set
TABY PGx

Parameter		<75 Years		≥75 Years		All Subjects	
		ITT Set N=7243	Genetic ITT Set N=4447	ITT Set N=2083	Genetic ITT Set N=1289	ITT Set N=9326	Genetic ITT Set N=5736
Ethnicity (%)	n	7242	4447	2083	1289	9325	5736
	Caucasian	65.4	73.8	73.9	80.8	67.3	75.4
	Asian	22.4	15.9	14.9	10.8	20.7	14.8
	Hispanic	9.2	7.9	9.4	7.1	9.2	7.7
	African	2.2	1.8	1.3	1.2	2.0	1.7
	Other	0.8	0.5	0.5	0.2	0.8	0.5
Geographic Region (%)	n	7243	4447	2083	1289	9326	5736
	North America	13.7	15.4	13.3	13.9	13.6	15.1
	Central/Eastern Europe	33.5	47.0	31.7	44.0	33.1	46.3
	Western Europe	8.7	8.4	17.5	16.0	10.7	10.1
	Latin America	13.4	9.6	14.8	10.9	13.7	9.9
	Mediterranean Basin	7.3	2.8	6.3	2.4	7.1	2.7
	East Asia	7.9	7.5	8.7	8.0	8.0	7.6
	Indian Subcontinent	14.1	8.0	5.8	2.4	12.2	6.8
	Rest of World	1.4	1.4	2.0	2.4	1.5	1.6

(source: page 91 PG Substudy Report for the TABY Clinical Study)

The treatment groups were well matched for baseline characteristics, both between genotype groups (except for race and geographic regions), and between both treatment arms (Table 3).

Table 3. Demographics and Baseline Characteristics Summary by Treatment and by CYP2C19 Predicted Phenotype Genetic ITT Set from TABY.

Parameter		<75 Years				≥75 Years				All Subjects			
		Pras N=2210		Clop N=2237		Pras N=639		Clop N=650		Pras N=2849		Clop N=2887	
		EM	RM	EM	RM	EM	RM	EM	RM	EM	RM	EM	RM
Age (years)	n	1500	537	1480	577	452	141	438	165	1952	678	1918	742
	Mean	62.0	61.6	62.3	60.7	80.3	80.5	80.2	79.7	66.3	65.5	66.4	64.9
	SD	8.29	8.66	8.12	8.65	4.24	4.41	4.45	4.29	10.77	11.07	10.59	11.17
Categorical Age (%)	n	NA				NA				1952	678	1918	742
	<75 years									76.8	79.2	77.2	77.8
	≥75 years									23.2	20.8	22.8	22.2
Weight (kg)	N	1500	537	1479	577	452	141	438	165	1952	678	1917	742
	Mean	80.4	76.9	80.9	78.5	72.9	70.3	71.6	71.1	78.7	75.5	78.8	76.8
	SD	16.15	18.92	17.66	18.58	14.24	12.98	13.59	15.08	16.04	18.04	17.26	18.12
Categorical Weight (%)	N	1500	537	1479	577	452	141	438	165	1952	678	1917	742
	<60 kg	9.1	17.9	9.2	13.2	17.3	19.9	17.6	20.6	11.0	18.3	11.1	14.8
	≥60 kg	90.9	82.1	90.8	86.8	82.7	80.1	82.4	79.4	89.0	81.7	88.9	85.2
BMI (kg/m^2)	n	1485	527	1466	571	442	136	429	162	1927	663	1895	733
	Mean	28.4	27.7	28.7	28.0	27.0	26.6	26.5	26.5	28.1	27.5	28.2	27.7
	SD	4.86	5.68	5.48	5.79	4.52	4.94	4.34	4.19	4.81	5.55	5.32	5.51
Categorical BMI (%)	n	1485	527	1466	571	442	136	429	162	1927	663	1895	733
	<18.5 kg/m^2	0.7	2.9	1.1	0.7	1.4	3.7	1.4	3.7	0.8	3.0	1.2	1.4
	18.5-25 kg/m^2	23.2	28.5	23.5	32.1	36.0	37.5	39.9	30.9	26.2	30.3	27.2	31.8
	25 to<30 kg/m^2	42.8	41.4	40.4	37.8	39.6	40.4	39.6	46.3	42.0	41.2	40.2	39.7
	≥30 kg/m^2	33.3	27.3	35.0	29.4	23.1	18.4	19.1	19.1	31.0	25.5	31.4	27.2
Gender (%)	n	1500	537	1480	577	452	141	438	165	1952	678	1918	742
	Male	63.1	63.9	62.0	65.3	49.8	46.8	49.3	47.3	60.0	60.3	59.1	61.3
	Female	36.9	36.1	38.0	34.7	50.2	53.2	50.7	52.7	40.0	39.7	40.9	38.7
Ethnicity (%)	n	1500	537	1480	577	452	141	438	165	1952	678	1918	742
	Caucasian	80.1	53.8	78.9	61.9	83.4	72.3	83.8	70.9	80.8	57.7	80.0	63.9
	Asian	8.9	38.2	8.9	30.5	6.2	21.3	8.0	23.6	8.3	34.7	8.7	29.0
	Hispanic	8.3	6.7	10.2	5.2	9.3	5.0	7.3	4.9	8.6	6.3	9.5	5.1
	African	2.0	1.3	1.5	1.7	0.9	1.4	0.7	0.6	1.7	1.3	1.3	1.5
	Other	0.7	0	0.5	0.7	0.2	0	0.2	0	0.6	0	0.5	0.5
Geographic Region (%)	n	1500	537	1480	577	452	141	438	165	1952	678	1918	742
	North America	15.3	14.3	16.2	14.7	13.5	19.9	11.6	16.4	14.9	15.5	15.2	15.1
	Central/Eastern Europe	52.9	32.2	50.2	35.5	45.6	36.2	47.5	35.2	51.2	33.0	49.6	35.4
	Western Europe	9.1	5.6	8.0	9.9	17.3	12.1	16.4	15.8	11.0	6.9	9.9	11.2
	Latin America	10.4	6.9	12.2	6.4	13.1	5.0	12.1	6.7	11.0	6.5	12.2	6.5
	Mediterranean Basin	2.7	2.6	3.5	1.4	2.7	4.3	1.8	0.6	2.7	3.0	3.1	1.2
	East Asia	3.9	20.3	4.2	16.6	3.8	18.4	6.9	17.6	3.9	19.9	4.8	16.9
	Indian Subcontinent	4.9	16.4	4.5	13.0	1.8	2.1	1.1	6.1	4.2	13.4	3.7	11.5
	Rest of World	0.9	1.7	1.2	2.4	2.4	2.1	2.5	1.8	1.2	1.8	1.5	2.3
Tobacco Usage (%)	n	1491	536	1467	575	443	139	434	163	1934	675	1901	738
	Never	52.2	55.6	53.3	51.0	67.5	68.4	70.5	67.5	55.7	58.2	57.2	54.6
	Not used within 30 days	25.2	24.3	25.0	23.0	26.0	25.9	22.8	25.2	25.4	24.6	24.5	23.4
	Used within 30 days:	22.6	20.2	21.7	26.1	6.6	5.8	6.7	7.4	18.9	17.2	18.3	22.0
	<10 cigarettes/day	5.0	5.4	4.4	5.2	2.7	0	2.3	2.5	4.5	4.3	3.9	4.6
	10-20 cigarettes/day	13.2	11.6	12.5	15.3	3.2	4.3	2.8	4.9	10.9	10.1	10.3	13.0
	>20 cigarettes/day	3.7	1.9	3.5	4.5	0.2	0.7	1.2	0	2.9	1.6	3.0	3.5
	Other tobacco products	0.7	1.3	1.3	1.0	0.5	0.7	0.5	0	0.6	1.2	1.1	0.8

(source: page 97. PG Substudy Report for the TABY Clinical Study)

The primary efficacy endpoint was the composite of CV death, MI, and stroke. The primary safety endpoint was non-CABG-related TIMI bleeding. The ITT group (< 75 years of age) of the PG substudy of TABY was utilized for the primary analyses by the sponsor. The findings of both efficacy and safety were similar between the PG substudy and the overall ITT population.

No significant CYP2C19 genotype by treatment interactions were observed for efficacy

or safety. RMs tended to have a higher event rate on prasugrel, but such an effect was not observed for clopidogrel. Additionally, when broken down into 4 genotype groups, again no significant differences were observed.

Table 4. Primary Efficacy Composite Endpoint (CV death, MI or Stroke) – CEC Adjudicated by CYP2C19-Predicted Phenotype Genetic ITT Subjects <75 Years of Age

Subset	2-Level Phenotype	4-Level Phenotype	Prasugrel			Clopidogrel			Hazard Ratio (95% CI)	P-Value
			n	N	%	n	N	%		
Overall ITT		N/A	364	3662	**10.1**	397	4351	**11.0**	**0.92 (0.79 – 1.01)**	0.21
PG Substudy			202	2037	**9.9**	226	2057	**10.9**	**0.97 (0.85 – 1.10)**	0.24
	EM		139	1500	**9.3**	164	1480	**11.1**	**0.84 (0.67-1.05)**	0.14
		UM	58	642	9.0	66	682	9.7	0.95 (0.66-1.35)	0.75
		EM	81	858	9.4	98	798	12.3	0.77 (0.57-1.03)	0.08
	RM		63	537	**11.7**	62	577	**10.8**	**1.08 (0.76-1.53)**	0.68
		IM	47	439	10.7	47	467	10.1	1.05 (0.70-1.58)	0.81
		PM	16	98	16.3	15	110	13.6	1.16 (0.58-2.36)	0.64

Table 5. Non-CABG-related TIMI Major/Minor Events While at Risk – CEC-Adjudicated by CYP2C19-predicted Phenotype Genetic Treated Set TABY PGx

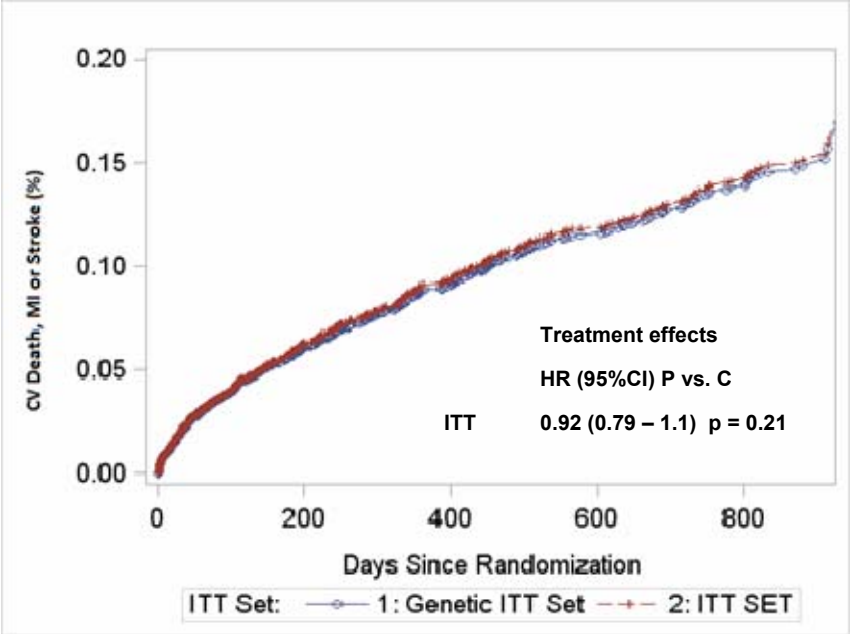
Subset	Predicted Phenotype	Genotype	Prasugrel			Clopidogrel			Hazard Ratio (95% CI)	P-Value
			n	N	%	n	N	%		
Overall ITT		N/A	70		**2.0**	46		**1.3**	**1.54 (1.06-2.23)**	0.02
PG Substudy										
	EM		32	1497	**2.1**	25	1477	**1.7**		0.34
		UM	11	641	1.7	14	679	2.1	0.84 (0.38-1.86)	0.76
		EM	21	856	2.5	11	798	1.4	1.82(0.88-3.78)	0.11
	RM		9	533	**1.7**	6	575	**1**		0.35
		IM	9	435	2.1	6	465	1.3	1.59 (0.57-4.47)	0.36
		PM	0	98	0	0	110	0		

3.1.2 Reviewer's analysis

The sponsor's analyses presented above were confirmed. Because the findings of the substudy are generally inconsistent with published literature in ACS, additional analyses were conducted to explore the effects of 1) the timing of DNA collection and 2) CYP2C19 inhibitors (omeprazole and esomeprazole).

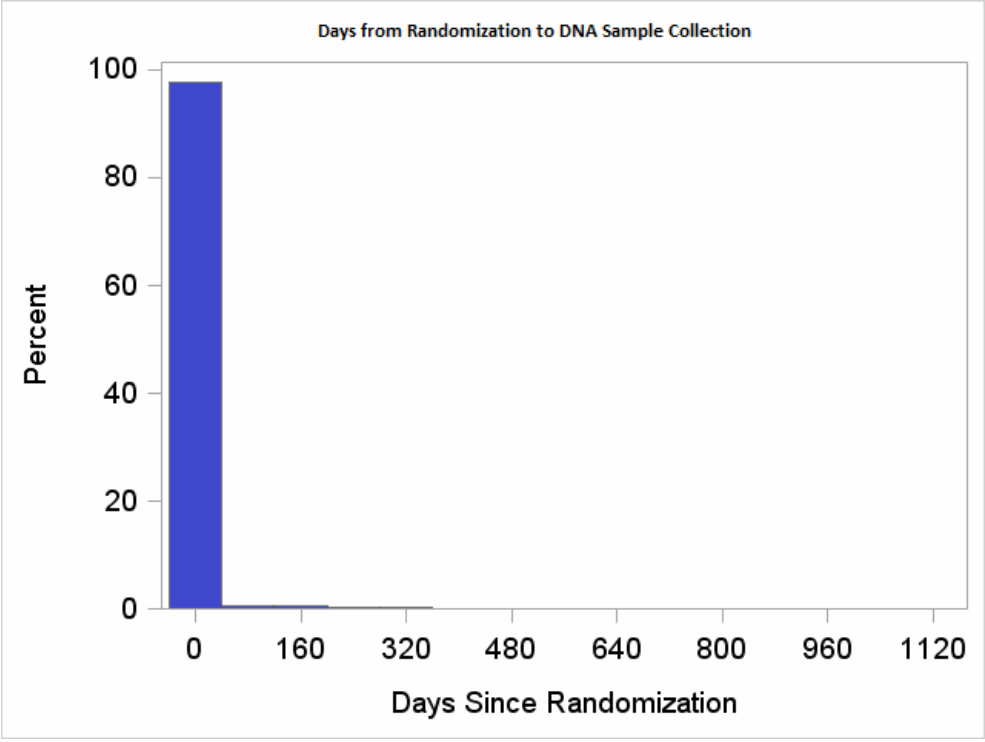
The PG substudy did not differ from the overall study in terms of efficacy. The hazard ratios and effect sizes were similar (Figure 2).

Figure 2. Overall Primary Endpoint Event Rate ITT vs. PG substudy



Additionally, to assess the potential for selection bias, DNA collection times were plotted. Overall, 97% of samples were collected at baseline (Figure 3), and as such, delayed collection is unlikely to have significantly affected the results.

Figure 3. Time of DNA Sample Collection



Use of CYP2C19 inhibitors, specifically omeprazole or esomeprazole, could phenotypically converting EMs to RMs by enzyme inhibition. In the PG substudy, 21% of subjects were receiving a proton-pump inhibitor (PPI); use of omeprazole and esomeprazole was much lower (Table 6). There were no significant differences in PPI use between CYP2C19 EMs and RMs receiving either clopidogrel or prasugrel. Given the low utilization of omeprazole or esomeprazole no further analyses related to the pharmacogenetic interactions within users and nonusers were performed.

Table 6. Omeprazole or Esomeprazole use by CYP2C19 Phenotype Group

	2-Level	Prasugrel				Clopidogrel				
Subset	Phenotype	Total	Yes	No	%Use	Total	Yes	No	%Use	P-Value
PG Substudy										
	EM	1500	52	1448	**3.5**	1480	63	1417	**4.2**	**0.30**
	RM	537	35	502	**4.5**	577	26	551	**6.5**	**0.15**

Reviewer's comments

In the TABY PG substudy, CYP2C19 genotype did not demonstrate any associations with either the efficacy or safety of either agent. CYP219 genotype was not significantly associated with either efficacy or safety in both the 2-level and 4-level predicted phenotype analyses. The findings of the PG substudy does not appear to have been affected by bias or confounding that would result in significant differences compared to the findings of the overall TABY substudy. Moreover, timing of DNA sample collection (~ 97% at baseline) or omeprazole/esomeprazole use (given the low prevalence) did not likely influence the overall findings.

3.2 Was CYP2C19 genotype associated with differential pharmacodynamic responses to clopidogrel or prasugrel?

No. Platelet activity was significantly decreased when switching from clopidogrel to prasugrel regardless of CYP2C19 genotype, although the magnitude of the change in platelet function was greater in RMs because of high baseline activity on clopidogrel.

3.2.1 Sponsor's analyses

(b) (4) the sponsor chose to utilize data from strata 3 (strata 3 subjects received commercial clopidogrel treatment prior to the index event, were deemed to be at steady state at time of onset of index event, and maintained on commercial clopidogrel daily up until time of randomization) (b) (4) In strata 3, subjects <75 years who switched to prasugrel after randomization, there was a significant mean change in LS mean PRU from baseline to day 30 for EMs (-114.2; SD=90.34, p<0.0001) and for RMs (-139.2; SD=82.23, p<0.0001). Similar results were observed for subjects ≥75 years and for the cohort of all subjects, with significantly reduced LS mean PRU from baseline to Day 30 (Table 7).

Table 7. Comparison of P2Y12 Reaction Units (PRU) Change from Baseline at Day

30 by CYP2C19 Predicted Phenotype Genetic PD Set for Subjects Switching from Clopidogrel to Prasugrel after Randomization

Population	Time Points	Statistics	EM	RM	P-value*
Age < 75 Years Old	Day 30	n	106	57	0.0837
		Mean	-114.2	-139.2	
		SD	90.34	82.23	
		Minimum	-348	-330	
		Median	-119.0	-147.0	
		Maximum	285	9	
		P-value**	<0.0001	<0.0001	
All Subjects	Day 30	n	134	67	0.0048
		Mean	-99.9	-137.7	
		SD	92.12	80.35	
		Minimum	-348	-330	
		Median	-103.5	-144.0	
		Maximum	285	9	
		P-value**	<0.0001	<0.0001	
Age >= 75 Years Old	Day 30	n	28	10	0.0061
		Mean	-46.0	-128.9	
		SD	79.02	71.94	
		Minimum	-194	-244	
		Median	-34.0	-107.5	
		Maximum	80	-34	
		P-value**	0.0047	0.0003	

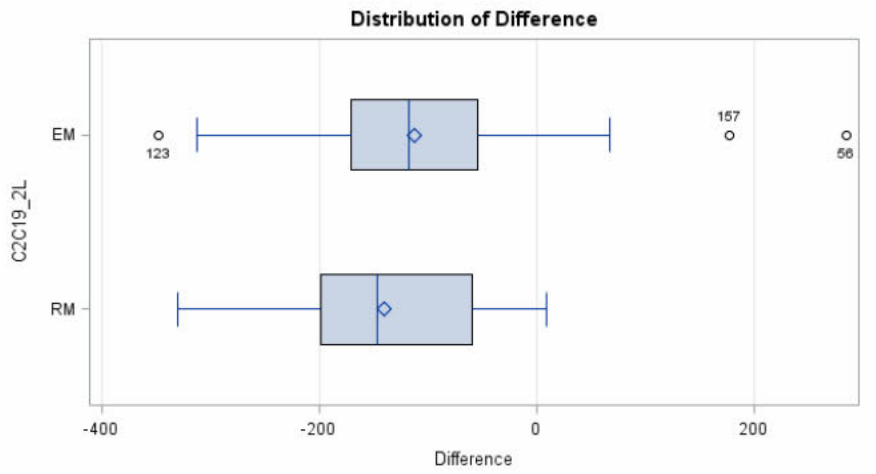
(source: page 208. PG Substudy Report for the TABY Clinical Study

3.2.2 Reviewer's Analysis

(b) (4)

A graphic depiction of the sponsor's data is shown below.

Figure 4. Decrease in PRU When Switching from Clopidogrel 75 to Either Prasugrel 5 or 10 mg at 30 days in CYP2C19 EMs and RMs



Difference = Change in PRU at 30 days
(source: reviewer)

Reviewer's Comments

Subjects switched from clopidogrel 75 mg to prasugrel 5 or 10 mg did have a decrease (113 for EMs, 140 for PMs, p < 0.0001 for both) in platelet reactivity as measured by platelet reactivity at 30 days. (b) (4) *This decrease in platelet*

reactivity occurred regardless of CYP2C19 genotype and is consistent with current knowledge that prasugrel is a more potent inhibitor of platelet reactivity compared to clopidogrel.

4 SUMMARY AND CONCLUSIONS

The sponsor conducted a PG substudy of the TABY study to fulfill a PMC requested by the Agency. The sponsor genotyped 62% of the subjects in the TABY study. Overall, 97% of these samples were collected at baseline. The PG substudy was similar to the overall TABY study and for a number of baseline and demographic factors. No associations between CYP2C19 genotype and either the efficacy or safety of clopidogrel or prasugrel were observed in both 2-level and 4-level CYP2C19 predicted phenotype analyses. These findings of no associations between CYP2C19 genotype and clinical outcomes in those treated with clopidogrel are not consistent with the current body of evidence. One potential explanation is the differences in the underlying populations studied. The TABY study was unique in that is consisted of acute coronary syndrome (ACS) subjects who were medically managed rather than undergoing PCI.

(b) (4)

Notably, the relationship between platelet inhibition and clinical outcomes has not been established.

5 RECOMMENDATIONS

The sponsor has fulfilled the PMC from the perspective of the Genomics and Targeted Therapy Group. No additional action is required except minor explicit changes to the sponsor's proposed labeling language noted below.

5.1 Post-marketing studies

None

5.2 Label Recommendations

The following proposed language should be removed from the label:

(b) (4)

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

/s/

MARTINA D SAHRE
08/19/2013

HOBART ROGERS
08/19/2013

MICHAEL A PACANOWSKI
08/19/2013

RAJANIKANTH MADABUSHI
08/19/2013

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

Prasugrel (Effient) was approved for use in patients with acute coronary syndrome who are to be managed with percutaneous coronary intervention on July 10, 2009. The present submission contains five studies conducted by the sponsor, Eli Lilly and Co. One study is a phase 3 trial (TRILOGY ACS, aka H7T-MC-TABY) conducted to compare treatment with prasugrel and aspirin to clopidogrel and aspirin in patients with unstable angina (UA)/non-ST-elevation myocardial infarction (NSTEMI), who are medically managed and not scheduled to undergo PCI. The four remaining studies are PK/PD or PD studies in specific populations or to assess platelet function when switching from clopidogrel to prasugrel. The protocol for H7T-MC-TABY had been submitted as a SPA on September 13, 2007.

	Information		Information
NDA/BLA Number	**22,307 S008**	**Brand Name**	**Effient**
OCP Division (I, II, III, IV, V)	**I**	**Generic Name**	**Prasugrel hydrochloride**
Medical Division	**Division of Cardiovascular and Renal Products**	**Drug Class**	**Platelet inhibitor**
OCP Reviewer	**Martina Sahre, PhD**	**Indication(s)**	**Acute coronary syndrome**
OCP Team Leader	**Rajanikanth Madabushi, PhD**	**Dosage Form**	**Film tablet, coated**
Pharmacometrics Reviewer		**Dosing Regimen**	
Date of Submission	**12/14/2012**	**Route of Administration**	**Per os**
Estimated Due Date of OCP Review	**9/9/2013**	**Sponsor**	**Eli Lilly and Co.**
Medical Division Due Date	**9/9/2013**	**Priority Classification**	**No**
PDUFA Due Date	**10/14/2013**		

Clinical Pharmacology and Biopharmaceutics Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies				**Not updated**
HPK Summary				
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:	**X**	**2**		**H7T-CR-TAEH H7T-MC-TABM**
Phase 3:	**X**	**1**		**H7T-MC-TABY**
PK/PD -				
Phase 1 and/or 2, proof of concept:	**X**	**2**		**H7T-MC-TACY H7T-MC-TADI**
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies	**X**	**1**		**Sub-study for H7T-MC-TABY**
Chronopharmacokinetics				
Pediatric development plan				
Impact of new formulation	**X**	**1**		**Sub-study for H7T-MC-TABY**
Total Number of Studies				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?			X	
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			Except for some figures in text
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	X			
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	N/A	Comment
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?		X		

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

Yes

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Please provide the following documents (or the location of the documents in submission 173 (12.14.2012)):

Full bioanalytical reports for TADI and TACY
Instruction for handling of bio-samples

Martina Sahre, PhD
Reviewing Clinical Pharmacologist Date

Rajanikanth Madabushi, PhD
Team Leader/Supervisor Date

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

/s/

MARTINA D SAHRE
02/11/2013

RAJANIKANTH MADABUSHI
02/11/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-307/S008

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

Memorandum

****PRE-DECISIONAL AGENCY MEMO****

Date: October, 10, 2013

To: Alison Blaus
Regulatory Project Manager
Division of Cardiovascular and Renal Products

From: Zarna Patel, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **Effient (prasugrel) Tablets**
NDA: 22-307-S008
Comments on draft product labeling

OPDP has reviewed the draft Package Insert (PI) submitted for consult on January 24, 2013, for Effient (prasugrel) Tablets. Please note that OPDP has reviewed the version emailed to us on October 8, 2013 and that comments are limited to the proposed changes for S-008.

OPDP does not have any comments on the proposed PI at this time.

Thank you for the opportunity to comment on the proposed PI.

17 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

ZARNA PATEL
10/10/2013

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title	**EFFIENT (prasugrel) tablets**
Applicant	Eli Lilly and Company
Application/Supplement Number	NDA 22307/S-008
Type of Application	Efficacy Supplement
Indication(s)	reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with acute coronary syndrome who are to be managed with PCI
Established Pharmacologic Class[1]	$P2Y_{12}$ platelet inhibitor
Office/Division	ODE I/DCRP
Division Project Manager	Alison Blaus
Date FDA Received Application	December 17, 2012
Goal Date	October 14, 2013
Date PI Received by SEALD	October 7, 2013
SEALD Review Date	October 8, 2013
SEALD Labeling Reviewer	Elizabeth Donohoe
SEALD Division Director	Laurie Burke

PI = prescribing information

[1] The established pharmacologic class (EPC) that appears in the final draft PI.

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, draft prescribing information (PI) for critical format elements reveals **outstanding labeling format deficiencies that must be corrected** before the final PI is approved. After these outstanding labeling format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

Guide to the Selected Requirements of Prescribing Information (SRPI) Checklist: For each SRPI item, one of the following 3 response options is selected:

- **NO:** The PI **does not meet** the requirement for this item **(deficiency)**.
- **YES:** The PI **meets** the requirement for this item **(not a deficiency)**.
- **N/A** (not applicable): This item does not apply to the specific PI under review.

Highlights (HL)

GENERAL FORMAT

YES 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

YES 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been is granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period (for RPMs)**
  - *For efficacy supplements:* If a waiver was previously granted, select "**YES**" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "**NO**" in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of Cycle Period (for SEALD reviewers)**
  - The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

YES 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

YES 4. White space must be present before each major heading in HL.

Comment:

NO 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment: *Although the BW includes some references, it is recommended that all "bulleted" information summaries have a reference. See the LRT, page 3.*

- *Each labeling information summary must reference the section(s) or subsection(s) of the FPI that contains more detailed information. The preferred presentation of referencing in HL is the numerical identifier in parentheses [e.g., (1.1)] following the summarized labeling information, corresponding to the location of information in the FPI.*

Consider adding references for each of the bullets.

YES 6. Section headings are presented in the following order in HL:

Selected Requirements of Prescribing Information

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a Boxed Warning is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*****
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

NO 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**."

Comment: *The statement is not on the line immediately beneath the HL heading and the name of the drug product is not in UPPER CASE.*

Product Title

YES 10. Product title in HL must be **bolded.**

Comment:

Initial U.S. Approval

NO 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded,** and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment: *The statement is not immediately below the product title.*

Boxed Warning

YES

Selected Requirements of Prescribing Information

12. All text must be **bolded**.

Comment:

YES 13. Must have a centered heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

YES 14. Must always have the verbatim statement "***See full prescribing information for complete boxed warning***." in *italics* and centered immediately beneath the heading.

Comment:

NO 15. Must be limited in length to 20 lines (this does not include the heading and statement "***See full prescribing information for complete boxed warning.***")

Comment: *Regarding the length of the BW, 21 CFR 201.57(a)(4)states: Must be limited in length to 20 lines (this does not include the heading and statement "See full prescribing information for complete boxed warning." The text is greater than 20 lines; it is 31 lines including the white spaces between bullets.*

YES 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

YES 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

N/A 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

NO 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Dosage and Administration, Coronary Stenting (2.2) --- 3/2012".

Comment: *The subheading "General Risk of Bleeding" should be added so that the line reads: "Warnings and Precautions, General Risk of Bleeding (5.1) 11/2012". [see 21 CFR 201.57(a)(5)]*

YES 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

YES 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment:

Dosage Forms and Strengths

N/A 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

YES 23. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known.

Comment:

YES 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

YES 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement

YES 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling."**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide."**

Comment:

Revision Date

NO 27. **Bolded** revision date (i.e., "**Revised: MM/YYYY** or **Month Year**") must be at the end of HL.

Comment: *The revision date is missing and should read: 10/2013; the clean version of the agreed-upon PI should include the revision date. [see the Draft Labeling Review MAPP; a link is on the SEALD internal website]*

Contents: Table of Contents (TOC)

GENERAL FORMAT

YES 28. A horizontal line must separate TOC from the FPI.

Comment:

Selected Requirements of Prescribing Information

YES 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: "**FULL PRESCRIBING INFORMATION: CONTENTS"**.

Comment:

YES 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

YES 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

YES 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

YES 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

YES 34. When a section or subsection is omitted, the numbering does not change.

Comment:

YES 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "**FULL PRESCRIBING INFORMATION: CONTENTS"** must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: "**FULL PRESCRIBING INFORMATION".**

Comment:

YES 37. All section and subsection headings and numbers must be **bolded**.

Comment:

YES 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS

Selected Requirements of Prescribing Information

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

NO 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, "*[see Warnings and Precautions (5.2)]*".

Comment: *There are 2 references to "7" (in Section 2 and subsection 5.1); if applicable, cross-references to a subsection is preferred (e.g., 7.3); in subsection 5.3 the cross-reference has an edit that should be removed ("and" is crossed through) and subsection 6.2 cross-references "17.3" which would not be appropriate given receommendations to not use subsection numbers in Section 17.*

YES 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

YES 42. All text is **bolded**.

Comment:

YES

Selected Requirements of Prescribing Information

43. Must have a heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

YES 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

N/A 45. If no Contraindications are known, this section must state "None".

Comment:

Adverse Reactions

YES 46. When clinical trials adverse reactions data is included (typically in the "Clinical Trials Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment:

YES 47. When postmarketing adverse reaction data is included (typically in the "Postmarketing Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

Patient Counseling Information

NO 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- "See FDA-approved patient labeling (Medication Guide)"
- "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information)"
- "See FDA-approved patient labeling (Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

Comment: *The statement currently states: "See Medication Guide"; this is not adequate. The recently released draft Patient Counseling Information Section guidance provides recommendations that differ from the statements listed above; according to the guidance, the recommended statement would read: Advise the patient to read the FDA-approved patient labeling (Medication Guide).*

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

/s/

ELIZABETH A DONOHOE
10/08/2013

LAURIE B BURKE
10/08/2013

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 22307 BLA# n/a	NDA Supplement #:S- 008 BLA Supplement # n/a	Efficacy Supplement Type SE- 2
Proprietary Name: EFFIENT Established/Proper Name: prasugrel hydrochloride Dosage Form: Tablets Strengths: 5, 10, & 60 mg		
Applicant: Eli Lilly Agent for Applicant (if applicable): n/a		
Date of Application: 14 December 2012 Date of Receipt: 14 December 2012 Date clock started after UN: n/a		
PDUFA Goal Date: 14 October 2013	Action Goal Date (if different): n/a	
Filing Date: 12 February 2013	Date of Filing Meeting: 28 January 2013	
Chemical Classification: (1,2,3 etc.) (original NDAs only) : n/a		

Proposed indication(s)/Proposed change(s): Section 2, Dosage & Administration (in maroon). There are other changes to Sections 6.1, 8, 12, and 14 (no changes to the MG):

Dosing in Low Weight Patients

Compared to patients weighing ≥60 kg, patients weighing <60 kg have an increased exposure to the active metabolite of prasugrel and an increased risk of bleeding on a 10 mg once daily maintenance dose. Consider lowering the maintenance dose to 5 mg in patients <60 kg. The effectiveness and safety of the 5 mg dose have not been prospectively studied (b) (4)

(b) (4)

Type of Original NDA: AND (if applicable)	☐ 505(b)(1) ☐ 505(b)(2)
Type of NDA Supplement: Efficacy ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.***	☒ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.***	☒ Standard ☐ Priority

If a tropical disease priority review voucher was submitted, review classification is Priority.	☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)
☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☒ PMC response ☒ PMR response: ☒ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*): n/a	
List referenced IND Number(s): 63449	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	X			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:***		X		

http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm				
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified: n/a				n/a
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	**X**			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) (NDAs/NDA Efficacy Supplements only)	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?			**X**	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**			**X**	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs***			**X**	
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm **If yes**, please list below:			**X**	

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***		X		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***			X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*		X		
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?			X	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***			X	

Format and Content	
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?	

Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	X			
Index: Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.	X			
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #			X	
Applications in "the Program" (PDUFA V) (NME NDAs/Original BLAs)	**YES**	**NO**	**NA**	**Comment**
Was there an agreement for any minor application components to be submitted within 30 days after the original submission?			X	
• If yes, were all of them submitted on time?			X	
Is a comprehensive and readily located list of all clinical sites included or referenced in the application?			X	
Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?			X	
Forms and Certifications				
***Electronic** forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, **paper** forms and certifications with hand-written signatures must be included. **Forms** include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); **Certifications** include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR***	X			

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

314.50(a)(5)].				
Are all establishments and their registration numbers listed on the form/attached to the form?	**X**			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	**X**			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	**X**			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***		**X**		Sponsor will submit.
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*		**X**		Sponsor used alternative language. They will resubmit.
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	**X**			

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff*:			X	

Pediatrics	YES	NO	NA	Comment
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	X			
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	X			
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***			X	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***			X	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]		X		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the***			X	

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm
[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

supporting document category, "Proprietary Name/Request for Review."				
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***		**X**		
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☐ Carton labels ☐ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	**X**			
Is the PI submitted in PLR format?[4]	**X**			
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***			**X**	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	**X**			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)			**X**	No changes to the MG and there is not a REMS
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?		**X**		
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample			

[4] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

	☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***		**X**		
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** n/a ***If yes, distribute minutes before filing meeting***		**X**		No EoP2 meeting for this efficacy supplement.
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** advice letters dated 5Jan12, 1Feb12, and 19June12 (there was no "pre-NDA" meeting for this supplement). Top-line meeting 8August12 ***If yes, distribute minutes before filing meeting***	**X**			Minutes from the top-line meeting dated 28Aug12
Any Special Protocol Assessments (SPAs)? **Date(s):** n/a ***If yes, distribute letter and/or relevant minutes before filing meeting***		**X**		

ATTACHMENT

MEMO OF FILING MEETING

DATE: 28 January 2013

BLA/NDA/Supp #: 22307 / s-008

PROPRIETARY NAME: EFFIENT

ESTABLISHED/PROPER NAME: prasugrel hydrochloride

DOSAGE FORM/STRENGTH: 5, 10, & 60 mg Tablets

APPLICANT: Eli Lilly

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): (b) (4)

[redacted]

Dosing in Low Weight Patients

Compared to patients weighing ≥60 kg, patients weighing <60 kg have an increased exposure to the active metabolite of prasugrel and an increased risk of bleeding on a 10 mg once daily maintenance dose. Consider lowering the maintenance dose to 5 mg in patients <60 kg. The effectiveness and safety of the 5 mg dose have not been prospectively studied (b) (4)

[redacted]

BACKGROUND: We have met with the applicant on a few occasions & provided a number of correspondences regarding TRILOGY. Please refer to the preNDA advice letters dated 5 January 2012, 1 February 2012, and 19 June 2012 (there was no "pre-NDA" meeting for this supplement). Please also refer to the minutes from the top-line meeting with the sponsor on 8 August 2012 (minutes dated 28 August 2012). Lastly, TRILOGY is related to the last two PMR/PMCs:

95-2 You will gather baseline cancer history and cancer adverse event data from the ongoing trial TRILOGY, a 10,300-subject trial being conducted in patients with acute coronary syndrome who are being managed medically (without coronary revascularization). The final report on cancers in this trial is to be submitted to IND 63,449 (PMR)

95-6 You commit to the collection of samples at baseline for genotyping CYP450 enzymes in TRILOGY subjects, to allow a comparison of effectiveness and bleeding in prasugrel and clopidogrel subgroups by metabolizer status. These

data will be submitted with the final study report of TRILOGY. The periodic reports will include the fraction of subjects who consented to genetic testing (PMC)

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Alison Blaus	Y
	CPMS/TL:	Edward Fromm	N
Cross-Discipline Team Leader (CDTL)	Karen Hicks		Y
Clinical	Reviewer:	Karen Hicks	Y
	TL:	Avi Karkowsky	N
Social Scientist Review (*for OTC products*)	Reviewer:	n/a	n/a
	TL:	n/a	n/a
OTC Labeling Review (*for OTC products*)	Reviewer:	n/a	n/a
	TL:	n/a	n/a
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	n/a	n/a
	TL:	n/a	n/a

Clinical Pharmacology	Reviewer:	Martina Sahre	Y
	TL:	Raj Madabushi	Y
Biostatistics	Reviewer:	Ququan Liu (Cherry)	Y
	TL:	Jim Hung	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	n/a	n/a
	TL:	n/a	n/a
Statistics (carcinogenicity)	Reviewer:	n/a	n/a
	TL:	n/a	n/a
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:	n/a	n/a
	TL:	n/a	n/a
Product Quality (CMC)	Reviewer:	n/a	n/a
	TL:	n/a	n/a
Quality Microbiology *(for sterile products)*	Reviewer:	n/a	n/a
	TL:	n/a	n/a
CMC Labeling Review	Reviewer:	n/a	n/a
	TL:	n/a	n/a
Facility Review/Inspection	Reviewer:	n/a	n/a
	TL:	n/a	n/a
OSE/DMEPA (proprietary name)	Reviewer:	n/a	n/a
	TL:	n/a	n/a
OSE/DRISK (REMS)	Reviewer:	n/a	n/a
	TL:	n/a	n/a
OC/OSI/DSC/PMSB (REMS)	Reviewer:	n/a	n/a
	TL:	n/a	n/a

Bioresearch Monitoring (OSI)	Reviewer:	n/a	n/a
	TL:	n/a	n/a
Controlled Substance Staff (CSS)	Reviewer:	n/a	n/a
	TL:	n/a	n/a
Other reviewers	Hobart Rogers		Y
Other attendees	Norman Stockbridge (Division Director), Stephen Grant (Deputy Director), Mike Pacanowski (Team Leader, Pharmacogenomics)		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☒ Not Applicable ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**: No Comments	☐ Not Applicable
CLINICAL **Comments**: Dr. Hicks had a few requests for more information and additional analyses. These were requested and the sponsor submitted these or is in the process of submitting.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☐ YES ☒ NO
• Advisory Committee Meeting needed? **Comments**:	☐ YES Date if known: ☒ NO ☐ To be determined

If no, for an NME NDA or original BLA , include the reason. For example: o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	Reason: n/a
• Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**: no 74-day letter issues as of the filing meeting.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**: no 74-day letter issues as of the filing meeting.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)	☒ Not Applicable ☐ FILE

Comments:	☐ REFUSE TO FILE ☐ Review issues for 74-day letter
IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
<u>Quality Microbiology</u> (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☒ Not Applicable ☐ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO

Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review **Comments**: n/a	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Norman Stockbridge, M.D., Ph.D.

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in "the Program" PDUFA V): 22 May 2013

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review ☐ Priority Review

ACTIONS ITEMS

☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by

	Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for NME NDAs in "the Program")
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
☒	Other – Check new Debarment Certification and Form 3674.

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

ALISON L BLAUS
02/11/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-307/S008

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 22307 SUPPL # 008 HFD # 110

Trade Name: EFFIENT

Generic Name: prasugrel

Applicant Name: Eli Lilly

Approval Date, If Known: Week of 14 October 2013

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

SE2

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

n/a

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

As part of this efficacy supplement, the sponsor presented the data from the TRILOGY study. This study was planned to inform prescribers regarding dosing for low-weight patients managed by PCI and Patients ≥75 Years of Age at High Risk (diabetes or prior MI).

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

n/a

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

n/a

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 22307

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# n/a

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

n/a

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☒ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

n/a

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

n/a

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

TRILOGY

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 (TRILOGY) YES ☐ NO ☒

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

n/a

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 (TRILOGY) YES ☐ NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

n/a

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

TRILOGY data was submitted as part of this efficacy supplement.

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
IND # 63449 YES ☒ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

n/a

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Alison Blaus, RAC
Title: Regulatory Health Project Manager
Date: 8 October 2013

Name of Office/Division Director signing form: Norman Stockbridge, M.D., Ph.D.
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

ALISON L BLAUS
10/08/2013

NORMAN L STOCKBRIDGE
10/08/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022307/S-008

FULFILLMENT OF POSTMARKETING REQUIREMENT/COMMITMENT

Eli Lilly and Company
Attention: Peter Morrow, MS
Director, Global Regulatory Affairs - US
Lilly Corporate Center
Indianapolis, IN 46285

Dear Mr. Morrow:

Please refer to your Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Effient (prasugrel hydrochloride) 5 mg and 10 mg Tablets.

We have received your submission dated December 14, 2012, containing the final reports for the following postmarketing requirement and commitment listed in the July 10, 2009 approval letter.

95-2 You will gather baseline cancer history and cancer adverse event data from the ongoing trial TRILOGY, a 10,300-subject trial being conducted in patients with acute coronary syndrome who are being managed medically (without coronary revascularization). The final report on cancers in this trial is to be submitted to IND 63,449.

The timetable you submitted on July 8, 2009 states that you will conduct this trial according to the following timetable:

Protocol Submission: Received 06/20/2008
Trial Completion Date: 12/2012
Final Report Submission: 01/2013

95-6 You commit to the collection of samples at baseline for genotyping CYP450 enzymes in TRILOGY subjects, to allow a comparison of effectiveness and bleeding in prasugrel and clopidogrel subgroups by metabolizer status. These data will be submitted with the final study report of TRILOGY. The periodic reports will include the fraction of subjects who consented to genetic testing.

Final Protocol Submission: Received 06/20/2008
Trial Completion Date: 12/2012
Final Report Submission: 01/2013

We have reviewed your submission and conclude that the above requirement and commitment were fulfilled.

We remind you that there is a postmarketing commitment listed in the April 16, 2010 Supplement Approval (S-001) letter that is still open.

1633-1 You agreed to have, on an interim basis, an acceptance criterion for the dissolution test of Q of (b) (4)% in 20 minutes for this formulation for one year. You also agreed to collect 15 minutes dissolution data for the remaining primary stability time points (18 and 24 months), and within 14 months of approval date submit these data to the FDA for re-evaluation and setting of the final dissolution acceptance criterion for your re-formulated product.

Submission Date: 06/2011

If you have any questions, please call:

Lori Anne Wachter RN, BSN, RAC
Regulatory Project Manager for Safety
(301) 796-3975

Sincerely,

{See appended electronic signature page}

Mary Ross Southworth, PharmD.
Deputy Director for Safety
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/

MARY R SOUTHWORTH
10/23/2013

PeRC PREA Subcommittee Meeting Minutes
August 14, 2013

PeRC Members Attending:
Lynne Yao
Wiley Chambers
Robert "Skip" Nelson
Patricia Dinndorf
Tom Smith
Julia Pinto (Volteran & Egranli reviews only)
William J. Rodriguez
Gregory Reaman
Peter Starke
Andrew Mulbery
Dianne Murphy
Kevin Krudys
Rosemary Addy
Lisa Kammerman
Dionna Green
Maura O'Leary
George Greeley
Barbara Buch
Karen Davis-Bruno (Egranli review only)
Hari Cheryl Sachs
Andrew Mosholder

Guests Attending:

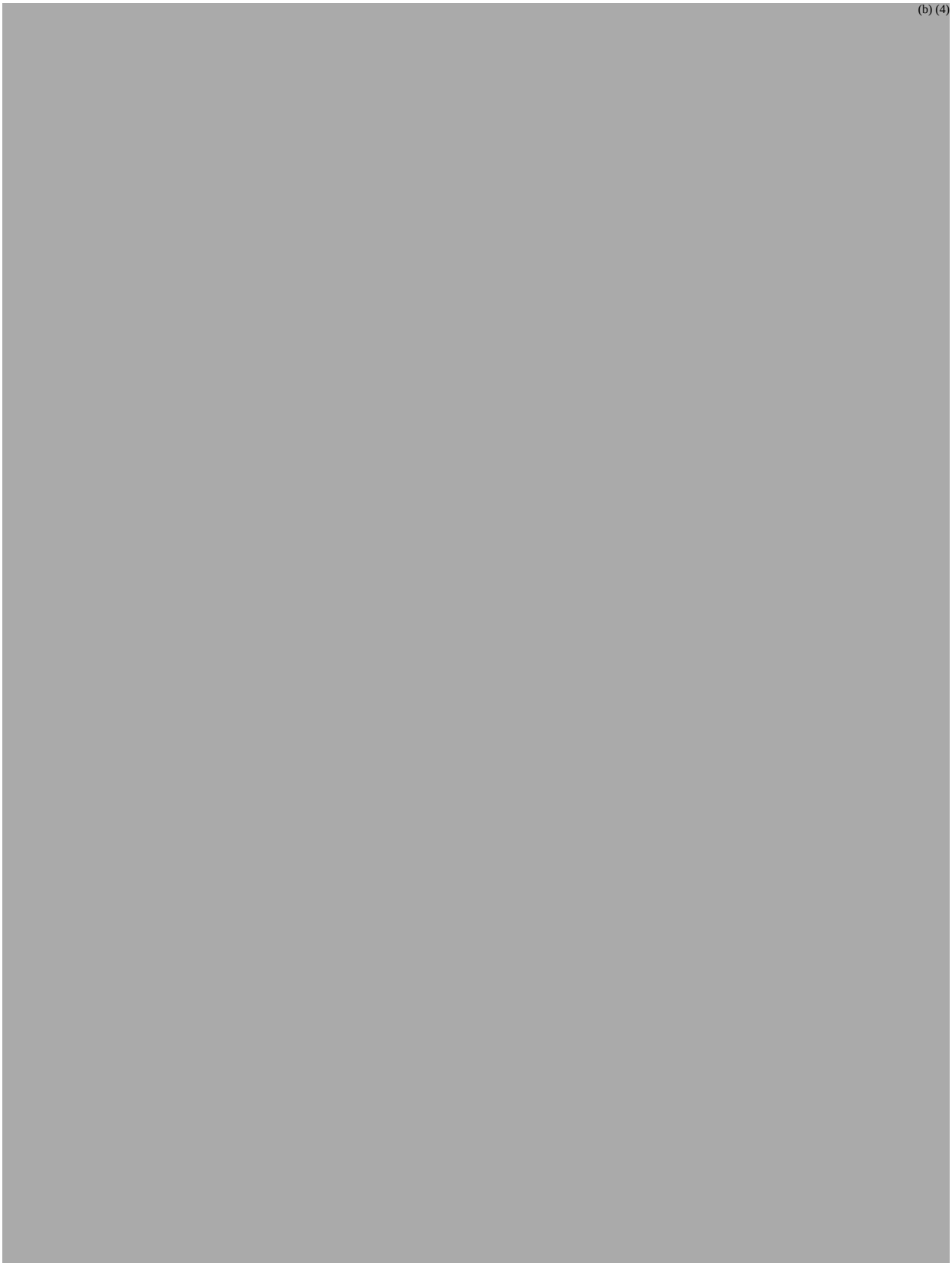
Amy Taylor (PMHS)	Gilbert Burckart (OCP)
Nichella Simms (PMHS)	Alyson Karesh (PMHS)
Courtney Suggs (OCP)	Gerold Wharton (OPT)
Melissa Tassinari (PMHS)	Lori Gorski (PMHS)
Eleanor Mayer (OCC)	Theresa Finn (CBER)
Philantha Bowen (DPARP)	Christina Marshall (DTOP)
Linda Onaga (DAVP)	Sharon Hertz (DAAAP)
Linda Lewis (DAVP)	Yodit Belew (DAVP)
Jian Wang (OCP)	Kathy Robie Suh (DHP)
Islam Younis (OCP)	Lucie Yang (DNCE)
Jade Pham (DNCE)	Yun Xu (OCP)
Wei Qiu (OCP)	Nina Mani (DAVP)

Agenda

(b) (4) (b) (4)	
NDA 22180	Feraheme (ferumoxytol) Partial Waiver/Deferral/Plan
BLA 125160	Cimzia (certolizumab pegol) Full Waiver
NDA 20912	Aggrastat (tirofiban hydrochloride) Full Waiver

NDA 22307 Effient (prasugrel) Full Waiver
NDA 203975 Anoro Ellipta (umeclidinium and vilanterol) Full Waiver

(b) (4)



Feraheme Partial Waiver/Deferral/Plan

- NDA 22180, Feraheme (ferumoxytol) solution for injection, was studied for the treatment of iron deficiency anemia in adult patients with a history of unsatisfactory oral iron therapy or in whom oral iron cannot be used.
- The application was submitted on December 21, 2012 and has a PDUFA goal date of October 21, 2013.
- The application triggered PREA as new indication.
- The sponsor submitted a partial waiver request in children ages birth through less than 2 years because studies would be impossible or highly impractical.
- *Sponsor Waiver Justification:*
- The sponsor requests a waiver from conducting a study with ferumoxytol in neonates (0-1 month) and infants (1 month-2 years) based on the limited projected use of ferumoxytol in patients of this age group and the extremely low incidence and prevalence of IDA in this population.

PeRC Recommendations:

- The PeRC agreed with the Division to grant a partial waiver in patients ages birth to less than 1 year and a deferral in patients 1-17 years. PeRC noted that the study proposed by the sponsor includes patients down to 6 months of age. However, the Division and PeRC both agree that it is unlikely to obtain sufficient numbers of patients less than 1 year of age can be enrolled and therefore a waiver for patients less than one year of age is justified.
- When the protocol synopsis is received the Division will pay particular attention to the safety monitoring plan.

Cimzia Full Waiver

- BLA 125160/213 & 215, Cimzia (certolizumab) powder for prefilled syringe, was studied for the treatment of psoriatic arthritis and axial spondyloarthritis.
- The application was submitted on October 17, 2012 and has a PDUFA goal date of September 29, 2013.
- The application triggers PREA as a new indication.
- A full waiver is being requested because there are too few children with disease/condition to study.

PeRC Recommendations:

- The PeRC agreed with the Division to grant a full waiver in pediatric patients because studies are impossible or highly impractical because there are too few children with disease/condition to study.

Aggrastat Full Waiver

- NDA 20912/19, Aggrastat (tirofiban hcl) injection, was studied for the treatment of ACS, including patients to be medically managed and those undergoing PTCA or Atherectomy.
- The application was submitted on December 14, 2012 and has a PDUFA goal date of October 14, 2013.
- The application triggers PREA as a new dosing regimen.
- A full waiver is being requested because there are too few children with disease/condition to study.

PeRC Recommendations:

- The PeRC agreed with the Division to grant a full waiver in pediatric patients because studies are impossible or highly impractical because there are too few children with disease/condition to study.

Effient Full Waiver

- NDA 22307/8, Effient (prasugrel) film coated tablet, was studied for the indication of acute coronary syndrome (ACS).
- The application was submitted on December 17, 20123 and has a PDUFA goal date of October 17, 2013.
- The application triggers PREA as a (b) (4)
- A full waiver is being requested because there are too few children with disease/condition to study.

PeRC Recommendations:

- The PeRC agreed with the Division to grant a full waiver in pediatric patients because studies are impossible or highly impractical because there are too few children with disease/condition to study.

Anoro Ellipta Full Waiver

- NDA 203975, Anoro Ellipta (umeclidinium and vilanterol) powder for inhalation, was studied for the maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.

- The application was submitted on December 18, 2012 and has a PDUFA goal date of December 18, 2013.
- The application triggers PREA as a new active ingredient.
- A full waiver is being requested because the disease/condition does not exist in pediatric patients.

PeRC Recommendations:

- The PeRC agreed with the Division to grant a full waiver in pediatric patients because studies are impossible or highly impractical because the disease/condition does not exist in pediatric patients.

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

/s/

JANE E INGLESE
10/21/2013

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 22307 BLA # n/a	NDA Supplement # 008 BLA Supplement # n/a	If NDA, Efficacy Supplement Type: SE 2
Proprietary Name: EFFIENT Established/Proper Name: prasugrel Dosage Form: 5 & 10 mg Tablets		Applicant: Eli Lilly Agent for Applicant (if applicable): n/a
RPM: Alison Blaus, RAC		Division: Division of Cardiovascular & Renal Products

NDAs and NDA Efficacy Supplements:

NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☒ 505(b)(1) ☐ 505(b)(2)

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:

Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

Provide a brief explanation of how this product is different from the listed drug.

☐ This application does not reply upon a listed drug.
☐ This application relies on literature.
☐ This application relies on a final OTC monograph.
☐ This application relies on (explain)

For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☐ No changes ☐ Updated Date of check:

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is 17 October 2013	☒ AP ☐ TA ☐ CR

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

[2] For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., nrew listed drug, patent certification revised).

• Previous actions *(specify type and date for each action taken)*	☐ None Original NDA approved on 10July2009; S001 (CMC) 16Apr10; S002 (Labeling) 1Jun11; S003 (Labeling) 27Sep11; S004 (CMC) 21Feb12; S005 (CMC) 17Jul12; S006 (REMS) 23Mar12; S007 (Labeling) 30Nov12
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics [3]	

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☒ Submitted in response to a PMR
☒ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments: PMR 95-2 and PMC 95-6

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Press Office notified of action (by OEP)	☐ Yes ☒ No

[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include*	☐ N/A (no paragraph IV certification) ☐ Verified

*any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other*

*paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**No**," continue with question (5).*	
(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No

CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[4]	Included
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s): Included
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	Included
• Original applicant-proposed labeling	Included
• Example of class labeling, if applicable	n/a

[4] Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☒ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	Medication Guide was unchanged
• Original applicant-proposed labeling	Medication Guide was unchanged
• Example of class labeling, if applicable	n/a
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)* • *Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.*	n/a
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☐ RPM ☐ DMEPA ☐ DMPP/PLT (DRISK) ☒ ODPD (DDMAC) 10Oct13 ☒ SEALD 8Oct13 ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[5]/Memo of Filing Meeting) (indicate date of each review)* ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	RPM Filing Review 11Feb13; Clinical Filing Review 11Feb13; Clinical Pharmacology Filing Review 11Feb13; Statistics Filing Review 11Feb13; RPM Overview 17Oct13 ☒ Not a (b)(2) ☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action

[5] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Pediatrics *(approvals only)* • Date reviewed by PeRC _____ If PeRC review not necessary, explain: _____ • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☐ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)*	Included
❖ Internal memoranda, telecons, etc.	n/a
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☒ No mtg Top-line meeting 8August12
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None 15Oct13
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 10Sep13 and 17Sep13
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical Information[6]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	n/a
• Clinical review(s) *(indicate date for each review)*	See CDTL Review; Supplemental Clinical Reviews dated 22Aug13 and 19Sep13
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	See CDTL Review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable

[6] Filing reviews should be filed with the discipline reviews.

❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☒ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ None
Statistical Review(s) *(indicate date for each review)*	☐ None 9Sep13
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 19Aug13 and 11Sep13
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None
Nonclinical ☒ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ None
• Supervisory Review(s) *(indicate date for each review)*	☐ None
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☐ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☐ No carc
❖ ECAC/CAC report/memo of meeting	☐ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☐ None requested

Product Quality ☒ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☐ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ None
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☐ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☐ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☐ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☐ NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[7])*	Date completed: ☐ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☐ Not needed (per review)

[7] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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

/s/

ALISON L BLAUS
10/16/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22307/S-008

FILING COMMUNICATION

Eli Lilly and Company
Attention: Peter Morrow, MS
Director, Global Regulatory Affairs - US
Lilly Corporate Center
Indianapolis, IN 46285

Dear Mr. Morrow:

Please refer to your Supplemental New Drug Application (sNDA) dated December 14, 2012, received December 17, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Effient (prasugrel hydrochloride) 5 mg and 10 mg Tablets.

We also refer to your amendments dated January 31 and February 5, 8, and 18th, 2013. These submission contained a pediatrics waiver rationale and several documents originally requested in our February 1, 2012 pre-NDA Advice Letter.

This supplemental application (b) (4) the inclusion of safety and clinical pharmacology data from the recently completed clinical trial, TRILOGY.

We have completed our filing review and have determined that your supplemental application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this supplemental application is considered filed 60 days after the date we received your supplemental application. The review classification for this supplemental application is **Standard**. Therefore, the user fee goal date is **October 17, 2013**.

We are reviewing your supplemental application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by **September 19, 2013**.

At this time, we are notifying you that we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the supplemental application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information:

1. Please provide the full bioanalytical reports for the pharmacokinetic analyses for the following studies:
    a. H7T-MC-**TADI** entitled, "A Pharmacokinetic and Pharmacodynamic Comparison of Prasugrel and Clopidogrel in Low Body Weight versus Higher Body Weight Aspirin-Treated Subjects with Stable Coronary Artery Disease."
    b. H7T-MC-**TACY** entitled, "A Pharmacokinetic and Pharmacodynamic Comparison of Prasugrel and Clopidogrel in Very Elderly versus Non-Elderly Aspirin-Treated Subjects with Stable Coronary Artery Disease."

2. Please explain the applicability of foreign data to U.S. population and practice of medicine. This piece of information was previously requested via email on February 11, 2013.

3. Please provide a "define" file that details all of the parameters used to identify the qualifying events for each TOSNP (variable names, etc.). This piece of information was previously requested via email on February 4, 2013

4. Per our request, you have provided DSMB charter, amendments, minutes, some results of all interim analyses, and any communications. We acknowledge that you are inquiring with the DSMB statistician about the full interim analyses.

Please respond only to the above requests for 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.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and Medication Guide. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and Medication Guide, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, please call:

Alison Blaus, RAC
Regulatory Project Manager
(301) 796-1138

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular & 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 L STOCKBRIDGE
02/27/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

Please send immediately following the Filing/Planning meeting

TO: **CDER-DDMAC-RPM**			FROM: (Name/Title, Office/Division/Phone number of requestor) Alison Blaus, ODE 1/DCaRP, (301)796-1138
REQUEST DATE 24 January 2013	IND NO. 63449	NDA/BLA NO. 22307-S008	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)

NAME OF DRUG: EFFIENT (prasugrel) Tablets	PRIORITY CONSIDERATION: Standard	CLASSIFICATION OF DRUG: n/a	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting):
NAME OF FIRM: Eli Lilly		PDUFA Date: 14 October 2013	

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
X PACKAGE INSERT (PI)
☐ PATIENT PACKAGE INSERT (PPI)
☐ CARTON/CONTAINER LABELING
☐ MEDICATION GUIDE
☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
☐ ORIGINAL NDA/BLA
☐ IND
X EFFICACY SUPPLEMENT
☐ SAFETY SUPPLEMENT
☐ LABELING SUPPLEMENT
☐ PLR CONVERSION

REASON FOR LABELING CONSULT
☐ INITIAL PROPOSED LABELING
X LABELING REVISION

EDR link to submission:

Submission can be obtained in the EDR (submission dated 14 December 2012).

Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to DDMAC. Once the substantially complete labeling is received, DDMAC will complete its review within 14 calendar days.

COMMENTS/SPECIAL INSTRUCTIONS:

Mid-Cycle Meeting: TBD – DDMAC will be invited

Labeling Meetings: TBD – Will invite DDMAC to all meetings

Wrap-Up Meeting: TBD – Will invite DDMAC to all meetings

SIGNATURE OF REQUESTER: Alison Blaus

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) X eMAIL ☐ HAND

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

/s/

ALISON L BLAUS
01/24/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 22307/S-008

Eli Lilly and Company
Attention: Peter Morrow, M.Sc.
Sr. Advisor, Global Regulatory Affairs-US
Lilly Corporate Center
Indianapolis, IN 46285

Dear Mr. Morrow:

We have received your Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA Number: 22307

Supplement Number: 008

Product Name: Effient (prasugrel hydrochloride) Tablets, 5 mg and 10 mg

Date of Submission: December 14, 2012

Date of Receipt: December 17, 2012

This supplemental application proposes revisions to the Effient Prescribing Information (PI) based on the results of the TRILOGY Study (TABY) and several pharmacokinetic/ pharmacodynamic studies.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 15, 2013, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3).

SUBMISSION REQUIREMENTS

Please cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have questions, please contact:

Alison Blaus, RAC
Regulatory Health Project Manager
(301) 796-1138

Sincerely,

{See appended electronic signature page}

Edward Fromm, R.Ph., RAC
Chief, Project Management Staff
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/

EDWARD J FROMM
01/15/2013