# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 204958Orig1s000

# MEDICAL REVIEW(S)

# Addendum to Clinical Review for NDA 204958

Drug: Cangrelor
Sponsor: The Medicines Company
Indication: 1) Reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with coronary artery disease undergoing percutaneous coronary intervention (PCI),

Division: Division of Cardiovascular and Renal Products
Reviewer: B. Nhi Beasley, Pharm.D.

Subject: Site reported events in the ITT population in CHAMPION PHOENIX
Date: June 16, 2015

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The purpose of this addendum is to clarify the differences between the Applicant's site reported primary endpoint events in the Intention-to-Treat (ITT) population of the CHAMPION PHOENIX trial and Dr. Tom Marciniak's, the Cross Disciplinary Team Leader during the first review cycle for this application.

## 1 Background

Table 1 shows the adjudicated, applicant site reported, and Dr. Marciniak's site reported number of subjects with primary endpoint events (composite of death, myocardial infarction, ischemia driven revascularization, and stent thrombosis) in the ITT population.

**Table 1. Primary endpoint event, ITT – CHAMPION PHOENIX**

| Index event type | Adjudicated | | Applicant Site-reported | | Dr. Marciniak Site-reported | |
|---|---|---|---|---|---|---|
| | Clopidogrel | Cangrelor | Clopidogrel | Cangrelor | Clopidogrel | Cangrelor |
| All | 325 / 5564 (5.8) | 260 / 5581 (4.7) | 122/ 5564 (2.2) | 101/ 5581 (1.8) | 126/ 5564 (2.3) | 115/ 5581 (2.1) |
| OR (95%CI) | 0.79 (0.67, 0.93) | | 0.82 (0.63, 1.07) | | Not calculated | |

**n/N (%), index patient type is based on investigator's assessment at the time of clinical presentation**
**Source: Adapted from Dr. Jialu Zhang's review (3/2015), Dr. Marciniak's benefit risk review (1/2014)**

**Materials Used**

1. Dr. Marciniak's benefit risk review, dated 13 January 2014
2. Dr. Marciniak's dataset that was extracted from DARRTS into a usable dataset.
3. Dr. Jialu's statistical review, dated March 2015.

## 2 Review

Dr. Marciniak's described analysis is close to the applicant's described analysis #2 shown in Table 2. His review states that he identified site reported events based on answers to the following questions found in the 48-hour and 30-day follow-up CRFs. A site reported MI was counted if yes was checked next to "Did patient experience an MI?". A site reported revascularization was counted if no was checked next to "Was the revascularizaton



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planned?". Marciniak also included deaths in his site reported analysis (but did not explain this in his review). Thus, their results should have been identical. However, Dr. Marciniak's results included the applicant's entire site reported events plus an additional 18 events. A review of the excess 18 events (14 cangrelor, 4 clopidogrel) shows that six subjects (5 cangrelor, 1 clopidogrel) met his criteria. In the remaining 12 subjects, Dr. Marciniak counted 11 as having a major cardiovascular adverse event (MACE) event/primary endpoint event at 48 hours and death at 30 days, and one as having an MI and ST. It appears that for subjects that withdrew consent and/or were missing follow-up information, Dr. Marciniak assumed an endpoint event. This was true despite the 48 hour follow-up CRF indicating that there was no event for 2 of these 11 subjects.

The Applicant's original statistical analysis plan (SAP) stipulated that "site reported data from the PCI procedure performed within the index hospitalization period will be summarized…" (p. 40/145). Thus, the Applicant's site reported events occurred during the index hospitalization period. Specific fields on the case report form were not part of the original definition. The Applicant's Complete Response SAP stipulated two additional site reported analyses shown in the table below. The second analysis in Table 2 produces the applicant's site reported results shown in Table 1 with the provision that they also excluded the six subjects (identified by Dr. Marciniak) whose events actually occurred after 48 hours from randomization. According to the sponsor's description of analysis 2, these six subjects should have been included in the applicant's analysis. However, including these six subjects does not change the conclusions [OR (95% CI) after including these six subjects: 0.86 (0.66, 1.11)].

The applicant did not have any additional events that were not reported by Dr. Marciniak. Analysis 1 results in 3 additional events in the clopidogrel arm and 2 additional events in the cangrelor arm (source: applicant's complete response document, Table 105.1.2.1).

**Table 2. Complete response site reported analyses definitions**

| Analysis | Definition |
|---|---|
| 1. Site reported death, MI, IDR, ST | • All deaths<br>• MIs recorded by the site on the MI eCRF page<br>• IDR recorded by the site on the Revascularization eCRF page<br>• ST from death, MI, IDR, follow-up and PCI eCRF page |
| 2. Site reported death, MI, IDR, ST (on IDR eCRF) | • All deaths<br>• MIs recorded by the site on the MI eCRF page<br>• Unplanned revascularizations recorded by the site on the Revascularization eCRF page<br>• ST from IDR eCRF page |

Source: Adapted from Table 13 (p 50/837) from the Complete Response document.
MI = myocardial infarction, IDR = ischemia driven revascularization, ST = stent thrombosis
eCRF = electronic case report form



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**Table 3. Number and subject IDs in Dr. Marciniak's site reported ITT population that are not in the Applicant's site reported ITT population**

| | Clopidogrel | Cangrelor |
|---|---|---|
| **Site reported primary endpoint event, but potential event occurred more than 48 hours after index PCI** | **1**<br>449001009 | **5**<br>439001076<br>439001085<br>439004181<br>443002052<br>443002145 |
| **Site reported primary endpoint event forms blank, subject withdrew consent. Dr. Marciniak attributed as having a MACE event at 48 hours and died at 30 days.** | **3**<br>449004029<br>449017033<br>495005567 | 6<br>401021013<br>401030289<br>449012005<br>495002197<br>495005197<br>495005476 |
| **Site reported primary endpoint event forms checked 'no', unable to contact subject. Dr. Marciniak attributed as having a MACE event at 48 hours and died at 30 days.** | **0** | **2**<br>449005002<br>449005032 |
| **Site reported primary endpoint event forms checked 'no', Clinical Events Committee adjudicated as an event.** | **0** | **1**<br>449021003 |
| **Total** | **4** | **14** |

# 3 Summary and Conclusion

The identification of site reported events as described in Dr. Marciniak's review is appropriate, however, he should have checked the actual time of the event. Moreover, it appears that he applied additional rules in his analysis. Ascribing a MACE event at 48 hours and mortality at 30 days for all subjects that withdrew consent and/or are missing follow-up information seems inappropriate – even for the conservative FDA reviewer. Moreover, some of the subjects that withdrew consent had no ischemia, no angiography, no PCI, or did not receive study drug. The reviewer believes that the applicant's site reported analysis is appropriate, and is the one that should be used to describe site reported events.



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/s/

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BACH N BEASLEY
06/17/2015

STEPHEN M GRANT
06/18/2015

# CLINICAL REVIEW OF RESUBMISSION

| | |
|---|---|
| Application Type | NDA, Class 2 resubmission |
| Application Number(s) | 204958 |
| Initial Submission Date | 30 April 2013 |
| Advisory Committee Meeting Dates | 12 February 2014, 15 April 2015 |
| Complete Response Letter Date | 30 April 2014 |
| Resubmission Date | 23 December 2014, submission 063 |
| PDUFA Goal Date | 23 June 2015 |
| Division / Office | Division of Cardiovascular and Renal Products /Office of Drug Evaluation 1 |
| Reviewer Names | Fred Senatore, MD, PhD, FACC (efficacy)<br>B. Nhi Beasley, Pharm.D. (safety) |
| Review Completion Date | 19 March 2015 |
| Established Name | Cangrelor |
| (Proposed) Trade Name | Kengreal™ |
| Therapeutic Class | $P2Y_{12}$ platelet inhibitor |
| Applicant | The Medicines Company |
| Formulation(s) | Intravenous |
| Dosing Regimen | 30 ug/kg IV bolus followed by 4 ug/kg/min infusion for a minimum of 2 hours or the duration of PCI |
| Indication(s) | Reduction of thrombotic cardiovascular events in patients undergoing percutaneous coronary intervention (PCI) |
| Intended Population(s) | Patients with coronary artery disease undergoing PCI (b) (4) |

Template Version: March 6, 2009

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## List of Abbreviations

| | |
|---|---|
| ARC | Academic Research Consortium |
| ARC-ST | ARC-defined ST |
| CDTL | Cross-Discipline Team Leader (FDA role) |
| CEC | Clinical Endpoint Committee (i.e. adjudication committee) |
| CHAMPION | Cangrelor versus standard therapy to achieve optimal management of platelet inhibition |
| CI | Confidence Interval |
| CK-MB | Creatinine kinase myocardial b fraction |
| COR | Class of Recommendation |
| CR | Complete Response |
| CSR | Case Study Report |
| IPA | Inhibition of Platelet Aggregation |
| IPST | Intraprocedural Stent Thrombosis |
| IR | Information Request |
| ITT | Intention to treat |
| LOE | Level of Evidence |
| MI | Myocardial Infarction |
| mITT | Modified Intention to treat |
| NSTE-ACS | Non-ST segment elevation acute coronary syndrome |
| NSTEMI | Non-ST segment elevation myocardial infarction |
| OR | Odds Ratio |
| OSI | Office of Scientific Investigation |
| PEP | Primary endpoint |
| QW | Q-wave |
| QWMI | Q-wave Myocardial Infarction |
| SA | SA |
| SAP | Statistical Analysis Plan |
| SCAI | Society for Cardiac Angiography and Interventions |
| SOP | Standard Operating Procedure |
| ST | Stent Thrombosis |
| STEMI | ST segment elevation myocardial infarction |
| UA | Unstable Angina |
| ULN | Upper limit of normal |



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# 1 Recommendations/Risk Benefit Assessment

## 1.1 Recommendation on Regulatory Action

We recommend that cangrelor be approved as an adjunct to percutaneous coronary intervention (PCI) for the reduction in risk of periprocedural (b) (4) including myocardial infarction and stent thrombosis in patient (b) (4)

## 1.2 Benefit Risk Assessment

The primary efficacy endpoint (PEP) included death, myocardial infarction (MI), ischemia driven revascularization (IDR), and stent thrombosis (ST) at 48 hours after randomization. Secondary endpoints included components of the composite; they were ordered and tested sequentially. The applicant won on the PEP (p=0.005), the MI component (p=0.02), and the ST component (p=0.01). ***Table 1*** shows the PEP, its components and various subtypes for the modified Intention-to-Treat population (mITT).

**Table 1. CHAMPION PHOENIX endpoints, mITT population[1]**

| | Cangrelor N=5472 (%) | Clopidogrel N=5470 (%) | OR (95% CI) |
|---|---|---|---|
| **Death, MI, IDR, ST (Primary endpoint)** | 257 (4.7) | 322 (5.9) | 0.78 (0.66, 0.93)[a] |
| **Death** | 18 (0.3) | 18 (0.3) | -- |
| **Myocardial infarction (MI)[2]** | 207 (3.8) | 255 (4.7) | 0.80 (0.67, 0.97) |
| **Type 1** | 1 (0.0) | 1 (0.0) | -- |
| **Type 3** | 3 (0.1) | 0 (0.0) | -- |
| **Type 4a (associated with PCI)** | 194 (3.5) | 239 (4.4) | 0.80 (0.66, 0.98) |
| **Type 4b (associated with ST)** | 9 (0.2) | 15 (0.3) | 0.60 (0.26, 1.37) |
| **MI by SCAI** | 53 (1.0) | 81 (1.5) | 0.65 (0.46, 0.92)[b] |
| **Q-wave** | 11 (0.2) | 18 (0.3) | 0.61 (0.29, 1.29) |
| **Ischemia Driven Revascularization** | 28 (0.2) | 38 (0.7) | 0.74 (0.45, 1.20) |
| **Stent Thrombosis** | 46 (0.8) | 74 (1.4) | 0.62 (0.43, 0.90) |
| **Intraprocedural ST** | 35 (0.6) | 54 (1.0) | 0.65 (0.42, 0.99) |
| **Academic Research Consortium ST[3]** | 12 (0.2) | 22 (0.4) | 0.54 (0.27, 1.10) |

Adapted from CHAMPION PHOENIX CSR Table 5.1.1.1
a=adjusted prespecified primary endpoint analysis
b=adapted from Applicant's Complete Response document, Table 12.
-- Not calculated or reviewer chose not to show
SCAI=Society for Cardiovascular Angiography and Interventions, OR=odds ratio.
MI types and SCAI MI[3] defined in *Section 7.2*.

Each component will be discussed separately in order of clinical import. Mortality in CHAMPION PHOENIX was the same in both arms at 48 hours (18 vs. 18). At 30 days, there were 60 deaths in the cangrelor arm (1.1%) and 55 deaths in the clopidogrel arm (1.0%) in the mITT population.[4] Because death was balanced between arms, it did not impact our benefit risk assessment.

Myocardial infarction was defined by the Universal Definition of MI (UDMI).[5] Most of the MIs were associated with PCI (Type 4a). Periprocedural myocardial necrosis was defined as elevations of cardiac biomarkers 3x above the 99$^{th}$ percentile upper limit of normal (ULN) in patients with normal baseline cardiac biomarkers. Thus, angiographic evidence, ECG changes, or ischemic symptoms were not required for the diagnosis of a periprocedural MI. The Society for Cardiovascular Angiography and Interventions

1 The mITT population was defined as subjects that received at least one dose of study drug and had the index PCI. The number of subjects that did not complete follow-up in the mITT population were 2 and 1, cangrelor and clopidogrel, respectively. The ITT results for the PEP included 3 additional events in each arm. The incidence and OR were similar among the ITT and the mITT population.

2 Total MI= Type 1+Type 3+Type 4a+Type 4b. Type 1, 3, 4b, and all Q-wave MIs except one Q-wave MI are included in the subjects with SCAI MI.

3 ARC-ST data were all Definite ST. There was no Probable or Possible ST.

4 Reviewer's analysis: rb\nnt, Dataset: endpoint

5 Thygesen et al. Circulation 2007; 116: 2634-2653.



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(SCAI) endorsed an Expert Consensus Document[6] that states that in patients with normal baseline cardiac biomarkers prior to PCI the "preponderance of the best scientific evidence supports post-PCI elevation of CK-MB ≥ 10x ULN as being clinically relevant". This document therefore questions the clinical meaningfulness of periprocedural MIs in CHAMPION PHOENIX that were diagnosed solely by 3x ULN< CK-MB < 10x ULN. Consequently, in our benefit risk analysis we included MIs as defined by SCAI.

Ischemia driven revascularization represents a failed PCI. In CHAMPION PHOENIX, IDR was defined as rest pain (presumed to be ischemic) resulting in urgent (not planned/staged) repeat PCI or urgent coronary artery bypass graft surgery. In the absence of pain, other ischemic symptoms (e.g., ventricular arrhythmia) sufficed if they occurred after completion of the index PCI and guide wire removal.[7] Avoidance of revascularization is a clinical benefit.

Like IDR, stent thrombosis represents a failed PCI. Stent thrombosis is a rare event but can lead to MI or death, so avoidance of ST is also a clinical benefit. Several drugs (including glycoprotein IIb/IIIa inhibitors (GPI) and other $P2Y_{12}$ inhibitors) reduce the occurrence of ST. The applicant's definition of ST included ARC ST and intraprocedural ST (IPST). ARC ST occurs after the patient has left the catheterization lab and is an established definition developed by the Academic Research Consortium (ARC).[8] IPST represented an angiographic finding identified during PCI, but its prognostic significance has never been demonstrated.

***Table 2*** shows the benefit of cangrelor relative to clopidogrel in CHAMPION PHOENIX. There were a total of 79 subjects on cangrelor and 114 subjects on clopidogrel that died, or had an MI defined by SCAI, or had IDR, or had ARC-ST within 48 hours of randomization. We believe that the clinical meaningfulness of these endpoints is unlikely to be disputed. In the benefit analysis shown in ***Table 2***, subjects are counted by worst event and are counted only once. If a subject had more than one event in 48 hours, the worst event was counted as death>SCAI MI > IDR > ST (e.g., a subject with an SCAI MI and an ARC-ST is counted only in SCAI MI.). The number needed to treat was not calculated for deaths and ARC-ST since it was neutral.

6 Moussa ID et al. Journal of American College of Cardiology 2013; 62: 1563-70.
7 Unlike the ARC definition of a target lesion revascularization that requires symptoms and target lesion severity of >50% diameter stenosis, there was no minimum diameter stenosis required. Percent diameter stenosis was recorded in ~ 75% of subjects who were revascularized with PCI; there was no difference between treatment arms (mean stenosis~89%).
8 Cutlip DE et al., Academic Research Consortium. Circulation 2007;115:2344-2351



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**Table 2. PHOENIX Subjects with efficacy event and number needed to treat**

| | Cangrelor N=5470 (%) | Clopidogrel N=5469 (%) | Number Needed to Treat |
|---|---|---|---|
| **Death** | 18 (0.33) | 18 (0.33) | --- |
| **SCAI MI, IDR, ARC-ST** | 61 (1.12) | 96 (1.76) | 156 |
| **SCAI MI** | 48 (0.88) | 80 (1.46) | 171 |
| **IDR** | 13 (0.24) | 16 (0.29) | 1822 |
| **ARC-ST** | 0 (0.00) | 0 (0.00) | --- |

Reviewer's analysis: rb\nnt, mITT population. Dataset: ep_scai. Subjects counted only once and by worst event. For subjects with more than one event in 48 hours, the worst event was counted (death>SCAI MI > IDR > ARC-ST).

***Table 3*** shows the number need to harm, with the primary safety concern being major bleeding. Subjects are counted only once within each bleed classification.

**Table 3. PHOENIX Subjects with bleeding event and number needed to harm**

| | Cangrelor N=5529 (%) | Clopidogrel N=5527 (%) | Number Needed to Harm |
|---|---|---|---|
| **GUSTO severe or moderate** | 32 (0.58) | 20 (0.36) | 461 |
| **GUSTO severe** | 11 (0.20) | 6 (0.11) | 1106 |
| **GUSTO moderate** | 21 (0.38) | 14 (0.25) | 790 |
| **TIMI major or minor** | 45 (0.81) | 17 (0.31) | 198 |
| **TIMI major** | 12 (0.22) | 6 (0.11) | 922 |
| **TIMI minor** | 33 (0.60) | 11 (0.20) | 251 |

Reviewer's analysis: rb\nnt.

Our conclusions regarding the benefit risk of cangrelor remain the same as in our original NDA review. The benefit of cangrelor compared to clopidogrel is small, but the risk is smaller. Treating 171 patients prevents one clinically meaningful periprocedural MI. In comparison, treating 1106 patients causes one GUSTO severe bleed, a safety factor of ~ 6.5 fold.[9] Using a less severe bleed to assess benefit risk, such as a GUSTO moderate or TIMI minor bleed still favors the use of cangrelor. (Please see ***Section 5 Bleeding Summary*** for more discussion on the utility of the bleeding classifications.)

# 2 Introduction

In 2013 The Medicines Company submitted NDA 204958 for approval to market cangrelor for two indications:

9 GUSTO severe bleed is an intracranial hemorrhage or bleeding resulting in hemodynamic compromise.



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1. For the reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with coronary artery disease undergoing percutaneous coronary intervention (PCI indication), and
2. To maintain $P2Y_{12}$ inhibition in patients with acute coronary syndromes or patients with stents who are at increased risk of thrombotic events (such as stent thrombosis) when oral $P2Y_{12}$ therapy is interrupted due to surgery (bridging indication).

The Applicant conducted three large outcome trials intended to provide substantial evidence of efficacy and safety for the PCI indication; CHAMPION PCI, CHAMPION PLATFORM, and CHAMPION PHOENIX. All three trials were randomized, double-blind, superiority trials in which patients following coronary angiography were randomized prior to percutaneous coronary intervention to either a) intravenous (IV) cangrelor followed by clopidogrel 600 mg after the 2 hour cangrelor infusion or b) IV placebo + clopidogrel. CHAMPION PCI started 7 months prior to CHAMPION PLATFORM. Both trials were stopped early for futility; however CHAMPION PCI nearly completed enrollment. CHAMPION PHOENIX was designed with knowledge of the first two trials; the Applicant modified the ascertainment of periprocedural myocardial infarction and included ST in the primary endpoint (See ***Table 4.*** See ***Section 7.1*** for the flow of the CHAMPION PHOENIX trial).

**Table 4: Summary of CHAMPION Program for the PCI Indication**

| | | PCI | PLATFORM | PHOENIX |
|---|---|---|---|---|
| Subjects randomized (% of planned enrollment) | | 8,846 (99%) | 5,346 (85%) | 11,145 (100%) |
| Primary endpoint at 48 hours | | Death, MI, or IDR | Death, MI, or IDR | Death, MI, IDR, or ST |
| Outcome of primary analysis, OR (95% CI) | | 1.05 (0.88, 1.24) p-value=0.59 | 0.87 (0.71, 1.07) p-value=0.18 | 0.78 (0.66, 0.93) p-value=0.005 |
| Clopidogrel timing in placebo arm | | 600 mg immediately before PCI | 600 mg after PCI | 300 or 600 mg immediately before or after PCI |
| Population enrolled (%) | Stable angina | 15 | 5 | 58 |
| | NSTE-ACS | 64 | 95 | 26 |
| | STEMI | 11 | excluded | 16 |

The Division of Cardiovascular and Renal Products (Division) and Cardiovascular Advisory Committee (AC) members had a number of issues regarding the approvability and labeling of cangrelor. The AC members voted 2 yes, 7 no, (with 0 abstentions) on the approvability of cangrelor for the PCI indication. The Division issued a Complete Response (CR) letter to the Applicant on 30 April 2014 identifying the reasons for not approving cangrelor at that time.



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The Applicant conducted one phase 2 pharmacodynamic study in support of the bridging indication. The AC members voted unanimously against approval of cangrelor for the bridging indication because of the lack of clinical data. (b) (4)

# 3 List of Issues

The issues raised during the review process and during the AC meeting leading to a complete response letter are listed here:

- Some subcomponents of the primary endpoint in CHAMPION PHOENIX may not represent clinical benefit
- Relevancy of CHAMPION PHOENIX data to current American practice
- General approvability
- Transition from cangrelor to an oral $P2Y_{12}$ antagonist
- Uncertainty about cangrelor utility in patients with stable angina undergoing PCI
- Baseline clinical diagnosis: "derived patient type" vs. investigator assessment at time of enrollment
- Database management

# 4 Assessment of Issues

## 4.1 Some subcomponents of the primary endpoint in CHAMPION PHOENIX may not represent clinical benefit

**Problem**: The PHOENIX trial demonstrated superiority of cangrelor over clopidogrel for the primary endpoint (composite of death, MI, ST, and IDR) in the mITT population (OR 0.78, 95% CI 0.66-0.93, p=0.005). However, it was noted that IPST, a new biomarker included as a secondary endpoint in a protocol amendment, was incorporated post-hoc into the ST component of the primary endpoint. There was no description of IPST in the angiographic core lab charter, and it was not clear from the documents submitted with the NDA how IPST was adjudicated. We recognized that IPST was associated with post procedure ischemic events, perhaps an argument for including them, but it was not clear they were a cause of such events. Investigators were instructed to record the timing of an IPST diagnosis at the end of diagnostic angiography prior to the start of PCI. The Applicant opined that any thrombotic event occurring in the cardiac catheterization laboratory was automatically assigned a diagnosis of IPST. It was not clear whether the angiographic appearance of a thrombosis was due to stent placement or due to the pathophysiology of coronary artery disease.

The FDA reviewers and the AC members questioned the clinical significance of periprocedural myocardial infarction. Periprocedural myocardial infarction was generally based on chemical biomarker elevations in the absence of other signs or symptoms. One of the AC members questioned the benefit risk of cangrelor based on:



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1) failure to prevent symptomatic myocardial infarction in the previous failed studies, 2) showing efficacy in lowering the rate of generally asymptomatic elevations in CK-MB, which are not routinely evaluated in clinical practice, and 3) increased bleeding. We also were concerned that attainment of statistical significance favoring cangrelor for the adjudicated primary endpoint may have been an artifact of: 1) Clinical Endpoint Committee (CEC) adjudication rules that led to counting many cases with small increments in CK-MB as periprocedural MIs, and 2) IPST diagnoses defined as any thrombotic event occurring in the catheterization laboratory when all of them were documented to have occurred before the commencement of PCI.

The Applicant was asked to perform a series of sensitivity analyses that modified the primary analysis of PHOENIX by first removing IPST, then removing MIs not meeting the definition of clinically relevant periprocedural MI as defined in the SCAI Consensus document (Moussa 2013), and finally removing both variables. The Applicant was also asked to perform an analysis analogous to the primary analysis, but using site-reported events, defined as death, MIs noted on the checkbox on the MI Case Report Form (CRF), and unplanned revascularization or ST noted on the checkboxes on the Revascularization CRF.

**Applicant Information**: The Applicant performed the requested sensitivity analyses as shown in ***Table 5***. Removal of IPST still yielded a significant difference between the study groups in favor of cangrelor. Removal of both IPST and MI not meeting the definition of a clinically relevant periprocedural MI also yielded a difference between cangrelor and clopidogrel in favor of cangrelor.



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**Table 5. CHAMPION PHOENIX Sensitivity analyses of primary endpoint**

| Endpoints | Cangrelor N=5470 (%) | Clopidogrel N=5469 (%) | OR (95% CI) | Nominal p-value |
|---|---|---|---|---|
| **Death, MI, IDR, ST**<br><br>(primary endpoint) | 257 (4.7) | 322 (5.9) | 0.78 (0.66-0.93) | 0.005 |
| **Death, SCAI MI, IDR, ARC-ST**<br><br>(primary endpoint excluding IPST and MI not meeting SCAI definition)[1] | 79 (1.4) | 114 (2.1) | 0.69 (0.52-0.92) | 0.0110 |
| **SCAI MI** | 53 (1.0) | 81 (1.5) | 0.65 (0.46-0.92) | 0.0149 |
| **ARC-ST** | 12 (0.2) | 22 (0.4) | 0.54 (0.27-1.10) | 0.0858 |
| **Death, MI (CK-MB ≥ 10x ULN), IDR, ARC-ST**<br><br>(primary endpoint excluding IPST and MIs with CK-MB < 10xULN)[2] | 77 (1.4) | 111 (2.0) | 0.69 (0.51-0.92) | 0.0123 |
| **MI (CK-MB ≥ 10x ULN)** | 50 (0.9) | 78 (1.4) | 0.64 (0.45-0.91) | 0.0128 |

Source: Applicant's Compete Response document (Table 12) - verified by the Office of Biostatistics
1. SCAI MI defined in *Section 7.1.*
2. Moussa et al, 2013.

The Applicant performed the suggested sensitivity analysis of the primary endpoint by site-reported events and compared the results to CEC adjudicated events as shown in *Table 6.* The site-reported primary endpoint was determined two different ways:

- MI recorded by the site on the MI CRF page; IDR recorded by the site on the Revascularization CRF page; and ST from death, MI, IDR, follow-up, and PCI CRF pages.
- MI recorded by the site on the MI CRF page; unplanned revascularizations recorded by the site on the Revascularization CRF page; and ST recorded by the site on the IDR CRF page.



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### Table 6. Sensitivity analysis of primary endpoint: site reported events

| | Cangrelor (N=5472) | Clopidogrel (N=5470) | OR and 95% CI | p-value |
|---|---|---|---|---|
| **Protocol-Defined Primary Endpoint** | | | | |
| Death/MI/IDR/ST[1] | 257/5470 (4.7) | 322/5469 (5.9) | 0.78 (0.66, 0.93) | 0.0049 |
| **Site-Reported Events** | | | | |
| Death/MI/IDR/ST[2] | 96/5470 (1.8) | 121/5469 (2.2) | 0.79 (0.60, 1.03) | 0.0862 |
| Death/MI/IDR/ST (IDR eCRF)[3] | 94/5470 (1.7) | 118/5469 (2.2) | 0.79 (0.60, 1.04) | 0.0957 |

[1]Includes ARC-ST and IPST. Adjusted for loading dose and baseline patient status in logistic regression.

[2]Includes MIs recorded by the site on the MI eCRF page, IDR recorded by the site on the Revascularization eCRF page, and ST from death, MI, IDR, Follow-up, and PCI eCRF pages.

[3]Includes MIs recorded by the site on the MI eCRF page, unplanned revascularizations recorded by the site on the Revascularization eCRF page, and ST recorded by the site on the IDR eCRF.

ARC-ST=Academic Research Consortium-stent thrombosis; CI=confidence interval; CK-MB=creatine kinase-myocardial band; IDR=ischemia driven revascularization; MI=myocardial infarction; OR=odds ratio; ST=stent thrombosis; ULN=upper limit of normal.

Source: Applicant's Complete Response Document (Table 15)

The Applicant opined that the results showed no significant difference between the site-reported events and adjudicated events for the comparison between cangrelor and clopidogrel. The odds ratios for adjudicated endpoints and site reported endpoints were identical.

**Reviewer Evaluation**: The Office of Biostatistics independently confirmed the sensitivity analyses the Applicant provided in ***Table 5***. The results of the sensitivity analyses showed that the 48 hour composite endpoint of death, clinically relevant periprocedural MI (SCAI MI), IDR, and ARC-ST was lower in the cangrelor arm (OR 0.69, 95% CI 0.52-0.92, nominal p-value 0.01).

The Applicant's data showed similar odds ratios between the site-reported and adjudicated 48-hour protocol-defined primary endpoint (***Table 6***). This finding attenuated the concern that the adjudication process biased the results of the trial. The 95% confidence intervals crossed the line of unity for the site reported events.

The Office of Biostatistics performed an independent analysis of the 48 hour primary endpoint as reported by the sites compared to adjudicated endpoints for the ITT population. The results are shown in ***Table 7***. The difference between cangrelor and clopidogrel was evaluated for the entire cohort as well as for subjects presenting with SA, NSTE-ACS and STEMI. The results showed a lower incidence of the primary endpoint in the cangrelor arm compared to the clopidogrel arm for the entire cohort using either site-reported or adjudicated endpoints. This trend was observed for the population presenting with SA and NSTE-ACS. In the STEMI population, the incidence

for the adjudicated primary endpoint was equal in both arms (2.8%), whereas the incidence of site-reported endpoints was slightly higher in the cangrelor arm (2.4%) compared to the clopidogrel arm (2.2%).

**Table 7. Site-reported vs. adjudicated 48 hr. primary endpoint analysis**

| | Adjudicated primary endpoint | | Site-reported primary endpoint | |
|---|---|---|---|---|
| | Clopidogrel | Cangrelor | Clopidogrel | Cangrelor |
| **SA** | 217/3208 (6.8%) | 182/3220 (5.7%) | 65/3208 (2.0%) | 53/3220 (1.7%) |
| **NSTE-ACS** | 82/1435 (5.7%) | 53/1479 (3.6%) | 37/1435 (2.6%) | 27/1479 (1.8%) |
| **STEMI** | 26/921 (2.8%) | 25/882 (2.8%) | 20/921 (2.2%) | 21/882 (2.4%) |
| **all** | 325/5564 (5.8%) | 260/5581 (4.7%) | 122/5564 (2.2%) | 101/5581 (1.8%) |

Source: Office of Biostatistics. Population: ITT.

**Conclusion**: We believe that cangrelor was demonstrated to be effective when only endpoints whose clinical meaningfulness is undisputed were analyzed. There was no difference in the odds ratios between the adjudicated and site-reported 48 hour primary endpoint.

## 4.2 Relevance of PHOENIX data to current American Practice

**Problem**: Uncertainty was expressed about whether or not the data from PHOENIX was relevant to current American practice. The PHOENIX protocol restricted the use of glycoprotein IIb/IIIa receptor antagonists, which was not consistent with either current practice guidelines or practice, although many patients are not given these drugs. Clopidogrel was initiated only at the start of PCI despite a presentation to the CHAMPION-PCI and PLATFORM Executive Committee by the Applicant dated 07 May 2007 stating that clopidogrel must be loaded at least 2 hours before PCI to have an adequate effect. The Applicant was asked to explain why PHOENIX data were relevant to current American practice.

**Applicant Information**: The Applicant's response to this question was summarized as follows:

- Ad-hoc PCI is a feature of American practice. Ad-hoc PCI is defined as PCI performed at the same session as diagnostic catheterization, compared to staged-PCI where PCI is performed at a subsequent session scheduled after diagnostic angioplasty. The Applicant stated that 63 US sites (41% of all sites enrolling 38% of all subjects) routinely performed ad-hoc PCI.



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- Timing of clopidogrel administration is variable and likely due to the absence of firm guidelines.
- Prasugrel was approved by the FDA based on a similar ad-hoc PCI paradigm.
- GP IIb/IIIa receptor antagonist use "upstream" is declining in American practice. Its use as a concomitant medication was excluded in PHOENIX in order to avoid the possibility of additive bleeding.

**Reviewer Evaluation**:

Ad-hoc PCI:

We agree that ad-hoc PCI is a feature of American practice. It has become the default strategy for treating acute coronary syndrome, and it is the recommended strategy for patients presenting with STEMI and UA/NSTEMI (Blankenship et al, 2013).

Timing of clopidogrel:

We agree that there are no firm guidelines regarding the optimal timing of $P2Y_{12}$ therapy relative to PCI, and that the timing of clopidogrel in the PHOENIX trial was within the variability of the treatment paradigm.

The ACCF/AHA/SCAI Guideline for PCI (Levine et al, 2011) stated that "the efficacy of clopidogrel remains controversial. Although some studies have suggested that pretreatment with clopidogrel is associated with decreased platelet aggregation and a significantly lower incidence of periprocedural MI after elective PCI, others have suggested no benefit to pretreatment compared with administration of the drug in the catheterization laboratory" (section 5.7.2 of guideline).

A recently published prospective randomized double-blind trial (ACCOAST-PCI) evaluated the effect of prasugrel pre-treatment in patients undergoing PCI for NSTEMI (Montalescot et al, 2014). A total of 4033 subjects were randomized: prasugrel pre-treatment (30 mg upon admission to the hospital, and 30 mg at time of PCI, n=2037) vs. no pre-treatment (60 mg at time of PCI, n=1996). (b) (4)

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(b) (4)

[redacted]

Use of GP IIb/IIIa receptor antagonists

The guidelines for patients with stable ischemic heart disease (Levine et al, 2011) stated that "in patients undergoing elective PCI with stent implantation treated with unfractionated heparin and adequately treated with clopidogrel, it might be reasonable to administer a GP IIb/IIIa inhibitor (abciximab, double-bolus eptifibatide, or high dose bolus tirofiban)". The Class of Recommendation (COR) and Level of Evidence (LOE) for the use of GP IIb/IIIa receptor antagonists without clopidogrel pretreatment in PCI was COR IIa, LOE A in the STEMI population; COR I, LOE A in



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the UA/NSTEMI population, and COR IIa, LOE B in the stable ischemic population. The use of GP IIb/IIIa receptor antagonists with clopidogrel pretreatment was COR IIa, LOE C in the STEMI population; COR IIa, LOE B in the UA/NSTEMI population, and COR IIb, LOE B in the stable ischemic population. Based on the guideline recommendations and supportive evidence from the guideline, the benefit greatly outweighs the risk with high level of evidence for the use of GP IIb/IIIa agents without clopidogrel in patients presenting with STEMI and UA/NSTEMI. The benefit also outweighs the risk when GP IIb/IIIa receptor antagonists are used in concert with clopidogrel pre-treatment although the evidence is limited.

In the CHAMPION PLATFORM and CHAMPION PCI trials, the use of GP IIb/IIIa receptor antagonists (GPI) was originally allowed at the discretion of the investigator. On May 8, 2007, both PCI and PLATFORM protocols were amended to exclude use of GPI within the previous 12 hours prior to enrollment. The use of GPI as an elective concomitant medication was still allowed but the investigators were cautioned that “the use of these agents should be considered carefully based on the anti-platelet effect already provided by the study drug, i.e. clopidogrel 600mg or cangrelor”. In a series of Executive / Steering Committee meetings (September 2007, November 2007, and March 2008), the Applicant reported the results of GPI use in the NSTEMI population at discrete time points during the course of the PLATFORM and PCI trials. These reports are compiled in ***Table 8***. The data shows that following the protocol amendments of CHAMPION PLATFORM and CHAMPION PCI, the number of NSTEMI subjects in PLATFORM increased from 19% to 53% and the use of GPI in NSTEMI subjects decreased from 37% to 12%. Similarly in the PCI trial, the number of NSTEMI subjects increased from 22% to 58% and the use of GPI in NSTEMI subjects decreased from 53% to 35%. In the PHOENIX trial, a total of 380 subjects (153 in the cangrelor arm and 227 in the clopidogrel arm) were administered GPI as bailout medication, representing 3.4% of the ITT population. The data from the antecedent CHAMPION trials suggest that common practice would deploy GPI agents at a much higher incidence than that seen in PHOENIX, as well as in the PCI and PLATFORM trials post-amendment. It is not clear what the outcome of PHOENIX would have been if patients who might have required GPI therapy were enrolled in PHOENIX, especially when the concomitant use of GPI and clopidogrel has been recommended with a COR IIa, LOE B in the UA/NSTEMI population.



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**Table 8. Use of GP IIb/IIIa receptor antagonists in NSTEMI subjects over time in CHAMPION PCI and CHAMPION PLATFORM**

| CHAMPION | April 2007 | September 2007 | November 2007 | March 2008 |
|---|---|---|---|---|
| **PCI** | | N= 4338 | N= 4684 | N=5541 |
| -NSTEMI | 22% | 43% | 45% | 58% |
| -GPI use in NSTEMI | 53% | 38% | 38% | 35% |
| **PLATFORM** | | N=1387 | N=1556 | |
| -NSTEMI | 19% | 34% | 38% | 53% |
| -GPI use in NSTEMI | 37% | 14% | 14% | 12% |

Source: Slide presentations from CHAMPION Executive Committee/Steering Committee Meetings dated March 27, 2007; September 2, 2007; November 3, 2007; March, 2008 (day not specified)

The Applicant's argument that the use of GP IIb/IIIa receptor antagonists is in decline, and the evidence provided by the Applicant to support this argument, has not been accompanied by any evidence signaling a concern about relative efficacy or safety of this class of antiplatelet drug compared to other classes of antiplatelet drugs.

**Conclusion**: We believe that ad-hoc PCI is a common feature of American practice. The timing of $P2Y_{12}$ therapy is variable and the guidelines have not provided firm instructions. (b) (4) The concomitant use of cangrelor with a GP IIb/IIIa agent has not been tested, but combination therapy using clopidogrel and a GP IIb/IIIa agent showed a benefit outweighing risk with limited population studies as a guideline for American practice. Based on previous CHAMPION trials, it appears that if patients who might have required GPI therapy were enrolled in PHOENIX, the rate of use probably would have been much higher and the outcome of the trial might have been different.

## 4.3 General Approvability

**Problem**: Concern was expressed about whether the PHOENIX trial could serve as the basis of approval in the setting of two previously failed clinical trials.

**Applicant Information**: The Applicant argued that CHAMPION-PCI and CHAMPION-PLATFORM, although failed studies, served as the basis for the hypothesis tested in the PHOENIX trial.



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**Reviewer Evaluation**: Post-hoc analyses of these two failed studies showed a potential utility for cangrelor in preventing periprocedural myocardial infarction. The consequent hypothesis was proven in the PHOENIX trial. We do not consider the failed studies to offset the successful PHOENIX trial because the hypotheses and endpoints in PHOENIX were different from the two failed studies. Clopidogrel, as an approved $P2Y_{12}$ agent, was an appropriate active comparator. An established basis for approvability from a single Phase 3 trial, a very small p-value, was met. The outcome in PHOENIX was significant with a p value of 0.0049. Following the exploratory sensitivity analysis for outcomes whose clinical relevance is not in dispute, the results were still significant with a p value of 0.0123.

**Conclusion**: The PHOENIX study as a stand-alone trial was sufficient to warrant approval of cangrelor in patients undergoing PCI for the prevention of periprocedural MI and stent thrombosis.

### 4.4 Transition from cangrelor to an oral $P2Y_{12}$ agent

**Problem**: Concern was expressed that there was a window of pharmacodynamic vulnerability between the time when cangrelor was discontinued and the time when there was a therapeutic effect of clopidogrel, which was started when cangrelor was stopped. Clopidogrel took at least 2 hours to reach therapeutic effect, even if the loading was doubled to 600 mg. Therefore subjects in PHOENIX had a period of at least 2 hours after cessation of cangrelor infusion during which platelets were inadequately inhibited. This indicated that use of cangrelor delays, but does not eliminate, a time-period during which clopidogrel is ineffective. The question therefore is what the consequence of the later delay is.

**Applicant Information**: The Applicant responded by opining that “when clopidogrel is loaded at the end of the cangrelor infusion as proposed, antiplatelet effects are not anticipated to be below the desirable level for very long-if at all-compared to loading clopidogrel at the time of PCI”. The Applicant provided the following additional arguments:

- Even at 2-4 hours, clopidogrel effects are not fully developed. Studies among patients undergoing coronary artery stenting and given clopidogrel 600 mg orally have shown that platelet aggregation in response to 20 uM ADP stimulation ex-vivo ranged from 30% (SD 10%)--52% (SD 16%) at 2-4 hours. The Applicant provided a figure that is reproduced here as ***Figure 4***. This figure shows platelet aggregation ranging from approximately 70% to 50% between 30 minutes to 360 minutes following a clopidogrel loading dose of 600 mg.
- Administration of clopidogrel while cangrelor is being infused may be associated with diminished clopidogrel effects consequent to pharmacodynamic interactions. However, administration of clopidogrel after the end of a cangrelor infusion does not lead to clinically important loss of effects. Following a 2-hour infusion of



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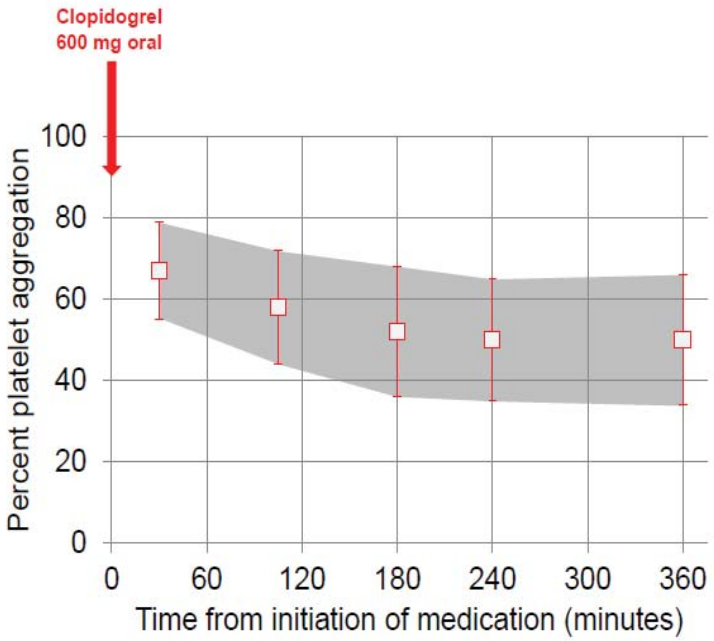
cangrelor during which platelet aggregation was effectively eliminated, and a post-infusion clopidogrel 600mg load, platelet aggregation in response to 20 uM ADP stimulation ex-vivo ranged from 26% to 58% at 2-4 hours post cessation of cangrelor infusion and clopidogrel load (***Figure 5***). However, there was a window of pharmacodynamic vulnerability where platelet aggregation rose to approximately 60% between 2-3 hours post initiation of cangrelor (approximately 1 hour post cessation of cangrelor). Platelet aggregation returned to 20% at 6 hours post initiation of cangrelor (4 hours post-termination of cangrelor). The Applicant provided several arguments regarding this apparent window of pharmacodynamic vulnerability (ref: Applicant's Response Document section 5.5): "Any differences during the 2-4 hour period of transition between platelet inhibition on clopidogrel after cangrelor compared with platelet inhibition on clopidogrel started immediately are (a) modest and not clinically important (b) of short duration (< 1 hour), (c) fall within the expected wide variability of antiplatelet effect at 2-4 hours normally observed among patients dosed with clopidogrel 600 mg orally at the time of PCI and (d) occur at a time of lower thrombotic risk relative to the peri-PCI period".

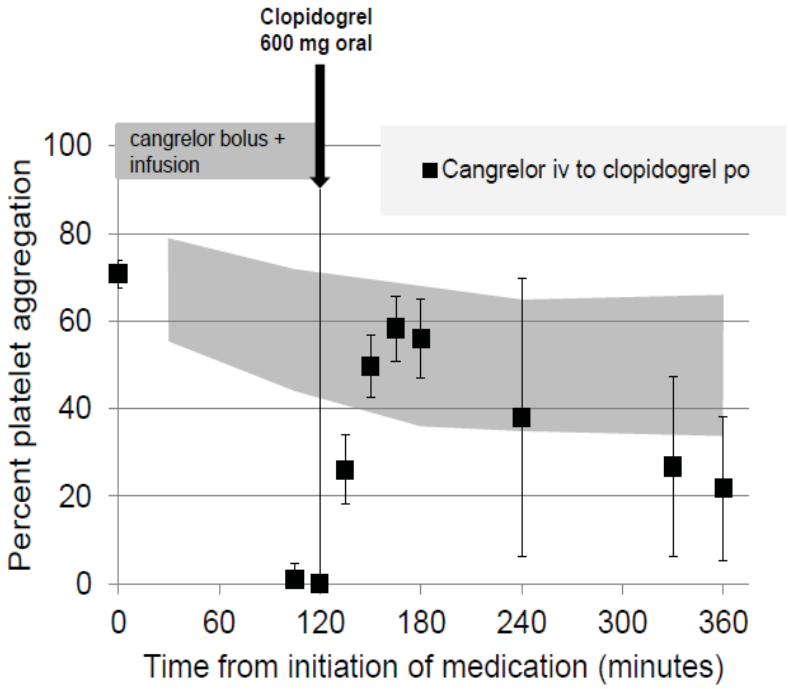
- Most events occurred within the initial 6 hours post randomization in PHOENIX (CSR, Table 10 Landmark Analysis). Further analysis by the Applicant showed that most of these 6-hour post randomization events occurred within the first 2 hours post randomization (see Applicant's Complete Response Figure 6) at a time when cangrelor would be effective compared to clopidogrel. The 2-4 hour infusion of cangrelor therefore provided coverage during the most important risk period.
- Transitions to other $P_2Y_{12}$ inhibitors:
    - Prasugrel also exhibited an interaction with cangrelor but if given 30 minutes before the end of cangrelor infusion, platelet reactivity briefly increased to 49%, thus minimizing platelet reactivation (study MDCO-CAN-13-02).
    - Ticagrelor did not interact with cangrelor. Platelet function in the cangrelor-ticagrelor transition period was reportedly less than 20% (study MDCO-CAN 12-13).

### Figure 4. Platelet aggregation ex-vivo after clopidogrel 600 mg given for PCI




Source: Applicant's Complete Response Document (Figure 3)

### Figure 5. Platelet aggregation with cangrelor followed by clopidogrel 600 mg




Source: Applicant's Complete Response Document (Figure 4)

**Reviewer Evaluation**:

Transition Data

The Office of Clinical Pharmacology performed a transition analysis assessing inhibition of platelet aggregation as a function of time when cangrelor was replaced by various $P2Y_{12}$ agents. ***Figure 6*** shows the percent inhibition of platelet aggregation (IPA) for loading doses of clopidogrel, prasugrel, and ticagrelor as a function of time. The IPA-time profile for prasugrel and ticagrelor are similar where each had a higher IPA compared to clopidogrel for all time points. ***Figure 7*** shows cangrelor→prasugrel transition data for a prasugrel 60 mg load provided at various time points after the start of a 2-hour cangrelor infusion. The data suggested that the loss of IPA during the cangrelor→prasugrel transition was minimized when prasugrel 60 mg load was provided 1.5 hours after the start of the 2-hour cangrelor infusion (i.e. 30 minutes before the end of the cangrelor infusion). ***Figure 8*** shows cangrelor→ticagrelor transition data for ticagrelor 180 mg provided 0.5 hours and 1.25 hours after the start of a cangrelor 2-hour infusion. The data suggested an overlapping loss of IPA 30 minutes after the end of cangrelor infusion (from > 90% IPA to 60% IPA when ticagrelor was given 85 minutes after the start of the 2-hour cangrelor infusion; from > 90% IPA to ≈ 80% IPA when ticagrelor was given 30 minutes after the start of cangrelor infusion). ***Figure 9*** shows the combined time-course of IPA for clopidogrel, prasugrel, and ticagrelor using the OCP recommended transition strategies for each oral $P2Y_{12}$ agent. The data shows that the OCP recommendation of ticagrelor 180 mg administered 30 minutes after the start of a 2-hour cangrelor infusion minimizes the loss of IPA. The OCP also recommended prasugrel 60 mg immediately after the end of a 2-hour cangrelor infusion as well as clopidogrel 600 mg immediately after the end of a 2-hour cangrelor infusion. However, the use of prasugrel or clopidogrel as the transition agent showed a significant loss of IPA for approximately 2 hours after the end of cangrelor infusion. We believe that ticagrelor should be the preferred agent of choice when transitioning from cangrelor to an oral $P2Y_{12}$ agent. However, clinical outcome data are not available to assess bleeding risk for this transition strategy.



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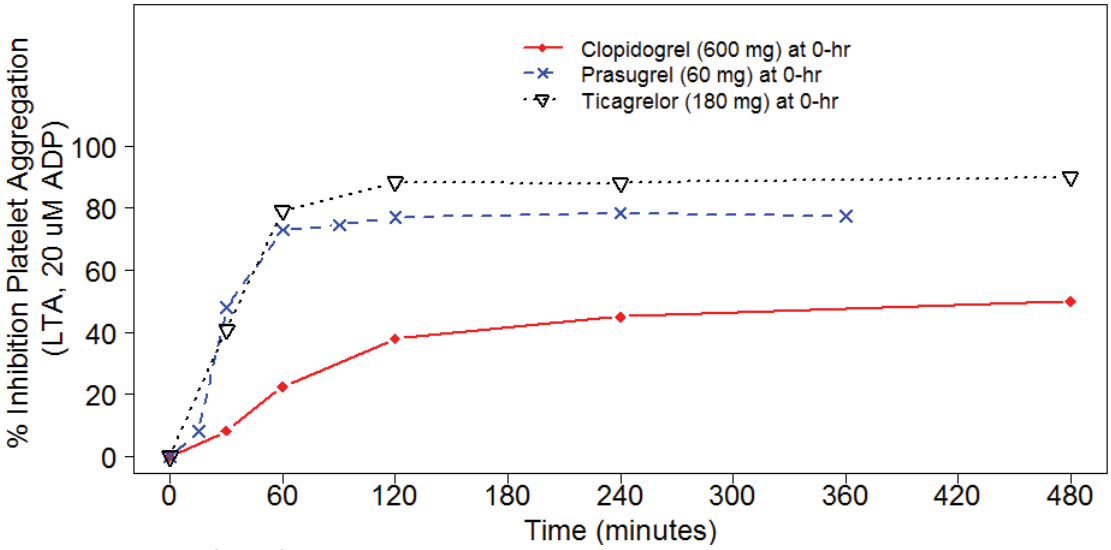
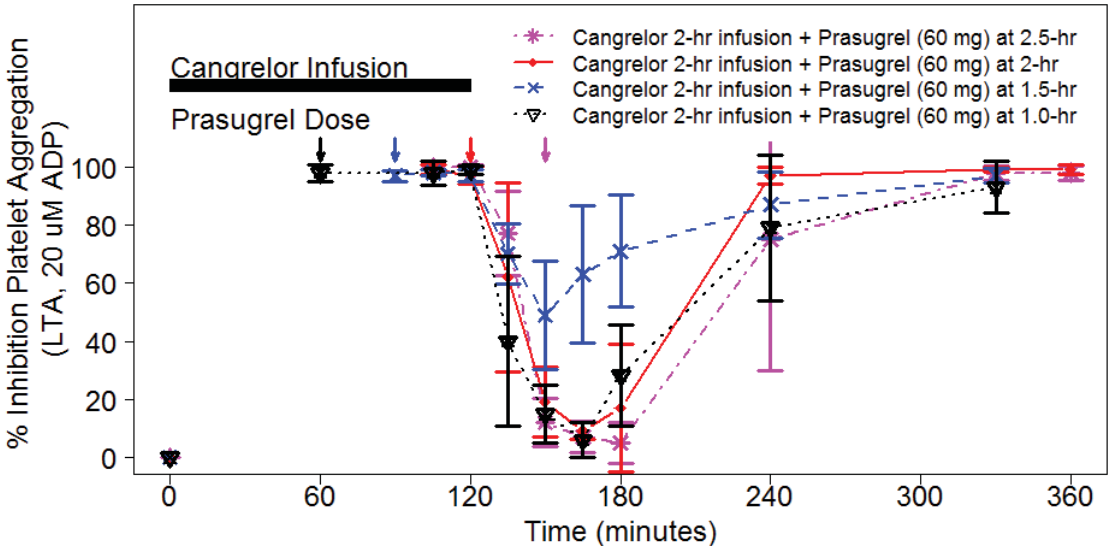
**Figure 6. Percent Inhibition of platelet aggregation for clopidogrel, prasugrel and ticagrelor loading doses**



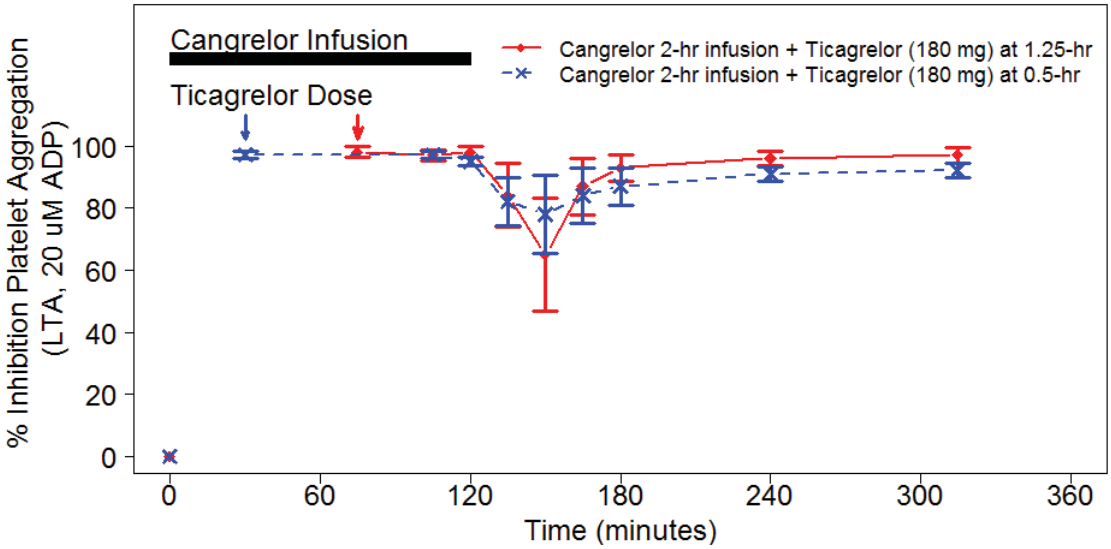

Source: OCP Review-Fig 1

**Figure 7. Percent inhibition of platelet aggregation for cangrelor and transition to prasugrel at various times from start of cangrelor infusion**



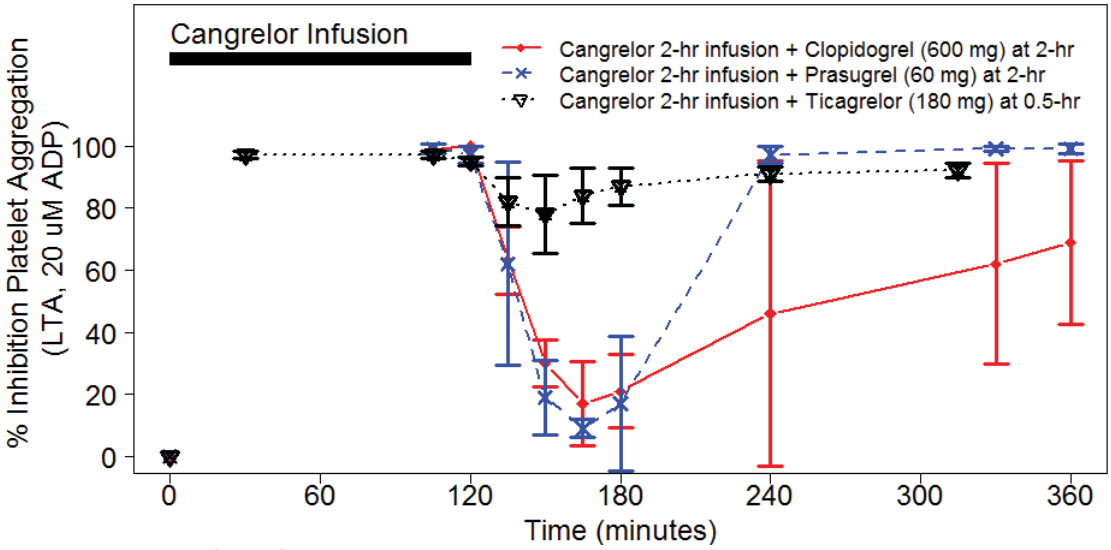

Source: OCP Review-Fig 4

**Figure 8. Percent inhibition of platelet aggregation for cangrelor and transition to ticagrelor at various times from the start of cangrelor infusion**




Source: OCP Review-Fig 6

**Figure 9. Time-course of antiplatelet effect with recommended transition strategies**




Source: OCP Review-Fig 8

Clinical Relevance of the Pharmacodynamic Window of Vulnerability

The Office of Biostatistics verified the Applicant's re-evaluation of the landmark analysis using a primary endpoint that excluded IPST and using a more conservative definition of MI (SCAI-MI). The largest separation between the arms of PHOENIX occurred in the initial 2 hours of treatment. The Office of Biostatistics noted that among the 138 endpoints (death, SCAI-MI, IDR, ARC-ST), 41 events (25 in the clopidogrel arm and 16 in the cangrelor arm) occurred within 2 minutes from infusion of the study drug. It is not clear how a periprocedural MI could be diagnosed on the basis of a CK-MB rise 2 minutes into the infusion of study drug when PCI has likely just commenced. The amount of time required for CK-MB to rise would imply that the MI occurred prior to catheterization laboratory entry. If a periprocedural MI occurred, it is expected that the CK-MB would begin rising at the time of PCI, with peaks occurring post-PCI. Therefore, while the transition from cangrelor to an oral $P2Y_{12}$ agent is taking place, the patient might be sustaining a periprocedural MI when platelet reactivation is simultaneously occurring. In order to minimize the probability of post-PCI cardiac adverse events, the question remains as to whether it is necessary to maintain continued adequate inhibition of platelet aggregation (i.e. above 80%) during the transition period, or whether a transient 2-4 hour time period of empirical pharmacodynamic vulnerability is allowable because it poses a negligible clinical risk to the patient. In order to ensure complete coverage post-PCI, pre-treatment loading with a $P2Y_{12}$ agent might be preferable, thereby obviating the utility of cangrelor. The Applicant argued that the 2-4 hour period of inadequate platelet inhibition was similar between clopidogrel after cangrelor and clopidogrel 600 mg started at the time of PCI. The approval of cangrelor should not rest on this argument in a setting where pre-PCI treatment with clopidogrel or ticagrelor is within the practice paradigm.

**Conclusion**: The use of cangrelor produced a window of pharmacodynamic vulnerability but its clinical relevance has not been established.

## 4.5 Uncertainty about cangrelor utility in patients with stable angina undergoing PCI

**Problem**: Uncertainty was expressed over the utility of cangrelor in patients with SA undergoing PCI. These patients could be preloaded with a $P2Y_{12}$ receptor inhibitor before coronary angiography. This would avoid the approximately 2-hour post-PCI decrease in platelet inhibition that occurs after administration of cangrelor followed by clopidogrel. If cangrelor were to be approved, it is not clear which patients with SA could be given clopidogrel only when PCI is initiated, the population in which an effect has been shown rather than before PCI. The Applicant was asked to explain why they believe the data from PHOENIX support use of cangrelor as an adjunct to PCI in patients with SA.



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**Applicant Information**: The Applicant reiterated that cangrelor can be useful in the ad-hoc setting where $P2Y_{12}$ receptor inhibitor was not administered prior to angiography.

**Reviewer Evaluation**: We acknowledge variability in American clinical practice. In patients undergoing PCI, there are clinical scenarios where a delay in the use of a $P2Y_{12}$ receptor inhibitor until the time of PCI is warranted. Two such scenarios are: 1) ad-hoc PCI in the absence of antecedent $P2Y_{12}$ receptor inhibitor treatment, and 2) delineation of coronary anatomy in order to make a clinical decision prior to giving a $P2Y_{12}$ receptor inhibitor.

**Conclusion**: Cangrelor has utility in the clinical setting where patients are not pretreated with $P2Y_{12}$ receptor inhibitor: ad-hoc PCI in the absence of antecedent $P2Y_{12}$ receptor inhibitor treatment, and clinical scenarios where knowledge of coronary anatomy is desired prior to treatment.

## 4.6 Baseline Clinical Presentation: Derived Patient Type vs Investigator Diagnosis

**Problem**: After database lock the Applicant defined a “derived patient type”. Upon query, this term was used as a baseline diagnosis of subjects randomized to PHOENIX (i.e. SA, NSTE-ACS, STEMI), based on an algorithm which partly included information that was obtained after the patient’s initial presentation. The derived patient type algorithm resulted in altering the investigators’ initial diagnosis at the time of enrollment without the investigator’s knowledge. The purpose of the derived patient type algorithm was not clearly explained in the original submission, as well as the meaning of the derived patient type and the justification for ignoring the investigators’ original diagnosis. In clinical practice, the decision to prescribe antiplatelet therapy would customarily be based on the clinical impression at the time of diagnosis. The derived patient type algorithm served to incorporate post hoc information that the prescribing physician would not ordinarily have at the time of making an initial clinical judgment. In practice, prescribers would likely have similar data as the investigators had at the time of randomization. Thus, the initial baseline diagnosis as per investigator judgment rather than the Applicant’s diagnosis from the derived patient type algorithm would be the most useful information on which to base prescription instructions. Furthermore, the algorithm was designed and executed after unblinding, raising the possibility of bias when deploying the patient derived type algorithm. The Applicant was asked to provide an exact and detailed description of the process, including when and why the Applicant decided it was necessary to deploy it, the calendar dates during which it was performed, and the name of the group or groups responsible for performing it. In addition, the Applicant was asked to provide a tabular data-set that listed all subjects for whom the clinical presentation entered into the IVRS differed from the results of the derived type algorithm.



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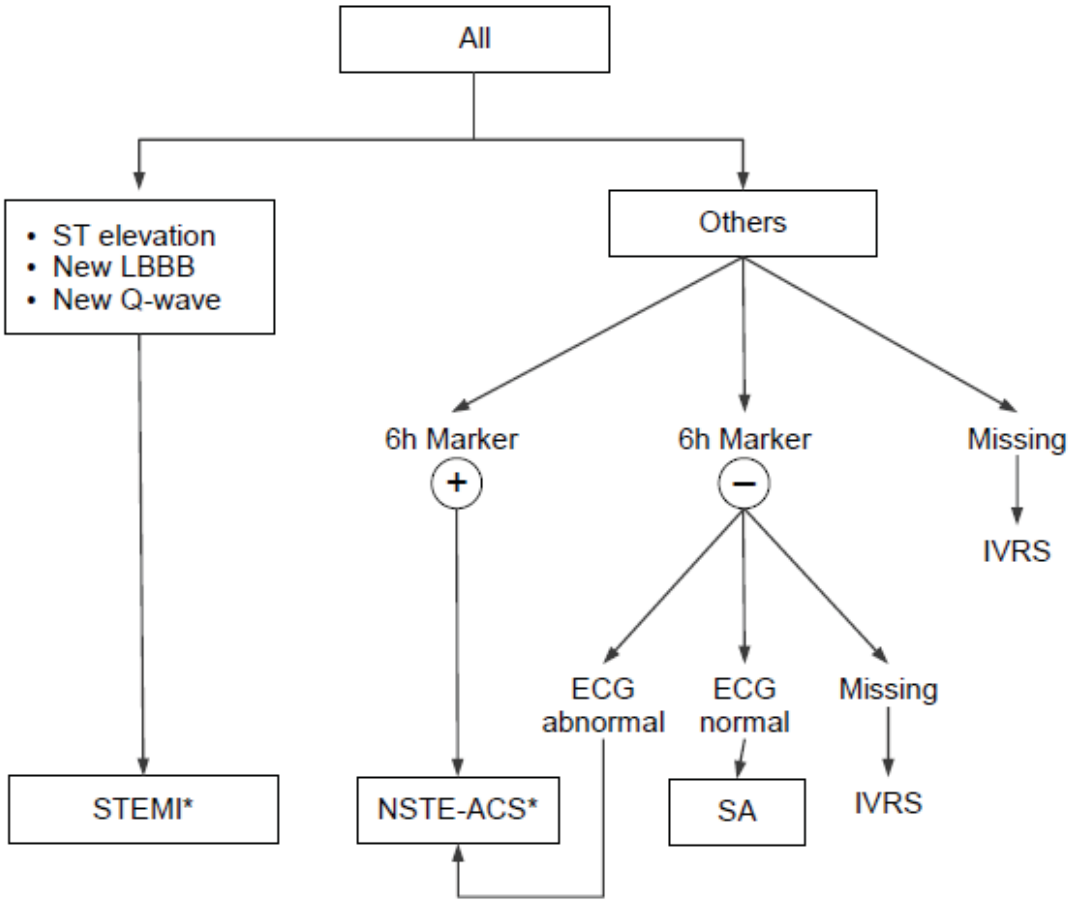
**Applicant Information**: The Applicant described the algorithm used to change the baseline diagnosis of enrolled subjects and is illustrated in ***Figure 10***. After database lock, the program algorithm searched the database for cardiac markers and ECG results. Based on the data, the subject was re-assigned a baseline clinical diagnosis. If data were missing, the algorithm defaulted to the investigator's clinical baseline diagnosis retrieved from the IVRS.

**Figure 10. Algorithm for derived patient type using baseline eCRF data**




*UDMI definitions (Thygessen)

Source: Applicant's Complete Response Document (Figure 11) - confirmed by the Office of Biostatistics

The Applicant explained the reasons for the difference between site-reported and Applicant-derived clinical presentations as shown in ***Table 9***. In those instances where the site-reported diagnosis was NSTE-ACS, subjects who maintained normal biomarkers within 6 hours of randomization were reclassified as SA. In those instances where the site-reported diagnosis was SA, the development of abnormal biomarkers or

ST segment depression indicative of ischemia during screening resulted in a reclassification to NSTE-ACS. Subjects with a site-reported diagnosis of SA, who developed a new Q-wave or new Left Bundle Branch Block (LBBB) or ST-segment elevation during screening, were reclassified as STEMI. Subjects with a site-reported diagnosis of STEMI were reclassified as SA if ECG criteria for STEMI were not met and there were with normal biomarkers within 6 hours of randomization.

**Table 9. Changes in baseline diagnosis from investigator (or IVRS) to derived patient type**

| Clinical Presentation/ Patient Type | | | | |
|---|---|---|---|---|
| **IVRS** | **eCRF Derived** | **Reason for Difference** | **No. of Patients** | **% of N N=10,942** |
| NSTE-ACS | SA | Normal BL biomarkers within 6 hours of randomization | 864 | 7.9 |
| SA | NSTE-ACS | Abnormal BL biomarkers within 6 hours of randomization | 583 | 5.3 |
| SA | NSTE-ACS | ST segment depression or Other ECG abnormality indicative of ischemia during screening | 397 | 3.6 |
| NSTE-ACS | STEMI | New Q wave, or new LBBB or ST segment elevation during screening | 229 | 2.1 |
| SA | STEMI | New Q wave, or new LBBB or ST segment elevation during screening | 101 | 0.9 |
| STEMI | NSTE-ACS | ECG criteria for STEMI not met and abnormal BL Biomarker within 6 hours of randomization or ST segment depression of other ECG abnormality during screening | 24 | 0.2 |
| STEMI | Stable | ECG criteria for STEMI not met and normal BL biomarkers within 6 hours of randomization | 6 | 0.05 |

BL=baseline; ECG=electrocardiogram; LBBB=left bundle branch block; NSTE-ACS: non-ST segment elevation-acute coronary syndrome; STEMI=ST segment elevation myocardial infarction.
Source: Applicant's Complete Response Document (Table 18)

The Applicant agreed with our concerns and elected to forgo the derived patient type algorithm in favor of the investigators' baseline diagnosis at the time of randomization.

**Reviewer Evaluation**: The Office of Biostatistics reproduced the Applicant's derived patient type algorithm and shown in ***Table 10***. The results matched that of the Applicant.

### Table 10. Investigator diagnosis vs. derived patient type

| | | site-reported patient type | | |
|---|---|---|---|---|
| | | Stable Angina | NSTE-ACS | STEMI |
| Derived patient type | Stable Angina | 5347 | 864 | 6 |
| | NSTE-ACS | 980 | 1821 | 24 |
| | STEMI | 101 | 229 | 1773 |

Source: Statistical Review and Evaluation Addendum (Reviewer's Analysis, Table 4)

Results for the primary endpoint using the derived patient type algorithm for the baseline diagnosis are shown on ***Table 11***. Similarly, results for the primary endpoint using the site-reported database are shown on ***Table 12***. When using the Applicant's algorithm, the odds ratio for the adjudicated primary endpoint favored cangrelor for all clinical presentations, and was significant for subjects with SA. For site-reported baseline diagnoses, the odds ratio for the adjudicated primary endpoint favored clopidogrel in subjects with STEMI, but significantly favored cangrelor in subjects with NSTE-ACS and trended in favor of cangrelor in subjects with SA. The pathophysiology of coronary artery disease is common to all clinical presentations. It is therefore unlikely that cangrelor would be effective only in the NSTE-ACS population but not in patients with SA or STEMI. Notably, there were relatively few endpoint events in the patients with STEMI (22 and 23 in the cangrelor and clopidogrel arms, respectively).

### Table 11. Primary endpoint analysis by derived patient type

| | cangrelor | | | Clopidogrel | | | | |
|---|---|---|---|---|---|---|---|---|
| | N | event | % | N | event | % | OR | 95% CI |
| stable angina | 3120 | 181 | 5.8 | 3018 | 222 | 7.4 | 0.78 | (0.63, 0.95) |
| UA/NSTEMI | 1389 | 49 | 3.5 | 1421 | 62 | 4.4 | 0.8 | (0.55, 1.18) |
| STEMI | 961 | 27 | 2.8 | 1030 | 38 | 3.7 | 0.76 | (0.46, 1.25) |

Source: Statistical Review and Evaluation Addendum (Reviewer's Analysis, Table 2)

**Table 12. Primary endpoint analysis by clinical presentation as assessed by the investigator at the time of enrollment**

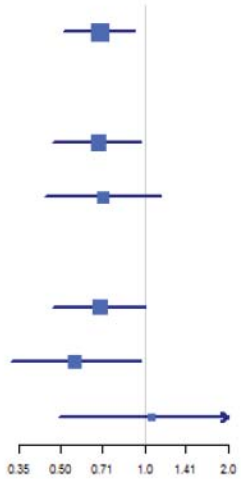
| | cangrelor | | | Clopidogrel | | | | |
|---|---|---|---|---|---|---|---|---|
| | N | event | % | N | event | % | OR | 95% CI |
| stable angina | 3185 | 182 | 5.7 | 3171 | 217 | 6.8 | 0.83 | (0.67, 1.01) |
| UA/NSTEMI | 1464 | 53 | 3.6 | 1428 | 82 | 5.7 | 0.62 | (0.43,0.88) |
| STEMI | 821 | 22 | 2.7 | 870 | 23 | 2.6 | 1.01 | (0.56,1.83) |

Source: Statistical Review and Evaluation Addendum (Reviewer's Analysis, Table 3)

The Office of Biostatistics created a Forest Plot using the investigators' baseline diagnosis. The results for the endpoint of death, MI (CK-MB ≥ 10x ULN), IDR, and ARC-ST were sub-grouped by baseline diagnosis and is shown in ***Figure 11***. Consistent with our results, the reported OR (1.06) subtended the line of unity when using the investigators' baseline diagnosis of STEMI. When using the derived patient diagnosis, the OR (0.76) favored cangrelor for patients with STEMI. In both cases, the 95% CI crossed the line of unity, thereby making these results not significant. The Forest plot shows the overall benefit of cangrelor for clinically relevant endpoints. The subgroups classified as "normal" (i.e. SA and asymptomatic ACS) or "abnormal" (symptomatic ACS and STEMI) did not reach significance, but did trend in favor of cangrelor.

**Figure 11. Forest plot for subgroup analysis of Death / SCAI MI / IDR / ARC-ST at 48 hours by baseline stratum and IVRS clinical presentation**

| | Cangrelor | Clopidogrel | OR (95% CI) |
|---|---|---|---|
| Overall | 79/5470 | 114/5469 | 0.69 (0.51, 0.92) |
| **Subject Stratum** | | | |
| Normal | 50/3549 | 73/3524 | 0.68 (0.47, 0.97) |
| Abnormal | 29/1921 | 41/1945 | 0.71 (0.44, 1.15) |
| **Clinical Presentation** | | | |
| Stable Angina | 45/3185 | 65/3171 | 0.69 (0.47, 1.01) |
| NSTE-ACS | 21/1464 | 36/1428 | 0.56 (0.33, 0.97) |
| STEMI | 13/821 | 13/870 | 1.06 (0.49, 2.30) |




Source: The Office of Biostatistics

**Conclusion**: There was no overall significant difference in outcome between the patient derived type and investigators' baseline diagnoses. The difference in the OR for STEMI between the derived patient algorithm baseline diagnosis and the investigator baseline



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diagnosis was not significant because of the wide confidence intervals crossing the line of unity for each OR estimate. The pathophysiology which subtends the spectrum of coronary artery disease (SA, NSTE-ACS, and STEMI) makes it unlikely that cangrelor would be effective in only one subgroup. The Applicant agreed to use the investigator baseline clinical diagnosis in lieu of the derived patient type algorithm.

### 4.7 Database Management

**Problem**: The Applicant unlocked the database to incorporate missing concomitant anticoagulation medication. This involved 553 subjects from 84 sites. The Applicant was asked to provide a detailed description of their database unlocking process and explain the root cause of missing key data.

**Applicant Information**: The Applicant provided relevant documentation supporting the database unlocking process. The Applicant explained the cause of missing information: transcription error, unfamiliarity with drug names, and site-specific SOP violations.

**Reviewer Evaluation**: The Office of Scientific Investigation (OSI) conducted a review and determined that the data was acceptable in support of the claimed indication.

**Conclusion**: The questions about database unlocking have been answered, and there are no issues about database unlocking.

## 5 Bleeding Summary

The reader should refer to the original clinical review for a complete discussion of the safety findings. This review presents the overall findings of the primary adverse event, major bleeding (see ***Table 13***). There were more bleeds on cangrelor (15.5%) compared to clopidogrel (10.9%); this was true overall as well as within each bleeding classification. The primary safety endpoint was the incidence of GUSTO severe bleeding (intracranial hemorrhage or bleeding resulting in hemodynamic compromise) (see ***Appendices Table 14*** for bleeding definitions). The incidence of a GUSTO or TIMI bleed was less than 1% in each treatment arm with the risk of a GUSTO bleed ranging from 50-83% higher, and the risk of a TIMI bleed being 2-3 fold higher on cangrelor compared to clopidogrel. The incidence of ACUITY major bleeding was higher than either GUSTO or TIMI classifications. This was primarily because of access site hemorrhages and hematomas which are part of the ACUITY major definition.



Reference ID: 3718758

**Table 13. CHAMPION PHOENIX Non-CABG bleeding classification at 48 hours**

| | Cangrelor N=5529 | | Clopidogrel N=5527 | | Cangrelor vs. Clopidogrel | |
|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | OR | (95% CI) |
| Non CABG bleeds | 857 | (15.5) | 602 | (10.9) | 1.50 | (1.34, 1.68) |
| | | | | | | |
| GUSTO | | | | | | |
| Severe or Moderate | 32 | (0.6) | 20 | (0.4) | 1.60 | (0.92, 2.81) |
| Severe | 11 | (0.2) | 6 | (0.1) | 1.83 | (0.68, 4.96) |
| Moderate | 21 | (0.4) | 14 | (0.3) | 1.50 | (0.76, 2.96) |
| Mild | 825 | (14.9) | 582 | (10.5) | 1.49 | (1.33, 1.67) |
| TIMI | | | | | | |
| Major or Minor | 45 | (0.8) | 17 | (0.3) | 2.66 | (1.52, 4.65) |
| Major | 12 | (0.2) | 6 | (0.1) | 2.00 | (0.75, 5.34) |
| Minor | 33 | (0.6) | 11 | (0.2) | 3.01 | (1.52, 5.96) |
| Acuity | | | | | | |
| Major | 249 | (4.5) | 145 | (2.6) | 1.75 | (1.42, 2.16) |

Reviewer code: bleed\resub\primary safety. Applicant's datasets: raw\bld, iss\fda_bld, iss lab

*Reviewer comment 1: Which bleeding classification should be used for the assessment of safety? Perhaps that is a matter of preference and so three classifications are included in this review. It is the reviewer's belief that the GUSTO severe and moderate are more clinically driven (there are no lab values in its definition) than TIMI major or minor (includes a hemoglobin change). Since both are widely used, the reviewer includes both in this review. The ACUITY major definition includes access site bleeding and hematomas, and in the CHAMPION PHOENIX trial this was the majority of the reason for the ACUITY major bleeds. Since most of the other reasons for an ACUITY major bleed were captured in the GUSTO and TIMI classifications, ACUITY major bleeds were not considered in the reviewer's benefit risk analyses. (See* **Section 1.2** *for more discussion on the utility of the bleeding classifications).*

*Reviewer comment 2: There were differences between the reviewer's and the applicant's initial report of major bleeds (with generally excess bleeds in the reviewer's analysis). The bleeding risk and the differences between the reviewer's and the applicant's numbers did not preclude the approval of cangrelor in 2014, but it was a*

*topic of discussion at the AC meeting. After the AC meeting, the Applicant and the reviewer thoroughly discussed the reasons for the differences, agreed on the interpretation of published bleeding classifications, and independently reviewed the data again.* ***Table 13*** *is the result of the review, and it should replace Table 59 in the original clinical review.*

Because the incidence of major bleeding is low, subgroup analysis within each classification is unlikely to produce any meaningful results. However, it was done for the combined GUSTO moderate or severe bleeds (even though the combined incidence was less than 1% in each arm). Although the numbers are small, females and patients < 75 years old tended to be at greater risk of bleeding with cangrelor compared to clopidogrel.

# 6 Summary

Cangrelor was still effective when only endpoints whose clinical meaningfulness is undisputed were analyzed (nominal p-value = 0.0123). The PHOENIX study as a stand-alone trial was sufficient to warrant approval of cangrelor for the prevention of periprocedural MI and stent thrombosis in patients undergoing PCI.

Ad-hoc PCI is a common feature of American practice. Cangrelor has utility in the ad-hoc PCI setting where $P2Y_{12}$ receptor inhibitor was not administered prior to angiography.

The timing of $P2Y_{12}$ therapy is variable and the guidelines have not provided firm evidence of optimal timing. The only prospective randomized clinical trial testing the hypothesis that pre-treatment of PCI patients with $P2Y_{12}$ inhibitors is more efficacious than treatment at the time of PCI showed no difference in efficacy between prasugrel pre-treatment and prasugrel treatment at the time of PCI, but a greater safety risk in the pre-treatment arm. The concomitant use of cangrelor with a GP IIb/IIIa agent has not been tested, but combination therapy using clopidogrel and a GP IIb/IIIa agent showed the benefit outweighing the risk with limited population studies as a guideline for American practice. Based on previous CHAMPION trials, it appears that if subjects likely to require GP IIb/IIIa antagonists were enrolled in PHOENIX, the rate of use probably would have been much higher and the outcome of the trial might have been different.

The use of cangrelor produced a window of pharmacodynamic vulnerability that could be clinically relevant but did not seem to abort results in PHOENIX.

Our conclusions regarding the benefit risk of cangrelor remain the same as in our original NDA review. The benefit of cangrelor compared to clopidogrel is small, but the risk is smaller. Treating 171 patients prevents one clinically meaningful periprocedural MI. In comparison, treating 1106 patients causes one GUSTO severe bleed, a safety



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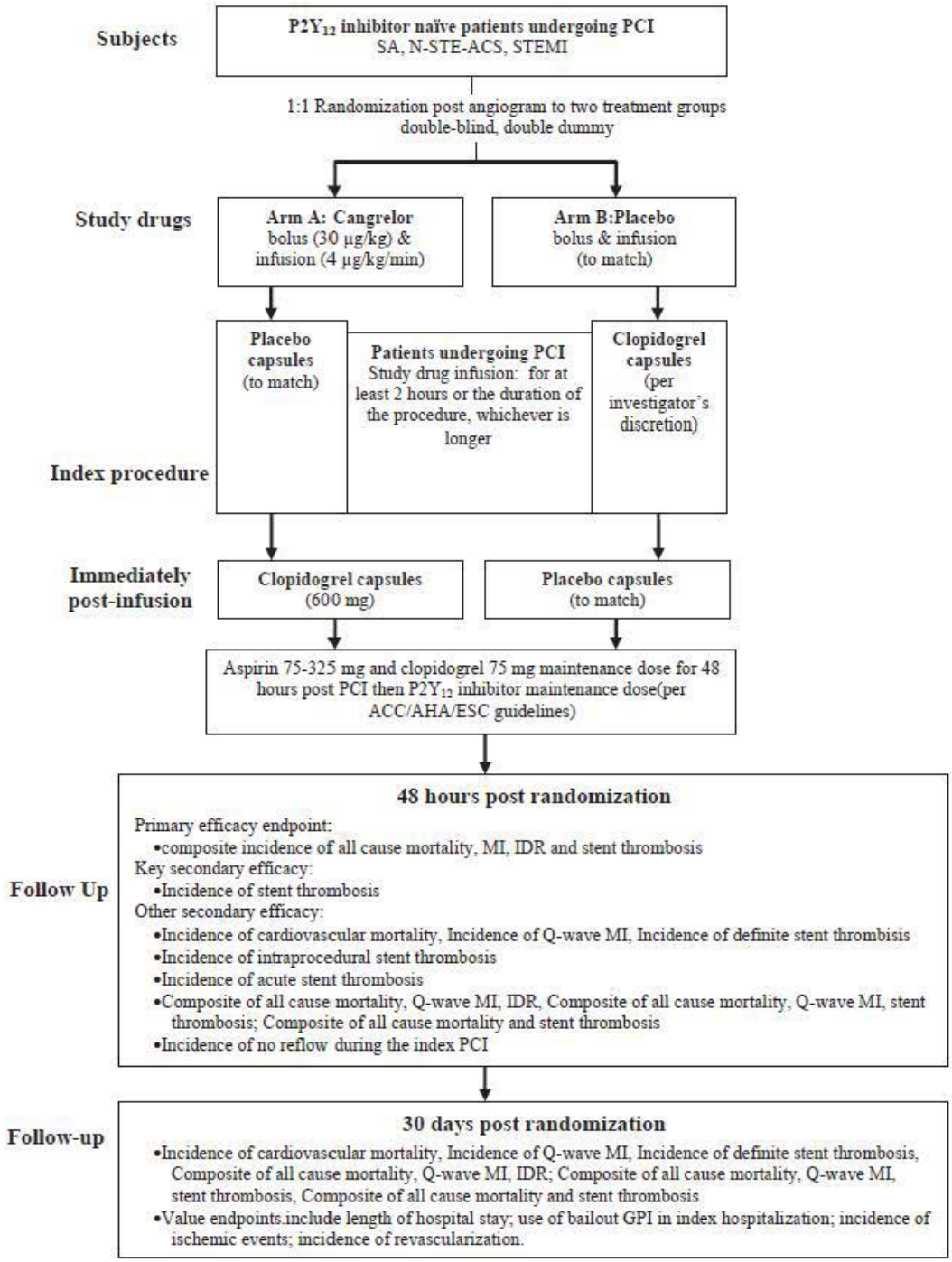
factor of ~ 6.5 fold.[10] Using a less severe bleed to assess benefit risk, such as a GUSTO moderate or TIMI minor bleed still favors the use of cangrelor.

We recommend that cangrelor be approved as an adjunct to PCI for the reduction in risk of periprocedural (b) (4) including myocardial infarction and stent thrombosis in patients (b) (4)

10 GUSTO severe bleed is an intracranial hemorrhage or bleeding resulting in hemodynamic compromise.

# 7 Appendices

## 7.1 CHAMPION PHOENIX Trial design and follow-up




Source: CHAMPION PHOENIX CSR

## 7.2 Definitions

### Table 14. Bleeding definitions in CHAMPION PHOENIX

| Bleed Classification | Definition |
|---|---|
| GUSTO severe | • Intracranial bleeding or<br>• Resulting in hemodynamic compromise requiring treatment (includes fatal bleeding) |
| GUSTO moderate | • Requiring blood transfusion |
| GUSTO mild | • Other bleeding requiring intervention, but not requiring transfusion or causing hemodynamic compromise |
| TIMI major† | • Intracranial bleeding or<br>• Any bleeding associated with clinically overt signs associated with a drop in hemoglobin of > 5 g/dL (or when hemoglobin is not available, an absolute drop in hematocrit > 15%) |
| TIMI minor† | • Clinically overt sign of bleeding (including observations by imaging techniques) that is associated with a fall in hemoglobin of ≥3 g/dL and ≤5 g/dL (or when hemoglobin is not available, an absolute drop in hematocrit ≥9% and ≤15%) |
| ACUITY major† | • Intracranial bleeding or<br>• Intraocular bleeding or<br>• Retroperitoneal or<br>• Access site hemorrhage requiring intervention or<br>• ≥ 5 cm diameter hematoma or<br>• Reduction in Hg ≥ 4 g/dL without an overt source of bleeding or<br>• Reduction in Hg ≥ 3 g/dL with an overt source of bleeding or<br>• Reoperation for bleeding or<br>• Use of any blood product transfusion |
| ACUITY minor | • All other bleeding not listed as major |

**Myocardial Infarction Definition in CHAMPION PHOENIX (UDMI, 2007)**
Type 1 = Spontaneous MI related to ischemia due to primary coronary event
Type 3 = Sudden unexpected cardiac death, often with symptoms suggestive of myocardial ischemia accompanied by new ECG changes or with ischemic evidence by angiography or autopsy.
Type 4a = MI associated with PCI
Type 4b = MI associated with ST.
There was no Type 2 or Type 5 MIs.

**Society for Cardiovascular Angiography and Interventions (SCAI) MI Definition**
SCAI MI in patients with normal baseline cardiac biomarkers is a post PCI MI with CK MB ≥10x ULN or CK MB ≥5x ULN (or cardiac troponin ≥35x ULN) with new pathologic Q-waves in ≥ 2 contiguous leads (or new persistent left bundle branch block) or cardiac Troponin I or T ≥70x ULN.

To diagnose post-PCI MI in ACS patients in whom the baseline level has not returned to normal:
1) In patients with elevated cTn (or CK-MB) in whom the biomarker levels are stable or falling, there should be a new CK-MB elevation by an absolute increment of ≥10x ULN (or ≥70x ULN for cTn I or T) from the previous nadir level;
2) In patients with elevated cTn (or CK-MB) in whom the biomarker levels have not been shown to be stable or falling, there should be a further rise in CK-MB or troponin beyond the most recently measured value by an absolute increment of ≥10x ULN in CK-MB or ≥70x ULN in cTn plus new ST-segment elevation or depression plus signs consistent with a clinically relevant MI, such as new onset or worsening heart failure or sustained hypotension.

## 7.3 Literature Review/References

Blankenship, JC, et al., 2013, Ad hoc percutaneous coronary intervention: a consensus statement from the Society for Cardiovascular Angiography and Interventions, Catheter Cardiovascular Interventions, 81(5): 748-758

Cutlip, D, et al., 2007, Clinical endpoints in coronary stent trials: a case for standardized definitions, Circulation, 115: 2344-2351

Farooq, V, et al., 2013, Short-term and long-term clinical impact of stent thrombosis and graft occlusion in the SYNTAX trial at 5 years, JACC, 62 (25): 2360-2369

Ibanez, B & Dangas, G, 2014, Prasugrel in NSTEMI-Loading after Seeing, JACC, 64 (24): 2572-2574

Levine, G, et al., 2011, 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention, JACC, 58 (24): e44-e122

Montalescot, G, et al., 2014, Effect of Prasugrel Pre-Treatment Strategy in Patients Undergoing Percutaneous Coronary Intervention for NSTEMI: the ACCOAST-PCI Study, JACC, 64 (24): 2563-2571

Montalescot, G, et al., 2013, Pretreatment with prasugrel in non-ST-segment elevation acute coronary syndromes, supplementary appendix, NEJM, 369:999-1010

Moussa, I, et al., 2013, Consideration of a new definition of clinically relevant myocardial infarction after coronary revascularization, JACC, 62 (17): 1563-1670

Thygesen, K, et al., 2007, Universal Definition of Myocardial Infarction, Circulation, 116:2634-2653

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BACH N BEASLEY
03/19/2015

FORTUNATO F SENATORE
03/19/2015

STEPHEN M GRANT
03/19/2015

**Subject: Review of Cangrelor Response Letter to the CR**

**From: Sharon Gershon Pharm.D.**

**Through: Susan Thompson, M.D. and Kassa Ayalew, M.D.**

FDA's Complete Response Question (in black type)

Sponsor's response (in blue type)

OSI Reviewer Comments (in red type)

You state in the CHAMPION-PHOENIX clinical study report that the database was initially locked and unblinded on January 4, 2013 and then later unlocked between February 2, 1013 and February 18, 2013 so as to include missing data regarding anticoagulant therapy prior to or during PCI for 5% (553) subjects at 84 investigational sites.

a. Please provide the documents that stipulate the procedures followed during this process and verify the procedures were followed.

Sponsor's response – the sponsor provides a response in Section 8.2.1, 8.2.2 and 8.2.3 of their response letter. The sponsor provided the following documents in their resubmission:

- SOP -130: Process for Locking a Clinical Trial Database - signed and dated December 16, 2011 and December 16, 2011 (Appendix 15.6).
- Database Locking Authorization Form – blank form
- Agreement to Unlock a Database – blank form
- Agreement to Unlock a Database form for PHOENIX study - signed and dated February 1, 2013 (Appendix 15.7),
- Vendor Sign Off Form – signed and dated February 1, 2013 (Appendix 15.8)
- Process describing Confirmation of Other Meds CRF page data - identifies the location of original CRFs and returned CRFs with anticoagulant data as Section 9.8 of the Trial Master File (Appendix 15.9)
- Letter of Clarification that was sent to the clinical investigator sites that had one or more subjects with missing anticoagulant data – dated February 6, 2013 (Appendix 15.10)
- Tracking spreadsheet used by sponsor's data management group to track site replies – includes site names, dates sent and dates received (Appendix 15.11).
- PHOENIX Reauthorization for Relock form - signed and dated February 18, 2013 (Appendix 15.12).
- Vendor Approval form to Relock the database – signed February 18, 2013 (Appendix 15.13)

OSI Reviewer Comments: The sponsor has provided the requested documents.

b. Please provide datasets from before unlocking and after unlocking for any datasets that were changed during the unlocking. Please also provide the AE, BLDH, BLDEVT, DISP, DTH, ENDPOINT, IDRH, MIH, and SAECASE datasets before and after regardless of whether there were any changes.

Sponsor's response – the sponsor provides a response in Section 8.2.4 of their response letter. The MEDS and CECMI datasets before database unlock and after relock are provided. Specifically, the following datasets are provided:

- Raw datasets for AE, BLDH, DTH, IDRH, MIH, and SAECASE.
- Derived datasets for AE, BLDEVNI, DISP, DTH, and ENDPOINT.

OSI Reviewer Comment: The sponsor has provided the requested datasets, which will be reviewed by DCRP.

c. Please provide a list of any other changes made to the database between February 1, 2013 and February 18, 2013, other than the anticoagulant changes.

Sponsor response: the sponsor provides a response in Section 8.2.4 of their response letter. The sponsor's database management group identified a data entry error for the clinical endpoint committee (CEC) reported date of an MI for Patient 495005131. This patient had an MI on (b) (6), but this date was mistakenly recorded as (b) (6). The CEC corrected this error during the database unlock period.

OSI Reviewer Comments: The sponsor has provided a list of changes in the database, as requested.

d. Please provide a dataset identifying the 553 patients, by site, who were missing anticoagulant data when the database was unlocked and whether or not the site provided updated anticoagulant use data via the paper CRF query that you utilized.

Sponsor's response: The sponsor provides a response in Section 8.2.5 of their response letter. A listing of the 553 patients by site was provided (Appendix 15.14). A corresponding SAS dataset (MEDSCHG.XPT) was also submitted.

OSI Reviewer Comments: The sponsor has provided the requested dataset.

e. Please provide a summary table identifying the percentage of sites that responded to the data query, and percent of subjects for which this data was obtained by treatment arm.

Sponsor's response: the sponsor provides a response in Section 8.2.6 of their response letter Table 24 in Section 8.2.6 documented that the response rate was 81 of 84 sites (96%) and that of the 81 responding sites, 68 sites submitted paper CRFs with data corrections for some or all of the patients who had missing anticoagulant use. The sponsor provided Table 25 that displayed the information according to treatment arm.

OSI Reviewer Comments: The subject has provided the requested summary table..

f. Please provide responses to the following questions:

i. Whether a subject was administered heparin or bivalirudin does not appear to be critical for interpreting the efficacy or safety outcomes of PHOENIX, especially as the data was missing for only about 5% of subjects. Why was the missing information thought to be important enough to require unlocking the database?

Sponsor's Response: The sponsor provides a response in Section 8.2.7 of the response letter. Their response indicates that anticoagulant administration during PCI procedure is standard of care, and because this data was missing the sponsor assumed it was a collection error. Because bleeding was an important adverse event during this study, the sponsor considered it important to know the anticoagulant use during the study.

OSI Reviewer Comments: The sponsor has provided an answer to the review division's query.

Please provide the reason(s) (i.e., root cause) that some sites did not record information about anticoagulant therapy administered prior to or during the PCI procedure for only some subjects, and why this was not identified during on-site, remote, or central monitoring during the conduct of the study?

Sponsor's Response: The sponsor provides a response in Section 8.2.8 of their response letter. The sponsor contacted the five sites (495001, 401055, 455002, 455019, and 443002) that had the largest volume of enrolled patients with missing anticoagulant use. Table 26 lists those reasons by site, with a more comprehensive explanation given below the table. Four of five sites provided explanations. Reasons included: misunderstanding of eCRF data entry to include drugs administered both in the Cath Lab and/or outside the Cath Lab (197 patients); data entry error (55 patients) in that anticoagulant was recorded on the anesthesia chart and not in the prescription chart; new study coordinator unfamiliar with generic names on the Other Meds eCRF (bivalirudin, LMWH) compared with the trade names recorded in the patient's chart (eg, Angiomax, Lovenox) (35 subjects).

However, Site 443002 that enrolled 246 patients had no explanation for why the site did not document anticoagulant use during the PCI procedure.

OSI Reviewer Comments: There were four sites that gave plausible reasons for why they did not document anti-coagulant use during the PCI procedure. However, there is no explanation given for why Site 443002 did not provide this information, or why monitoring did not pick this up. This site enrolled 246 subjects.

ii. The clinical study report states that it is "believed that there may have been some confusion on how to collect these data within the eCRF." If the CRF was confusing,

then why was the information missing for only about 5% of subjects?

Sponsor's Response: The sponsor provides a response in Section 8.2.9 of their response letter. The site in question was Site 495001 which only documented the anticoagulants that were administered in the Catheterization Laboratory on the Other Meds CRF page. Anticoagulants administered outside the Catheterization Lab or in the ER were not documented.

OSI Reviewer Comments: The sponsor has provided the requested information

iii. The reason(s) you elected to return paper CRF pages to sites on which the site was to make corrections as opposed to issuing data queries to sites and requesting that they update and resign eCRFs.

Sponsor's Response: the sponsor provides a response in Section 8.2.10 of their response letter. The reasons they provided were to restrict the number of people having access to the database and to avoid logistical issues with eCRF user accounts or personnel changes which would have added more time to the process.

OSI Reviewer Comments: The sponsor has proved the requested information.

iv. The reason(s) you elected to unlock the database, and leave it unlocked while you were obtaining corrected data from sites, as opposed to first collecting this information from sites and then unlocking database to make corrections.

Sponsor's Response: The sponsor provides a response in Section 8.2.11 of their response letter. In summary, the sponsor believed that collecting and entering the data on a rolling basis would be the most acceptable and more efficient way. All persons who interacted with the database remained unblended, and their names captured in the audit trail.

OSI Reviewer Comments: The sponsor has provided the requested information.

v. What process did you use to ensure that for those sites that responded, the data provided were accurate?

Sponsor's Response: The sponsor provides a response in Section 8.2.12 of their response letter. A visual review of the revised Other Meds eCRF page against the signed paper page was made.

OSI Reviewer Comments: The sponsor has provided an answer to the request.

vi. A more detailed summary of how it was initially determined that a systemic issue was present that some sites had not recorded anticoagulant therapy prior to or during the PCI procedure for some subjects

Sponsor's Response: the sponsor provides a response in Section 8.2.13 of their response letter. The response indicates that the database was initially locked on January 4, 2013 and unblinded on January 7, 2013 with study results available for review shortly thereafter. During the initial review, it was found that 5% of patients did not have documented anticoagulant administration.

OSI Reviewer Comments: In general, it appears that all items requested by the Review Division are addressed adequately by the sponsor in their response to Question 2 in the CR. The sponsor does not address the issue of why monitoring did not pick up this issue prior to database lock, or why data queries were not issued to sites to collect the information during the study. The sponsor indicated this could be due to data collection errors. Based on inspectional findings as previously detailed in our Clinical Inspection Summary, OSI does not change its recommendation that the data is acceptable in support of the claimed indication.

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SHARON K GERSHON
03/03/2015

SUSAN D THOMPSON
03/03/2015

# CDTL REVIEW ADDENDUM

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: May 28, 2014

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

NDA: 204-958

Drug: cangrelor (Kengreal)

Subject: Revised directions for extracting datasets from PDF files

An earlier CDTL Review Addendum provided the datasets for the cangrelor CHAMPION studies in PDF format and included directions for extracting the datasets. The earlier directions were incomplete in that they failed to include a step for removing the "Reference ID:" string that DARRTS inserts at the bottom of every page. This review provides the revised directions including how to remove the Reference ID string.

**Revised Directions for Extracting the Datasets**

1. Open the review with Adobe Acrobat (not the Acrobat Reader). From the Tools, Pages, Extract menu item extract out the pages from one of the sections 3 to 7 corresponding to one dataset. A quick way to determine the correct page numbers for a dataset is to click the Bookmarks icon at the left of the screen. Select the bookmark for the dataset you wish to extract. Note the starting page number. Then click the bookmark for the next dataset and note the starting page number (or, for the last dataset, the number of pages in the file.) Extract the pages from the starting page number for the desired dataset to the starting page number minus 1 for the next dataset (or the number of pages in the file minus 1 for the last dataset). Save the extracted pages as a .PDF file with the same filename as the section bookmark.

2. Open the saved file in Acrobat. From the File, Save As, More options menu item select Text (Plain). Save the file as a .TXT file. Acrobat may take several minutes to save the file.

3. Open the .TXT file with WordPad. When the .PDF dataset was filed in DARRTS, DARRTS added the string "Reference ID:" and a number at the bottom of every page. You must remove the entire Reference ID string, including the number, to restore the valid XML. Find an occurrence of the Reference ID string and highlight it, including the number. Click Replace on the menu bar, copy the entire string to the Find what box, leave the Replace with box blank, and click Replace All. WordPad may take a few minutes to Replace all. When WordPad completes the Replace all, save the edited .TXT file.

4. Using Windows Explorer change the .TXT extension to .XML.

5. Double click on the .XML file. The file should open in Excel. Verify that all variables are present and that the number of records is the same as that indicated in the DEFINE.PDF section.



Reference ID: 3513663

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THOMAS A MARCINIAK
06/02/2014

# CDTL REVIEW ADDENDUM

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: May 28, 2014

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

NDA: 204-958

Drug: cangrelor (Kengreal)

Subject: Revised directions for extracting datasets from PDF files

An earlier CDTL Review Addendum provided the datasets for the cangrelor CHAMPION studies in PDF format and included directions for extracting the datasets. The earlier directions were incomplete in that they failed to include a step for removing the "Reference ID:" string that DARRTS inserts at the bottom of every page. This review provides the revised directions including how to remove the Reference ID string.

**Revised Directions for Extracting the Datasets**

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4. Using Windows Explorer change the .TXT extension to .XML.

5. Double click on the .XML file. The file should open in Excel. Verify that all variables are present and that the number of records is the same as that indicated in the DEFINE.PDF section.



Reference ID: 3513751

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THOMAS A MARCINIAK
05/28/2014

# CDTL REVIEW ADDENDUM

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: May 23, 2014

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

NDA: 204-958

Drug: cangrelor (Kengreal)

Subject: Master datasets supporting cangrelor CDTL reviews

This review provides, in XML Excel format embedded in PDF files, the master datasets supporting all of the analyses in my cangrelor CDTL reviews. It is organized into seven sections: (1) this brief introduction including comments on some variables and directions for extracting the XML Excel format datasets from this document; (2) a DEFINE.PDF file, including numeric code definitions; and (3-7) providing the XML Excel format datasets in PDF format, one for CHAMPION PLATFORM and two each (by treatment arm) for PHOENIX and PCI. Bookmarks delineate the sections. I use XML Excel format because it is a format usable by most people, i.e., it opens in Excel. Most statistical packages have the capability to import Excel worksheets. One disadvantage of Excel is that the XML file sizes are large. Converting back (from PDF to XML text format) takes several minutes. I divided the larger studies, i.e., PHOENIX and PCI, into two datasets each (by treatment arm) to make the conversion back more manageable. All datasets have the same structure and have full key variables uniquely identifying the records. The datasets can be appended together freely. Another disadvantage of Excel is that the long variable names and the translations for numeric coded variables do not import into Excel. I provide the long variable names and the translations for numeric coded variables in the DEFINE.PDF file in section 2.

**Comments on Variables**

All three datasets include the same variables. I define the variables briefly in the DEFINE.PDF in section 2. While for most variables the derivation from the sponsor's submissions should be obvious, for some variables the derivation is more complex and may be dependent upon manual overrides based on my reviews of the case report forms. I try to include an abbreviated description of the override in the *comment* free text variable. If the derivation is particularly complex I will include the programs (Stata) for deriving the variable, although I did not do so for this application.

Stata has several conventions worth mentioning:

- Binary indicator variables typically use 0 for no or false and 1 for yes or true. In DEFINE.PDF I indicate them usually by the yesno value coding.

- The Stata symbol for a missing numeric value is a period (“.”) and Stata uses the highest positive value to store missing values. Hence, code checking for “<.” or “!=.” is checking for a nonmissing numeric value. (“!” is the “not” operator in Stata.) Note also that the “or” operator is the “|” character in Stata. I use these symbols in DEFINE.PDF.

- Stata time variables are double precision numeric variables counting milliseconds from 01jan1960. This time format is similar to that used by SAS except SAS uses seconds from 01jan1960. To convert to SAS format divide by 1,000. Because the Stata time values are large with many significant digits you must use a double precision numeric format for storing them rather than a lower precision float or long integer format. Stata date variables count days from 01jan1960 and can be represented with an integer variable.

I follow certain conventions of my own design for some variables. They are the following:

- *patid* – I convert the numeric unique portion of the *usubjid* (or whatever variable the application uses to identify patients in the datasets) into the shortest numeric variable that uniquely identifies a patient for a study. Usually this is a combination of a site ID and a sequential number for the site. I do this for ease of entry when working with datasets. Usually *patid* is the full key for my master datasets. For this application, because I include all three CHAMPION trials in one dataset, the full key is the combination of *patid* and the *study* variable.

- *study* – This variable identifies the study, in this case one of the CHAMPION studies PCI, PLATFORM, or PHOENIX. I describe the coding in DEFINE.PDF in section 2.

- *rx* – I provide the study drug identity (or treatment or arm) in the *rx* variable. For a two arm study I use 0 for the control and 1 for the new drug. I describe the coding in DEFINE.PDF in section 2.

- *time0* – I use *time0* for the randomization time. I count time from randomization typically regardless of whether the sponsor counts time from the first dose of study drug. The values for *time0* are Stata times, i.e., the number of milliseconds from 01jan1960, as I discuss above.

- *pepi48h* – I use *pep* to designate the primary endpoint. A character following pep indicates who ascertained the endpoint, e.g., *i* designates the investigator, *a* designates adjudicated (by sponsor—also without any qualifier), *f* designates FDA, etc. For the CHAMPION studies the primary endpoint was evaluated at 48 hours but 30 day outcomes are also of interest. So for CHAMPION I include a trailer indicated the time at which the endpoint was evaluated, i.e., 48h or 30d.



Reference ID: 3512121

- *comment* – I store miscellaneous free text comments about a patient in the *comment* variable.

**Directions for Extracting the Datasets**

1. Load the review into Adobe Acrobat (not the Acrobat Reader). From the Tools, Pages, Extract menu item extract out the pages from one of the sections 3 to 7 corresponding to one dataset. Save the pages to the same filename as the section bookmark.

2. Open the saved file in Acrobat. From the File, Save As, More options menu item select Text (Plain). Save the file as a .TXT file. This may take several minutes.

3. From Windows Explorer change the .TXT extension to .XML.

4. Double click on the .XML file. The file should open in Excel. Verify that all variables are present and that the number of records is the same as that indicated in the DEFINE.PDF section.

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Reference ID: 3512121

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/s/

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THOMAS A MARCINIAK
05/23/2014

Deputy Office Director Decisional Memo

| | |
|---|---|
| **Date** | (electronic stamp) |
| **From** | Robert Temple, MD |
| **Subject** | Deputy Office Director Decisional Memo |
| **NDA/BLA #**<br>**Supplement #** | 204958 |
| **Applicant Name** | The Medicines Company |
| **Date of Submission** | 01 May 2013 |
| **PDUFA Goal Date** | 30 April 2014 |
| **Proprietary Name / Established (USAN) Name** | KANGREAL/ cangrelor |
| **Dosage Forms / Strength** | Single-use 10 ml vial containing 50 mg cangrelor as a lyophilized powder for reconstitution |
| **Proposed Indication(s)** | I. Reduction of thrombotic events (including stent thrombosis) in patients with coronary artery disease undergoing percutaneous coronary intervention (PCI).<br>II. To maintain $P2Y_{12}$ inhibition in acute coronary syndromes (ACS) patients or patients with stents who are at increased risk for thrombotic events (such as stent thrombosis) when oral $P2Y_{12}$ therapy is interrupted due to surgery. |
| **Action:** | Complete Response for both indications |

| **Material Reviewed/Consulted OND Action Package, including:** | **Names of discipline reviewers** |
|---|---|
| Medical Officer Review<br><br>Medical Team Leader Review | Fred Senatore, Nhi Beasley |
| Statistical Review | Jialu Zhang |
| Pharmacology Toxicology Review | Belay Tesfamariam |
| CMC Review/OBP Review | David J. Claffey |
| Microbiology Review | Steven P. Donald |
| Clinical Pharmacology Review | Sreedharan Sabarinath |
| OSI | Sharon Gershon |
| CDTL Review | Thomas Marciniak |
| OSE/DMEPA | Janine Stewart |
| OSE/DRISK | Somya Dunn |
| Deputy Division Director | Stephen Grant |

OND=Office of New Drugs
OPDP=Office of Prescription Drug Products
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management



Reference ID: 3498637

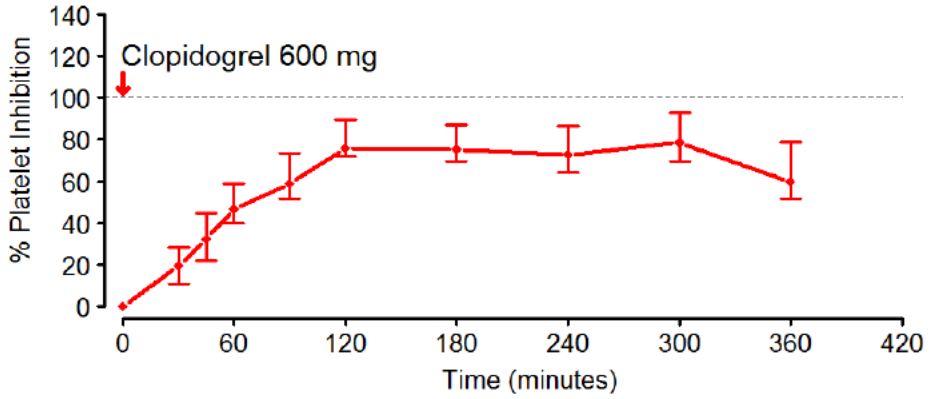
I. Introduction

Cangrelor is a parenterally administered inhibitor of adenosine-diphosphate (ADP)-induced platelet aggregation, inhibiting binding of ADP to the platelet P2Y12 receptor, the same receptor inhibited by clopidogrel's active metabolite and by prasugrel's active metabolites and reversibly inhibited by ticagelor. Cangrelor has a short half-life and its inhibition is rapidly reversible after infusion is stopped. Both of its proposed uses are intended to ameliorate problems associated with the PK/PD problems of clopidogrel when it is used 1) to treat patients undergoing percutaneous coronary intervention (PCI) or 2) to provide maintenance treatment in patients with a history of acute coronary syndromes or who have coronary stents in place, and who are going to surgery and need to stop drug.

1. PCI

In the first case, supported by the CHAMPION-PHOENIX study, it is well-recognized that platelet inhibition by clopidogrel takes about 2 hours to maximize, even with a 600 mg dose (twice the labeling-recommended dose) as shown in Dr. Grant's Figure 1, taken from Dr. Sabarinath's review. This is not an issue in a maintenance setting, but it can be in an acute setting. Thus, the striking early advantage of prasugrel over clopidogrel in the acute coronary syndrome (ACS) setting (TRITON Study) has been attributed in part to its rapid (no delay) effect, with a lesser difference seen later, attributed to prasugrel's overall greater platelet inhibition. Cangrelor is, in this case, being used to "cover" the 1-2 hour delay in attaining the full platelet-inhibiting effect of clopidogrel. This is, on its face, a pharmacologically and clinically reasonable approach, although one whose benefit cannot be expected to be large, as it would reduce, principally, events occurring in the first 1-2 hours of anti-platelet therapy. Indeed, as described below, this is where its effect appeared to occur.

**Figure 1: Platelet inhibition over time of a 600 mg dose of clopidogrel**




2. "Bridging" in maintenance clopidogrel therapy

Although there can be debate about how essential it is, [redacted] (b) (4)



Reference ID: 3498637

(b) (4)

It is noted also that the use of cangrelor as a bridge led to increased bleeding.

II. Effectiveness in PCI

A variety of issues have arisen in the analysis and interpretation of the CHAMPION-PHOENIX results, principally relating to

1. The appropriateness of the study design, including timing of the control agent (clopidogrel) in relation to percutaneous coronary intervention (PCI), the dose of clopidogrel chosen (300 mg or 600 mg), and the ability to use 2b/3a inhibitors.

2. The meaningfulness of the observed effect on the 48 hour primary endpoint: death, new heart attack (MI), ischemia-driven revascularization (IDR), or stent thrombosis (ST). The primary endpoint assessed the comparative rates of occurrence of any of these events as the first event but secondary endpoint analyses included each event separately. An important concern was the clinical meaningfulness of some components of the primary endpoint, namely non-symptomatic (biomarker-based) myocardial infarctions and "intra-procedural stent thrombosis" (IPSTs), which together represent a substantial fraction of the primary endpoint events. It should be noted that we have accepted biomarker-based MIs as pertinent in assessment of prasugrel and ticagrelor.

   The study included 3 different populations: a) patients with stable angina (SA), b) patients with non-ST elevation acute coronary syndrome (NSTE-ACS), and c) patients with ST-elevation MI (STEMI). As will be considered further below, the need to delay clopidogrel until the start of PCI in the SA setting is open to question.

3. The importance of 2 other CHAMPION trials, CHAMPION-PLATFORM and CHAMPION-PCI, in different populations that failed to show a benefit of added Cangrelor (b) (4)

   A. Study Design of CHAMPION-PHOENIX
   An issue discussed in detail was whether initiation of clopidogrel was inappropriately delayed, giving cangrelor "more room" to show an advantage. It has been suggested that, particularly in the case of stable angina, clopidogrel could be started earlier, before angiography, and CABG delayed if angiography revealed a need for the surgical procedure If CABG were not indicated, PCI could proceed with the effect of clopidogrel fully manifested.

   Clopidogrel initiation was not markedly delayed but it was not given longer enough before PCI to be fully effective (which was, of course, why cangrelor was being used). Clopidogrel appears to have been started promptly, either before or shortly after PCI began, in most cases, as shown in Dr. Senatore's review pages 93-94. The sponsor contends (March 17, 2014, letter, p 19), and this is also shown in the forest plot on p 106 of Dr. Senatore's review, that hazard ratios for clopidogrel given before or after the start of PCI were essentially identical.



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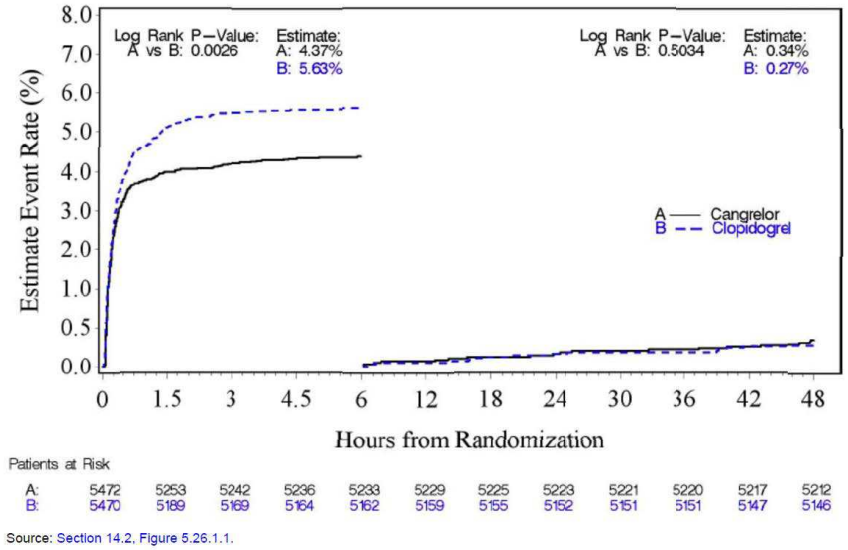
There is no doubt that the anti-platelet effect of clopidrogrel is somewhat greater, and occurs somewhat faster, with 600 mg of clopidogrel than with 300 mg, although clinical trials have generally not shown differences in effect. In CHAMPION-PHOENIX the dose of clopidogrel (600 or 300 mg) did not seem to make a difference in results (April 2, 2014 submission, p 18), with cangrelor somewhat better (HR 0.77) vs. 600 mg than 300 (HR 0.84), with about 75% of patients getting the 600 mg dose.

After 2 hours or completion of PCT, cangrelor was stopped and patients were given 600 mg of clopidogrel. It is stated in both the stats review and Dr. Senatore's review that the "loading dose" of clopidogrel was thus unbalanced, with 300 or 600 in the clopidogrel control group vs 600 in the Cangrelor group when Cangrelor was tapered and clopidogrel started. That, however, is not a loading dose, and is not part of the treatments being compared, and it followed the occurrence of most of the events of interest, as shown in the figure on p 60 of Dr. Senatore's review. The analysis of ST events above was similar.

**Figure 9. Landmark analysis of first occurrence of death/MI/IDR/ST in 48 hours (mITT population)**




It is of interest, as stressed by Dr. Grant, that stopping cangrelor at 2 hours, then starting clopidogrel, leaves a relatively unprotected period from about 2-4 hours. This occurs because you cannot start clopidogrel until the cangrelor is gone from the blood. Although this could be troublesome, as it leaves the patient without anti-platelet coverage for 1-2 hours, most events had already occurred by 2 hours.

B. Importance of Endpoints and Effect

The primary endpoint in CHAMPION-PHOENIX was death, MI, ischemia-driven revascularization (IDR), and stent thrombosis (ST). There is no doubt as to the importance of death and IDR, nor of certain kinds of MI and ST, but the details bear discussion.



Reference ID: 3498637

MI's with clear pain, q-wave effects, ST elevation, etc. are acknowledged to be bad events. But many MIs associated with procedures do not have such consequences. The PHOENIX trial used the "Universal definition of MI (UDMI), wherein an MI can be diagnosed if there were no prior enzyme elevations and CK-MB goes to 3xULN. If there was evidence of ischemia at baseline, a new MI needed either clear resolution of the baseline ischemia or new findings (ECG changes, symptoms, etc).

Although there was some skepticism as to the importance of these "biomarker MIs," FDA has accepted them in the TRITON study of prasugrel and the applicant argues that they have adverse consequences, a matter the applicant will need to address fully.

The ST endpoint included intra-procedural stent thrombosis (IPST), i.e., new or worsened thrombosis during the procedure, as well as post procedural ST, which all accept as a significant event. The applicant argues that these IPST events predict a bad outcome but that leaves open the question of whether it was the event or the patient's susceptibility to such an event that was critical. This too will need to be addressed further.

Of interest is a table in Dr. Grant's review, based on Dr. Zhang's analysis,

**Table 2: Outcomes up to 48 hours in CHAMPION-PHOENIX (mITT)**

| Outcome | Cangrelor N = 5472 | | Clopidogrel N = 5470 | | |
|---|---|---|---|---|---|
| | events | % | events | % | OR (95% CI) |
| **Death/MI/IDR/ST** (primary endpoint) | 257 | 4.7 | 322 | 5.9 | 0.78 (0.66, 0.93) |
| **Death/MI/IDR/ARC* ST** (i.e., primary endpoint excluding IPST) | 230 | 4.2 | 286 | 5.2 | 0.79 (0.66, 0.95) |
| **Death/MI (CKMB > 10x ULN for subjects with baseline normal CKMB)/IDR/ARC ST (i.e., primary endpoint excluding MIs with < 10 X ULN CKMB)** | 86 | 1.6 | 116 | 2.1 | 0.74 (0.56, 0.98) |

* Academic Research Consortium
** Death, MI (checkbox on MI CRF), unplanned revascularization or stent thrombosis (checkboxes on revasc CRF)

that removes the questioned endpoints, notably any MI with < 10x ULN increase in CKMB and any intra-procedural ST (IPST), leaving only bona fide ST's. The HRs remain unaltered, although confidence intervals widen. There is thus nominal significance for the endpoint that includes death, real ST, IDR, and a reasonably strongly supported MI. This important result will need to be assessed and confirmed by the applicant.

It is also notable, as shown in Dr. Senatore's forest plot (p 106), that effects on the primary endpoint are quite similar for all 3 subgroups of the population. These are also presented in the sponsor's March 17, 2014 submission.



Reference ID: 3498637

| Group | Cangrelor | Clopidogrel | OR (95% CI) |
|---|---|---|---|
| All Patients | 257/5470 (4.7%) | 322/5469 (5.9%) | 0.79 (0.67, 0.93) |
| Stable Angina | 181/3120 (5.8%) | 222/3018 (7.4%) | 0.78 (0.63, 0.95) |
| NSTE/ ACS | 49/1389 (3.8%) | 62/1421 (4.4%) | 0.80 (0.55,1.17) |
| STEMI | 27/961 (2.8%) | 38/1030 (3.7%) | 0.75 (0.46, 1.25) |

I note, however, that there is some uncertainty as to classification of patients, as discussed fully in Dr. Zhang's statistical Review Addendum. The table above is based on the "derived" patient type, a determination that modified the site-reported patient type based on additional information not available to the site investigator. Somewhat surprisingly, the results were quite different.

| | Cangrelor | Clopidogrel | OR (95% CI) |
|---|---|---|---|
| Stable Angina | 182/3185 (5.7%) | 217/3171 (6.8%) | 0.83 (0.67, 1.01) |
| NSTE/ACS | 53/1464 (3.0%) | 82/1428 (5.7%) | 0.62 (0.43, 0.88) |
| STEMI | 22/821 (2.7%) | 23/870 (2.0%) | 1.01 (0.56, 1.83) |

This will need further discussion and explanation by the applicant, (b) (4)

III. Previous Trials

The critical features of the CHAMPION-PCI and CHAMPION-PLATFORM trials are set out in Dr. Grant's Deputy Director review. Both trials entered patients with much more aggressive CAD, 95% NSTEMI/ACS in PLATFORM and 75% NSTEMI/ACS or STEMI in CHAMPION-PCI. Both used a clopidogrel dose of 600 mg, just prior to PCI in CHAMPION-PCI and after PCI in CHAMPION-PLATFORM and used endpoints of death, MI, IRR at 48 hours (but not ST). In PCI about 1/3 of patients were already receiving clopidogrel and 2b/3a inhibitors were used in about 25%. The PCI study did not suggest any effect (HR 1.05) but PLATFORM "leaned" (HR 0.87). It seems likely that prior use of clopidogrel and use of 2b/3a inhibitors worked against cangrelor in the PCI study. The applicant also believes many pre-existing MIs (surely more likely in these more acutely ill patients) were mistakenly counted as "new MIs," undermining any cangrelor effect. To avoid this in PHOENIX, patients with elevated CKMB were generally not counted as new MIs.

Like Dr. Grant, if PHOENIX were persuasive at a reasonably strong significance level, I believe the two negative studies would not weigh heavily against a conclusion of effectiveness.

IV. Bridging Study

I am less negative than the Advisory Committee on the possibility of a pharmacologically based conclusion that bridging is effective, given the clear evidence of an ability to replace the anti-platelet effect lost when clopidogrel is stopped prior to surgery. It is clear, however, that the added 2 or so days of coverage will not prevent very many stent thromboses and there clearly will be some excess of bleeding. Whether this use represents a reasonable benefit-risk tradeoff clearly



Reference ID: 3498637

needs further consideration and perhaps more use data, at least to define risk. It seems unlikely that a study large enough to show an actual reduction in ST in this short period is feasible.

V. Data Issues

Apart from the analysis of results in the entry subsets (see IIB above) there needs to be further evaluation of the late "unlocking" of the database (see Dr. Grant's review) and of results omitting the questionable endpoints of IPST and small CKMB MIs. The potential importance of those endpoints can also be further addressed by the applicant.

VI. Conclusion

I do not believe cangrelor can be approved at this time for use in reducing thrombotic events in patients undergoing PCI or as a bridge to maintain platelet inhibition in patients with a history of ACS or patients with stents when clopidogrel therapy must be interrupted because of pending surgery. There is evidence that tends to support the first of these claims but there remain important questions of what populations would benefit from the use of cangrelor (stable angina, NSTE/ACS, STEMI) and in what patients clopidogrel should be delayed until PCI is begun (although it does appear this is relatively common practice. It will be critical to assess the effect of cangrelor on clearly pertinent endpoints (death, post procedure ST, IDR and longer CKMB MIs) even if the drug's effect on IPST and smaller MIs is given some weight. The applicant will be asked to address these issues further.



Reference ID: 3498637

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ROBERT TEMPLE
04/30/2014

# Summary Review for Regulatory Action

| | |
|---|---|
| **Date** | 30 April 2014 |
| **From** | Stephen M Grant |
| **Subject** | Deputy Division Director Summary Review |
| **NDA #** | 204958 |
| **Applicant Name** | The Medicines Company |
| **Date of Submission** | 30 April 2013 |
| **PDUFA Goal Date** | 30 April 2014 |
| **Proprietary Name / Established (USAN) Name** | KANGREAL/ cangrelor |
| **Dosage Forms / Strength** | Single-use 10 ml vial containing 50 mg cangrelor as a lyophilized powder for reconstitution |
| **Proposed Indications** | 1. Reduction of thrombotic events (including stent thrombosis) in patients with coronary artery disease undergoing percutaneous coronary intervention (PCI).<br>2. To maintain $P2Y_{12}$ inhibition in acute coronary syndromes (ACS) patients or patients with stents who are at increased risk for thrombotic events (such as stent thrombosis) when oral $P2Y_{12}$ therapy is interrupted due to surgery. |
| **Action** | Complete Response for both indications |

| **Reviews Consulted** | **Names of primary reviewers** |
|---|---|
| Cross-Discipline Team Leader | Thomas Marciniak |
| CMC | David J. Claffey |
| Biopharmaceutics | Kareen Riviere |
| Microbiology | Steven P. Donald |
| Pharmacology Toxicology | Belay Tesfamariam |
| Clinical Pharmacology | Sreedharan Sabarinath |
| Clinical | Fred Senatore, Nhi Beasley |
| Statistical | Jialu Zhang |
| Office of Scientific Investigations | Sharon Gershon |
| Division of Medication Error Prevention and Analysis | Janine Stewart |
| Division of Risk Management | Somya Dunn |



Reference ID: 3498649

# 1. Introduction

Cangrelor, an analogue of adenosine triphosphate (ATP), is a parenteral, short-acting inhibitor of adenosine diphosphate (ADP)-induced platelet aggregation. It directly and competitively inhibits ADP binding to the platelet $P2Y_{12}$ receptor, one of the pathways that result in activation of the platelet glycoprotein 2b/3a complex. (b) (4) It is from a different chemical class and has a different mechanism of action than the currently marketed oral platelet $P2Y_{12}$ receptor inhibitors, which include the thienopyridines ticlopidine, clopidogrel, and prasugrel (which are irreversible inhibitors) and the cyclopentyltriazolopyrimidine, ticagrelor (which is a reversible inhibitor).

The Medicines Company has submitted an NDA seeking approval to market cangrelor for two quite different indications:

1. Reduction of thrombotic events (including stent thrombosis) in patients with coronary artery disease undergoing percutaneous coronary intervention (PCI) (hereafter referred to as the "PCI indication") and
2. To maintain $P2Y_{12}$ inhibition in acute coronary syndromes (ACS) patients or patients with stents who are at increased risk for thrombotic events (such as stent thrombosis) when oral $P2Y_{12}$ therapy is interrupted due to surgery (hereafter referred to as the "Bridging indication").

The applicant conducted three trials that were intended to provide substantial evidence of efficacy and safety to support approval for the PCI indication; CHAMPION-PCI, CHAMPION-PLATFORM, and CHAMPION-PHOENIX. All three were large, randomized, double-blind superiority trials in which patients who had undergone coronary angiography were randomized immediately before percutaneous coronary intervention (PCI) to cangrelor administered as 30 µg/kg IV bolus followed by a 4 µg/kg/min infusion for at least 2 hours or until the conclusion of the index procedure (whichever was longer), followed by a 600 mg dose of clopidogrel, or to clopidogrel alone for prevention of peri-procedural thrombotic events. The first two trials, PCI and PLATFORM, were conducted concurrently and were stopped at the same time prior to completion for futility. The third trial, PHOENIX, was designed with knowledge of the results of the first two trials. The applicant emphasizes that that a more specific definition for ascertaining peri-procedural myocardial infarction (MI) was used in PHOENIX. However there are other potentially relevant differences between the first two trials and the third, which are summarized in table 1 on the next page.

The applicant has not conducted an outcomes trial to provide substantial evidence of efficacy and safety for the Bridging indication. Rather, the applicant proffers a double-blind pharmacodynamic study, BRIDGE, in which 210 patients previously treated with a thienopyridine within 72 hours and requiring coronary artery bypass grafting (CABG) no sooner than 48 hours and no later than 7 days were randomized 1:1 to cangrelor infused at 0.75 µg/kg/min for a minimum of 48 hours and discontinued 1 to 6 hours prior to surgery or to matching placebo for the same period of time. The primary objective of the study was to demonstrate that IV cangrelor maintains levels of platelet reactivity below a threshold measurement (as determined by the Accumetrics VerifyNow™ PRUTest) up to the time of surgery, without increasing surgical bleeding. The applicant asserts that the threshold of platelet reactivity chosen, > 240 P2Y12 Reaction Units (PRU), is "known to be associated with a low risk of thrombotic events."



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## Table 1: Differences amongst Champion Trials

| | | PHOENIX | PLATFORM | PCI |
|---|---|---|---|---|
| Dates of conduct | | Sept 2010 – Nov 2012 | Oct 2006 – July 2009 | March 2006 – June 2009 |
| Number of subjects (% of planned enrollment) | | 11145 (100%) | 5364 (84%) | 8846 (99%) |
| Primary endpoint | | Death, MI, ischemia-driven revascularization (IDR), or stent thrombosis at 48 hours | Death, MI, or IDR at 48 hours | Death, MI, or IDR at 48 hours |
| Outcome of primary analysis | | OR: 0.79 (95% CI: 0.67, 0.93) p-value = 0.006 | OR: 0.87 (95% CI: 0.71, 1.07) p-value = 0.18 | OR: 1.05 (95% CI: 0.88 to 1.24) p-value = 0.59 |
| Patients taking clopidogrel prior to enrollment | | Not eligible to enroll | Not eligible to enroll | Eligible to enroll - 34% taking clopidogrel at baseline |
| Administration of study clopidogrel | | 300 or 600 mg either immediately before or after PCI | 600 mg after PCI | 600 mg immediately before PCI |
| Protocol restriction on use of glycoprotein 2b/3a inhibitors use | | Bailout only | Initially at investigator discretion; use discouraged after May 8 2007 | Initially at investigator discretion; use discouraged after May 8 2007 |
| Actual glycoprotein 2b/3a use | | Cangrelor: 2.3%<br>Clopidogrel: 3.5% | 8%<br>(16% prior to May 8 2007) | 22%<br>(33% prior to May 8 2007) |
| Population enrolled | Stable angina | 58% | 5% | 15% |
| | Non-ST elevation ACS | 26% | 95% | 64% |
| | ST-elevation MI | 16% | Not eligible to enroll | 11% |
| Definition of MI used for primary endpoint | | **Normal baseline CKMB**: CKMB > 3x ULN<br>**Abnormal baseline CKMB**: CKMB re- elevation + ischemic symptoms, angiographic evidence, or ECG changes<br>**STEMI**: Not assessed | • Q-MI or<br>• Post-procedure CKMB ≥ 3x ULN and CKMB > 50% above baseline if CKMB elevated prior to PCI | • Q-MI or<br>• Post-procedure CKMB ≥ 3x ULN and CKMB > 50% above baseline if CKMB elevated prior to PCI |



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# 2. Background

## A. PCI Indication

Drugs that inhibit platelet aggregation are routinely administered during (and after) PCI to prevent thrombosis at the site of coronary intervention. Aspirin is always administered except in the event of serious aspirin allergy. Generally at least one additional anti-platelet drug is administered as well. The additional anti-platelet drugs currently administered are

1. Glycoprotein 2b/3a receptor inhibitors, which inhibit cross-linking of activated glycoprotein 2b/3a receptors on the surface of platelets and thereby interfere with platelet aggregation and
2. Platelet $P2Y_{12}$ receptor inhibitors, which indirectly inhibit platelet aggregation by preventing ADP from binding to the platelet $P2Y_{12}$ receptor. Binding of ADP results in activation of the glycoprotein 2b/3a complex.

There are at least two other important platelet receptors in addition to the $P2Y_{12}$ receptor that activate the glycoprotein 2b/3a complex. Hence glycoprotein 2b/3a receptor inhibitors are more potent inhibitors of platelet aggregation because they inhibit the final common pathway of aggregation. The currently available glycoprotein 2b/3a receptor inhibitors are administered intravenously and so act rapidly. The currently available platelet $P2Y_{12}$ receptor antagonists are administered orally and platelet inhibition is delayed until they are absorbed and, for the thienopyidines, until they undergo metabolic activation. Ticagrelor and prasugrel require about an hour and clopidogrel requires a few hours to reach maximal effect.

The current guidelines from American cardiology societies do not make particularly clear recommendations about how to use these drugs as adjuncts to PCI because comparative studies directly testing them have not been performed (the current PIs for these drugs provide no useful guidance either). In general, the guidelines seem to recommend selective use of glycoprotein 2b/3a inhibitors in situations in which their more potent inhibition of platelet aggregation provides a benefit that justifies the increased risk of bleeding. Examples given in the guidelines of such situations include large thrombus burden in the coronary artery being treated, ongoing myocardial ischemia/infarction as evidenced by increased serum biomarkers of myonecrosis, and "inadequate" oral $P2Y_{12}$ receptor antagonist loading.

## B. Bridging Indication

Currently there is little information to guide pre-operative dosing of clopidogrel in patients who are taking clopidogrel and require an elective or urgent operation. The PI for clopidogrel advises "If a patient is to undergo surgery and an antiplatelet effect is not desired, discontinue Plavix five days prior to surgery." However, that advice appears to be based solely on the observation that bleeding in phase 3 studies in which clopidogrel was compared to placebo was increased in clopidogrel subjects compared to placebo subjects who underwent operation prior to 5 days; the PI does not indicate whether waiting increases thrombotic or other undesirable events.

The current treatment strategies for peri-surgical use of clopidogrel include:

1. Discontinue clopidogrel for some period of time based on the average half-life of the antiplatelet effect of clopidogrel or on the period of time required in trials for bleeding



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risk to return to baseline and then operate. Restart clopidogrel with or without a loading dose when adequate hemostasis is achieved.

2. Perform surgery without discontinuing clopidogrel for an extended period of time. Resume clopidogrel without a loading dose when adequate hemostasis is achieved.
3. Discontinue clopidogrel and daily measure platelet activity using some diagnostic device. When the platelet activity increases to some value, perform surgery. Restart clopidogrel with or without a loading dose when adequate hemostasis is achieved.

It should be noted that no diagnostic device has been approved in the USA for use to determine timing of surgery and there are no adequate data for choosing the level of platelet activity at which surgery may be performed without an increased risk of bleeding. In fact the device most commonly used for this purpose, Accumetrics VerifyNow™, has been cleared solely "to measure the level of platelet $P2Y_{12}$ receptor blockade." It has not been approved for any more specific use such as adjusting the dose of drugs that block the platelet $P2Y_{12}$ receptor or for assessing prognosis of patients based on the level of platelet inhibition.

## 3. CMC

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. The provided stability data support the proposed (b) (4) month expiration period for this product. There are no outstanding issues.

## 4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

## 5. Clinical Pharmacology/Biopharmaceutics

While I concur with the conclusions reached by the clinical pharmacology reviewer that there are no outstanding clinical pharmacology issues that preclude approval, a few relevant issues about the dosing of cangrelor as an adjunct to PCI are worth discussion.

### A. Duration of infusion for the PCI indication

I could not find a stated rationale for testing a two-hour infusion of cangrelor in the CHAMPION trials, and the choice is not obvious. It appears that the previous sponsor developing cangrelor, Astra-Zeneca, (b) (4) And the PI for the short-acting glycoprotein 2b/3a receptor inhibitor eptifibatide (which is specifically indicated for treatment of patients undergoing PCI) recommends that it be infused for several hours.

After discontinuation of cangrelor, its inhibition of platelet aggregation diminishes within minutes. Because clopidogrel cannot be administered until after cangrelor is discontinued (see discussion in section 5.B. below), there is a period of a few hours during which the anti-platelet effect of clopidogrel gradually increases and during which there is no further anti-platelet effect from cangrelor. It would seem logical that the duration of cangrelor should have been chosen based on a consideration of the time course of the risk for thrombotic events post-procedure. If



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that risk is substantially less after say, 24 hours, then 24 hours might have been the appropriate time to discontinue cangrelor and transition to clopidogrel. Although I am not aware of any definitive information about the time course of thrombotic risk after PCI, it seems unlikely that the risk would disappear immediately after the procedure is completed. Previous trials of anti-platelet agents in ACS indicate that a there is period of high risk for a few days after an event. So it may be that studying a longer duration of cangrelor would have resulted in better outcomes.

Although this discussion would have no regulatory implication if an effect that outweighs the risk were shown in clinical trials, it may explain why the demonstrated benefit of cangrelor in the CHAMPION trials was modest. It also suggests it would be prudent to study a longer duration of infusion if future trials of cangrelor are conducted.

## B. Anti-platelet drug effect over time in the PCI indication

Clopidogrel is not administered until after discontinuation of cangrelor (see section 5.c. below). So the two hour delay required for 600 mg of clopidogrel to achieve its antiplatelet effect is still present; administering cangrelor for two hours merely shifts the period during which clopidogrel has little anti-platelet effect from the time PCI is being performed to two hours later, as shown by the figures below provided by Dr. Sabarinath, the clinical pharmacology reviewer:

**Figure 1: Platelet inhibition over time of a 600 mg dose of clopidogrel**

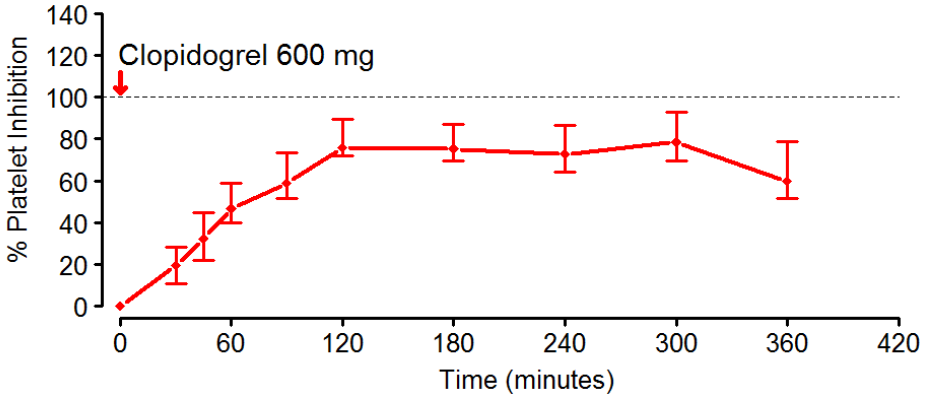
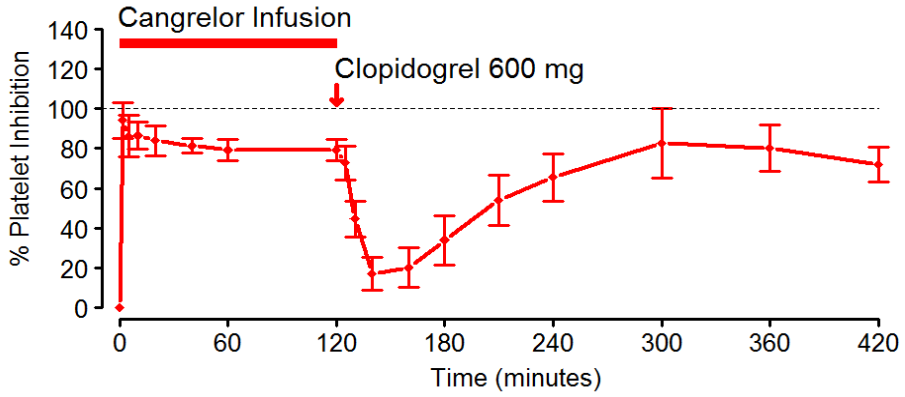



**Figure 2: Platelet inhibition over time of cangrelor 30 µg/kg IV bolus + 4 µg/kg/min for 2 hours followed by 600 mg of clopidogrel**



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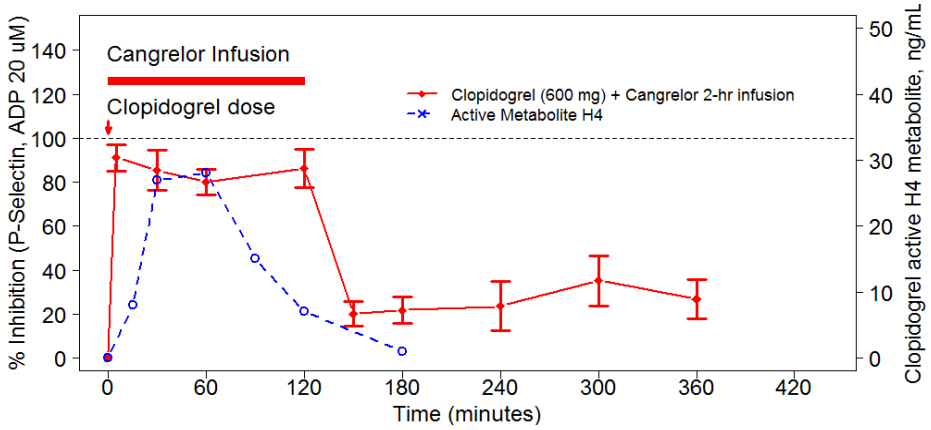
The maximal platelet inhibition achieved by cangrelor at the dose administered in the CHAMPION trials is somewhat higher (consistently greater than 80% inhibition) than that achieved by a single 600 mg dose of clopidogrel (maximal effect less than 80%). But if the AUC of the two figures above is examined, it appears that the average platelet inhibition over the first 6 hours of administering clopidogrel alone is not much different from that of administering cangrelor followed by clopidogrel and is no different after that time period. The small difference in pharmacological effect may limit the magnitude of the difference in clinical effects (both efficacy and safety) between cangrelor followed by clopidogrel compared to clopidogrel alone. The principal reason to expect any increased clinical efficacy is that the risk for thrombotic events is expected to be higher during the period PCI is being performed than immediately after. If the difference in risk during these two time periods is not large, shifting the time period over which the antiplatelet effect of clopidogrel increases to maximal from hours 0-2 to hours 2-4 is unlikely to result in a large difference in efficacy outcomes.

### C. Timing of clopidogrel administration for the PCI indication

It would be preferable if a decrease in platelet inhibition after discontinuation of cangrelor infusion could be avoided but the pharmacology of clopidogrel prevents clopidogrel from having an effect if administered concomitantly with cangrelor. If the platelet $P2Y_{12}$ receptor is occupied by cangrelor, then the short-lived active metabolite of clopidogrel cannot access it and administration will not result in any additional anti-platelet effect. Figure 12 from the Clinical Pharmacology review illustrates the situation:

**Figure 3: Platelet inhibition over time of administering cangrelor 30 µg/kg IV bolus + 4 µg/kg/min for 2 hours concomitantly with 600 mg of clopidogrel**




It is the inability to start clopidogrel before discontinuing cangrelor that leads to the problem discussed in 5.B.

## 6. Clinical Microbiology

I concur with the conclusions reached by the Product Quality microbiology reviewer that there are no outstanding microbiology or sterility issues that preclude approval except for restricting in labeling the in-use period for D5W diluted product to 12 hours.



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# 7. Clinical/Statistical-Efficacy

## A. PCI Indication

The Division prospectively agreed that a single well-conducted trial demonstrating superiority of cangrelor to clopidogrel could provide sufficient evidence of efficacy and safety to support an NDA for the PCI indication. If a comparator in an active-controlled trial is known to be effective, then the Division generally accepts that a single trial successful at p-value < 0.05 is adequate support for efficacy because that result provides strong evidence that the test drug is superior to placebo. The review team seems to concur that PHOENIX was statistically successful at a p-value of ~ 0.006. No novel safety issues are identified. Nonetheless, they do not recommend approval of this NDA at this time. I will discuss the issues that appear to be impeding approval at this time.

### i) Clinical Import of the Components of the Primary Endpoint

The primary endpoint in PHOENIX was a composite of death, MI, ischemia driven revascularization, and stent thrombosis. The clinical import of each of these components varies greatly. Each will be discussed below.

#### a. Stent thrombosis

Several of the anti-platelet drugs approved for marketing in the USA either have a separate claim in the PI for reduction of the occurrence of stent thrombosis (glycoprotein 2b/3a inhibitors and ticlopidine) or such a reduction is mentioned in the indication (prasugrel and ticagrelor). Stent thrombosis can result in death or MI and represents failure of the procedure, which is performed solely to maintain coronary artery patency, so avoidance of it can be interpreted as a clinical benefit.

However, the applicant's definition of stent thrombosis includes a novel event termed "intraprocedural stent thrombosis" (IPST), which represents an angiographic finding identified during PCI. The Division has never considered a similar claim and the applicant did not seek the Division's concurrence to its inclusion as a subcomponent of the primary endpoint. The applicant has provided observational data indicating patients who have IPST have worse outcomes but, of course, observational data cannot distinguish whether IPST independently causes worse outcomes or just distinguishes patients at higher risk for worse outcomes. Therefore the relationship of the occurrence of IPST to a clinical benefit is unknown. In fact the results of PHOENIX itself make it unlikely that prevention of IPST had an important effect on mortality. 18 subjects died by 48 hours in both treatment groups but at 30 days more cangrelor subjects had died, 60 vs. 55.

#### b. Ischemia-driven revascularization

Similar to post-procedural stent thrombosis, ischemia-driven revascularization (IDR) or a similar indication is included in the indications in the PIs of all three glycoprotein 2b/3a inhibitors and ticlopidine. Like stent thrombosis, IDR represents failure of the procedure so avoidance of it can be interpreted as a clinical benefit.

#### c. MI

The clinical import of post-procedural MIs identified solely by increases in serum biomarkers of myocardial necrosis is a matter of continuing controversy in the cardiology community. The current assays for troponin are so sensitive that up to 30% of patients have post-procedural



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elevations. While increases in post-procedural biomarkers are associated with some increase in risk for subsequent events, it is unclear if they increase the risk of subsequent events or are simply a marker for subsequent events. Pre- and post-procedure measurement of serum biomarkers after uncomplicated PCI is not recommended in guidelines and apparently is not routine. So it appears that practicing interventional cardiologists are not persuaded that measurement of serum biomarkers in the absence of symptoms and/or ECG changes provides useful diagnostic or prognostic information.

The interventional cardiology professional society, the Society for Cardiovascular Angiography and Interventions (SCAI), recently endorsed an Expert Consensus Document (JACC 2013; 62:1563–70) written to address the issue what level of biomarker elevation post-PCI is "clinically meaningful;" i.e., should be considered prognostic. It notes that "adoption of a MI definition not based on meaningful correlation with adverse consequences in clinical trials may result in false conclusions regarding the relative risk-benefit ratio of comparative therapeutic strategies." In discussing the differences between the significance of biomarker elevations during MI resulting from spontaneous plaque rupture and biomarker elevation post-PCI, they state "peri-procedural myonecrosis is induced by a single procedure in a controlled setting, and in most cases its consequences (if any) are immediately addressed." After systematically examining various clinical studies for the relationship peri-procedural biomarker elevation and mortality, these authors conclude that in patients without biomarker elevation prior to PCI the "preponderance of the best scientific evidence support(s) post-PCI elevation of CK-MB to > 10x ULN as being clinically relevant."

In PHOENIX, MIs in patients with normal baseline CKMB were defined as peri-procedural increases > 3x ULN. The SCAI document represents the consensus opinion of interventional cardiologists about the meaningfulness of peri-procedural biomarker elevation not accompanied by symptoms or ECG changes and so casts doubt on the clinical meaningfulness of MIs as defined by the applicant, or at least those defined by CKMB > 3x ULN and < 10x ULN.

### d. Death

The clinical importance of avoidance of death is obvious but as mentioned above the number of deaths in the cangrelor and clopidogrel subjects in PHOENIX were identical at 48 hours (18 vs. 18) and there were 5 more deaths in cangrelor subjects at 30 days (60 vs. 55).

### e. Summary discussion of primary endpoint

Components of a composite primary endpoint in cardiovascular trials are often of differing clinical import. Analyses of individual components or some combination of components considered most clinically important are perilous because trials are not powered to show an effect on less than the combination of all components of the primary endpoint. So we recognize that *post-hoc* analyses that exclude the less clinically meaningful components of a composite primary endpoint are treacherous. But it is critical to believe that the components at least are clinically meaningful and the problem here is that measurement of two subcomponents of the composite endpoint, specifically avoidance of IPST and small increases in peri-procedural biomarkers unaccompanied by symptoms and/ or ECG changes, have not been demonstrated to be clinical benefits.

The sensitivity analysis below provided by Dr. Zhang, the statistical reviewer, shows the primary endpoint with step-wise removal of first the subcomponents that do not definitely represent a clinical benefit and then the less clinically important components of ST and IDR; the final line is



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site reported events as defined by Dr. Marciniak:

**Table 2: Outcomes up to 48 hours in CHAMPION-PHOENIX (mITT)**

| Outcome | Cangrelor N = 5472 | | Clopidogrel N = 5470 | | |
|---|---|---|---|---|---|
| | events | % | events | % | OR (95% CI) |
| **Death/MI/IDR/ST** (primary endpoint) | 257 | 4.7 | 322 | 5.9 | 0.78 (0.66, 0.93) |
| **Death/MI/IDR/ARC* ST** (i.e., primary endpoint excluding IPST) | 230 | 4.2 | 286 | 5.2 | 0.79 (0.66, 0.95) |
| **Death/MI (CKMB > 10x ULN for subjects with baseline normal CKMB)/IDR/ARC ST** | 86 | 1.6 | 116 | 2.1 | 0.74 (0.56, 0.98) |
| **Death/MI (CKMB > 10x ULN for subjects with baseline normal CKMB)** | 71 | 1.3 | 98 | 1.8 | 0.72 (0.52, 0.98) |
| **Site-reported events**** | 115 | 2.1 | 126 | 2.3 | 0.91 (0.7, 1.2) |

* Academic Research Consortium

** Death, MI (checkbox on MI CRF), unplanned revascularization or stent thrombosis (checkboxes on revasc CRF)

The table above demonstrates that removal of IPST and smaller post-procedural biomarker increases, the subcomponents that are not clearly clinical benefits, does not significantly change the apparent reduction in relative risk attributable to cangrelor. The 95% CI is below one (i.e., the nominal p-value is < 0.05) for all analyses above except for site-reported events. However, it does change the apparent benefit as measured by reduction in absolute risk, from 1.2% to 0.5%. This latter number seems best for determination of the absolute benefit demonstrated in PHOENIX.

### ii) Two previous unsuccessful phase 3 trials

PHOENIX was the third trial conducted to demonstrate a clinical benefit of cangrelor in patients undergoing PC. The first two trials which were conducted concurrently, CHAMPION-PCI and PLATFORM, failed to demonstrate a benefit.

The applicant asserts that the PCI and PLATFORM failed because the biomarker definition of MI used to ascertain peri-procedural MI in patients with abnormal biomarkers at baseline identified many subjects as having peri-procedural MI who actually did not and the "false" peri-procedural MIs added noise to the primary analysis, obscuring the true effect of cangrelor. The applicant provides *post hoc* analyses of the occurrence of type 4a MI using the universal definition of MI (UDMI: 3x ULN in troponin or CKMB) and MIs resulting in Q-waves (Q MI) and states the effect of cangrelor is apparent using these definitions. The table below shows that the actual results are somewhat inconsistent with this assertion. One would expect that identification of "false" peri-procedural MIs to be randomly distributed between the two treatment groups. However, the sum of MIs in CHAMPION-PCI and PLATFORM as defined in the protocol is slightly higher in cangrelor patients. But the number of the protocol MIs that do not meet the definition of UDMI is considerably higher in the cangrelor subjects. And Q MIs comprise less than 3% of protocol-defined MIs; loss of that much information makes any resulting analysis unreliable.



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**Table 3: Number of MIs up to 48 hours by Type in CHAMPION-PCI and PLATFORM**

| | Cangrelor | Clopidogrel |
|---|---|---|
| MI as defined in protocols | 455 | 447 |
| UDMI | 171 | 194 |
| Not UDMI | 284 | 253 |
| Q MI | 8 | 18 |
| Not Q MI | 447 | 429 |

Finally there are other potentially important differences between PCI + PLATFORM and PHOENIX in addition to the definition of MI used (see table 1 above). The applicant's assertion that the results of PCI + PLATFORM provide supportive evidence for the use of cangrelor as an adjunct to PCI cannot be accepted. However, for similar reasons (i.e., the first two trials are quite different from PHOENIX) their failure should not be viewed as undermining the results of PHOENIX either.

### iii) Population studied in PHOENIX

An important part of the rationale for developing cangrelor was to make available an intravenously administered platelet $P2Y_{12}$ receptor inhibitor with a rapid onset of action and short half-life that can be administered after coronary angiography. If administration of oral platelet $P2Y_{12}$ receptor blockers is delayed until after angiography, their maximum anti-platelet effect will not be achieved until after completion of PCI. If administered before angiography, so that their maximum anti-platelet effect is achieved by the time of PCI, and emergent/ urgent CABG is required based on angiographic findings, then peri-operative bleeding will be increased because the anti-platelet effects of these drugs last days.

Emergent/ urgent CABG is most likely to be required in patients with acute coronary syndrome (ACS), who undergo angiography in anticipation of emergent/ urgent revascularization. However, the majority of subjects actually studied in PHOENIX were not patients with ACS but rather were patients with stable angina. Stable angina patients require emergent CABG after angiography or PCI only for procedural misadventure, which fortunately is rare. In general therefore, patients with stable angina can be preloaded with a platelet $P2Y_{12}$ receptor inhibitor prior to angiography if revascularization is thought likely and CABG, if needed, can be delayed for the week or so until the anti-platelet effects have diminished. In fact, based on the pharmacology discussed in section 5.B above, oral loading prior to PCI may be preferable because it avoids the post-PCI decrease in platelet inhibition that occurs after administration of cangrelor followed by clopidogrel. An analysis performed by Dr. Beasley suggests that in PHOENIX, 1231 of the 6231 subjects categorized by the site as having stable angina had their angiogram more than an hour before PCI and 545 had angiography more than 24 hours before PCI. Because their coronary anatomy was known to be amenable to PCI, they could have been loaded with clopidogrel before PCI. Of course it is easier to detect minor post-procedural CKMB elevations in patients with stable angina because they have normal CKMB at baseline; that may be the reason that PHOENIX targeted enrollment of stable angina subjects.



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## iv) Comparator in PHOENIX

While there is no regulatory requirement that the active control in a comparative trial designed to show superiority be best therapy available, it is somewhat unusual that the worst is used. In PHOENIX the weakest anti-platelet regimen available was used as the comparator.

- The use of the most potent and rapid acting anti-platelet drugs available, glycoprotein 2b/3a inhibitors (GPIs), was prohibited except as bailout.
- The use of prasugrel, a drug demonstrated in TRITON to be superior to clopidogrel for prevention of early MIs as well as prevention of stent thrombosis, was prohibited although it had been approved for marketing in the USA 2009; i.e., prior to the initiation of PHOENIX.
- The use of ticagrelor, a drug demonstrated in PLATO to be superior to clopidogrel for prevention of stent thrombosis, was prohibited (although it was not approved for marketing in the USA until 2011; i.e., after the initiation of PHOENIX).
- Administration of clopidogrel at least a few hours prior to PCI increases the anti-platelet effect at the time of PCI because generation of the active metabolite of clopidogrel takes some time. The following slide describing when patients in practice were administered clopidogrel relative to PCI was presented at the Sept 7 2007 Executive Committee meeting for CHAMPION-PCI and PLATFORM. It makes clear that the presenters also believed that "adequate" administration required giving clopidogrel hours before PCI.

**Figure 4: Slide from May 7 2007 Presentation to CHAMPION-PCI and PLATFORM Executive Committee**

(b) (4)



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In PHOENIX patients who were administered clopidogrel prior to angiography were not eligible to enroll. (b) (4)

## v) Effect of cangrelor in STEMI

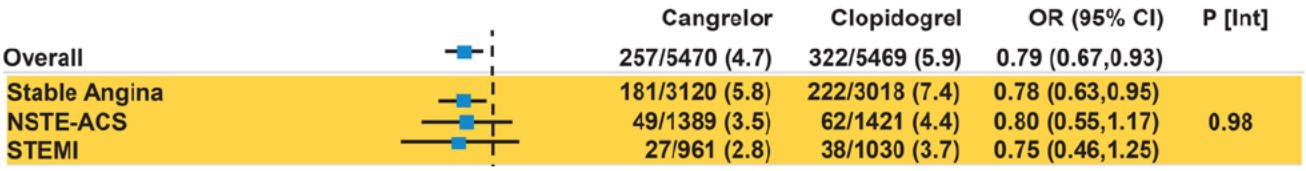
The Division has for a number of years questioned whether effects of drugs in the treatment of ST elevation MI (STEMI) are similar enough to effects in non-ST elevation Acute Coronary Syndrome (NSTE-ACS, which is composed of non-ST elevation MI + unstable angina) to allow both groups to be analyzed together as a single group. Thrombolytic therapy was found useful in STEMI, but not so in NSTE-ACS. On the other hand, in PLATO ticagrelor was found to have effects in both conditions similar enough that the indication in the PI lumps them together. The ACC-AHA produces separate guidelines for STEMI and NSTE-ACS so clearly the cardiology community considers the two conditions clinically distinct. In the absence of any clear conclusion about this issue, it appears that the Division does not object to analyzing both together but also appears to have had special interest in reviewing subgroup analyses of both.

Two of the three CHAMPION trials, PCI and PHOENIX, enrolled subjects with STEMI. In PCI the primary analysis of the 11% of subjects with STEMI (OR 1.06 with 95% CI 0.54 - 2.09) was similar to the overall population (OR 1.06 with 95% CI 0.89 - 1.25). However in PHOENIX the results were not as obviously similar, as shown below in an analysis provided by Dr. Zhang, the statistical reviewer:

**Table 4: Occurrence of Primary Efficacy Events in PHOENIX by Clinical Presentation as entered in IVRS during Randomization (mITT)**

| | Cangrelor N = 5470 | | | Clopidogrel N = 5469 | | | OR (95% CI) |
|---|---|---|---|---|---|---|---|
| | N | event | % | N | event | % | |
| **Stable angina** | 3185 | 182 | 5.7 | 3171 | 217 | 6.8 | 0.83 (0.67, 1.01) |
| **NSTE-ACS** | 1464 | 53 | 3.6 | 1428 | 82 | 5.7 | 0.62 (0.43, 0.88) |
| **STEMI** | 821 | 22 | 2.7 | 870 | 23 | 2.6 | 1.01 (0.56, 1.83) |

The applicant provided a different analysis of outcomes by subject presentation in slide CE-80 titled "Consistent Effect across All Subgroups," which was presented to the advisory committee at which this application was discussed:




The reason the two analyses are different is that the applicant did not use the information entered in IVRS at the time of randomization to classify clinical presentation. Instead they used "derived type" based in part from the CRF in addition to that entered in the IVRS during randomization.



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For about 20% of the subjects the clinical presentation entered in the IVRS differs from the derived clinical presentation as shown in the following analysis provided by Dr. Zhang, the statistical reviewer:

**Table 5: IVRS vs Derived Clinical Presentation in PHOENIX (ITT)**

| | | Clinical presentation entered in IVRS | | | |
|---|---|---|---|---|---|
| | | Stable Angina | NSTE-ACS | STEMI | Total |
| Derived clinical presentation | Stable Angina | 5347 | 864 | 6 | 6217 |
| | NSTE-ACS | 980 | 1821 | 24 | 2825 |
| | STEMI | 101 | 229 | 1773 | 2103 |
| | Total | 6428 | 2914 | 1803 | 11145 |

The discrepancy between these two analyses is of some interest, at least for labeling. If the applicant's analyses are a better description of the outcomes in PHOENIX, then the indication in any resulting PI is likely to indicate cangrelor is for treatment of PCI performed during ACS, both STEMI and NSTE-ACS. If the Agency's analyses are a better description, then neither PHOENIX nor PCI suggest a clinical benefit of using cangrelor as an adjunct to PCI during STEMI. The indication in any resulting label may exclude STEMI from the population for whom the drug is indicated and certainly the discrepancy in results between NSTE-ACS and STEMI will be provided in the description of the outcomes in PHOENIX in section 14.

The review team asked the applicant to provide details of the process used to derive the clinical presentation but so far the applicant has failed to provide a comprehensible explanation. Without knowing what additional information and process were used to derive clinical presentation, it is not possible to know whether the clinical presentation as entered in the IVRS or as subsequently derived by the applicant is more useful. However, the IVRS clinical presentation presumably captures all the information available to the investigator when the decision was made to enroll the patient in the trial. If approved, practitioners probably would have about the same information when they decide whether to administer cangrelor to their patients.

### vi) Ethics and use of other anti-platelet therapies in PHOENIX

Dr. Marciniak asserts in one of his reviews that PHOENIX was unethical because the protocol did not stipulate that clopidogrel be administered prior to PCI, and so concluded that the NDA should not be approved. He provides analyses that suggest that delaying administration of clopidogrel in PCI and PLATFORM results in worse outcomes and that the applicant was aware of the need to administer clopidogrel early. As noted above in section 2, however, the current guidelines for use of anti-platelet drugs during PCI are not very clear and practices in the USA appear to vary widely (as shown in the slide in figure 4 above), even though the pharmacology of clopidogrel strongly suggests that clopidogrel should be administered hours before PCI because the antiplatelet effect is delayed by at least two hours (see figure 1 above). The Division was concerned about delaying administration of clopidogrel and requested that the protocol be altered to allow administration of clopidogrel earlier.

Of equal concern is that the PHOENIX protocol prohibited use of GPIs. Prior to being amended on May 8 2007, the protocols for PCI and PLATFORM allowed investigators to use GPIs if they



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deemed useful. The following table provided by Dr. Zhang, the statistical reviewer, shows the use of GPIs in PCI and PLATFORM:

**Table 6: Use of Glycoprotein 2b/3a Receptor Inhibitors (GPI) in CHAMPION-PCI and PLATFORM**

| | Cangrelor | | Clopidogrel | |
|---|---|---|---|---|
| | N | GPI use (%) | N | GPI use (%) |
| **PCI** (before 8 May 2007) | 1746 | 583 (33.3) | 1720 | 589 (34.2) |
| **PCI** (after 8 May 2007) | 2600 | 565 (21.7) | 2599 | 571 (22.0) |
| **PLATFORM** (before 8 May 2007) | 418 | 67 (16.0) | 425 | 73 (17.1) |
| **PLATFORM** (after 8 May 2007) | 2235 | 174 (7.8) | 2217 | 171 (7.7) |

The protocol for PHOENIX prohibited the use of GPIs except for "bailout;" i.e., for treatment of an intraprocedural thrombotic complication. In PHOENIX glycoprotein 2b/3a receptor inhibitors were used in fewer than 4% of subjects, which is quite different from the use in clinical practice and in PCI and PLATFORM.

For the restriction on use of glycoprotein 2b/3a receptor inhibitors and the delayed administration of clopidogrel to be unethical, it would be necessary to conclude that subjects received worse care than they would have received had they not participated in PHOENIX. If an investigator knowingly provided what he or she considered worse care for a subject in order to allow participation in PHOENIX, then the investigator behaved unethically. The review team does not provide any information suggesting that this occurred or that anyone involved in the conduct of PHOENIX was aware that an investigator provided worse care in order to allow a subject to participate.

I think that it can be concluded that the protocol provided the opportunity for investigators to behave unethically and it does appear that the DSMB or personnel conducting PHOENIX made no effort to detect such behavior. However, PHOENIX is not the only trial that has provided an opportunity for investigators to act in ways not in the best interests of the subjects. Absent a clear demonstration that unethical behavior occurred, I am unaware that the Agency has refused to approve an application on this basis.

Finally, it should be noted PHOENIX was far from a 'real-world' study; the eligibility requirements and use of concomitant anti-platelet drugs were constrained in ways that made it easier to detect any effect of administering cangrelor. If approved, cangrelor is likely to be frequently used in patients on more potent anti-platelet regimens. And the eligibility criteria were not meant to enrich for patients with worse baseline prognoses and so more likely to have events of interest. In fact, patients with stable angina with better prognoses were the majority of patients enrolled but may well not be the patients in whom cangrelor would be used.

## B. Bridging Indication

BRIDGE succeeded in one of its two objectives (it failed to meet its safety objective –see section 8.B. below). 99% of cangrelor-treated patients maintained levels of platelet inhibition below the prespecified target of < 240 PRU as measured by the Accumetrics VerifyNow™ P2Y12 assay



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for all measured time points compared to 19% of placebo patients. This result means that a much higher proportion of subjects administered an active platelet $P2Y_{12}$ receptor blocker had a certain percentage of their platelet $P2Y_{12}$ receptors blocked than did those administered a placebo, which is hardly a surprising outcome. Blocking the $P2Y_{12}$ receptor and thereby inhibiting platelet aggregation is clearly the mechanism by which these drugs reduce stent thrombosis so it can be assumed that during the preoperative period (or any other period for that matter) administering cangrelor instead of placebo will reduce the risk of stent thrombosis in patients at significant risk for stent thrombosis without requiring it be directly demonstrated in a prospective controlled trial. But that is all it demonstrates. Among the questions unanswered are:

- What is the magnitude of risk reduction of stent thrombosis and other thrombotic outocomes? $P2Y_{12}$ receptor blockers such as cangrelor increase bleeding. Without knowing the magnitude of risk reduction for stent thrombosis, no risk benefit analysis can be performed.
- What is the right dose and duration to optimize benefit-risk? How long after discontinuation of clopidogrel should cangrelor be started?
- Which patients are at high enough risk for stent thrombosis to justify the bleeding risk?
- Finally, and most importantly, whether the strategy of waiting for the anti-platelet effect of clopidogrel to diminish substantially prior to surgery to lessen the risk of bleeding is correct. It is obvious that emergent surgery required to preserve life (e.g., repair of a type A aortic dissection) in a patient taking clopidogrel should not be delayed because the risk of increased bleeding caused by operating immediately is less than the risk of loss of life if operation is delayed. But delaying even urgent operations may expose patients to an increased risk of a bad outcome.

# 8. Safety

## A. PCI Indication

For the PCI indication the only relevant safety issue identified by the clinical reviewers was bleeding. Dr. Beasley, the clinical safety reviewer, identified two flaws in the applicant's assessment of bleeding in PHOENIX:

- Although not prespecified in the protocol or analytic plan, the applicant utilized only specific checked fields on a specific bleeding case report form to derive the number of bleeding events. Dr. Beasley's analyses also included other information, such as laboratory datasets.
- The applicant proffered analyses of bleeding that were labelled as being based on TIMI and GUSTO bleeding scales but the criteria used differed slightly from the published criteria. Dr. Beasley based her analyses on the published criteria.

As a result of the above, Dr. Beasley's analyses of the bleeding outcomes in PHOENIX identified a few more bleeding events than those of the applicant. She sent her analyses to the applicant, who agreed that they were technically correct. Hence I believe the following table abstracted from Table 1 in the clinical review safety addendum represents the best description of bleeding outcomes in PHOENIX. Administration of cangrelor does increase bleeding but the absolute increase is not large; 12 more GUSTO severe or moderate bleeds in cangrelor subjects compared to placebo.



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**Table 7: Non-CABG Bleeding up to 48 hours in PHOENIX**

| | Cangrelor N=5529 | Clopidogrel N=5527 | RR (95% CI) |
|---|---|---|---|
| Non-CABG bleeds | 857 (15.5%) | 601 (10.9%) | 1.42 (1.29, 1.56) |
| GUSTO severe or moderate | 32 (0.6%) | 20 (0.4%) | 1.57 (0.90, 2.74) |
| GUSTO severe | 10 (0.2%) | 6 (0.1%) | 1.64 (0.60, 4.52) |
| GUSTO moderate | 22 (0.4%) | 14 (0.6%) | 1.54 (0.79, 3.00) |
| GUSTO mild | 825 (14.9%) | 581 (10.5%) | 1.41 (1.28, 1.56) |
| TIMI Major or Minor | 40 (0.7%) | 14 (0.3%) | 2.83 (1.54, 5.19) |
| TIMI Major | 10 (0.2%) | 5 (0.1%) | 1.99 (0.68, 5.83) |
| TIMI Minor | 30 (0.5%) | 9 (0.2%) | 3.29 (1.56, 6.93) |

## B. Bridging Indication

Operating during the time there is residual antiplatelet effect of an oral platelet $P2Y_{12}$ receptor inhibitor increases the risk of bleeding. Cangrelor was developed for the Bridging indication to decrease the risk of peri-operative bleeding while maintaining effective platelet oral platelet. Because the half-life of cangrelor is a few minutes, it should not increase the risk of bleeding if discontinued an hour or so before operation. Hence one of the primary objectives of BRIDGE was to demonstrate that cangrelor did not result in more bleeding as measured by "excessive CABG-related bleeding." However, excessive CABG-related bleeding as defined in the protocol was slightly more frequent in cangrelor subjects than in placebo subjects; 12 (11.8%) vs 10 (10.4%). The numbers are too small to reach a firm conclusion but the observed result cannot be construed as demonstrating that administration of cangrelor does not increase bleeding.

Another example of a safety issue not resolved by the BRIDGE data is dyspnea. Dr. Tesfamariam, the pharmacology-toxicology reviewer, notes that because cangrelor is structurally similar to ATP, it may cause respiratory distress, especially in patients with COPD or asthma. Review of the reported in SAEs in BRIDGE reveals that two subjects (242004004 and 242007005) randomized to cangrelor and none randomized to placebo had to discontinue cangrelor because of dyspnea. The first developed bronchospasm about 30 minutes after cangrelor was started. The wheezing was severe enough to be assessed by the investigator as life-threatening; it resolved after discontinuation of cangrelor. The second developed mild dyspnea after several hours of cangrelor administration and the dyspnea resolved after discontinuation. Based on pharmacology cangrelor may have caused these subjects respiratory distress, but given the very limited safety information provided by BRIDGE, it may also be a chance finding.

For the Bridging indication, there is inadequate safety information to make any reasonable assessment. While not entirely irrelevant to the Bridging indication, the safety information from the CHAMPION studies is of limited utility because cangrelor was administered in the



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CHAMPION studies at a higher dose and for a much shorter duration (2 hours vs. days).

# 9. Advisory Committee Meeting

This application was discussed by the Cardiovascular and Renal Advisory Committee on February 12, 2014. The Committee voted 7-2 against approval for the PCI indication. The committee members who voted "No" indicated concern about the design of PHOENIX, about the two negative trials (PLATFORM and PCI), and felt that the increased risk of bleeding was not outweighed by the small clinical benefit. In particular, the committee did not believe that reduction in the risk of IPST was clinically important and expressed uncertainty about the clinical import of peri-procedural MI's detectable only by rises in serum biomarkers.

The committee voted 9-0 against approval for the Bridging indication. The committee unanimously concluded that the measure of platelet inhibition in this setting is an unproven surrogate and expressed concern that without a clinical trial in patients that assesses clinical outcome, the risks and benefits could not be known.

# 10. Pediatrics

DCaRP recommended a waiver for performance of pediatric studies required under PREA (Pediatric Research Equity Act) because PCI is performed so infrequently in the pediatric population and because so few pediatric patients are prescribed $P2Y_{12}$ inhibitors that studies relevant to the indications sought would be impossible.

# 11. Other Relevant Regulatory Issues

## A. Unlocking of PHOENIX Database after Unblinding

The database for PHOENIX was initially locked and unblinded on January 4 2013. On pages 81 - 83 of the clinical study report the applicant discloses that the database was unlocked from February 1 2013 to February 18 2013. The applicant states the database was unlocked because 553 subjects enrolled at 84 investigative sites were recorded in the locked trial database as not having received any anticoagulant therapy prior to or during PCI. The applicant states paper CRFs were generated for these subjects and distributed to the 84 sites. These were apparently returned, the data entered, and the database was again locked. The applicant indicates this process was conducted in accordance with a "documented agreement between the Sponsor's data management team, biostatistician, and study management team."

Reviewers in the Office of Scientific Investigations (OSI) indicate that unlocking a database after unblinding is not unusual and not problematic so long as procedures to maintain integrity are documented and followed. Nonetheless the information provided by the applicant raises several questions:

- Why was the information missing thought important enough to require unlocking the database? Whether a subject was administered heparin or bivalirudin was not critical for interpreting the efficacy or safety outcomes of PHOENIX, especially as the data was missing for only about 5% of subjects.
- Why was the information missing? The applicant mentions they "believed that there may have been some confusion on how to collect these data within the eCRF." If the CRF



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was confusing, then why was the information missing for only about 5% of subjects? Also, given the number of sites, it appears that the information must have been completed correctly for some subjects at those sites, indicating they were not confused about how to complete the CRF.

- Why did monitoring during the trial fail to detect that the information was not entered on the CRF?
- Why was the database unlocked before the paper CRFs were sent to the sites? Couldn't the subjects missing the data have been identified without unlocking the database? If so, why not wait until the data from the sites were returned and then unlock the database just long enough to enter it?
- 17 days seems like a brief amount of time to get all 84 sites to respond. Did they all respond? Was there a process in place to ascertain the accuracy of the responses?

This issue needs to be satisfactorily resolved before this application can be approved. OSI will provide input to the review team to help elicit from the applicant the information necessary to resolve. Hopefully, the applicant has before unlocking and after re-locking images of the databases used for the primary efficacy and safety outcomes documenting there were no changes to these critical databases.

### B. Bioequivalence of overencapsulated clopidogrel clinical supplies to approved clopidogrel

The Division requested appropriate bioequivalence studies on the actual clinical supplies in an Advice Letter (under IND 56812) dated September 9, 2010. The applicant has not provided the requested information and will need to do so before this application can be approved.

## 12. Labeling

No review of the sponsor's draft labeling has been performed because the application as currently submitted is not approvable. However if cangrelor is eventually approved for the PCI indication the following should be incorporated:

- [redacted] (b) (4) Loading an oral $P2Y_{12}$ receptor inhibitor far enough in advance of PCI to attain maximal anti-platelet effect is preferable to administering cangrelor followed by clopidogrel because it avoids the 2-hour dip in anti-platelet activity that occurs after cangrelor is discontinued.
- The indication should state that [redacted] (b) (4)
- [redacted] (b) (4)

For the Bridging indication, the claim sought is not consistent with current labeling guidance, which states an indication should describe the condition or population being treated and the



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clinical benefit expected. The population is not well-defined; characteristics that identify patients at "increased" risk for thrombotic events are not provided. And the only stated "benefit", maintenance of $P2Y_{12}$ inhibition, is not a clinical benefit but rather is a laboratory measurement whose relation to a clinical benefit is uncertain.

# 13. Decision /Risk Benefit Assessment

## A. PCI Indication

### i) Risk Benefit Assessment

The efficacy demonstrated in PHOENIX was modest as was the increase in bleeding. If events of IPST and MIs defined solely by CKMB < 10x ULN are not included (see table 2 above), then the difference in endpoints events is only 30 in a trial of over 11,000 subjects. There were 12 more GUSTO severe and moderate bleeds in the cangrelor subjects than in the clopidogrel subjects. So a simple subtracting of safety events from efficacy events (30 − 12) will result in a positive number. This method of assessing net clinical benefit is probably too simple because it does not properly account for severity of bleeding and the permanent clinical consequences of the efficacy events. And it does not take into consideration that at 30 days there were a few more deaths in cangrelor than clopidogrel subjects, although admittedly it is unlikely cangrelor, which is pharmacologically active only during the few hours it is administered, has any clinical effect 30 days later.

### ii) Recommended Regulatory Action

The main issues here are

- The magnitude of the clinical benefit demonstrated in PHOENIX of administering cangrelor to patients undergoing PCI is quite modest,
- The primary endpoint included components not clearly clinically meaningful,
- The comparator and adjunctive anti-platelet therapies administered were the least potent available, and
- The majority of subjects studied, stable angina, is not the one for whom cangrelor is most likely to be useful.

PHOENIX was statistically successful for the prespecified primary endpoint at a p-value < 0.01 and even if only larger post-procedural MIs and death (i.e., excluding IPST, ST, IDR, and MIs defined by CKMB < 10x ULN from the endpoint) are analyzed it appears that the nominal p-value is < 0.05, below the level of persuasiveness generally required for a single superiority trial with an active comparator. But the question of clinical meaningfulness remains. The clinical pharmacology of cangrelor suggests the clinical benefit is likely to be small as indeed it was. The demonstrated benefit is primarily a reduction of peri-procedural increases of CKMB with some reduction in ST and IDR events that did not result in MI or death. There was no reduction in death.

Further, in PHOENIX cangrelor was studied in a contrived setting that does not mirror the expected use if approved for marketing. The utility of cangrelor in patients chronically taking oral $P2Y_{12}$ receptors and those being administered glycoprotein 2b/3a receptor inhibitors was not studied and therefore is unknown. The majority of patients studied in PHOENIX were stable



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angina patients and for reasons discussed in section 5.A.iii) above, the comparator in this population should have been clopidogrel administered well in advance of PCI.

Therefore there are several problems that prevent approval of the PCI indication at this time. To be approved, the applicant will need to confirm that PHOENIX is statistically successful even if the components which have not been demonstrated to be clinically useful are excluded from the primary analysis or provide a demonstration that they are clinically useful. Approval will then hinge on a making a successful argument that the small benefit demonstrated is clinically meaningful in a specific population that can be usefully described in labeling.

## B. Bridging Indication

BRIDGE does not provide the substantial evidence of efficacy and safety required for approval under current regulatory standards; only a prospective adequate and well-controlled study in which outcomes are assessed can be useful here. Without the information provided by a prospective trial with clinically meaningful outcomes, no risk- benefit assessment can be made. In fact, the occurrence of the one of two primary endpoints in BRIDGE that measured a clinical event, "excessive CABG-related bleeding," was not better (actually slightly numerically worse) in subjects randomized to cangrelor and so BRIDGE does not provide any data suggesting the risk-benefit for use of cangrelor for bridging is positive.

If the applicant chooses to conduct a trial of cangrelor for use after discontinuing clopidogrel (and potentially other oral platelet $P2Y_{12}$ receptor inhibitors) prior to surgery, then I believe the following should be assessed:

1. Adverse events related to condition for which surgery is planned,
2. CV thrombotic events during any delay and peri-procedural CV thrombotic events, and
3. Bleeding during any delay and peri-procedural bleeding.

Additionally the trial should ideally have three arms; 1) one in which surgery is performed after a brief interruption of clopidogrel, 2) one in which clopidogrel is discontinued for several days, and 3) one in which clopidogrel is discontinued for several days and cangrelor is infused until shortly before surgery.



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/s/

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STEPHEN M GRANT
04/30/2014

# CDTL REVIEW ADDENDUM

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: April 28, 2014

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

NDA: 204-958

Drug: cangrelor (Kengreal)

Indications: For reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with coronary artery disease undergoing percutaneous coronary intervention (PCI); to maintain $P2Y_{12}$ inhibition in patients with acute coronary syndromes (ACS) or patients with stents who are at increased risk for thrombotic events (such as stent thrombosis) when oral $P2Y_{12}$ inhibitor therapy is interrupted due to surgery

Subject: Additional analyses and clarifications since filing of CDTL review

**Summary and Recommendations**
Since filing my CDTL review on March 23, 2014, we have had further discussions with the applicant and performed additional analyses to clarify issues. Many primary reviewers have filed addendums to their reviews describing the additional analyses. I summarize the updated issues below. The additional information regarding these issues (except the CMC update) reinforce my recommendation to issue a complete response rather than approval for the PCI indication.

**CMC Recommendation for Approval**
The CMC reviewer Dr. David Claffey filed a memorandum on April 15, 2014, that the Office of Compliance issued an overall acceptable recommendation (based on the manufacturing site inspections and communications from the applicant.) He stated that an overall approval recommendation can now be made from a CMC perspective.

**PHOENIX Sites That Were Also PCI or PLATFORM Sites**
A slide presented at the January 2013 PHOENIX Executive Committee Update listed that "Approx. 70% were CHAMPION sites." We requested confirmation of this statement and the applicant submitted a dataset in which about 54% of the PHOENIX sites were matched to CHAMPION sites. When we queried the applicant about the discrepancy between the January

2013 slide and the dataset the applicant responded that the dataset was correct and the slide was in error. However, I examined the site names and identified 8 additional PHOENIX sites that appeared to match PCI or PLATFORM sites. We queried the applicant about these 8 additional sites and the applicant confirmed that 7 of them were PCI or PLATFORM sites. The applicant also identified an additional 8 PHOENIX sites that were also PCI or PLATFORM sites. With these additional sites about 61% of the PHOENIX sites are identified as PCI or PLATFORM sites. These 61% of sites contributed about 67% of the PHOENIX patients.

*COMMENT: We still don't understand the discrepancy between 70% and now 61% nor am I certain that we know all of the PHOENIX sites that were PCI or PLATFORM sites. Because this issue is not a critical issue I don't believe further resolution is mandatory. Examining the available data should still be informative.*

The issue regarding which examining PHOENIX sites that were PCI or PLATFORM sites may be informative is the issue whether sites were following their standard of care or following the protocol. I show in Table 1 the clopidogrel timing for patients categorized by whether their sites participated in one or more of the CHAMPION trials.

**Table 1: Clopidogrel Timing for Patients Categorized by Sites Participating in the CHAMPION Trials**

| | PCI PHOENIX sites | | | PHOENIX | | | PLATFORM PHOENIX sites | | |
|---|---|---|---|---|---|---|---|---|---|
| | patients | pre-PCI | post-PCI | patients | pre-PCI | post-PCI | patients | pre-PCI | post-PCI |
| PHOENIX only | | | | 3,700 | 51% | 44% | | | |
| & PLATFORM | | | | 2,705 | 80% | 17% | 1,310 | 0.0% | 100% |
| & PCI | 2,818 | 77% | 12% | 2,847 | 63% | 30% | | | |
| & PLATFORM & PCI | 1,695 | 70% | 23% | 1,893 | 62% | 35% | 866 | 0.5% | 98% |
| All sites | 8,882 | 79% | 11% | 11,145 | 63% | 32% | 5,364 | 0.1% | 99% |

Clopidogrel timing was similar for all patients enrolled in a trial regardless of whether the site participated in one or more CHAMPION trials with some minor variations: PCI sites participating in both PLATFORM and PCI had more patients with clopidogrel administered post-PCI, i.e., like PLATFORM rather than PCI, than other PCI patients. PHOENIX sites that were also PLATFORM sites administered clopidogrel post-PCI less frequently than other PHOENIX sites.

*COMMENT: These data suggest to me that sites administered clopidogrel according to the protocol rather than per their standard of care. The PHOENIX clopidogrel timings for the PHOENIX sites that were also PCI or PLATFORM sites are similar to the overall PHOENIX clopidogrel timings rather than their clopidogrel timings in PCI and PLATFORM. One could postulate that the PLATFORM sites participating in PHOENIX may have learned from their PLATFORM experience that administering clopidogrel post-PCI is bad and hence they changed their standard of care, but such an argument isn't available for the other sites. As I discussed in my review of the ethicalness of the cangrelor development program, a CHAMPION newsletter from September 2008 states that "Other than the fact that we are conducting a research protocol, what is the rationale for not loading subjects with clopidogrel?" I postulate that sites believed that any variation in the timing of clopidogrel was acceptable because they were participating in a research protocol. Regardless, because delayed clopidogrel timing can cause*



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*irreversible harm to patients and because the informed consent documents did not inform patients regarding this possibility, I judge that delaying clopidogrel in PLATFORM and PHOENIX was unethical.*

**Patient Type (Index Event)**
In PHOENIX the sites entered into the IVRS system the patient type, i.e., whether the index event motivating the PCI and qualifying the patient for PHOENIX was stable angina, UA/NSTEMI, or STEMI. If the patient was stable angina, the patient was classified as "normal"; if the patient was STEMI, the patient was classified as "abnormal". If the patient was UA/NSTEMI, then the site entered indicators for biomarkers, ischemia, and ECG changes. If any were present than the patient was classified as "abnormal"; otherwise the patient was classified as "normal". "Abnormal" vs. "normal" was used, along with proposed clopidogrel loading dose and site, as a stratification factor for randomization.

*Post hoc* and post-unblinding the applicant defined a "derived patient type". The greatest impact of the new "patient type" was that, while with the original patient type used for stratification STEMI patients fared poorly with cangrelor, by the new "derived patient type" the cangrelor benefit for the applicant's primary endpoint was consistent across "derived" patient types. The Statistical Review Addendum dated April 23, 2014, discusses some aspects of "derived patient type" in more detail. The most relevant details regarding "derived patient type" are the following:

- The applicant defined "derived patient type" in a SAS program updated January 11, 2013, and then modified its definition for biomarker use on January 18, 2013. The last PHEONIX patient was randomized on October 3, 2012. The applicant reported the database locked on January 13, 2013, but then unlocked it between February 1 and 18, 2013. The protocol and statistical analysis plan do not define "derived patient type".

- The discrepancies between IVRS patient type and "derived patient type" are substantial. They differ for about 20% of the patients.

- While the primary endpoint rates at 48 hours look favorable for cangrelor in STEMI patients by "derived patient type", the site-reported endpoint rates at 48 hours are unfavorable for cangrelor in STEMI patients as shown in Table 2 and the mortality rates at 30 days are also unfavorable in STEMI patients as shown in Table 3.

**Table 2: Site-reported Primary Endpoint Rates at 48 Hours by "Derived Patient Type" in PHOENIX**

| | clopidogrel | cangrelor |
|---|---|---|
| angina | 2.0% | 1.7% |
| UA/NSTEMI | 2.6% | 2.4% |
| STEMI | 2.5% | 2.6% |
| Total | 2.3% | 2.1% |



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**Table 3: Mortality Rates at 30 Days by "Derived Patient Type" in PHOENIX**

| | clopidogrel | cangrelor |
|---|---|---|
| angina | 0.2% | 0.4% |
| UA/NSTEMI | 1.6% | 1.3% |
| STEMI | 2.6% | 3.0% |
| Total | 1.0% | 1.1% |

*COMMENT: I see no justification for abandoning the index event classification entered by the sites at randomization for a post hoc, post-unblinding classification. The index event classification entered by the sites should be the one by which they intended to treat the patients and corresponds to the classification we have used to analyze other trials. Conversely, if one believes that the site-reported classification is seriously flawed, e.g., derived patient type differs for about 20% of patients, then how can we trust the site actions for other activities, such as referring events for adjudication? Regardless, there is evidence that cangrelor was not effective in STEMI patients by "derived patient type" as well as by the site-reported index event.*

**Glycoprotein IIb/IIIa Inhibitor (GPI) Use**

The PHOENIX protocol prohibited GPI use except for bailout. The original PCI and PLATFORM GPI protocols allowed GPI use but amendments to both protocols dated May 8, 2007, excluded use of GPIs within the previous 12 hours prior to enrollment. The amendments cautioned investigators that "the use of these agents should be considered carefully based on the anti-platelet effect already provided by the study drug, i.e. clopidogrel 600mg or cangrelor". GPI use declined in PCI and PLATFORM after the amendments as documented in the Clinical Review Addendum and in the Statistical Review and Evaluation Addendum.

The statistical addendum has tables with primary endpoint rates for each of the CHAMPION trials by GPI use. The statistical reviewer observes that "The use of GPI did not appear to affect the treatment effect of cangrelor." I will not repeat the tables here—please see the statistical addendum for the details. I do note the following:

- The point estimate for the odds ratio of the primary endpoint with GPI use in PCI, the trial with the highest rates of GPI use, was less favorable for cangrelor. However, there is not a significant interaction between cangrelor and GPI use for the primary endpoint.

- GUSTO moderate/severe bleeding rates were substantially higher with GPI use, about 2-fold in PCI for both arms and with cangrelor in PLATFORM and 3-fold higher for clopidogrel in PLATFORM. Bleeding rates were higher with cangrelor than with clopidogrel regardless of GPI use.

*COMMENT: The major relevance of GPI use to approvability is that GPI use does not appear to explain the differing results among the three trials. The one factor that does is clopidogrel timing. GPI use was not randomized, so we do not know what factors influenced investigators to use them and how the factors might affect efficacy. I think it is reasonable to conclude that GPI use was responsible for the increased bleeding rates. Because GPI use was not randomized, the trials do not provide evidence that GPI use should have been restricted for clopidogrel.*



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**PHOENIX Database Unlock**
The Clinical Review Addendum describes an occurrence of the PHOENIX database being unlocked: "The database, which was locked on 14 January 2013, was unlocked on 01 February 2013 and relocked on 18 February 2013 because of 533 cases of missing anticoagulation concomitant medication data over 84 of the total of 153 sites in the PHOENIX trial." The Clinical Review Addendum provides the details so I will not repeat them here.

*COMMENT: I favor unlocking the database for legitimate corrections but, because late changes in my experience always seem to favor new drug, I'd also favor only including corrections that favor control. If we implemented that policy I project we would see few late changes. Regardless, as the Clinical Review Addendum describes, the PHOENIX database unlocking is unusual because of unlocking prior to the problem being defined and because of the duration of the unlocking. While I suspect that we will not be able to establish that the unlocking resulted in any inappropriate changes, it is another example of a unusual conduct problem in the CHAMPION development program.*

**Clopidogrel Timing within PHOENIX**
The major limitation of the analyses of clopidogrel timing in PHOENIX is that the timing was not randomized. As I stated in my initial CDTL review, interpreting clopidogrel timing within PHOENIX is more problematic than the cross-trial comparisons because investigators were allowed some discretion in timing and loading dosage. We do not know what patient characteristics they considered. In my advisory committee (AC) presentation I briefly discussed two confounding factors evident in the data: (1) Investigators administered 300 mg loading doses predominantly pre-PCI while timing of 600 mg loading was variable. (2) Loading dosages used were correlated with sites and, for bleeding, reported rates of bleeding varied substantially by sites grouped by loading dose. Because clopidogrel timing only varied in the clopidogrel arm, to explore clopidogrel timing I focused my analyses for my benefit-risk review on the clopidogrel arm. I tried to control for confounding factors by performing logistic regression. By the logistic regressions both a 600 mg loading dose and early administration of clopidogrel are associated with better outcomes. (For details see my AC presentation and my CDTL review.)

The applicant has submitted other analyses that challenge my conclusions above. The two most relevant confounders that they identified are the following:

- I had analyzed the clopidogrel arm alone because clopidogrel timing only varied in that arm. The applicant is correct that, while analyzing dummy clopidogrel timing in the cangrelor arm is obviously not related to clopidogrel timing, it is informative regarding whether patient factors responsible for the timing variations are responsible for the differences in outcomes rather than the timing *per se*. For logistic regressions of the cangrelor arm the odds ratio and its confidence interval and p value for dummy clopidogrel timing are similar to those for logistic regressions of the clopidogrel arm for actual clopidogrel timing.

- Longer duration of PCI procedures is associated with worse outcomes. Because clopidogrel administration was frequently delayed in patients with longer PCI durations,



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> it is difficult to distinguish the effects of longer PCI duration from those of timing of clopidogrel administration.

*COMMENT: The clopidogrel timing within PHOENIX is difficult to interpret. As I stated in my CDTL review, because I judge that the PCI to PLATFORM comparison is the best evidence supporting that delaying clopidogrel use is bad and because the three trial comparisons by clopidogrel timing appear consistent, I do not rely upon the analyses of clopidogrel timing within PHOENIX to make a recommendation of a complete response.*

**PHOENIX Bleeding Rates**

At the advisory committee meeting the applicant confirmed that they had based bleeding rates on the bleed case report form only. The primary safety reviewer used all available data to determine bleeding rates. Hence there are some discrepancies between the applicant's and the safety reviewer's rates. She asserts that her "analysis results in a more accurate description of the bleeding outcomes in the CHAMPION PHOENIX trial, and so should be used for benefit-risk analysis of the CHAMPION PHOENIX trial and in any label for cangrelor." She summarizes her conclusions regarding bleeding rates as follow:

> "The overall conclusions regarding safety of cangrelor with respect to bleeding remains essentially unchanged from the original review. The overall risk of a non-CABG bleed is ~42% higher on cangrelor compared to clopidogrel. The risk of a GUSTO severe or moderate bleed is approximately 60% higher on cangrelor compared to clopidogrel, but the difference was not significant, likely because the absolute numbers were low. The absolute risk of a GUSTO severe or moderate bleed was 0.6% on cangrelor compared to 0.4% on clopidogrel. The risk of a TIMI major bleed was two-fold higher on cangrelor compared to clopidogrel. Again, the difference was not significant. The absolute risk was low (0.2% cangrelor versus 0.1% clopidogrel)."

*COMMENT: I agree with the primary safety reviewer that her bleeding rates are the more accurate representation of bleeding risk with the cangrelor regimen. Cangrelor clearly produces more bleeding of all severities than a clopidogrel only regimen. However, while she also notes that the absolute risk of a TIMI major bleed is low and I note that all major or severe or moderate bleeding rates were <1% (except for ACUITY major bleeds), there are suggestions that we should not ignore completely the increased bleeding rates with cangrelor: For example, intracranial hemorrhages and fatal bleeds were both 3 with cangrelor vs. 1 with clopidogrel. If cangrelor had shown superior efficacy these bleeding rates were not be an impediment to approval. With uncertain efficacy in STEMI and vs. early clopidogrel loading they tilt the benefit-risk towards unfavorable.*



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**Standard for Approval**

For many drugs the standard of approval is that the drug beats placebo, i.e., the drug is better than nothing. However, it would appear to be common sense that for indications involving irreversible harm we should require the drug to be as good as available alternatives. As I presented at the Advisory Committee meeting, this latter truism was formalized in a Federal Register notice dated August 1, 1995, in Docket No. 95N-0230 entitled "Statement Regarding the Demonstrations of Effectiveness of Human Drug Products and Devices." A relevant quote from that notice is the following:

> "However, for products intended to treat life-threatening diseases, diseases with irreversible morbidity, and contagious diseases that pose serious health risks to others, it is essential for public health protection that a new therapy be as effective as existing, approved therapies."

The examples the notice provides regarding "irreversible morbidity" are "e.g., stroke or heart attack".

*COMMENT: This is the standard by which we must judge cangrelor. The cangrelor development program has failed to establish that cangrelor is as effective as clopidogrel used early or as prasugrel, ticagrelor, or GPI use.*



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/s/

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THOMAS A MARCINIAK
04/28/2014

# Safety Addendum to Clinical Review for NDA 204-958

Drug: Cangrelor
Sponsor: The Medicines Company
Indication: 1) Reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with coronary artery disease undergoing percutaneous coronary intervention (PCI),
2) Maintain P2Y12 inhibition in patients with acute coronary syndromes (ACS) or patients with stents who are at increased risk for thrombotic events (such as stent thrombosis) when oral P2Y12 therapy is interrupted due to surgery

Division: Division of Cardiovascular and Renal Products
Reviewer: B. Nhi Beasley, Pharm.D.

Subject: Safety Addendum
Date: April 28, 2014

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The purpose of this addendum is to update major bleeding, renal toxicity in the pivotal Phase 3 trial CHAMPION PHOENIX, discuss the 120 day safety update, and to correct mistakes noted in the safety section of the original cangrelor clinical review dated January 14, 2014.

# 1 Major Bleeding

**CHAMPION PHOENIX**

Bleeding was a non-adjudicated primary safety endpoint in the PHOENIX trial. Both the Applicant and I derived the established bleeding classifications. The difference between the Applicant's analysis and mine was discussed at the February FDA Advisory Committee meeting. The main reasons for the differences were highlighted in Table 45 of the clinical review, but are discussed here in more detail.

1. The definitions the Applicant used for various bleeding classifications differed in some respects from the published definitions.[1-4] Some published definitions include the terms "clinically overt" or "an overt source". The Applicant defined "clinically overt or "an overt source" differently than the referenced papers. Although the applicant had a checkbox on the bleed CRF for "clinically overt", the applicant required that additional fields be checked on the bleed CRF to deem the bleed "clinically overt".[1] Their inclusion of many other possible terms to define "clinically overt" or "overt source" supports the notion that these terms are ambiguous in the medical community. Since there is not a widely accepted definition of "clinically overt" or "overt source", and the published papers did not define these terms, I defined an overt bleed based on the dictionary definition, as an apparent sign of bleeding (including bleeding seen on imaging). In addition, in

[1] Defined just prior to the last subject completing the trial, although before unblinding, in the final SAP.



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the final SAP, the applicant added that a GUSTO mild bleed "required intervention". The 1993 GUSTO paper defined a minor bleed as "other bleeding, not requiring transfusion or causing hemodynamic compromise." I classified a GUSTO mild bleed as bleeds that were not GUSTO severe or moderate.

2. The Applicant only used specific checked fields on the bleed CRF to programmatically derive each bleed classification. When classifying severity of bleeding based on change in hemoglobin concentration, I used the Integrated Summary of Safety (ISS) lab dataset to determine the change in hemoglobin from baseline.[2] I used this approach because the hemoglobin or hematocrit information was often missing from the bleed CRF or miscalculated. If there was disagreement between the Hg drop noted on the CRF and the ISS lab dataset and a query to the site to resolve the discrepancy was made, then I generally used the resulting information. If there was no query or if the information in the query was not informative, I used the information in the lab dataset because I believed human error was less likely to occur in the lab data set. In the Applicant's analysis, if the Hg or Hct information was missing from the particular Hg or Hct field of the bleed CRF, the Applicant did not attempt to use other sources of information such as information found in text fields of the bleed CRF or the lab dataset. Rather, the event became ineligible to be a TIMI bleed.[3] I also used information found in the text fields of the bleed CRF (e.g., a transfusion was noted in the text field of the CRF that was not noted in the "transfusion field").
3. I classified non-CABG bleeds as mutually exclusive within each class. Some subjects had multiple bleed CRFs (events just 15 minutes apart) for what appeared to be one event. I collapsed multiple bleed CRFs into one event; the applicant did not.

I believe my analysis results in a more accurate description of the bleeding outcomes in the CHAMPION PHOENIX trial, and so should be used for benefit-risk analysis of the CHAMPION PHOENIX trial and in any label for cangrelor. I reviewed (blindly) the discrepant cases and now agree with the Applicant on five of the cases. The revised non-CABG bleed classifications are shown in Table 1. An Information Request was sent to the Applicant on April 11 to resolve the differences between our analyses. The rationale for my classifications was provided for each discrepant case. On April 15 the Applicant agreed with my numbers.

The overall conclusions regarding safety of cangrelor with respect to bleeding remains essentially unchanged from the original review. The overall risk of a non-CABG bleed is ~42% higher on cangrelor compared to clopidogrel. The risk of a GUSTO severe or moderate bleed is approximately 60% higher on cangrelor compared to clopidogrel, but the difference was not significant, likely because the absolute numbers were low. The absolute risk of a GUSTO severe or moderate bleed was 0.6% on cangrelor compared to 0.4% on clopidogrel. The risk of a TIMI major bleed was two-fold higher on cangrelor

[2] variable LBCHGBLS that adjusts for transfusions from the December 2013 NDA submission
[3] In addition to a TIMI bleed, the event was also ineligible to be an ACUITY or BARC bleed.



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compared to clopidogrel. Again, the difference was not significant. The absolute risk was low (0.2% cangrelor versus 0.1% clopidogrel).

**Table 1. *Non-CABG bleeding classification risk at 48 hours in CHAMPION PHOENIX (revised)***

| | Cangrelor | | Clopidogrel | | Cangrelor vs. Clopidogrel | | Cangrelor vs. Clopidogrel | |
|---|---|---|---|---|---|---|---|---|
| | N=5529 | (%) | N=5527 | (%) | RR | (95% CI) | OR | (95% CI) |
| Non CABG bleeds | 857† | (15.5) | 601 | (10.9) | 1.42 | (1.29, 1.56) | 1.50 | (1.34, 1.67) |
| | | | | | | | | |
| GUSTO severe or moderate | 32 | (0.6) | 20 | (0.4) | 1.57 | (0.90, 2.74) | 1.57 | (0.90, 2.75) |
| GUSTO severe | 10 | (0.2) | 6 | (0.1) | 1.64 | (0.60, 4.52) | 1.64 | (0.60, 4.53) |
| GUSTO severe* | 9 | (0.2) | 6 | (0.1) | 1.50 | (0.53, 4.21) | 1.50 | (0.53, 4.22) |
| GUSTO moderate | 22 | (0.4) | 14 | (0.3) | 1.54 | (0.79, 3.00) | 1.54 | (0.79, 3.01) |
| GUSTO moderate* | 22 | (0.4) | 13 | (0.2) | 1.69 | (0.85, 3.35) | 1.69 | (0.85, 3.37) |
| GUSTO mild | 825 | (14.9) | 581 | (10.5) | 1.41 | (1.28, 1.56) | 1.49 | (1.33, 1.67) |
| GUSTO mild* | 150 | (2.7) | 88 | (1.6) | 1.70 | (1.31, 2.21) | 1.72 | (1.32, 2.25) |
| TIMI Major or Minor | 40 | (0.7) | 14 | (0.3) | 2.83 | (1.54, 5.19) | 2.84 | (1.55, 5.23) |
| TIMI Major | 10 | (0.2) | 5 | (0.1) | 1.99 | (0.68, 5.83) | 2.00 | (0.68, 5.84) |
| TIMI Major* | 5 | (0.1) | 5 | (0.1) | 1.00 | (0.29, 3.45) | 1.00 | (0.29, 3.45) |
| TIMI Minor | 30 | (0.5) | 9 | (0.2) | 3.29 | (1.56, 6.93) | 3.31 | (1.57, 6.97) |
| TIMI Minor* | 9 | (0.2) | 3 | (0.1) | 3.00 | (0.81, 11.07) | 3.00 | (0.81, 11.10) |
| Acuity Major | 242 | (4.4) | 143 | (2.6) | 1.67 | (1.36, 2.05) | 1.71 | (1.39, 2.11) |
| Barc2 | 110 | (2.0) | 66 | (1.2) | 1.65 | (1.22, 2.24) | 1.67 | (1.22, 2.27) |
| Barc3a | 41 | (0.7) | 12 | (0.2) | 3.37 | (1.77, 6.40) | 3.39 | (1.78, 6.45) |
| Barc3b | 16 | (0.3) | 9 | (0.2) | 1.74 | (0.77, 3.94) | 1.74 | (0.77, 3.95) |
| Barc3c | 3 | (0.1) | 1 | (0.0) | 2.98 | (0.31, 28.63) | 2.98 | (0.31, 28.68) |
| Bad‡ | 61 | (1.1) | 41 | (0.7) | 1.46 | (0.99, 2.17) | 1.47 | (0.99, 2.19) |

* Applicant's analysis
† Reviewer identified an extra bleed (CSUBJECT 401029051) based on SAE report (no BLD CRF page so subject was excluded from Applicant's report). Classified as GUSTO severe, TIMI major and BARC 3b.
‡ Bad defined as any of the following: ICH, transfused, cardiac tamponade, reoperation for bleeding, surgical intervention, retroperitoneal, requiring or extending hospitalization
Reviewer's analysis with factors patient status, gender. Reviewer code: bleed\postAC\primary safety ptstatus gender final. Datasets: raw\bld, iss\fda_bld, iss lab.

## CHAMPION PCI and CHAMPION PLATFORM

The safety endpoints in these two trials were the incidence of hemorrhage by GUSTO, TIMI, and ACUITY classification at 48 hours, and the incidence of blood product transfusions during the index hospitalization (distinguished by relationship to CABG surgery). Since the PHOENIX trial was of sufficient size and duration to characterize the safety of cangrelor, I did not scrutinize the bleeding in PCI and PLATFORM as assiduously as the PHOENIX trial. Table 2 shows the Applicant's programmatic derivation of the GUSTO, TIMI, and ACUITY bleeding classifications.



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The risk of major bleeding is generally greater with cangrelor compared to clopidogrel. Note that the applicant's definition of a GUSTO mild bleed in PCI and PLATFORM was similar to the published GUSTO trial (in other words, an "intervention" was not required). The incidence of bleeding with cangrelor does not appear much different between trials. However, the relative risk of bleeding with cangrelor compared to clopidogrel appeared slightly greater in PLATFORM than in PCI or PHOENIX. The later administration of clopidogrel in PLATFORM (thus lowering the incidence of bleeding with clopidogrel) might have contributed to this finding. Because of the difference in clopidogrel administration, I recommend not combining the three trials to display relative risk. If cangrelor were to be approved, the Applicant should apply the same derivation to CHAMPION PCI and PLATFORM that I used for PHOENIX and compare the results.

**Table 2. Applicant's bleeding classification in CHAMPION PCI and PLATFORM**

| | Cangrelor | | Clopidogrel | |
|---|---|---|---|---|
| | | (%) | | (%) |
| **PCI (TMC-CAN-05-02)** | **N=4374** | | **N=4365** | |
| GUSTO severe or moderate | 46 | (1.1) | 41 | (0.9) |
| GUSTO severe | 10 | (0.2) | 11 | (0.3) |
| GUSTO moderate | 36 | (0.8) | 30 | (0.7) |
| GUSTO mild | 853 | (19.5) | 736 | (16.9) |
| TIMI Major | 19 | (0.4) | 14 | (0.3) |
| TIMI Minor | 36 | (0.8) | 26 | (0.6) |
| Acuity Major | 151 | (3.5) | 120 | (2.7) |
| Transfusion | 41 | (0.9) | 38 | (0.9) |
| | | | | |
| **PLATFORM (TMC-CAN-05-03)** | **N=2662** | | **N=2650** | |
| GUSTO severe or moderate | 26 | (1.0) | 19 | (0.7) |
| GUSTO severe | 9 | (0.3) | 6 | (0.2) |
| GUSTO moderate | 18 | (0.7) | 13 | (0.5) |
| GUSTO mild | 427 | (16.0) | 308 | (11.6) |
| TIMI Major | 4 | (0.2) | 9 | (0.3) |
| TIMI Minor | 22 | (0.8) | 15 | (0.6) |
| Acuity Major | 145 | (5.4) | 91 | (3.4) |
| Transfusion | 24 | (0.9) | 16 | (0.6) |

Source: Table 6.1.4.1 from PLATFORM CSR. Table 6.1.4.3 from PCI CSR

## 1.1 Bleeding and use of Glycoprotein IIb/IIIa inhibitors (GPIs)

In CHAMPION PCI and PLATFORM, GPIs were allowed to be used per site standard of care, but in PHOENIX GPIs were only allowed to be used as bailout during the PCI procedure. Since GPIs are indicated as an adjunct to PCI to reduce the risk of cardiac ischemic complications and these agents may increase the risk of bleeding, it was important to examine the bleeding risk in subjects that received both GPI and cangrelor.



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Tables 3-4 show the risk of bleeding in subjects that received and did not receive a GPI in the three trials. The incidence of bleeding was greater with a GPI than without in both treatment arms. However, the relative risk of bleeding was higher without a GPI; this is likely a result of chance. Definitive conclusions regarding the relative risk of bleeding with cangrelor and a GPI cannot be made.

**Table 3. Periprocedural GPI use and bleeding risk in PHOENIX**

| Class<br>GPI use | Cangrelor | | | Clopidogrel | | | Cangrelor vs. Clopidogrel | |
|---|---|---|---|---|---|---|---|---|
| | n | N | % | n | N | % | OR | 95% CI |
| GUSTO severe or moderate | | | | | | | | |
| Yes | 5 | 153 | (3.3) | 5 | 229 | (2.2) | 1.49 | (0.42, 5.29) |
| No | 27 | 5376 | (0.5) | 15 | 5298 | (0.3) | 1.74 | (0.92, 3.27) |
| GUSTO severe | | | | | | | | |
| Yes | 1 | 153 | (0.7) | 1 | 229 | (0.4) | 1.74 | (0.10, 29.10) |
| No | 9 | 5376 | (0.2) | 5 | 5298 | (0.1) | 1.75 | (0.58, 5.21) |
| GUSTO moderate | | | | | | | | |
| Yes | 4 | 153 | (2.6) | 4 | 229 | (1.7) | 1.40 | (0.34, 5.75) |
| No | 18 | 5376 | (0.3) | 10 | 5298 | (0.2) | 1.73 | (0.80, 3.75) |
| GUSTO mild | | | | | | | | |
| Yes | 29 | 153 | (19.0) | 41 | 229 | (17.9) | 1.09 | (0.64, 1.87) |
| **No** | **796** | **5376** | **(14.8)** | **540** | **5298** | **(10.2)** | **1.52** | **(1.36, 1.71)** |
| Timi Major or Minor | | | | | | | | |
| Yes | 6 | 153 | (3.9) | 6 | 229 | (2.6) | 1.56 | (0.48, 5.05) |
| **No** | **34** | **5376** | **(0.6)** | **8** | **5298** | **(0.2)** | **4.17** | **(1.93, 9.01)** |
| Timi Major | | | | | | | | |
| Yes | 3 | 153 | (2.0) | 2 | 229 | (0.9) | 2.25 | (0.36, 13.91) |
| No | 7 | 5376 | (0.1) | 3 | 5298 | (0.1) | 2.29 | (0.59, 8.84) |
| Timi Minor | | | | | | | | |
| Yes | 3 | 153 | (2.0) | 4 | 229 | (1.7) | 1.19 | (0.25, 5.60) |
| **No** | **27** | **5376** | **(0.5)** | **5** | **5298** | **(0.1)** | **5.28** | **(2.03, 13.74)** |
| Acuity Major | | | | | | | | |
| Yes | 15 | 153 | (9.8) | 18 | 229 | (7.9) | 1.29 | (0.62, 2.68) |
| **No** | **227** | **5376** | **(4.2)** | **125** | **5298** | **(2.4)** | **1.81** | **(1.45, 2.26)** |
| Bad | | | | | | | | |
| Yes | 8 | 153 | (5.2) | 7 | 229 | (3.1) | 1.83 | (0.64, 5.25) |
| No | 53 | 5376 | (1.0) | 34 | 5298 | (0.6) | 1.51 | (0.98, 2.33) |

Reviewer's analysis: bleed\postAC\sub\primary safety_sub_gpi. 95% CI that do not cross 1 are bolded.



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**Table 4. Periprocedural Glycoprotein IIb/IIIa inhibitor use and bleeding risk in PCI and PLATFORM**

| Class<br>GPI use | Cangrelor | | | Clopidogrel | | | Cangrelor vs. Clopidogrel | |
|---|---|---|---|---|---|---|---|---|
| | n | N | % | n | N | % | OR | 95% CI |
| GUSTO severe or moderate | | | | | | | | |
| Yes | 20 | 1396 | (1.4) | 28 | 1414 | (2.0) | 0.72 | (0.40, 1.28) |
| **No** | **52** | **5640** | **(0.9)** | **32** | **5601** | **(0.6)** | **1.62** | **(1.04, 2.52)** |
| GUSTO severe | | | | | | | | |
| Yes | 5 | 1396 | (0.4) | 8 | 1414 | (0.6) | 0.63 | (0.21, 1.94) |
| No | 14 | 5640 | (0.2) | 9 | 5601 | (0.2) | 1.55 | (0.67, 3.58) |
| GUSTO moderate | | | | | | | | |
| Yes | 15 | 1396 | (1.1) | 20 | 1414 | (1.4) | 0.76 | (0.39, 1.48) |
| **No** | **39** | **5640** | **(0.7)** | **23** | **5601** | **(0.4)** | **1.69** | **(1.01, 2.83)** |
| GUSTO mild | | | | | | | | |
| Yes | 374 | 1396 | (26.8) | 378 | 1414 | (26.7) | 1.00 | (0.85, 1.19) |
| **No** | **906** | **5640** | **(16.1)** | **666** | **5601** | **(11.9)** | **1.42** | **(1.27, 1.58)** |
| Timi Major or Minor | | | | | | | | |
| Yes | 34 | 1396 | (2.4) | 32 | 1414 | (2.3) | 1.08 | (0.66, 1.76) |
| No | 47 | 5640 | (0.8) | 32 | 5601 | (0.6) | 1.46 | (0.93, 2.30) |
| Timi Major | | | | | | | | |
| Yes | 15 | 1396 | (1.1) | 10 | 1414 | (0.7) | 1.52 | (0.68, 3.41) |
| No | 8 | 5640 | (0.1) | 13 | 5601 | (0.2) | 0.61 | (0.25, 1.47) |
| Timi Minor | | | | | | | | |
| Yes | 19 | 1396 | (1.4) | 22 | 1414 | (1.6) | 0.87 | (0.47, 1.62) |
| **No** | **39** | **5640** | **(0.7)** | **19** | **5601** | **(0.3)** | **2.05** | **(1.18, 3.54)** |
| Acuity Major | | | | | | | | |
| Yes | 73 | 1396 | (5.2) | 74 | 1414 | (5.2) | 1.00 | (0.72, 1.39) |
| **No** | **223** | **5640** | **(4.0)** | **137** | **5601** | **(2.4)** | **1.64** | **(1.32, 2.04)** |

Reviewer's analysis: primary safety PLATPCI_sub_gpi_final. Applicant's data: ISS\bldevnt, disp.
Note that the bleed classifications are the applicant's. 95% CI that do not cross 1 are bolded.



Reference ID: 3496995

# 2 Adverse events leading to treatment discontinuations in CHAMPION PHOENIX

*Section 7.3.3 Dropouts and/or Discontinuations* of the clinical review discussed treatment discontinuations in PHOENIX and the three CHAMPION trials as a whole. While Table 50 in the clinical review provides the System Organ Class (SOC) that led to treatment discontinuations in PHOENIX, Table 5 provides a more granular summary of the adverse events. The events are consistent with the original review for both PHOENIX and the CHAMPION trials (Table 51 of original clinical review). Notably, dyspnea was a common reason for treatment discontinuation in subjects treated with cangrelor compared to subjects treated with clopidogrel. A common reason for treatment discontinuation in both arms was due to the intervention.

**Table 5. Adverse events leading to treatment discontinuation in PHOENIX**

| | Cangrelor N=5529 | Clopidogrel N=5527 |
|---|---|---|
| **Subjects that discontinued treatment** | **31 (0.6%)** | **21 (0.4%)** |
| Cardio-respiratory arrest/cardiac arrest | 5 | 1 |
| Dyspnea | 4 | 0 |
| Anaphylactic reaction | 2 | 0 |
| Nausea/vomiting | 2 | 0 |
| Cardiac tamponade | 1 | 0 |
| Dizziness | 1 | 0 |
| Dysphagia | 1 | 0 |
| Eye irritation | 1 | 0 |
| Hypotension | 1 | 0 |
| Panic attack | 1 | 0 |
| Pruritus | 1 | 0 |
| Thrombosis in device | 1 | 0 |
| Transient ischemic attack | 1 | 0 |
| Coronary artery /aortic dissection | 7 | 5 |
| Coronary artery perforation | 5 | 4 |
| Arterial rupture / Interventricular septum rupture | 2 | 3 |
| Bradycardia | 0 | 2 |
| Coronary artery occlusion | 0 | 2 |
| Hypersensitivity | 0 | 2 |
| Hypotension | 0 | 2 |
| Cardiogenic shock | 0 | 1 |
| Extravasation | 0 | 1 |
| Loss of consciousness | 0 | 1 |

Reviewer's analysis: ae\aedc. Applicant analysis dataset ae.xpt



Reference ID: 3496995

Missing from the possible AEs leading to treatment discontinuations are bleeds (the most common adverse event). This is because analysis of treatment discontinuations was derived from the AE case report form (CRF) and information on bleeds was not collected on this CRF. Bleeds were documented on a specific bleed CRF, however there was no field for treatment discontinuation due to bleed. Since the study drug infusion was to be administered for the longer of 2 hours or the duration of the PCI procedure, one way to estimate treatment discontinuations due to bleeding was to examine subjects whose infusion was stopped prior to 2 hours. Table 6 shows the number of subjects that had a bleed on the same day of the infusion and whose study drug infusion was less than 1.9 hours.[4]

**Table 3. Updated adverse events leading to treatment discontinuation**

| | Cangrelor N=5529 n (%) | Clopidogrel N=5527 n (%) |
|---|---|---|
| Subjects that might have discontinued treatment because of bleeding (Infusion duration is < 1.9 hours and < PCI duration) | 29 (0.5) | 13 (0.2) |
| Revised subjects with AE leading to treatment discontinuation | 51 (0.9) | 28 (0.5) |

Reviewer's analysis: bleed\dc bc bleed. Datasets: applicant analysis ae.xpt and reviewer's main bleed dataset r_bl.c_rev

# 3 Acute renal toxicity in CHAMPION PHOENIX

The primary clinical review included a summary of the Applicant's analysis of renal AEs in the entire ISS (see Table 52 of clinical review). While the number of events were generally higher in the cangrelor arm, they were small so definitive conclusions on risk of acute renal toxicity from cangrelor could not be made. The primary clinical review also included adverse events of SMQ for both PCI (Table 53) and PLATFORM (Table 54). There were more adverse events as renal function declined in the cangrelor arm compared to the clopidogrel arm in PCI, but not in PLATFORM. Missing from the primary clinical review was an analysis of the renal toxicity in PHOENIX. Table 6 shows various MedDRA analyses of acute renal toxicity in PHOENIX. These analyses indicate that there does not appear to be a clear signal of acute renal toxicity from cangrelor. My overall conclusion regarding acute renal toxicity is unchanged. That is, there are no clear safety signals indicating that the risk of acute renal toxicity is greater with cangrelor compared to clopidogrel.

[4] Includes some subjects whose time of bleed occurred after the time of infusion stop.



Reference ID: 3496995

**Table 7. Acute renal toxicity SMQ and MedDRA analysis in PHOENIX**

| Trial | Cangrelor | | | Clopidogrel | | | Cangrelor vs. Clopidogrel | |
|---|---|---|---|---|---|---|---|---|
| | n | N | % | n | N | % | RR | 95% CI |
| PHOENIX | | | | | | | | |
| Broad | 25 | 5529 | (0.5) | 20 | 5527 | (0.4) | 1.25 | (0.70, 2.25) |
| Narrow | 10 | 5529 | (0.2) | 9 | 5527 | (0.2) | 1.11 | (0.45, 2.73) |
| HLGT renal disorders (excluding nephropathies) | | | | | | | | |
| | 10 | 5529 | (0.2) | 6 | 5527 | (0.1) | 1.67 | (0.61, 4.58) |

Reviewer's Analysis: ae\maed phoenix\. Not restricted to 48 hours from drug infusion start.

# 4 120 day safety update

The 120 day safety update included a 12 subject prasugrel transition study. There was no new safety information.

# 5 Corrections to safety section in original clinical review

Page 149, Section 7.3.3. "Error! Reference source not found" should read, "Table 50".

Page 159, Table 59. The incidence of GUSTO moderate bleed should read "(0.3)". It is not 0.6%.

# 6 References


1. Antman EM, Morrow DA, McCabe CH et al. Enoxaparin versus unfractionated heparin as antithrombin therapy in patients receiving fibrinolysis for ST-elevation myocardial infarction. Design and rationale for the Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment-Thrombolysis In Myocardial Infarction study 25 (ExTRACT-TIMI 25). Am Heart J. 2005;149(2):217-226.

2. The GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. N Eng J Med. 1993;329:673-682.

3. Mehran R, Rao SV, Bhatt DL et al. Standardized bleeding definitions for cardiovascular clinical trials, A consensus report from the Bleeding Academic Research Consortium. *Circulation.* 2011;123:2736-2747.

4. Stone GW, Bertrand M, Colombo A et al. Acute Catheterization and Urgent Intervention Triage strategY (ACUITY) trial: study design and rationale. Am Heart J. 2004;148:764–775.

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/s/

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BACH N BEASLEY
04/28/2014

# CLINICAL REVIEW ADDENDUM

| | |
|---|---|
| **Application Type** | **NDA** |
| **Application Number(s)** | **204958** |
| **Priority or Standard** | **Standard** |
| | |
| **Submit Date** | **30 April 2013** |
| **Received Date** | **30 April 2013** |
| **PDUFA Goal Date** | **30 Apr 2014** |
| **Division / Office** | **DCaRP/ODE I** |
| | |
| **Reviewer Names** | **Fred Senatore MD, PhD, FACC** |
| | |
| **Review Completion Date** | **13 January 2014** |
| **Addendum Completion Date** | **11 April 2014** |

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**List of Abbreviations**

| | |
|---|---|
| AC | Advisory Committee |
| ACC | American College of Cardiology |
| ACCF | American College of Cardiology Foundation |
| AE | Adverse Event |
| AHA | American Heart Association |
| ARC | Academic Research Consortium |
| ARC-ST | ARC-defined ST |
| CABG | Coronary Artery Bypass Graft Surgery |
| CAD | Coronary Artery Disease |
| CEC | Clinical Endpoint Committee (i.e. adjudication committee) |
| CHAMPION | Cangrelor versus standard therapy to achieve optimal management of platelet inhibition |
| CHF | Congestive Heart Failure |
| CLARITY | Clopidogrel as Adjunctive Reperfusion Therapy |
| CR | Complete Response |
| CSR | Case Study Report |
| DMP | Data Management Plan |
| DRP | Data Review Plan |
| DRCP | Division of Cardio-Renal Products |
| DSMB | Data Safety Monitoring Board |
| IARC | Interim Analysis Review Committee |
| IPST | Intra-Procedural Stent Thrombosis |
| ITT | Intention to Treat population |
| IV | Intravenous |
| IVRS | Interactive Voice Response System |
| LOE | Level of Evidence |
| MACE | Major Adverse Cardiac Event |
| MI | Myocardial Infarction |
| NDA | New Drug Application |
| NSTEACS | Non-ST segment elevation acute coronary syndrome |
| NSTEMI | Non-ST segment elevation myocardial infarction |
| OR | Odds Ratio |
| PAD | Peripheral Arterial Disease |
| PCI | Percutaneous Coronary Intervention |
| PD | Pharmacodynamic |
| PO | Per Oral |
| PRU | $P2Y_{12}$ or Platelet Reactivity Unit (interchangeable) |
| QD | Once a day (i.e. scheduled administration of drug) |
| QW | Q-wave |
| QWMI | Q-wave Myocardial Infarction |
| SA | Stable Angina |
| SAP | Statistical Analysis Plan |
| SOC | Standard of Care |
| SOP | Standard Operating Procedure |
| ST | Stent Thrombosis |
| STEMI | ST segment elevation myocardial infarction |
| TIA | Transient Ischemic Attack |
| TMC | The Medicines Company |
| UA | Unstable Angina |
| UDMI | Universal Definition Myocardial Infarction |
| ULN | Upper Limit of Normal |



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# 1 ADDENDUM: EXECUTIVE SUMMARY and RECOMMENDATION

**Summary**:

CHAMPION PHOENIX

- The ADVISORY Committee (AC) has expressed concerns about the design and conduct of the PHOENIX trial. These concerns, which were similarly expressed by the review team and the deputy director of the Division of Cardio-Renal Products (DCRP), are:
    - The PHOENIX trial by itself, in the setting of two antecedent failed studies, was not sufficiently persuasive to warrant an approval of cangrelor.
    - The manner of clopidogrel and glycoprotein IIbIIIa receptor antagonist (GPI) administration in the PHOENIX trial were designed to optimize the probability of cangrelor showing superiority over clopidogrel:
        - Clopidogrel was permitted to be administered post-PCI whereas cangrelor was required to be administered pre-PCI.
        - Clopidogrel loading dose in the clopidogrel arm was flexible (i.e. 300mg or 600mg) as per investigator discretion, whereas a transition clopidogrel loading dose in the cangrelor arm was required to be 600mg. This created an imbalance in clopidogrel loading dose favoring cangrelor (i.e. cangrelor+600mg clopidogrel vs. placebo +clopidogrel + 300mg or 600mg load).
        - GPI was restricted except for bailout whereby the informed consent did not specify GPI as an alternative therapy.
    - The PHOENIX endpoints which drove the results of the study: Universal Definition of Myocardial Infarction (UDMI)-type 4a, and Stent Thrombosis (ST) driven by intra-procedural stent thrombosis (IPST) were not clinically relevant.
    - The applicant developed an algorithm which, in a significant number of cases, resulted in a post-randomization change in subject diagnosis (i.e. ST-elevation myocardial infarction {STEMI}, Non-ST-elevation acute coronary syndrome {NSTEACS}, Stable Angina {SA}) from the investigators' original report. This has called into question a number of issues, including investigator competence in making a diagnosis, lack of adjudication when the applicant's algorithm altered the investigator diagnosis, lack of process description in any of the documents (i.e. protocol, statistical analysis plan (SAP), adjudication committee (CEC) charter, data management plan (DMP)), and ultimately the integrity of the PHOENIX trial.
    - The database, which was locked on 14 January 2013, was unlocked on 01 February 2013 and relocked on 18 February 2013 because of 533 cases of missing anticoagulation concomitant medication data over 84 of the



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total of 153 sites in the PHOENIX trial. Although database unlocking is not uncommon especially in a mega-trial, questions arose over operational paradigms: monitoring, investigator education, process documentation, quality assurance, for which the Office of Scientific Investigations was consulted.

**Recommendation**:

For the PCI indication, I recommend that the PHOENIX trial serve as the sole basis of the NDA. The CHAMPION PLATFORM and PCI failed trials served to generate a hypothesis resulting in a carefully crafted efficacy endpoint successfully tested in PHOENIX, albeit with marginal benefit/risk, under conditions designed to optimize the probability of success. I also recommend that a decision whether or not to approve the NDA be delayed pending the applicant's response to the following requests:

- A document which conclusively shows superiority of cangrelor over clopidogrel for clinically relevant post-PCI MI for each stratified patient population. This request was made because when applying criteria for clinical relevance of post-PCI MI to the results of the PHEONIX trial, the outcome was mixed, depending on which criteria was used for the determination of clinical relevance.
- A document which justifies the use of UDMI as the criteria for post-PCI events when the consensus opinion (Moussa, I, et al.) suggests that the evidence to date does not support the use of the UDMI as the optimal criteria to identify clinically relevant post-PCI MI events.
- Resolution of the issues raised on the database unlocking event from February 01, 2013 to February 18, 2013.
- A document which clearly explains the "patient-derived type algorithm". Specifically:
    - Why the patient-derived type algorithm was developed in lieu of a more standard data correction algorithm based on queries and investigator-controlled corrections.
    - Why such a process affected a considerable subject population and why was it not described in the SAP or in more detail in the Case Study Report (CSR).
    - Why changes from investigator-based diagnoses to applicant-based diagnoses were not adjudicated.
    - Timing of process implementation relative to the IVRS qualification data entry.
    - The impact of the changes in diagnosis on the primary endpoint.



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# 2 ADDENDUM: EMERGING ISSUES WITH THE PCI INDICATION FOLLOWING ADVISORY COMMITTEE MEETING

## 2.1 Concern that the PHOENIX trial by itself may not have been sufficiently persuasive in the setting of two previous failed studies

The ideal paradigm for approval is two positive trials. One trial as the basis of approval usually requires a robust result. Given two previously failed trials and one non-robust positive trial assessed as having a marginal benefit-risk profile, the Advisory Committee opined that the preponderance of the evidence was not sufficiently persuasive to approve cangrelor for the PCI indication.

The failure of CHAMPION PCI and CHAMPION PLATFORM was postulated by the applicant to be due to the effect of pre-PCI MI on the outcome of the trials. The applicant opined that myocardial infarctions that occurred pre-PCI masked the benefit of cangrelor in the previous CHAMPION trials. Post-hoc analyses of the failed trials generated a hypothesis that cangrelor reduced the incidence of stent thrombosis and type 4a MI (myocardial infarction associated with PCI as per the universal definition of MI).

The review team conducted an investigation in order to understand why the CHAMPION PCI and PLATFORM trials were negative. The design of the PHOENIX trial, including the CEC adjudication process, focused on subjects who did not have pre-PCI evolving myocardial damage characterized as troponin or CPK-MB rising levels at baseline. Additionally, the use of GPI was disallowed except for bailout use. Other more potent $P2Y_{12}$ receptor antagonists as the active comparator were not considered for use. The pre-PCI use of thienopyridines was also disallowed for at least 7 days prior to randomization. These features were designed to maximize the empirical efficacy of cangrelor by elimination of potential confounders which are standard in clinical practice within the PCI setting. Consequently, the majority of subjects in PHOENIX were stable patients.

***Table 1*** displays the baseline patient types (i.e. SA, Unstable Angina {UA}, NSTE-ACS, and STEMI) in the three CHAMPION trials. Both CHAMPION PLATFORM and CHAMPION PCI consisted primarily of subjects presenting with NSTEACS and UA. CHAMPION PCI also randomized subjects presenting with STEMI. The patient type in the two failed studies differed from that in the PHOENIX trial where the majority of subjects in PHOENIX presented with SA. Differential subject presentation between PHOENIX and the antecedent CHAMPION trials might have been a cause for discrepant results between PHOENIX and the previous trials.



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**Table 1: Comparative baseline patient types in the CHAMPION Trials**

| | CHAMPION TRIALS | | | | | |
|---|---|---|---|---|---|---|
| | PLATFORM | | PCI | | PHOENIX | |
| | cangrelor | clopidogrel | cangrelor | clopidogrel | cangrelor | clopidogrel |
| N | 2695 | 2669 | 4433 | 4444 | 5581 | 5564 |
| | n (%) | | n (%) | | n (%) | |
| SA | 145 (5.4) | 142 (5.3) | 668 (15.1) | 665 (15.0) | 3220 (57.7) | 3208 (57.7) |
| UA | 949 (35.2) | 918 (34.4) | 1097 (24.7) | 1088 (24.5) | ----- | ----- |
| NSTEACS | 1599 (59.4) | 1609 (60.3) | 2181 (49.2) | 2182 (49.1) | 1479 (26.5) | 1435 (25.8) |
| STEMI | ----- | ----- | 487 (11.0) | 509 (11.5) | 882 (15.8) | 921 (16.6) |

N = ITT sample size; n (%) = sub-sample size (percentage of N): ITT population; SA = stable angina; UA = unstable angina; NSTEACS = non-ST elevation acute coronary syndrome; STEMI = ST Elevation Myocardial Infarction

***Table 2*** and continuing on ***Table 3*** show the baseline characteristics of the subjects in each of the CHAMPION trials. The subjects in all three CHAMPION trials were generally similar in baseline characteristics. However, there were some numerical differences. In the PLATFORM trial, the incidence of subjects with a history of percutaneous intervention and a history of hyperlipidemia were numerically lower than that of the CHAMPION PCI and CHAMPION PHOENIX trials. There was a higher number of Asians enrolled in PLATFORM compared to PCI and PHOENIX. There were a numerically higher number of CABG patients in CHAMPION PCI compared to PLATFORM and PHOENIX. Despite these differences, there was no compelling evidence that baseline characteristics were a cause of discrepant results between PHOENIX and the antecedent trials.

### Table 2: Comparative baseline characteristics of the CHAMPION Trials -1

| | CHAMPION TRIALS | | | | | |
|---|---|---|---|---|---|---|
| | PLATFORM | | PCI | | PHOENIX | |
| | cangrelor | clopidogrel | cangrelor | clopidogrel | cangrelor | clopidogrel |
| N (ITT) | 2695 | 2669 | 4433 | 4444 | 5581 | 5564 |
| | n (%) | | n (%) | | n (%) | |
| Age –median (years) | 63 | 63 | 62 | 62 | 64 | 64 |
| Gender | | | | | | |
| -Male | 1938 (72.0) | 1877 (70.3) | 3275 (73.9) | 3209 (72.2) | 3982 (71.3) | 4042 (72.6) |
| -Female | 755 (28.0) | 792 (29.7) | 1158 (26.1) | 1235 (27.8) | 1599 (28.7) | 1522 (27.4) |
| Race / Ethnic | | | | | | |
| -White | 2039 (75.7) | 2024 (75.8) | 3658 (82.5) | 3626 (81.6) | 5231 (93.7) | 5206 (93.6) |
| -Black | 80 (3.0) | 73 (2.7) | 215 (4.8) | 239 (5.4) | 156 (2.8) | 152 (2.7) |
| -Hispanic | 75 (2.8) | 85 (3.2) | 209 (4.7) | 218 (4.9) | 196 (3.5) | 202 (3.6) |
| -Asian | 482 (17.9) | 476 (17.8) | 311 (7.0) | 313 (7.0) | 173 (3.1) | 177 (3.2%) |
| -Other | 8 (0.3) | 5 (0.2) | 35 (0.8) | 42 (1.0) | 18 (0.3) | 22 (0.4) |
| Weight-median (kg) | 80.0 | 80.0 | 84 | 84 | 84 | 84 |
| Diabetes Mellitus | 828 (30.7) | 868 (32.5) | 1350 (30.5) | 1352 (30.4) | 1546 (27.7) | 1559 (28.0) |
| Current Smoker | 850 (31.5) | 806 (30.2) | 1247 (28.1) | 1283 (28.9) | 1533 (27.5) | 1573 (28.3) |
| Hypertension | 1994 (74.0) | 1979 (74.1) | 3181 (71.8) | 3139 (70.6) | 4460 (79.9) | 4406 (79.2) |
| Hyperlipidemia | 1342 (49.8) | 1347 (50.5) | 2825 (63.7) | 2777 (62.5) | 3412 (61.1) | 3380 (60.7) |
| Stroke or TIA | 162 (6.0%) | 160 (6.0) | 223 (5.0) | 227 (5.1) | 276 (4.9) | 252 (4.5) |
| FH of CAD | 918 (34.1) | 901 (33.8) | 1843 (41.6) | 1873(42.1) | 2121 (38.0) | 2108 (37.9) |

**Table 3: Comparative baseline characteristics of the CHAMPION Trials-2**

| | | | | | | |
|---|---|---|---|---|---|---|
| Hx of MI | 645 (23.9) | 683 (25.6) | 1075 (24.2) | 1089 (24.5) | 1111 (19.9) | 1191 (21.4) |
| Hx of PCI | 381 (14.1) | 411 (15.4) | 1266 (28.6) | 1261 (28.4) | 1281 (23.0) | 1344 (24.2) |
| Hx of CABG | 203 (7.5) | 223 (8.4) | 557 (12.6) | 552 (12.4) | 581 (10.4) | 509 (9.1) |
| Hx of CHF | 210 (7.8) | 192 (7.2) | 333 (7.5) | 338 (7.6) | 565 (10.1) | 592 (10.6) |
| Hx of PAD | 126 (4.7) | 143 (5.4) | 323 (7.3) | 315 (7.1) | 449 (8.0) | 390 (7.0) |

N = ITT sample size; n (%) = sub-sample size (percentage of N): ITT population; TIA = Transient Ischemic Attack; FH of CAD = Family History of Coronary Artery Disease; Hx =History of; MI = Myocardial Infarction; PCI =Percutaneous Coronary Intervention; CABG = Coronary Artery Bypass Graft; CHF = Congestive Heart Failure; PAD =Peripheral Vascular Disease

A question emerged concerning the differential use of GPI in the three trials as an etiology for the failure of PCI and PLATFORM compared to PHOENIX. In the PHOENIX trial, 2.3% (129/5581) ITT subjects in the cangrelor arm and 3.5% (194/5564) ITT subjects in the clopidogrel arm were reportedly administered a GPI. In the PLATFORM and PCI trials, the use of GPI was originally allowed as per investigator discretion. On May 8, 2007, both PCI and PLATFORM protocols were amended to exclude use of GPI within the previous 12 hours prior to enrollment. The use of GPI as an elective concomitant medication was still allowed but the investigators were cautioned that "the use of these agents should be considered carefully based on the anti-platelet effect already provided by the study drug, i.e. clopidogrel 600mg or cangrelor". The amendment, amongst others not mentioned here, also included:

- a sample size increase from 4400 to 6200 subjects in CHAMPION PLATFORM
- a cap on the enrollment of SA subjects in CHAMPION PCI until the expected balance of stable vs. urgent subjects was restored
- exclusion of STEMI subjects from the primary analysis in CHAMPION PCI but inclusion of them in the secondary analysis
- elective patients presenting for percutaneous intervention in CHAMPION PCI not requiring high risk anatomy to be included

In a series of Executive / Steering Committee meetings sponsored by the applicant (September 2007, November 2007, and March 2008), the applicant reported the results of GPI use in the NSTEMI population at discreet time points during the course of the PLATFORM and PCI trials. These reports are compiled in ***Table 4***. The data shows that following the protocol amendments of CHAMPION PLATFORM and CHAMPION PCI, the number of NSTEMI subjects in PLATFORM increased from 19% to 53% and the use of GPI in NSTEMI subjects decreased from 37% to 12%. Similarly in the PCI trial, the number of NSTEMI subjects increased from 22% to 58% and the use of GPI in NSTEMI subjects decreased from 53% to 35%. The data from the applicant indicates



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that GPI usage in PCI was approximately 12-18 times that used in PHOENIX. Similarly, GPI usage in PLATFORM was approximately 4-12 times that used in PHOENIX.

**Table 4: Use of GPI in NSTEMI Subjects as a Function of Time in PCI and PLATFORM**

| | Use of GPI in NSTEMI Subjects as Function of Time in PCI and PLATFORM | | | |
|---|---|---|---|---|
| CHAMPION | April 2007 | September 2007 | November 2007 | March 21008 |
| **PCI** | | N= 4338 | N= 4684 | N=5541 |
| -NSTEMI | 22% | 43% | 45% | 58% |
| -GPI use in NSTEMI | 53% | 38% | 38% | 35% |
| **PLATFORM** | | N=1387 | N=1556 | |
| -NSTEMI | 19% | 34% | 38% | 53% |
| -GPI use in NSTEMI | 37% | 14% | 14% | 12% |

Source: Slide presentations from CHAMPION Executive Committee/Steering Committee Meetings dated March 27, 2007; September 2, 2007; November 3, 2007; March, 2008 (day not specified)

The effect of the protocol amendment regarding GPI usage on the primary efficacy endpoint results based on our own analysis are shown in ***Table 5*** for PCI and ***Table 6*** for PLATFORM. In the PCI trial, GPI usage was approximately 33% prior to the amendment of May 8, 2007 and 22% after the amendment. Similarly, in the PLATFORM trial, GPI usage was approximately 16% prior to the amendment of May 8, 2007 and 8% after the amendment. By these numbers, the use of GPI in PHOENIX was 7-11 times less than that in PCI and 3-5 times less than that in PLATFORM. The data also indicated there was no difference in efficacy between cangrelor and clopidogrel in either PCI or PLATFORM whether or not GPI was a concomitant medication. ***Table 7*** shows the effect of GPI usage on the primary endpoint from the PHOENIX trial. The data shows that the concomitant use of GPI was associated with a significantly favorable outcome for cangrelor (Odds Ratio {OR} 0.82, 95%CI 0.68, 0.97). In the absence of GPI concomitant usage, the OR was also favorable for cangrelor (i.e. 0.84) but did not reach significance.



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**Table 5: Effect of GPI Usage on the results of the PCI trial**

| CHAMPION PCI | | | | |
|---|---|---|---|---|
| GPI use | TRT | N | # events (%) | OR (95% CI) |
| Yes | cangrelor | 1141 | 97 (8.5) | |
| | clopidogrel | 1155 | 100 (8.7) | |
| | total | 2296 | 197 (8.6) | 0.98 (0.73, 1.31) |
| No | cangrelor | 3193 | 211 (6.6) | |
| | clopidogrel | 3156 | 193 (6.1) | |
| | total | 6349 | 404 (6.4) | 1.09 (0.89, 1.33) |

| | cangrelor | | clopidogrel | |
|---|---|---|---|---|
| | N | GPI use (%) | N | GPI use (%) |
| Before May 8, 2007 | 1746 | 583 (33.3) | 1720 | 589 (34.2) |
| After May 8, 2007 | 2600 | 565 (21.7) | 2599 | 571 (22.0) |



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**Table 6: Effect of GPI Usage on the results of the PLATFORM trial**

| CHAMPION PLATFORM | | | | |
|---|---|---|---|---|
| GPI use | TRT | N | # events (%) | OR (95% CI) |
| Yes | cangrelor | 240 | 28 (11.7) | |
| | clopidogrel | 243 | 33 (13.6) | |
| | total | 483 | 61 (12.6) | 0.84 (0.49, 1.44) |
| No | cangrelor | 2411 | 156 (6.5) | |
| | clopidogrel | 2395 | 177 (7.4) | |
| | total | 4806 | 333 (6.9) | 0.87 (0.69, 1.08) |

| | cangrelor | | clopidogrel | |
|---|---|---|---|---|
| | N | GPI use (%) | N | GPI use (%) |
| Before May 8, 2007 | 418 | 67 (16.0) | 425 | 73 (17.1) |
| After May 8, 2007 | 2235 | 174 (7.8) | 2217 | 171 (7.7) |

**Table 7: Effect of GPI Usage on the results of the PHOENIX trial**

| CHAMPION PHOENIX | | | | |
|---|---|---|---|---|
| GPI use | TRT | N | # events (%) | OR (95% CI) |
| Yes | cangrelor | 153 | 27 (17.7) | |
| | clopidogrel | 227 | 46 (20.3) | |
| | total | 380 | 73 (19.2) | 0.82 (0.68, 0.97) |
| No | cangrelor | 5317 | 230 (4.3) | |
| | clopidogrel | 5242 | 276 (5.3) | |
| | total | 10559 | 506 (4.8) | 0.84 (0.50, 1.43) |

The differences between the two failed studies and the PHOENIX trial were:

- Primary Efficacy Endpoint: UDMI type 4a (compared to conventional MI), Stent Thrombosis (not present in the failed studies).
- Restriction of evolving pre-PCI MIs in the PHOENIX trial.
- Much lower use of GPI in PHEONIX (3-11 times less) compared to PLATFORM and PCI.
- Much higher enrollment of SA subjects in PHEONIX (58% compared to 5% in PLATFORM and 15% in PCI).

Another possible etiology for the failed CHAMPION studies was the lack of data cleanliness and lack of adjudicated data, as expressed by the DSMB in the Minutes from both the open and closed sessions held on March 24, 2007. It is unclear if the DSMB assessment about data quality was based on a snapshot in time focused on data readiness for the planned DSMB meeting, or a systemic issue which might have impacted trial integrity and data interpretation.

There was a question on the differential timing of clopidogrel amongst the three trials. As indicated in the original review, clopidogrel was administered post-PCI in PLATFORM, pre-PCI in the PCI trial, and variably pre/post-PCI in PHOENIX. It was opined that the empirical efficacy of cangrelor would be a direct function of delays in clopidogrel administration when comparing the two agents. Thus, the probability of a positive result in PLATFORM should have been higher than in PHOENIX or PCI. The



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results of the CHAMPION trials suggest to this reviewer that differential timing of clopidogrel did not have a significant impact on the results of the trials. Rather, a cath-lab based endpoint that would be impacted by a quick-acting agent (i.e. cangrelor) as opposed to a slower acting agent (i.e. clopidogrel), when each were initiated in the cath lab or after the procedure, was the etiology of the difference between the results of PHOENIX and the results of the PCI and PLATFORM trials.

It is this reviewer's opinion that the PCI and PLATFORM trials have no bearing on the NDA. The PHOENIX trial is the sole basis of the NDA. The CHAMPION PLATFORM and PCI failed trials served to generate a hypothesis resulting in a carefully crafted efficacy endpoint successfully tested in PHOENIX, albeit with marginal benefit/risk, under conditions designed to optimize the probability of success (see section 2.3 and 2.3 regarding optimizing probability of success).

## 2.2 Concern over the way clopidogrel was administered as a means toward optimizing the probability of success

The AC, in alignment with the Division review team, expressed concern over the timing of clopidogrel administration as well as the imbalance in the clopidogrel loading dose empirically favoring the cangrelor arm of the PHOENIX trial.

***Table 8*** shows the distribution of clopidogrel pre and post PCI for the 300mg and 600mg intended loading doses as per the double-dummy double-blinded strategy. The applicant explained that the term "intended dose" referred to the investigator-determined choice of 300mg or 600mg of clopidogrel to be given as soon as possible after randomization as per investigator discretion. The term "intended dose" did not refer to the protocol-mandated administration of 600mg clopidogrel to subjects in the cangrelor group at the conclusion of infusion. A review of the actual doses received by the PHOENIX subjects showed that in the cangrelor arm, virtually everyone received a 600mg clopidogrel loading dose following completion of cangrelor infusion (i.e. post PCI), as per protocol. In the clopidogrel arm where investigator discretion was utilized per protocol, 74% received the 600mg load dose divided equally between pre and post PCI. Of those subjects given clopidogrel 300mg load, 97% received the dose pre-PCI. As stated in the original clinical review, the imbalance in clopidogrel loading dose between the arms of PHOENIX may have biased the study in favor of cangrelor because the $P2Y_{12}$ Inhibitor regimen in the cangrelor arm involved cangrelor+ 600mg clopidogrel load + 75mg maintenance, whereas in the clopidogrel arm, the $P2Y_{12}$ Inhibitor regimen included 300 (26%) or 600mg (74%) clopidogrel load + 75mg clopidogrel maintenance.



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**Table 8: Time of clopidogrel administration: relative to PCI for two loading doses in PHOENIX.**

| Clopidogrel Loading Dose | | Intended Dose | | Actual Dose | |
|---|---|---|---|---|---|
| | | N | | N | |
| Dose | Relative to PCI | Cang | Clop | Cang | Clop |
| 300mg | Pre | 1355 | 1352 | 0 | 1354 |
| | Post | 49 | 49 | 4 | 49 |
| 600mg | Pre | 2105 | 2090 | 1 | 2058 |
| | Post | 1931 | 1947 | 5406 | 1948 |

Cang=cangrelor; Clop= clopidogrel; Source: PHOENIX CSR Table 3.2.1.1 (T_ORAL_DRUG.SAS); 9.106.1.1 (T_ENDP_SUBGRP.SAS), 9.107.1.1 (T_ENDP_SUBGRP.SAS)

The AC queried the applicant on the imbalance of the clopidogrel loading dose between the study arms empirically favoring cangrelor. The applicant replied that the 600mg clopidogrel loading dose in the cangrelor arm following infusion was postulated to more readily facilitate the transition between cangrelor to clopidogrel compared to the 300mg loading dose. The choice of loading dose in the clopidogrel arm was at physician discretion. Not providing equivalent discretion in the cangrelor arm was an issue with the AC as it may have biased the results of the PHOENIX trial in favor of cangrelor. This issue was recognized in the original clinical review.

The AC also queried the applicant on the timing of clopidogrel administration relative to PCI. The applicant told the AC (see applicant slide CI-10) that based on a meeting with the Division on SEP 2010, the Division requested the applicant to “revise the protocol to require the investigator to determine the timing of clopidogrel administration after definitive treatment decision is made”. Based on the meeting minutes dated 9 SEP 2010, the Division documented its communication to the applicant: “The protocol stipulates a loading dose of clopidogrel (300 to 600mg) will be administered to subjects randomized to clopidogrel “at the time of PCI”. The onset of action of clopidogrel is not rapid; therefore delaying administration of clopidogrel may result in inadequate platelet

inhibition at the time of PCI. Please revise your protocol to allow the investigator to determine the timing of clopidogrel administration". The final PHOENIX protocol dated 28 SEP 2010, as amended from the original protocol dated 15 JUNE 2010, specified study drug dispensation for cangrelor (section 5.1.1 of protocol) and for clopidogrel (section 5.1.2 of protocol). For cangrelor, "intravenous study drug infusion must be commenced prior to PCI (defined as the time of guidewire insertion), but not more than 30 minutes prior." For clopidogrel, "clopidogrel: to be administered as soon as possible following randomization as directed by the investigator. Clopidogrel will be provided in the study drug kit in an over-encapsulated form. In the control arm (Arm B), kits will contain 300 or 600mg of clopidogrel. In the cangrelor arm (Arm A), kits will contain 600mg of clopidogrel to be administered at the end of infusion". Although it appeared that the protocol was revised to comply with the Division's request to allow the investigator to determine the timing of clopidogrel administration, the wording of the protocol did not mandate clopidogrel administration pre-PCI. By not requiring that all PO and IV study drug be administered prior to PCI, the resulting lack of equipoise between the study arms resulted in possible bias in favor of cangrelor especially with also allowing a lower dose in the clopidogrel arm while mandating a higher dose in the cangrelor arm. In reply to the AC concern about potential bias, the applicant acknowledged that the design in hindsight should have enforced equipoise between the study arms.

Concern about potential applicant bias has historical precedence. In the course of the antecedent CHAMPION trials, there were concerns raised by the DSMB or the IARC regarding clopidogrel use, as reflected in the various minutes quoted below:

- DSMB meeting (open session) dated March 24, 2007:
  - "A question was raised concerning clopidogrel use pre-procedure for each study. A patient can be on chronic clopidogrel and still be enrolled in PCI. Conceptually, no patient in PLATFORM can be on clopidogrel in the 7 days prior to randomization based on the inclusion criteria. Surprise was expressed that PLATFORM is able to enroll patients in the U.S. since clopidogrel pre-procedure is pretty standard. The question of what is 'standard of care (SOC)' in the U.S. was asked. After some discussion, it was determined that the definition was not consistent. Clopidogrel was used by some pre-procedurally and not by others. It may be common practice but not standard."
  - "It was pointed out that it is the DSMB role to ensure safety of patient. In a country where clopidogrel use pre-procedure is pretty standard there is a concern over the ethics of excluding clopidogrel pre-procedure in the U.S. Dr. Bhatt acknowledged that criticism will be there. There is no FDA indication that clopidogrel is required pre-procedurally. It is not evidence-based medicine, therefore it is not considered unethical. Clopidogrel will be given in PLATFORM two hours after start of cangrelor."



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  - "The issue of not allowing pre-procedural clopidogrel continued to arise. It was recommended that TMC survey their PLATFORM sites and determine what is SOC. TMC responded by saying that they had done this during the site selection process. Sites couldn't participate if they couldn't treat patients per protocol. Each site IRB reviewed and approved the protocol".
  - "The question of what is standard of care when a patient is elective and has a diagnostic angiogram 1-2 days prior to their PCI. Whether clopidogrel is given pre-procedurally as SOC in the elective patient is the core issue. TMC could be altering SOC based on the protocol specifications or the sites could be doing so themselves to be able to complete the trial. The latter scenario is the concern. Ms. Skerjanec will review her site questionnaire data and get back to the DSMB. She will also look into the survey asked specifically about staged procedures, but she does not believe it did".
- IARC meeting dated 22 September 2008:
  - "A question was raised about the dose of cangrelor used in the PCI trial. The question was whether it was too low to be effective and would it be feasible to change the study design to increase the dose for the remaining patients left to enroll just so that drug/dose endpoint relationship could be explored. The answer was it would probably not be feasible since the protocol changes and regulatory hurdles would be expensive and time consuming to implement".

This reviewer could not locate any documentation pursuant to the commitment made by the applicant to elucidate the distinction between "standard of care" and "common practice" relating to pre-procedural administration of clopidogrel (DSMB minutes, open session, 24 March 2007).

A thorough review of all the DSMB minutes from the PHOENIX trial failed to reveal any concerns similar to those raised from the two antecedent trials with the exception of the definition of MI (see section 2.3 of this document).

The applicant emphasized that US practice patterns demonstrated a distribution in the timing of clopidogrel loading relative to PCI (Dean, BB et al, 2010). In 3922 patients undergoing elective PCI, 29% received clopidogrel up to 12 hours prior to PCI, 12 % received clopidogrel in the cath lab at PCI, and 59% received clopidogrel up to 6 hours after PCI. This pattern was similar in patients presenting with NSTE-ACS (n=972) where 43% received clopidogrel up to 12 hours prior to PCI, 16% received clopidogrel at PCI, and 41% received clopidogrel up to 6 hours after PCI. In 1359 patients presenting with STEMI, 30% received clopidogrel up to 12 hours prior to PCI, 33% received clopidogrel at PCI, and 37% received clopidogrel up to 6 hours after PCI. The applicant concluded from the reported practice pattern data that ADP-antagonist preloading showed uncertain benefit and potential harm, and that US practice patterns varied widely



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regarding the administration of ADP antagonists relative to PCI. These arguments by the applicant served to justify the timing of clopidogrel administration in PHOENIX.

The applicant also referenced several studies, presented herewith, purporting a lack of conclusive evidence favoring pre-PCI clopidogrel administration:

- Gurbel et al. (2005) studied GPI and clopidogrel in the CLEAR PLATELETS study. In this study, 4 antiplatelet regimens were evaluated: clopidogrel 300mg, clopidogrel 600mg, clopidogrel 300mg plus eptifibatide, and clopidogrel 600mg plus eptifibatide. Clopidogrel maintenance doses were 75mg daily. Clopidogrel was administered immediately after stenting. Eptifibatide was administered as per the ESPRIT trial (O'Shea et al., 2000): immediately before the PCI. The authors concluded that in elective stenting without clopidogrel treatment, use of GPI produced superior platelet inhibition and lower myocardial necrosis compared to high-dose (600mg) or standard dose (300mg) clopidogrel loading alone. In the absence of GPI, 600mg clopidogrel provided better platelet inhibition than the standard 300mg dose. These results "required confirmation in a large-scale clinical trial". The evidence from this trial, in the opinion of this reviewer, suggested the utility of pre-PCI treatment with GPI agents but in the absence of GPI therapy, clopidogrel 600mg was better than clopidogrel 300mg.

- Sabatine et al. (2005) studied patients with a recent STEMI who received fibrinolysis and study drug (clopidogrel versus placebo), and subsequent PCI 48-192 hours after study drug (PCI-CLARITY study). The authors concluded that clopidogrel pretreatment significantly reduced the incidence of cardiovascular death or ischemic complications both before and after PCI and without a significant increase in major or minor bleeding. The authors also concluded that the data from PCI-CLARITY added further support to the early use of clopidogrel in STEMI and the strategy of routine clopidogrel pre-treatment in patients undergoing PCI. In an editorial by Moliterno and Steinhubl (2005), the authors opined that from several post-hoc analyses of large-scale PCI trials, patients receiving clopidogrel hours to days before, rather than at the time of PCI, experienced substantially fewer periprocedural ischemic events. The CREDO trial (Steinhubl et al., 2002), referenced in the editorial, was designed to evaluate the benefit of 12 months treatment with clopidogrel after PCI and to determine the benefit of initiating clopidogrel with a pre-procedure loading dose versus no pre-procedure load, both in addition to aspirin. In this study, 2116 patients presenting for elective PCI were assigned (1:1) to one of two arms: 1) 300mg clopidogrel loading dose 3-24 hours pre-PCI, or 2) No pre-PCI loading dose. Immediately after PCI, both groups received clopidogrel 75mg and aspirin 325mg daily through day 28. Following this, subjects in the pre-PCI treatment group continued to receive clopidogrel 75mg daily and subjects in the no pre-PCI treatment group received matching placebo. The one year results showed that clopidogrel therapy (i.e. load plus maintenance) significantly reduced the risk of



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adverse ischemic events. A loading dose of clopidogrel administered at least 3 hours before the procedure did not reduce the events at 28 days, but a subgroup analysis suggested that longer intervals between loading dose and PCI may reduce events. Clopidogrel 300mg pre-treatment at least 15 hours prior to PCI versus no pre-treatment was required for a significant effect. Pre-treatment 24 hours pre-PCI was required for a maximum effect. This strategy, however, raised a concern which was suggested in the CURE trial that in patients with acute coronary syndrome randomized to clopidogrel within 5 days of surgical revascularization, there was a 53% increased risk of major bleeding compared with similar patients receiving placebo (Yusuf et al., 2001). The editorial concluded that the PCI-CLARITY study demonstrated that patients receiving thrombolytic therapy for STEMI should also receive a pre-PCI 300mg loading dose of clopidogrel followed by 75mg daily maintenance. Patients not receiving a loading dose within several days of angiography should be considered for a repeat loading dose at the time of PCI.

- Van der Heijden (2004) evaluated the effect of pre-treatment with clopidogrel in patients with stable coronary artery disease undergoing elective stent implantation. One group of patients (n=102) were given a 300mg clopidogrel loading dose immediately after coronary stent implantation. A second group (n=101) underwent pretreatment with 300mg clopidogrel three days prior to stent implantation followed by 75mg once daily. The authors concluded that no beneficial effect of pretreatment with clopidogrel on post-procedural elevation of troponin I and CK-MB or on clinical events after one and six months could be demonstrated.

- Di Sciascio et al. 2010 sought to evaluate the safety and efficacy of cath-lab pre-PCI treatment with clopidogrel 600mg load versus 6 hour pre-load (ARMYDA-5 PRELOAD trial). A total of 409 subjects were randomized 1:1 to receive clopidogrel 600mg either 4-8 hours pre-PCI or in the cath lab post angiography but pre-PCI. The primary endpoint was Major Adverse Cardiac Events (MACE) at 28 days. The results showed no difference in the incidence of MACE between the two arms. The authors concluded that in-cath lab administration of clopidogrel can be an alternative to routine pre-treatment.

- Widimsky et al. 2008 sought to compare clopidogrel pretreatment in patients with stable angina (either >6 hours before elective PCI or immediately prior to PCI after angiography) (PRAGUE-8 study). A total of 1028 subjects were randomized (1:1) to one of these two treatment strategy arms. In the > 6 hour group, the median time of clopidogrel load to PCI was 20 hours. Only 30% of the 513 subjects in this arm underwent PCI. In the immediately prior to PCI group, only 28% received clopidogrel due to the decision to perform a PCI. The primary endpoint was the composite of death, periprocedural MI, stroke, and re-intervention within 7 days of index PCI. The authors concluded that pre-

angiography treatment with clopidogrel increased the risk of minor bleeding complications while the benefit on peri-procedural infarction was not significant.

It is this reviewer's opinion that the body of evidence provided herewith, although not conclusive, suggests a benefit regarding pre-PCI treatment of clopidogrel. As stated to the applicant prior to the initiation of PHOENIX, the onset of action of clopidogrel is not rapid; therefore delaying administration of clopidogrel may result in inadequate platelet inhibition at the time of PCI. Although the applicant emphasized that the timing of clopidogrel was determined by the investigator, this reviewer agrees with the comment from the AC that the allowance to use clopidogrel post-PCI, knowing that the onset of action is not rapid compared to cangrelor, was part of a strategy to optimize the probability of showing superiority of cangrelor over clopidogrel when studied for use during the PCI.

## 2.3 Concern over whether or not the components of the primary endpoint which drove the results of the trial were clinically meaningful

An argument was raised concerning the clinical relevance of periprocedural MI (type 4a) as per the UDMI and ST (driven by IPST). Issues surrounding ST and IPST were thoroughly evaluated in the original clinical review, and there is no new information to be presented in this Addendum.

During AC discussion, it was opined that elevations in CKMB associated with PCI were not usually measured unless there were clinical symptoms or signs of ischemia: chest pain or ECG changes. Therefore, the relevance of endpoints which rested solely on elevation of biomarkers without concomitant signs or symptoms has been called into question.

Although the PHOENIX DSMB, also serving as the IARC later in the trial, did not document any objection to the trial design at various meetings or teleconferences (29 AUG 2011, 11 FEB 2012; 24 APR 2012, 27 JUN 2012), they questioned the MI definition. Dr. Harrington responded that "There is an angiographic component included in the MI definition. Dr. Harrington stated that the MI definition is a variant of WHO definition. Biomarker changes, ECG changes, symptoms, and angiographic core lab information are utilized in the determination of an MI. The previous trials utilized an MI definition that was more sensitive than specific. In this trial, a lower event rate is expected but the definition of MI will be more specific. A great deal of time is being invested to collect biomarker information in this trial" (DSMB teleconference 11 FEB 2012).

The AC raised questions about the validity or independence of post-PCI biomarkers as a predictor of mortality. The association between post-PCI biomarker and mortality was postulated to be an epiphenomenon due to the independence of the extent and



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complexity of coronary lesions as a predictor of mortality (Garg, S, et al., 2011; and Palmerini et al., 2011). Recent PCI studies have reported associations between peri-procedural MI and mortality only for very large infarcts. In one study (n=7147), only Q-wave MI or non-Q-wave MI with CKMB>8x upper limit of normal correlated with increased 2-year mortality (Stone et al., 2001). In another study (n=3,478), only CKMB >10x upper limit of normal was significantly associated with increased 1-year mortality (Brener et al., 2002). Troponin had greater sensitivity for myocardial necrosis than CKMB. However, troponin release was likely to occur without myocardial structural damage. Therefore, there was a suggestion that post-PCI CKMB was more strongly associated with subsequent cardiovascular events than c-troponin elevation (Moussa et al., 2013). A proposed definition of clinically relevant peri-procedural MI was postulated to be a function of baseline status (Moussa et al., 2013) and is summarized in ***Table 9***.

**Table 9: Post-PCI MI: proposed definition of clinically relevant MI.**

| | |
|---|---|
| Patients with normal baseline CKMB | Peak CKMB within 48 hours of PCI: ≥ 10x ULN or ≥ 5x ULN with new QW in ≥2 contiguous leads, or new persistent LBBB; OR in the absence of CKMB measurements and a normal baseline cTn, a cTn (I or T) level within 48 hours of PCI: ≥ 70x ULN or ≥ 5x ULN with new QW in ≥2 continuous leads or new persistent LBBB. |
| Patients with elevated baseline CKMB (or cTn) in whom the biomarker levels are stable or falling | CKMB (or cTn) rises by an absolute increment equal to those levels recommended above from the most recent pre-procedure level. |
| Patients with elevated CKMB (or cTn) in whom the biomarker levels have not been shown to be stable or falling | CKMB (or cTn) rises above an absolute increment equal to those levels recommended above plus new ST-segment elevation or depression plus signs consistent with a clinically relevant MI, such as new onset or worsening heart failure or sustained hypotension. |

ULN= upper limit of normal; LBBB=left bundle branch block; Source: Moussa, I, et al. 2013.

A sensitivity analysis was performed on the primary endpoint (Death/MI/IDR/ST) by focusing only on those myocardial infarcts where the CKMB exceeded 10x ULN or 5x ULN in the cases of Q-wave MI, and where ST diagnosis was limited to Academic Research Consortium (ARC)-ST. The loading dose of clopidogrel was restricted to the



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600mg in order to avoid the potential for bias due to the imbalance of clopidogrel loading dose empirically favoring cangrelor. The source of the data came from the adjudicated dataset. The results are shown in ***Table 10*** for MI restricted to CKMB ≥ 10x ULN, and in ***Table 11*** for MI restricted to Q-wave MI with CKMB ≥ 5x ULN. This analysis still yielded a benefit for cangrelor over clopidogrel when using the criteria of CKMB ≥ 10x ULN. However, the combination of all-cause death, Q-wave MI (with CKMB ≥ 5x ULN), IDR and ARC-ST showed no significant difference between cangrelor and clopidogrel. The combination of all-cause death, Q-wave MI, and ARC-ST, as discussed at a meeting with the Applicant on 09 NOV 2009, significantly but narrowly favored cangrelor.

**Table 10: Primary endpoint sensitivity analysis focused on ARC-ST and MI (CKMB > 10x ULN) in PHEONIX.**

| | Clopidogrel (600mg loading dose) | | Cangrelor | | | 95% CI | |
|---|---|---|---|---|---|---|---|
| **Endpoint** | **N** | **# events** | **N** | **# events** | **OR** | **Lower CL** | **Upper CL** |
| **D/MI/IDR/ST** | 4069 | 277 | 4067 | 176 | 0.763 | 0.623 | 0.934 |
| **D/MI (CKMB>10xULN)/ IDR/ST** | 4069 | 102 | 4067 | 64 | 0.623 | 0.454 | 0.854 |
| **D/MI (CKMB>10xULN)/ IDR/ARC-ST** | 4069 | 70 | 4067 | 45 | 0.639 | 0.438 | 0.932 |

D=all-cause mortality; OR= Odds Ratio; CL=confidence limit; QMI=Q-wave MI; ULN=upper limit of normal; 95% CI= 95% confidence interval

**Table 11: Primary endpoint sensitivity analysis focused on ARC-ST and MI (QW with CKMB > 5x ULN).**

| | Clopidogrel (600mg loading dose) | | Cangrelor | | | 95% CI | |
|---|---|---|---|---|---|---|---|
| Endpoint | N | # events | N | # events | OR | Lower CL | Upper CL |
| D/QMI/IDR/ARC-ST | 4069 | 39 | 4067 | 32 | 0.822 | 0.514 | 1.314 |
| D/QMI/ARC-ST | 4069 | 64 | 4067 | 42 | 0.656 | 0.443 | 0.97 |
| Death/QMI(CKMB >5x ULN)/IDR/ST | 4069 | 73 | 4067 | 52 | 0.712 | 0.497 | 1.019 |
| Death/QMI(CKMB >5x ULN)/IDR/ARC ST | 4069 | 38 | 4067 | 32 | 0.844 | 0.526 | 1.353 |
| Death/QMI(CKMB >5x ULN)/ARC ST | 4069 | 63 | 4067 | 42 | 0.666 | 0.45 | 0.987 |
| Death/QMI(CKMB >5x ULN) | 4069 | 18 | 4067 | 16 | 0.894 | 0.455 | 1.755 |

D=all-cause mortality; OR= Odds Ratio; CL=confidence limit; QMI=Q-wave MI; ULN=upper limit of normal; 95% CI= 95% confidence interval

These mixed results at best still provide a marginal benefit for cangrelor compared to clopidogrel for clinically relevant post-PCI myocardial infarction, but more likely render uncertain a therapeutic benefit which at least equals the risk.

The results from the sensitivity analysis were based on definitions associated with subjects who presented with normal baseline markers. It is unclear that the population used in the sensitivity analysis all had normal baseline biomarkers. For those subjects who did not have normal baseline biomarkers, there are additional criteria as outlined in *Table 9*. The assessment of the clinical relevance of MI as a function of stratified baseline status (i.e. normal or not normal) has not been performed by the applicant. The applicant should present a persuasive argument that the PHOENIX trial results

demonstrated a significant reduction of clinically relevant post-PCI myocardial infarction with the consensus definitions outlined for subjects with baseline normal and abnormal biomarkers. The applicant should also defend their use of UDMI as the criteria for post-PCI events when the consensus opinion (Moussa, I, Klein, L, Shah, B, Mehran, R, Mack, M, Brilakis, E, Reilly, J, Zoghbi, G, Holper, E, Stone, G, 2013) suggested that the evidence to date does not support the use of the UDMI as the optimal criteria to identify clinically relevant post-PCI MI events.

## 2.4 Operational Questions

### 2.4.1 “Patient Derived Type” in the PHOENIX Trial

During the initial review of the applicant’s NDA, it was noticed that the baseline diagnosis (i.e. STEMI, NSTEACS, and SA) was arrived at from a process developed by the applicant leading to a “patient-derived type” (i.e. reclassification of subjects from the investigator-based diagnosis of STEMI, NSTEACS, or SA). In the CSR, the applicant explained that “patient type was initially determined by the investigator at the time of randomization. Since this type of initial assessment might not have been precise and IV/WRS design prohibited change when new information became available, further assessments and analysis were also included in study methods incorporating additional information.” When queried about the difference between the investigator-based diagnosis and “patient-derived type” diagnosis (i.e. “please provide cross-tabulations of primary endpoint rates by treatment arm and baseline patient type and by treatment arm and your derived patient type”), the applicant replied that they were “puzzled by the question. The ‘derived patient type’ is the baseline patient type--it was the result of applying an algorithm to baseline data provided by the sites. Thus, there is no comparison to be made.”

This process initially appeared reasonable because of the rapidity in which IVRS data may need to be acquired in a PCI setting. Furthermore, an index ECG might not reflect an ST-segment elevation which might develop later in time, thereby precipitating a change in diagnosis. This process was originally construed by this reviewer to serve as a tool for programmatic quality control ensuring diagnostic accuracy. Although benefit of the doubt was given to the applicant in their assumption that the diagnosis of the investigator- cardiologist might be incorrect, or that key information might be missing in the index acquisition of data via the IVRS, it was assumed that the investigator assessment would not be questioned and that any correction by the applicant’s process would be based on a documentable query (program generated or via a medical monitor) with auditable data correction forms.

An exact and detailed description of the process was not provided by the applicant. The SAP did not describe this process, and there was no indication that any change from



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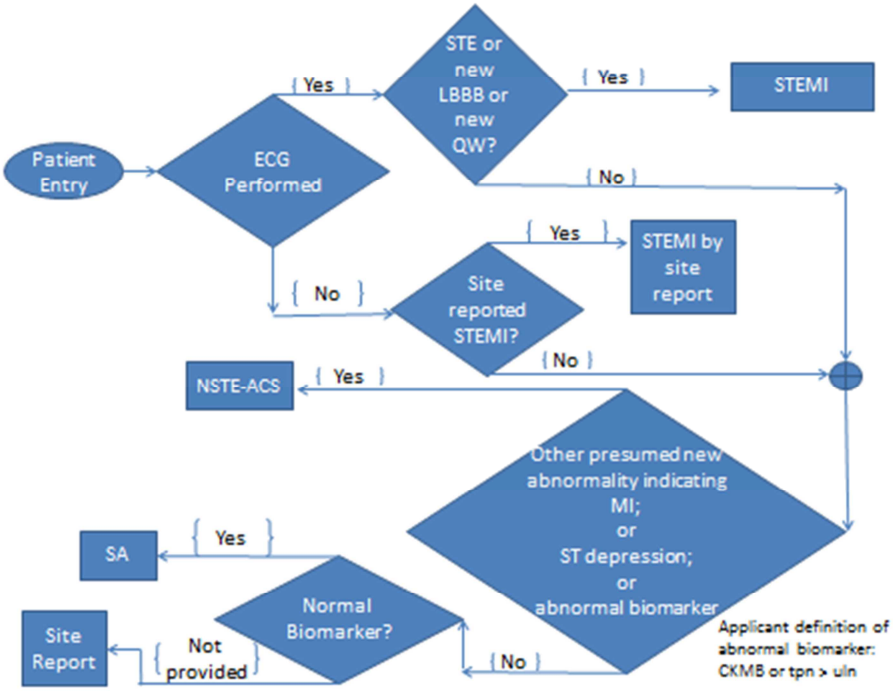
the investigators' diagnosis was adjudicated. There also was no evidence that the final diagnosis was endorsed by the investigator.

In reviewing the SAS programming by the team statistician, the description of the process was constructed and illustrated in ***Figure 1.*** This figure specifies that the diagnosis of STEMI required either ECG demonstration of ST-segment elevation or site reporting. If a STEMI was not reported or identified by an ECG, any abnormalities (other presumed ECG, laboratory biomarkers, "other abnormalities") would result in a diagnosis of NSTEACS. If there were no abnormalities, including no abnormal biomarker, then the diagnosis was SA.

**Figure 1: Patient Derived Type Algorithm described in PHOENIX**




*Source: interpretation of SAS program A_disp.sas*

***Table 12*** shows the results of an analysis demonstrating the change in baseline diagnosis (i.e. STEMI, NSTEACS, SA) from the investigator report to the applicant's patient-derived type. As the table indicates, 6428 subjects were diagnosed by the

investigators as having SA. Application of the patient-derived type algorithm resulted in changing the diagnosis of 980 of these subjects to NSTEACS and 101 of these subjects to STEMI. Similarly, 2914 subjects were diagnosed as NSTEACS by the investigators. Application of the patient-derived type algorithm resulted in changing the diagnosis of 864 subjects to SA and 229 subjects to STEMI. The investigators diagnosed 1803 subjects with STEMI. Application of the patient-derived type algorithm resulted in changing 24 of these subjects to NSTE-ACS and 6 subjects to SA. These corrections represented a considerable shift from investigator diagnoses to applicant-mediated patient-derived type diagnoses. It is counter-intuitive that so many misdiagnoses occurred by the investigators, who are presumably trained cardiologists. If investigator competency is called into question as a consequence of the apparently large number of applicant-mediated changes in the diagnosis of subjects randomized to PHOENIX, then the validity of the PHOENIX trial is placed into jeopardy.

**Table 12: Site-Reported Patient Type vs. Derived Patient Type**

| | | site-reported patient type | | |
|---|---|---|---|---|
| | | Stable Angina | NSTE-ACS | STEMI |
| Derived patient type | Stable Angina | 5347 | 864 | 6 |
| | NSTE-ACS | 980 | 1821 | 24 |
| | STEMI | 101 | 229 | 1773 |

The applicant should explain:

- Why the patient-derived type algorithm was developed in lieu of a more standard data correction algorithm based on queries and investigator-controlled corrections.
- Why such a process affected a considerable subject population and why was it not described in the SAP or in more detail in the CSR.
- Why changes from investigator-based diagnoses to applicant-based diagnoses were not adjudicated.
- Timing of process implementation relative to the IVRS qualification data entry.
- The impact of the changes in diagnosis on the primary endpoint.



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### 2.4.2 Database Unlock

The PHOENIX CSR documented that the database was locked on January 14, 2013, unlocked on February 1, 2013 and relocked on February 18, 2013. The applicant noticed missing anticoagulant concomitant medication data. Following procedures cited by the applicant as being described in the Data Management Plan (DMP) and Data Review Plan (DRP), the database was unlocked to “confirm” the missing data. Hard copies of the electronic case report form pages were created and dispatched to the sites. Following receipt of the missing data from the sites, the additional data was reentered into the database, the database was re-analyzed, and finally the database was re-locked. A total of 533 subjects were queried at 84 sites. There were 153 sites in the PHOENIX trial.

The applicant disclosed the database unlocking event in the CSR. Upon initial review, it was felt that database unlocking was not an uncommon procedure, especially in a mega-trial, and standard operating procedures for data-base unlock were commonplace. In the CSR (section 9.8.3), the DMP and DRP were referenced as the source describing database unlock. In reviewing the DMP (version 2 published 18 Feb 2013 on the day of database relock) and the DRP (finalized 12 Feb 2013 while the database was unlocked), a procedure describing database unlocking was not discoverable. The DRP referenced a Standard Operating Procedure (SOP)-DM-001 v4.0 as the source which described the process for locking a database. The contents of the SOP are not known.

Several questions arose concerning the database unlocking upon re-examination with the review team, including the deputy head of the division:

- Why was there confusion amongst 84 sites regarding data entry of anticoagulants in the eCRF?
- Why were the missing data not queried during routine monitoring or not discovered, even at site close-out?
- Why was db unlocking necessary to “confirm” missing data? Usually, db unlocking occurs to correct data errors following their discovery.
- Of the 533 subjects in 84 sites who were queried, how many of the eCRF data 1) were changed, or 2) were unchanged following confirmation that no anticoagulants were given and therefore no change, or 3) were unchanged because of no response from the site. What was the distribution of these subjects between the arms of PHOENIX? What were the anticoagulants?
- Why was there no QA certificate accompanying the database unlock- relock process to ensure adherence to the governing documents?

The deputy head of the Division has consulted OSI to review the incident of database unlocking.



Reference ID: 3493216

# 3 ADDENDUM: References

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

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/s/

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FORTUNATO F SENATORE
04/21/2014

THOMAS A MARCINIAK
04/22/2014
Please see my reviews for more complete discussions of clopidogrel timing and other issues.

# Cross-Discipline Team Leader Review Memo

| | |
|---|---|
| **Date** | March 23, 2014 |
| **From** | Thomas A. Marciniak, M.D. |
| **Subject** | Cross-Discipline Team Leader Review |
| **NDA/BLA #**<br>**Supp #** | NDA 204-958<br>000 |
| **Proprietary / Established (USAN) names** | Kengreal /<br>cangrelor |
| **Dosage forms / strength** | lyophilized powder for injection /<br>50 mg/vial |
| **Proposed Indication(s)** | for reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with coronary artery disease undergoing percutaneous coronary intervention (PCI); to maintain $P2Y_{12}$ inhibition in patients with acute coronary syndromes (ACS) or patients with stents who are at increased risk for thrombotic events (such as stent thrombosis) when oral $P2Y_{12}$ inhibitor therapy is interrupted due to surgery |
| **Recommended:** | complete response |

## 1. Introduction to Review

Cangrelor is an intravenously (IV) administered reversible $P2Y_{12}$ platelet inhibitor submitted for the two indications listed in the table above. I will reference the first indication above as the "PCI" indication and the second as the "bridging" indication. For the PCI indication the applicant studied cangrelor in three large clinical outcomes trial ("CHAMPION") in patients undergoing PCI. The two earlier trials, CHAMPION PCI and PLATFORM, failed to show superiority of a cangrelor regimen to a clopidogrel regimen.[1] The applicant alleges that the failure of these latter two trials was the result of problems with adjudicating new myocardial infarctions (MIs) in patients having baseline biomarker elevations. A third trial, CHAMPION PHOENIX, allegedly corrected this flaw and demonstrated superiority of the cangrelor regimen to a clopidogrel regimen. For the bridging indication the applicant submitted summaries of data from a Dutch stent thrombosis registry and of other published literature alleging the need for bridging and a pharmacokinetic (PK)/pharmacodynamic (PD) study in patients discontinuing clopidogrel or prasugrel in preparation for coronary artery bypass surgery (CABG) demonstrating that platelet inhibition can be maintained for several days by cangrelor infusion.

Because we presented cangrelor at the February 12, 2014, meeting of the Cardiovascular and Renal Drugs Advisory Committee (AC) I prepared reviews of the benefit-risk of cangrelor and of the ethicalness of the cangrelor development program for PCI to inform the AC members. In this review I will summarize and update the information in those reviews and comment

[1] In this review for brevity I refer to the "cangrelor" regimen or arm and the "clopidogrel" regimen or arm for the PCI indication. The more complete references are the "cangrelor infusion followed by clopidogrel" regimen or arm and the "clopidogrel alone" regimen or arm.



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upon the bridging indication. I have not had time to review all of the many submissions by the applicant since the AC meeting. I will comment upon them in an addendum after the primary reviewers file their reviews of them.

## 2. Background/Regulatory History/Previous Actions/Foreign Regulatory Actions/Status

I discussed the background and regulatory history in my review of the ethicalness of the cangrelor development program. There have been no previous FDA regulatory actions and no foreign approvals for cangrelor.

## 3. CMC/Microbiology/Device

The CMC reviewer, Dr. David Claffey, recommends approval of the application from a CMC perspective on receipt of an overall acceptable recommendation from CDER Office of Compliance. He concluded that the data provided in this application and the referenced DMFs were acceptable from a CMC perspective. The most clinically relevant findings are regarding incompatibilities with other IV administered drugs when co-administered in the same line. Incompatibilities include (b) (4) The incompatibility with (b) (4) should not be problematic because the ACS indication is for PCI. Coadministration of the other incompatible drugs is possible and should be avoided; the label will list all known incompatibilities.

The product quality microbiology reviewer, Mr. Steven Donald, M.S., recommends approvable pending a complete response to microbiology deficiencies. The deficiency he notes is that product labeling does not reflect the conclusions of the post constitution hold time study. (b) (4) the post constitution hold time study submitted on 10/09/2013 concludes that product diluted in 5% dextrose may be stored at room temperature for only 12 hours. The suggested hold period for saline, at 24 hours, is supported by the study and is acceptable.

## 4. Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology reviewer, Dr. Belay Tesfamariam, states that the extent and scope of the pharmacological and toxicological documentation provided are appropriate to assess the safety of cangrelor for the proposed clinical dosing regimens. In his review he does note that in the PCI setting, the Css values of 488 ng/ml achieved with a bolus injection of cangrelor 30 µg/kg followed by 4 µg/kg/min infusion for 2 hr is ~8-fold higher than the plasma concentration measured at the NOAEL in the dog (Css 61.5 ng/ml), and therefore in the absence of any margin of safety over the NOAEL, enhanced renal, urinary tract and liver function monitoring are recommended. He also has the following comments:

- Cangrelor is structurally similar to ATP and thus may aggravate conditions in patients with respiratory distress because inhibition of $P2Y_{12}$ receptors in the sensory neurons may increase the dyspnea sensation.



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- Cangrelor at high doses may cause slowing of heart rate (negative chronotropic effect), depression of the SA node and AV nodal conduction (negative dromotropic effect), and asynchronous premature ventricular contractions ('ectopics').

- In conscious beagle dogs infused continuously with cangrelor (40 μg/kg/min) for 7 days, ADP-induced aggregation was restored at about 60 min after cessation of cangrelor infusion. Transitioning from cangrelor (direct and reversible inhibitor) to orally active and irreversible thienopyridine $P2Y_{12}$ receptor inhibitors may delay onset of the latter's action if administered during the infusion. The reason is that cangrelor's high affinity for $P2Y_{12}$ receptors may prevent the thiol active metabolite from forming disulfide bridge with cysteine residues in the receptor. Thus, careful consideration should be given to the timing of administration of an oral thienopyridine in the cangrelor regimen.

*COMMENT: Dr. Tesfamariam raises some excellent issues that are partially addressed by the clinical experience:*

- *I am less concerned with the potential hepatic toxicity for the PCI setting both because of the short administration and because of the large numbers of patients exposed without significant toxicity. I don't consider cangrelor to have a signal for hepatotoxicity. Renal monitoring in the CHAMPION trials and in BRIDGE was less than optimal.*

- *Similarly, dyspnea or pulmonary toxicity did not appear to be problematic in the CHAMPION trials with the short duration exposure. While BRIDGE had longer exposure, it may be too small to produce definitive confirmation of safety for these adverse events.*

- *The clinical dosages are likely not high enough to show cardiac effects. Regardless, the cangrelor cardiac event rates in PHOENIX provide some reassurance that the direct cardiac effects of cangrelor are not significant compared to the antiplatelet effects (within the limitation that the antiplatelet effects were compared to clopidogrel used badly as I discuss in my benefit-risk review.)*

- *The problems with transitioning from cangrelor to an irreversible $P2Y_{12}$ receptor inhibitor may have led to real clinical problems. The gap in platelet inhibition occurring from infusion end until the clopidogrel inhibition kicks in could be responsible for the uncertain efficacy in STEMI patients.*

## 5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology reviewers, Drs. Sreedharan Sabarinath and Jeffry Florian, state that the NDA can be approved from a clinical pharmacology perspective. The most clinically relevant findings from their review are the following:



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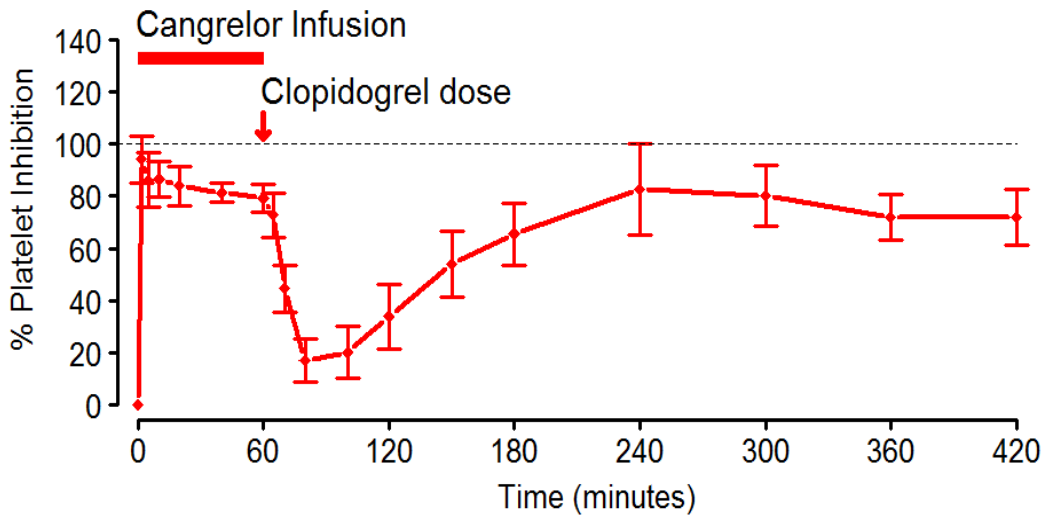
- Cangrelor has a rapid onset and offset for both PK and PD (platelet inhibition). The figure that I consider best represents the onset and offset for platelet inhibition as well as the transition to oral clopidogrel therapy is Figure 1.

**Figure 1: Time Course of Platelet Inhibition with Cangrelor Infusion followed by Oral Clopidogrel**




- While cangrelor's rapid onset and offset are desirable features, the transition to irreversible $P2Y_{12}$ inhibitors such as clopidogrel and prasugrel that have active metabolites with short half-lives is problematic. If clopidogrel is administered during the cangrelor infusion, cangrelor blocks access of the active metabolite to the $P2Y_{12}$ receptor. After the infusion is stopped there may be little active metabolite available to continue platelet inhibition, greatly reducing the effective platelet inhibition of clopidogrel administered during cangrelor infusion. To avoid this reduction clopidogrel was administered in the CHAMPION trials after the cangrelor infusion was stopped. However, this approach leaves a gap in platelet inhibition (the trough from 90 to about 240 minutes in Figure 1). We can not estimate theoretically how clinically relevant this gap is, but cangrelor appeared to be less effective in the STEMI subgroups of two CHAMPION trials as I discussed in my benefit-risk review and AC presentation.

- For the PCI indication the applicant based dosing on achieving an immediate high level (80-100%) of $P2Y_{12}$ inhibition. For the bridging indication the applicant based dosing to maintain residual platelet reactivity at or below the level that would be expected to be maintained if clopidogrel had not been discontinued (>60%). While these dose selection criteria are reasonable, because we do not know the dose-response or exposure-response relationships for either efficacy or safety, we do not know if they were optimal.



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- Of demographic and laboratory covariates evaluated, the applicant identified only body weight as having a significant effect upon PK (and so, because PD is dose-linear, upon PD). However, the sponsor did not study sufficient numbers of Asians and blacks to characterize racial differences in PK and PD. Cangrelor is dosed by body weight.

- Cangrelor is metabolized by nucleotidases in systemic circulation. No interactions with CYP enzymes were demonstrated in *in vitro* studies at levels corresponding to the proposed dosing. No significant clinical drug-drug interactions are anticipated.

## 6. Clinical Microbiology

Cangrelor is not an antimicrobial drug. See Section 3 for a summary of the product quality microbiology review.

## 7. Clinical/Statistical

### 7.1. Efficacy

#### 7.1.1. Dose identification/selection and limitations

See Section 5 for a discussion of the PD basis for dosing. The applicant conducted the phase 3 clinical trials with single dosages, so no adequate data on clinical effects by different dosages are available.

#### 7.1.2. Studies essential for approval

For the PCI indication the applicant conducted three large outcome trials referred to as the CHAMPION trials. The first two trials, PCI and PLATFORM, failed on their primary endpoint while the third, PHOENIX, succeeded. All three tested the same cangrelor regimen but differed in size, index event determining eligibility, clopidogrel timing, and results. I've summarized the most pertinent differences in Table 1.

**Table 1: CHAMPION Trials**

| | N | stable angina* | STEMI* | clopidogrel loading | Endpoint OR† |
|---|---|---|---|---|---|
| PCI | 8,877 | 15% | 11% | before PCI | 1.05 |
| PLATFORM | 5,301 | 5% | 0% | after PCI | 0.87 |
| PHOENIX | 11,145 | 58% | 16% | variable | 0.78 |

*rest UA/NSTEMI; †endpoint OR = primary endpoint odds ratio

For the bridging indication the most relevant clinical study is the BRIDGE PK/PD study in 207 patients discontinuing clopidogrel or prasugrel in preparation for CABG. The CHAMPION studies also provided supportive data for this indication regarding efficacy and safety.

#### 7.1.3. Other studies



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For the bridging indication the applicant also submitted summaries of data from a Dutch stent thrombosis registry and of other published literature alleging the need for bridging.

7.1.4. Primary clinical and statistical reviewers' findings and conclusions

7.1.4.1. PCI indication

The primary clinical efficacy reviewer, Dr. Fortunato Senatore, recommends approval for the PCI indication. The basis he gives regarding efficacy is that PHOENIX met its primary endpoint (OR 0.79; 95% CI [0.67, 0.93]; p=0.0053). He discusses some potential confounding issues that he believes do not negate efficacy. I will discuss the ones I judge to negate efficacy below.

The primary statistical reviewer, Dr. Jialu Zhang, also notes that PHOENIX demonstrated a statistically significant reduction in the primary endpoint. However, she questions whether the differential loading doses between the two arms contributed to the reduction. She did not provide a recommendation on approvability.

*COMMENTS: The confounding issues that the primary clinical reviewer dismisses that I judge do negate an efficacy benefit are the following:*

- *He considers the positive PHOENIX results to be based on lessons learned from PCI and PLATFORM, i.e., regarding endpoint ascertainment. I demonstrated that PHOENIX results are consistent with PCI and PLATFORM results with respect to the timings of clopidogrel administration as I present in Section 7.1.6.1. Cangrelor is not superior to clopidogrel administered after angiography but pre-PCI and it is unclear whether cangrelor is inferior to clopidogrel administered earlier.*

- *He summarizes that the periprocedural administration of clopidogrel was within guidelines. He appears to conclude from this observation that both the issue of loading dose and the issue of clopidogrel delay do not preclude approval. I discuss loading dose in Section 7.1.6.3 and clopidogrel delay in Section 7.1.6.1 and I conclude that they do preclude approval. I also discuss consistency with guidelines in detail in my ethical review of the cangrelor development program.*

- *He considers the benefit-risk of cangrelor to be narrowly marginally favorable for an endpoint restricting MIs to clinically meaningful MIs and excluding intraprocedural stent thrombosis. I found that cangrelor in PHOENIX did not show superior efficacy to clopidogrel for site-reported events and it is unclear whether cangrelor would be inferior to clopidogrel administered earlier.*



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*I did not find in the primary reviews discussions of the question of whether cangrelor is less effective in STEMI or, for this indication with irreversible impact upon morbidity and mortality, how the applicant has established that cangrelor is "as effective as existing, approved therapies" (including clopidogrel administered early, ticagrelor, prasugrel, and glycoprotein IIb/IIIa inhibitors) as specified by the August 1, 1995, Federal Register Notice [Docket No. 95N-0230]. These latter are additional reasons why I disagree with the primary efficacy reviewer and recommend a complete response rather than approval.*

7.1.4.2. Bridging indication

The primary clinical efficacy reviewer recommends a complete response for the bridging indication. He notes the following: There is lack of clinical data from BRIDGE to support the PD effect at the proposed bridging dose. The clinical efficacy observed in the PHOENIX trial is not applicable to the bridging indication because of the five-fold lower dose used in BRIDGE. Literature-based evidence suggests no relationship between the PD effect from the VerifyNow PRU data and clinical outcome as well as inconsistent and conflicting results regarding pre-CABG P2Y12 inhibition therapy and lack of an unmet need.

*COMMENT: I share his concerns and have an additional reason why I, too, recommend a complete response. Prior to reviewing BRIDGE I had thought that the only path to approval for the bridging indication was what the applicant has submitted: the combination of a PK/PD study, i.e., like BRIDGE, combined with clinical evidence of efficacy and safety from the large trials for the PCI indication and literature evidence for the need. I had presumed that the event rates for the short duration, i.e., max of about 5 days, during which bridging would be done would be too low to allow an outcomes trial to be feasible. However, from randomization to surgery about 2.8% of cangrelor and 4% of placebo patients (3:4) suffered the primary endpoint of death/MI/ischemia driven revascularization (IDR)/stroke; from post-surgery through 30 days 4 patients in each arm suffered the primary endpoint. We presume the benefit of cangrelor for bridging is during the pre-surgical period for reducing ischemic events. With a control rate of 4%, the sample size required for an 80% power of detecting a 50% reduction is 1239 subjects per arm. An outcomes trial of that size does not seem infeasible.*

7.1.5. Pediatric use

PCI is rarely done in children so that pediatric studies of it are not possible and not needed.

7.1.6. Discussion of notable efficacy issues

I discussed most of the notable efficacy issues for the PCI indication in my benefit-risk review and in my presentation at the February 12, 2014, AC meeting. Since then we have identified another issue: lack of dissolution data on the overencapsulated



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clopidogrel tablets used in all of the CHAMPION trials. I summarize the most relevant findings for all PCI issues below. I believe the bridging issues are summarized adequately in the primary reviews and in Section 7.1.4.2.

7.1.6.1. Clopidogrel delay

There are several lines of evidence supporting that delaying clopidogrel loading after the start of angioplasty is bad: timing in the clopidogrel trials; cross-comparisons of clopidogrel timing and outcomes in the CHAMPION trials; clopidogrel timing in PHOENIX; prasugrel trial results; and consistency among $P2Y_{12}$ inhibitor pharmacodynamics, coronary disease pathophysiology, and trial results. I believe the most valuable finding from the cangrelor development program is good evidence that delaying clopidogrel loading is hazardous to the patient. Because I plan to summarize all of the evidence in a review to be filed to the clopidogrel NDA to recommend modifying the clopidogrel label and because I summarized the evidence not related to cangrelor at the AC meeting, I will only summarize the data from the cangrelor program here.

7.1.6.1.1. PCI vs. PLATFORM comparison

The most significant difference between PCI and PLATFORM was that PCI specified clopidogrel loading in the clopidogrel arm prior to PCI while PLATFORM specified it after PCI. The results were that, while the point estimate for the primary endpoint in PCI favored clopidogrel, the point estimate favored clopidogrel in PLATFORM. More critical is that both deaths and stent thromboses were significantly higher in its clopidogrel arm by the end of the study. I show a DSMB-like view of deaths in PLATFORM in Figure 2 and of stent thromboses in Figure 3.

**Figure 2: Cumulative Deaths at 48 Hours by Enrollment Date in PLATFORM**

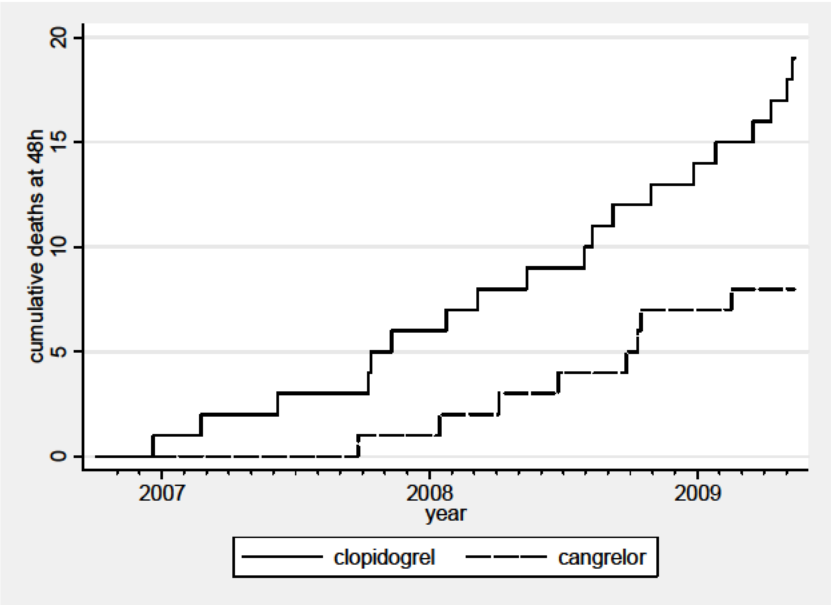




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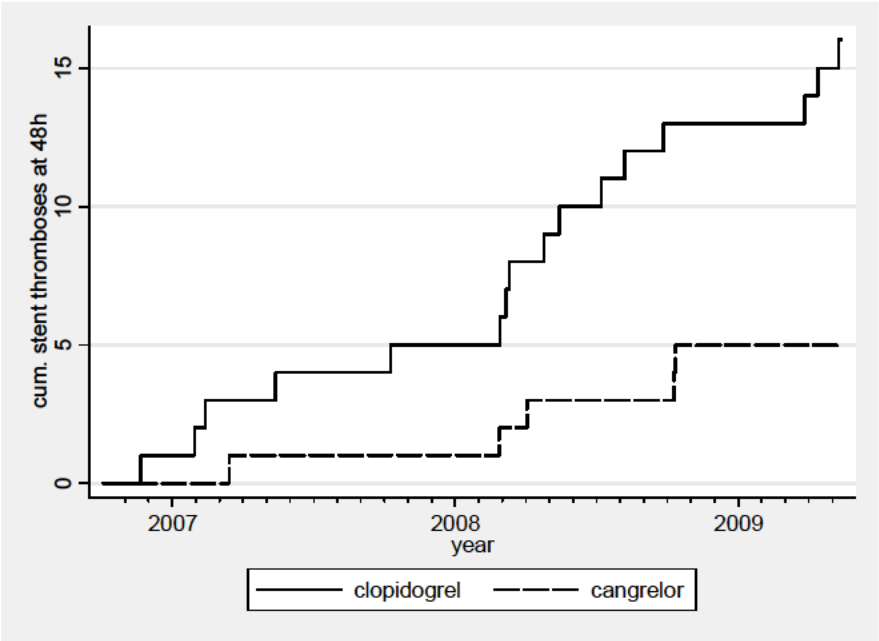
**Figure 3: Cumulative Stent Thromboses at 48 Hours by Enrollment Date in PLATFORM**




(b) (4)

. For a complete discussion of PLATFORM termination see my review of the ethicalness of the cangrelor development program.

*COMMENT: I conclude that the PCI to PLATFORM comparison establishes that delaying clopidogrel loading until after PCI is hazardous to patients' welfare. While the PCI to PLATFORM comparison is not a randomized comparison, the timing of clopidogrel loading was specified by their protocols rather than subject to investigator discretion as in PHOENIX. I consider the PCI to PLATFORM comparison to be the best evidence available regarding the hazards of delaying clopidogrel.*

*The lead author, Dr. Deepak Bhatt, for the NEJM PLATFORM article concluded similarly to my conclusion. In a 2009 interview (accessed at http://www.medscape.com/viewarticle/712388_print) Dr. Bhatt commented on the PLATFORM and PCI results:*

***"Give Antiplatelet Before PCI***

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Dr. Bhatt was also the lead author for the NEJM PHOENIX article. Both articles list his institutional affiliation as the VA (Veterans Affairs) Boston Healthcare System, which was one of three PHOENIX VA sites. I've listed relevant statistics for the VA and non-VA sites that participated in PHOENIX in Table 2.

**Table 2: Selected Statistics for VA and non-VA Sites for PHOENIX**

| | N | stable angina | clopidogrel | | primary endpoint | |
|---|---|---|---|---|---|---|
| | | | pre-PCI | post-PCI* | clopidogrel | cangrelor |
| Non-VA | 11,061 | 57.5% | 64.2% | 29.8% | 5.8% | 4.7% |
| All VA | 84 | 83.3% | 2.5% | 88.8% | 9.8% | 4.7% |
| Boston VA | 19 | 73.7% | 5.6% | 83.3% | 11.1% | 0.0% |
| Dallas VA | 43 | 90.7% | 2.4% | 90.2% | 4.5% | 9.5% |
| Jesse Brown VAMC | 22 | 77.3% | 0.0% | 90.5% | 20.0% | 0.0% |

*post-PCI = after the end of PCI (clopidogrel during-PCI percentages not shown)

The VA sites administered clopidogrel predominantly after the end of PCI. VA patients in the clopidogrel arm fared poorly (about 10% primary endpoint rate) while VA patients in the cangrelor arm fared comparable to the non-VA patients (both about 4.7% primary endpoint rate.)

*COMMENT: The VA experience in PHOENIX is consistent with delaying clopidogrel being hazardous to patient welfare.*

7.1.6.1.2. PCI, PLATFORM, and PHOENIX clopidogrel timing comparisons

In PHOENIX investigators employed various timings of clopidogrel loading in the clopidogrel arm, including pre-PCI, during PCI, and post-PCI. The average timing of clopidogrel loading in PHOENIX was intermediate between those of PCI and PLATFORM. I show a scatterplot of the primary endpoint ORs vs. mean clopidogrel timing in the stable angina subgroups in Figure 4.



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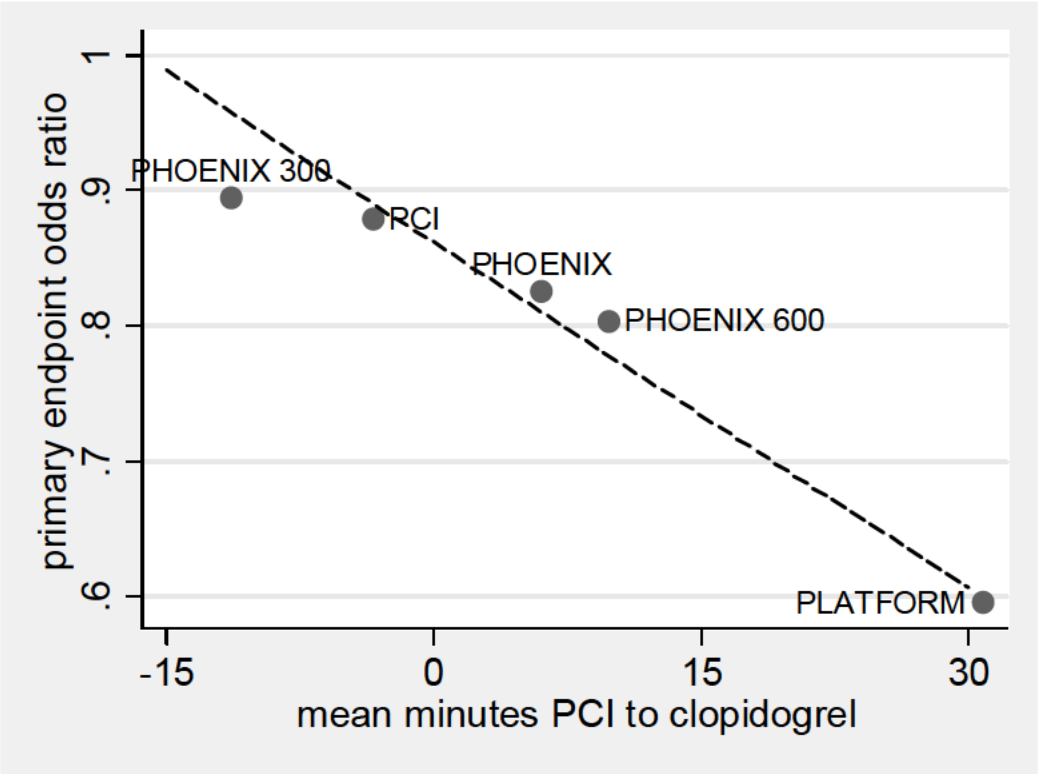
**Figure 4: Primary Endpoint Odds Ratios vs. Mean Clopidogrel Timing in the Stable Angina Subgroups of the CHAMPION Trials**




* negative numbers represent clopidogrel loaded pre-PCI; broken line is a least squares regression line of the three trials, i.e., not including the PHOENIX subgroups by loading dose

In Figure 4 I plotted only the stable angina subgroups because, as the applicant and principal investigators have proposed, the primary endpoint adjudication was flawed in PCI and PLATFORM in patients with elevated cardiac biomarkers at baseline, i.e., in the UA/NSTEMI and STEMI subgroups. I also include points for the subgroups loaded with 300 mg and 600 mg because efficacy may vary by loading dosage and, as Figure 4 suggests, patients loaded with 300 mg were loaded predominantly before PCI while patients loaded with 600 mg had variable timing, about 50% pre-PCI and 50% later.

*COMMENT: The PHOENIX primary endpoint results seem very consistent with the PCI and PLATFORM results when compared by clopidogrel timing. The results in the PHOENIX subgroups by 300 and 600 mg loading doses also suggest that 600 mg clopidogrel loading is more effective than 300 mg when the results are adjusted for the correlated clopidogrel timing.*

While the adjudicated primary endpoints in PCI and PLATFORM were problematic, the site-reported events should not share their limitations. I show



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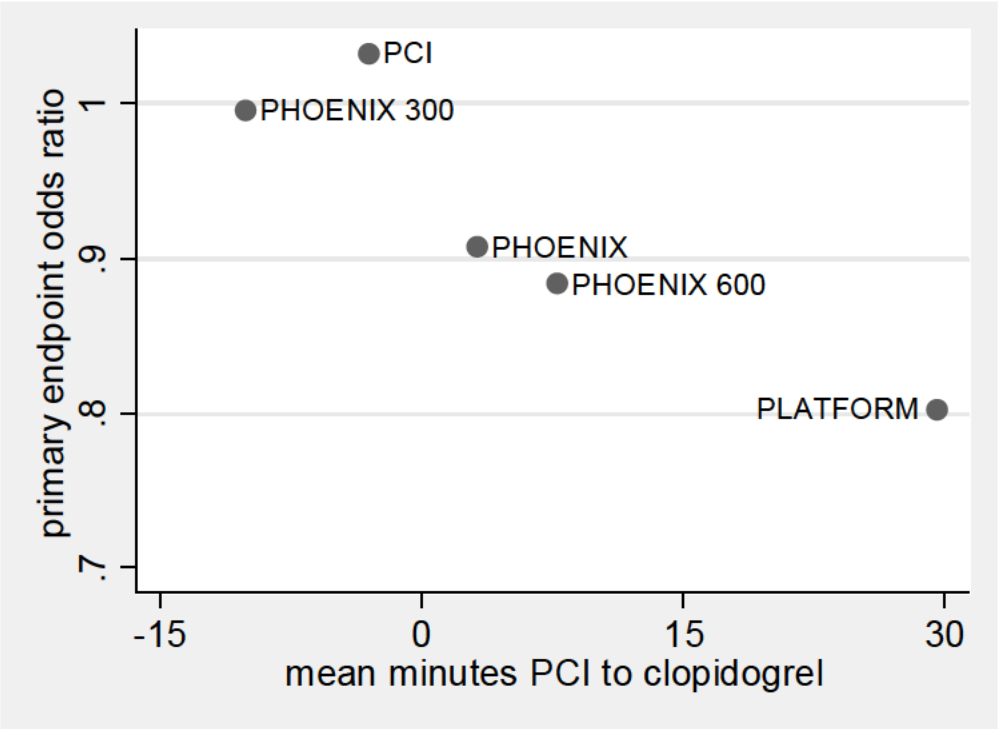
a scatterplot of the site-reported primary endpoint ORs vs. mean clopidogrel timing for all patients in the CHAMPION trials in Figure 5.

**Figure 5: Primary Endpoint Odds Ratios vs. Mean Clopidogrel Timing in the Stable Angina Subgroups of the CHAMPION Trials**




* negative numbers represent clopidogrel loaded pre-PCI

The results for site-reported endpoints vs. clopidogrel timing for all patients are also consistent among the three trials and PHOENIX loading dose subgroups.

*COMMENT: The results in Figure 5 at the left for the pre-PCI loading suggest that clopidogrel may be superior to cangrelor at mean administration times 5 or more minutes prior to PCI. From CHAMPION it is unclear that cangrelor is superior to clopidogrel if clopidogrel had been administered hours before PCI as, for example, the European guidelines recommend.*

7.1.6.1.3. Clopidogrel timing within PHOENIX

Interpreting clopidogrel timing within PHOENIX is more problematic than the cross-trial comparisons because investigators were allowed some discretion in timing and loading dosage. We do not know what patient characteristics they considered. In my AC presentation I briefly discussed two confounding factors evident in the data: (1) Investigators administered 300 mg loading doses predominantly pre-PCI while timing of 600 mg loading was variable. (2) Loading dosages used were correlated with sites and, for bleeding, reported rates of bleeding varied substantially by sites grouped by loading dose.



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Because clopidogrel timing only varied in the clopidogrel arm, to explore clopidogrel timing I focused my analyses for my benefit-risk review on the clopidogrel arm. I tried to control for confounding factors by performing logistic regression. I show in Table 3 the logistic regression that I judged to represent best the effects of clopidogrel timing and loading dose upon efficacy.

**Table 3: Logistic Regression of the Sponsor's Primary Endpoint at 48 Hours in the Clopidogrel Arm of PHOENIX**

```
Logistic regression                               Number of obs   =       5440
                                                  LR chi2(5)      =      35.17
                                                  Prob > chi2     =     0.0000
Log likelihood = -1179.9515                       Pseudo R2       =     0.0147

------------------------------------------------------------------------------
      pep48h | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
 600 mg load |   .6272858    .086665    -3.38   0.001     .4784808    .8223682
         age |   1.012741   .0055211     2.32   0.020     1.001977     1.02362
    diabetes |   .8068125   .1090964    -1.59   0.112     .6189763     1.05165
      angina |   1.615914   .2090219     3.71   0.000     1.254046    2.082202
  hrs to PCI |   .6894119   .1077956    -2.38   0.017     .5074414    .9366378
       _cons |   .0287312   .0106205    -9.60   0.000     .0139222    .0592926
------------------------------------------------------------------------------
```

By the logistic regression in Table 3 both a 600 mg loading dose and early administration of clopidogrel are associated with better outcomes.

*COMMENT: The major limitation of the analyses of clopidogrel timing in PHOENIX is that the timing was not randomized. There may be other confounding factors that explain the ORs in Table 3 other than loading dosage or clopidogrel timing. The applicant has submitted other logistic regressions that challenge my conclusions above. Some of the applicant's arguments appear reasonable, so I plan to address them in an addendum to this review. Because I judge that the PCI to PLATFORM comparison is the best evidence supporting that delaying clopidogrel use is bad and because the three trial comparisons by clopidogrel appear consistent, I do not rely upon the analyses of clopidogrel timing within PHOENIX to make a recommendation of a complete response.*

7.1.6.2. Severity of events in the primary composite endpoint

The primary clinical reviews (initial and addendum) address the details of the types of events included in the adjudicated primary endpoint. However, there are some simple statistics that summarize for me the clinical severity of the adjudicated composite endpoints. I show the primary endpoint rates, both adjudicated and site-reported, for PHOENIX by index event type in Table 4.

**Table 4: Primary Endpoint Rates by Index Event in PHOENIX**

| index event | adjudicated | | site-reported | |
|---|---|---|---|---|
| | clopidogrel | cangrelor | clopidogrel | cangrelor |
| angina | 6.8% | 5.7% | 2.1% | 1.8% |
| UA/NSTEMI | 5.7% | 3.6% | 2.6% | 2.2% |



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| index event | adjudicated | | site-reported | |
|---|---|---|---|---|
| | clopidogrel | cangrelor | clopidogrel | cangrelor |
| STEMI | 2.8% | 2.8% | 2.3% | 2.8% |
| all | 5.8% | 4.7% | 2.3% | 2.1% |

The index event classification ("patient type" by the applicant's terminology) in Table 4 is the classification entered by the sites in the IVRS at the time of randomization. The applicant presents the data by a "derived" patient type that is different than the IVRS entry and not defined in the protocol or in the statistical analysis plan.

The adjudicated primary endpoint rates are substantially higher in the stable angina subgroup than in the STEMI subgroup. The site-reported event rates are similar.

*COMMENT: Adjudicated event rates of 6% at 48 hours seem high for clinically overt problems in stable angina patients undergoing elective PCI. The primary clinical reviews document the rates of MIs adjudicated based on biomarker elevations and of angiographically-diagnosed intraprocedural stent thromboses. While I believe the adjudicated endpoints are useful for evaluations of antiplatelet effect, the site-reported endpoint rates are preferable for evaluations of benefit-risk.*

7.1.6.3. Exclusive use of 600 mg loading dose with cangrelor

*COMMENT: I included a detailed discussion of the effects of the differential clopidogrel loading doses in my benefit-risk review. I presented some of the differences related to efficacy in Section 7.1.6.1. The 600 mg clopidogrel loading dose appears to be slightly more effective than the 300 mg loading dose at the expense of slightly more bleeding. The exclusive use of the 600 mg loading dose in the cangrelor arm may explain some of the "superiority" of cangrelor.*

7.1.6.4. Uncertain benefit in STEMI

Clinical practice treats STEMI differently than other ACS: We believe "time is muscle" and rush the patient to PCI. Similarly, the CHAMPION trials, while specifying mandatory delays of clopidogrel loading for other ACS conditions, allowed immediate randomization and clopidogrel loading in STEMI. Furthermore, other recent antiplatelet effects have suggested differential benefits of different antiplatelet agents in STEMI: Prasugrel in TRITON showed a short-term mortality benefit in STEMI while ticagrelor in PLATO showed worse short-term mortality for STEMI patients treated with early PCI.

I show the endpoint rates for STEMI in PHOENIX in Table 4. For STEMI the point estimates for the adjudicated endpoint rates in the two arms are approximately the same while the site-reported endpoint rate of the cangrelor arm is higher than that for the clopidogrel arm.



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The PCI trial also enrolled STEMI patients. I show selected statistics comparing PCI and PHOENIX for STEMI patients in Table 5.

**Table 5: Selected Statistics for the STEMI Subgroups of PCI and PHOENIX**

| | PCI | PHOENIX |
|---|---|---|
| N | 996 | 1,803 |
| Clopidogrel post-angio | 79% | 71% |
| Adjudicated endpoint OR | 1.05 | 1.00 |
| Site-reported endpoint OR | 0.74 | 1.25 |

Clopidogrel loading was usually delayed until after angiography in both trials despite the protocols allowing earlier loading. While the point estimate of adjudicated endpoint OR for STEMI patients in PCI was slightly unfavorable for cangrelor the site-reported OR is favorable.

*COMMENT: The CHAMPION trials do not provide substantial evidence that, even with delayed clopidogrel loading, cangrelor is noninferior to clopidogrel in STEMI patients. Because STEMI is one of the conditions for which the desirable characteristics of cangrelor would be beneficial and therefore one of the conditions for which cangrelor is likely to be used, the neutral results for STEMI is another reason for insisting upon another trial with adequate STEMI representation prior to approval.*

7.1.6.5. Clopidogrel overencapsulation

All oral study drug in all three CHAMPION trials consisted of overencapsulated commercial clopidogrel tablets or microcellulose-filled dummy capsules. This approach does make it simple to unblind patients at the site (i.e., break open a capsule), but unblinding is only one of the concerns for this approach to blinding. The other is that the overencapsulation can affect the rate or completion of absorption of the study drug. We communicated both of these concerns to the applicant in a letter dated September 9, 2010, prior to PHOENIX enrollment:

> "You propose to provide clopidogrel or placebo in an over-encapsulated form. We believe it is easy for the investigators or the subjects to un-blind the study drug by opening the capsule. We suggest you instead use a placebo tablet. If you choose to provide clopidogrel in over-encapsulated forms, you should demonstrate bioequivalence of the study drug to clopidogrel tablet."

Despite this advice the applicant submitted the NDA without any data regarding bioequivalence of the study drug to clopidogrel tablet. When requested to provide such data, the applicant initially submitted a two page unsigned document briefly summarizing a dissolution study in acid media alleging complete dissolution of overencapsulated clopidogrel tablets at 30 minutes. The study apparently did not use actual clinical supplies from any of the CHAMPION trials. In response to



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further requests the applicant provided a more complete report of the same or similar study.

*COMMENT: We do accept dissolution studies for some oral formulations as evidence of bioequivalence of overencapsulated products. However, the actual clinical supplies should be used, multiple dissolution media may be required, and the studies should be rigorously performed and documented. This issue is another issue that must be resolved prior to approval.*

## 7.2. Safety

### 7.2.1. General safety considerations

The major safety concern for cangrelor is bleeding. Reversible $P2Y_{12}$ inhibitors that are ADP or ATP analogs have also been associated with dyspnea. Renal toxicity is also a theoretical concern based on the preclinical findings.

### 7.2.2. Safety findings

The most pertinent safety findings from the primary clinical review are the following:

- Four patients in the cangrelor arm of PHOENIX had a bleed and died within 48 hours of study drug initiation: 2 cardiac tamponades, an upper gastrointestinal bleed, and a patient with hematuria who then suffered a cardiac arrest and renal failure. Another cangrelor patient experienced shock 15 minutes after the end of infusion, had a retroperitoneal bleed, and died 4 days later.

- Overall bleeding was 42% greater in cangrelor treated subjects compared to clopidogrel treated subjects.

- The primary safety endpoint in the BRIDGE trial was CABG-related bleeds. The rates were similar in the two arms (cangrelor 11.8% vs. placebo 10.4%).

- Dyspnea was more frequent with cangrelor (1.3% vs. 0.4% control). The median onset time was 2 hours. In the CHAMPION trials discontinuation was attributed to dyspnea in 10 cangrelor vs. 1 clopidogrel patient.

- Renal function adverse events were more frequent with cangrelor (0.7%) then with control (0.5%).

*COMMENT: Bleeding is clearly greater with the cangrelor regimen than with clopidogrel alone and is the major safety concern. Regarding the PCI indication, serious bleeds are still rare such that they would be tolerable if cangrelor were clearly superior in efficacy to clopidogrel. The latter is not supported by the CHAMPION trial data. Regarding the bridging indication, BRIDGE does not establish (and was*



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*undersized to establish) that extended cangrelor use has a favorable safety or benefit-risk profile.*

7.2.3. Safety update

The 120-day safety update consists of a study report for a study of transitioning from cangrelor to prasugrel and from prasugrel to cangrelor in 12 patients. There were two minor adverse events reported.

7.2.4. Immunogenicity

Immunogenicity is not a significant concern for this small molecule.

7.2.5. Special safety concerns

Dyspnea and potential renal toxicity are special safety concerns that I discuss in Sections 4 and 7.2.2

7.2.6. Primary reviewers' comments and conclusions

The primary clinical reviewers, Drs. Senatore and Beasley, recommend approval for the PCI indication. They discuss safety with regard to approval in the context of a risk-benefit assessment. Their summary is the following:

> "In summary, the risk-benefit evaluation yielded mixed results. The benefit outweighed the risk using GUSTO, TIMI, and Bad Bleed criteria. One might consider these bleeds to be of greater clinical import. The risk outweighed the benefit in using all non-CABG bleeding and ACUITY major bleed. All non-CABG bleeding captured minor bleeds and a large component of the ACUITY major bleeds included hematomas. Thus, one might consider these bleeds to be of less clinical consequence. In conclusion, there was a marginal benefit over risk for the use of cangrelor in the PCI setting driven by periprocedural MI."

The primary clinical reviewers recommend a complete response for the bridging indication. The basis for this recommendation is based on uncertain need and efficacy rather than safety.

*COMMENT: Regarding the PCI indication, my assessment of risk-benefit is based on my conclusion that, if the effects of delaying clopidogrel are taken into account, there is no benefit of cangrelor when clopidogrel is loaded prior to PCI or earlier. Regarding the bridging indication, I agree that the benefit for bridging has not been established.*

7.2.7. Discussion of notable safety issues

There are no other notable safety issues.



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## 8. Advisory Committee Meeting

We presented cangrelor at the February 12, 2014, meeting of the Cardiovascular and Renal Drugs Advisory Committee (AC). The AC members voted 7 to 2 against approval of the PCI indication. The members who voted against approval indicated concern about the design of CHAMPION and about the two earlier negative trials (PLATFORM and PCI) and felt that the increased risk of bleeding was not outweighed by the small clinical benefit. Those who voted for approval stated that, despite issues with trial design, the trial was practical, showed net clinical benefit, and the primary endpoint was clinically significant.

The members voted 9 to 0 against approval of the bridging indication. They commented on the need for clinical data and a better sense of the unmet need.

## 9. Other Relevant Regulatory Issues

I stated the following in a review of the ethicalness of the cangrelor development program:

> "The ethicalness of all three trials is questionable because all three protocols specified delaying the use of clopidogrel to varying degrees. One of the two earlier trials, PLATFORM, delayed clopidogrel use until after the PCI; PLATFORM showed dramatically higher rates of stent thrombosis and of death in the clopidogrel arm. The last trial, PHOENIX, was unethical because it delayed use of clopidogrel until after coronary angiography or later and because it prohibited routine use of prasugrel, ticagrelor, and glycoprotein IIb/IIIa inhibitors (GPIs). The PHOENIX informed consent documents (ICDs) failed to inform patients regarding the advantages of earlier use of clopidogrel and the use of prasugrel, ticagrelor, and GPIs. The patients in PHOENIX were not informed about 'appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject' as required by 21 CFR §50.25."

The relevance to approvability is the question of whether we should refuse approval based on ethical considerations alone per 21 CFR §314.125(b)(16). My ethics review discusses most of the evidence regarding the ethicalness of the trials in detail and I will not repeat the evidence presented in that review and my discussion of approvability here.

There is one issue related to the ethicalness for which we have more information in addition to that discussed at the February 12, 2014, AC meeting: Whether the applicant and principal investigators were familiar with site practices and the sites followed their standard practices in PHOENIX. At that meeting the principal co-investigator Dr. Robert Harrington stated regarding PHOENIX that "We wanted to use clopidogrel as it was in the label at that time, as it was in the guidelines, and as it was being done already at the sites. . . the trial was overseen by academic clinical cardiologists very familiar with the practice of the local regions as well as at the particular sites."

The PHOENIX protocol states in Section 1.3 Study Rationale that "The comparator is clopidogrel standard of care. In line with guidelines and common practice, it is expected that



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the majority of patients will receive 600 mg loading dose given as soon as possible after randomization per investigator's discretion." The phrase "per investigator's discretion" was added in a pre-trial amendment with the following rationale: "Clarify language to assure that investigator's follow their standard approach to patients undergoing PCI." About 23% of patients had a 600 mg loading dose given within 10 minutes of randomization.

*COMMENT: One problem is that "clopidogrel as it was in the label" is not accurate: The US label has neither an indication for elective PCI in stable angina nor a recommendation for a 600 mg loading dose. However, both of these practices are common off-label uses and arguably standard of care. Regarding timing of clopidogrel, the US label does not explicitly state a loading time requirement but in CURE (the one trial supporting the indication for UA/NSTEMI, including PCI) clopidogrel was administered immediately after randomization without delaying for angiography.*

*Similarly, "as it was in the guidelines" is also not accurate. I discussed the inconsistencies between the CHAMPION trials and the US and European guidelines in my review of the ethicalness of the cangrelor program and I will not repeat those detailed discussions here.*

*Finally, given that the protocol projects that majority of patients will receive a 600 mg loading dose as soon as possible after randomization while the PHOENIX results document that about 23% of patients had a 600 mg loading dose given within 10 minutes of randomization, the protocol writers and principal investigators either did not understand common practice at the sites or the sites did not adhere to their common practices in PHOENIX.*

Another source of evidence for common practices should be the comparison of clopidogrel statistics at the PHOENIX sites that were also PCI or PLATFORM sites to their clopidogrel statistics in PCI and PLATFORM. A slide presented at the January 2013 PHOENIX Executive Committee Update listed that "Approx. 70% were CHAMPION sites." To perform the site comparisons I requested a dataset from the applicant identifying the sites in common among the three CHAMPION trials. The applicant submitted a dataset in which about 54% of the PHOENIX sites were matched to CHAMPION sites. When we queried the applicant about the discrepancy between the January 2013 slide and the dataset the applicant responded that the dataset was correct and the slide was in error. However, I examined the site names and identified 8 additional PHOENIX sites that appeared to match PCI or PLATFORM sites. The applicant is checking the discrepancies but had not submitted the verification of sites in time for this review.

**10. Financial Disclosure**

The primary clinical review describes that the applicant has certified that there are no financial arrangements with investigators defined by the regulations as potentially jeopardizing the integrity of the trial results.



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## 11. Labeling

### 11.1. Proprietary name

The latest proposed proprietary name Kengreal is under review. I have no objections to the name.

### 11.2. Physician labeling

Because I am not recommending approval I have no physician labeling recommendations at this time.

### 11.3. Carton and immediate container labeling

Because I am not recommending approval I have no carton and container labeling recommendations at this time.

### 11.4. Patient labeling/medication guide

Because I am not recommending approval I have no carton and container labeling recommendations at this time.

## 12. OSI Audits

OSI audited six sites. For one site OSI issued a VAI letter but recommended that the data are acceptable in support of the claimed indication.

## 13. Conclusions and Recommendations

### 13.1. Recommended regulatory action

Regarding the PCI indication I recommend a complete response. My main reason for this recommendation is that the CHAMPION program did not establish that cangrelor is superior to clopidogrel given after angiography but prior to PCI. The efficacy in STEMI patients is even more uncertain; STEMI patients are the better candidates for cangrelor use in clinical practice than the stable angina patients that comprised the majority of PHOENIX patients. It is unclear whether cangrelor would be inferior to clopidogrel given earlier. There is not substantial evidence that cangrelor is as effective as existing, approved therapies including clopidogrel given early, prasugrel, ticagrelor, and GPIs. Given the increased bleeding, the benefit-risk for cangrelor is unfavorable. There are other reasons for recommending a complete response that I discuss throughout this review.

Regarding the bridging indication I also recommend a complete response. BRIDGE was inadequate to establish the clinical benefit-risk. A clinical outcomes study is both feasible and needed prior to approval.



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13.2. Safety concerns to be followed postmarketing

Because I am not recommending approval I have no recommendations for safety concerns to be followed postmarketing.

13.3. Risk Minimization Plan

Because I am not recommending approval I have no recommendations for a risk minimization plan.

13.4. Postmarketing studies

Because I am not recommending approval I have no recommendations for postmarketing studies.

13.5. Comments to be conveyed to the applicant

We have had extensive discussions with about the major issues arguing against approval at the AC meeting and in teleconferences and meetings. We should summarize them again in a complete response letter.



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THOMAS A MARCINIAK
03/23/2014

# DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

| | |
|---|---|
| **NDA**: | 204958 |
| **Drug:** | Cangrelor |
| **Applicant:** | The Medicines Company |
| **Proposed Indication:** | **PCI** |
| | Cangrelor for injection is an intravenous (IV) $P2Y_{12}$ platelet inhibitor indicated for the reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI) [see *Clinical Studies* (14.1)]. In CHAMPION PHOENIX, cangrelor significantly reduced (relative risk reduction [RRR] 22%) the primary composite endpoint of all-cause mortality, myocardial infarction (MI), ischemia driven revascularization (IDR), and stent thrombosis (ST) compared to clopidogrel [see *Clinical Studies* (14.1)]. |
| | **Bridging** |
| | Cangrelor for injection) is indicated to maintain $P2Y_{12}$ inhibition in patients with acute coronary syndromes (ACS) or patients with stents who are at increased risk for thrombotic events (such as stent thrombosis) when oral $P2Y_{12}$ therapy is interrupted due to surgery [see *Clinical Studies* (14.2)]. |
| **Subject:** | Addenda to the *Benefit-risk of Cangrelor Review, the Clinical Review, the Statistical Review, the Clinical Pharmacology Review*, and *The Ethicalness of the Cangrelor Development Program* Review |

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The following tables and figures in the briefing book should be attributed as follows:

<u>Benefit-risk of Cangrelor</u>

- The following tables should have been noted as "created by the FDA":
  - Table 1 (pg.4)
  - Table 2 (pg.5)
    Table 4 (pg.7)
  - Tables on pg. 8 – 20

- The following tables should have contained these citations:
  - Table (not numbered) (on pg.6) – This table was copied from the New England Journal of Medicine publication. This publication was cited in the paragraph that precedes the table.

- Table 25 (pg.7) - This table was copied from TMC CAN-10-01 (CHAMPION PHOENIX) clinical study report. This citation appeared in the paragraph that precedes the table.

Clinical Summary

- The following figures and tables should have contained these citations:
  - Figure 1 (pg.14): retrieved from Google search on molecular structure images
  - Figure 2 (pg.28): taken from CSR TMC-CAN-05-02 (CHAMPION PCI), Figure 1, page 27
  - Figure 3 (pg.30): taken from CSR TMC-CAN-05-03 (CHAMPION PLATFORM), Figure 1, page 28
  - Figure 4 (pg.33): taken from Protocol TMC CAN-10-01 (CHAMPION PHOENIX), Figure 2, page 21
  - Table 5 (pg.49): taken from CSR TMC-CAN-10-01 (CHAMPION PHOENIX), section 10.3, Table 8, page 90
  - Table 15 (pg.67-68): Table 15 was produced by the primary reviewer
  - Table 16 (pg.69-70): Table 16 was produced by the primary reviewer
  - Table 17 (pg.74-76): Table 17 was produced by the primary reviewer
  - Table 18 (pg. 77-78): Table 18 was produced by the primary reviewer
  - Table 19 (pg.79): taken from Brener, S, et al., 2013, Intraprocedural Stent Thrombosis, JACC: Cardiovascular Interventions, 6(1): 36-43, Table 1
  - Table 20 (pg.80): taken from Brener, S, et al., 2013, Intraprocedural Stent Thrombosis, JACC: Cardiovascular Interventions, 6(1): 36-43, Table 2
  - Tables 66 - 70 (pg. 168 - 170): Tables 66-70 were created by the primary reviewer.
  - "Definition of myocardial infarction" (pg. 171): taken from Thygesen, K, et al., 2007, Universal Definition of Myocardial Infarction, Circulation, 116: 2634-2653, Abstract Summary Table (page 2365)
  - "Clinical classification of different types of myocardial infarction" (pg.172); taken from Thygesen, K, et al., 2007, Universal Definition of Myocardial Infarction, Circulation, 116: 2634-2653, Table 1
  - Tables on pg. 173 – 175:
    - Endpoint Definitions: taken from CEC Charter, Final version 2.0, 20 SEPT 2012, Table 2, page 21
    - Stent Thrombosis: taken from Cutlip, D, et al., 2007, Clinical Endpoint in Coronary Stent Trials, Circulation, 115: 2344-2351, Table 6
    - Definite, Probable, and Possible Stent Thrombosis: taken from Cutlip, D, et al., 2007, Clinical Endpoint in Coronary Stent Trials, Circulation, 115: 2344-2351, Table 7

- In the Clinical Summary Section of the CDRAC Briefing Document, the following clarifications are made herewith:
  - Figure 1 (page 14) illustrates molecular structures of ATP and cangrelor retrieved from a Google molecular image search.
  - Figure 2 (page 28) was taken from CSR TMC-CAN-05-02 (CHAMPION PCI), CSR Figure 1, page 27
  - Figure 3 (pg.30) was taken from CSR TMC-CAN-05-03 (CHAMPION PLATFORM), CSR Figure 1, page 28
  - Figure 4 (pg.33): was taken from Protocol TMC CAN-10-01 (CHAMPION PHOENIX), Protocol Figure 2, page 21
  - Table 5 (pg.49) was taken from CSR TMC-CAN-10-01 (CHAMPION PHOENIX), section 10.3, CSR Table 8, page 90

- Table 19 (pg.79) was taken from Brener, S, et al., 2013, Intraprocedural Stent Thrombosis, JACC: Cardiovascular Interventions, 6(1): 36-43, article Table 1
- Table 20 (pg.80) was taken from Brener, S, et al., 2013, Intraprocedural Stent Thrombosis, JACC: Cardiovascular Interventions, 6(1): 36-43, article Table 2
- "Definition of myocardial infarction" (pg. 171) was taken from Thygesen, K, et al., 2007, Universal Definition of Myocardial Infarction, Circulation, 116: 2634-2653, Abstract Summary Table (page 2365)
- "Clinical classification of different types of myocardial infarction" (pg.172) was taken from Thygesen, K, et al., 2007, Universal Definition of Myocardial Infarction, Circulation, 116: 2634-2653, article Table 1
- Tables on pg. 173 – 175:
  - Endpoint Definitions was taken from the CEC Charter, Final version 2.0, 20 SEPT 2012, Charter Table 2, page 21
  - Stent Thrombosis was taken from Cutlip, D, et al., 2007, Clinical Endpoint in Coronary Stent Trials, Circulation, 115: 2344-2351, article Table 6
  - Definite, Probable, and Possible Stent Thrombosis was taken from Cutlip, D, et al., 2007, Clinical Endpoint in Coronary Stent Trials, Circulation, 115: 2344-2351, article Table 7

Statistical Summary

- The following tables and figures should have been noted as "created by the FDA":
  - Tables 4 & 6 (pg.11)
  - Table 7 (pg.12)
  - Figure 3 (pg.17)
  - Tables 12&13 (pg.18)
  - Figure 4 (pg.20)
  - Table 18 (pg.22)
  - Figure 5 (pg.23)

- Page 25 of the statistical summary was intentionally left blank.

Clinical Pharmacology Review

- The following figures should have contained these citations:
  - Figure 1 (pg.9) - Figure 1A – Chemical Structure of ATP from Google web search: http://www.google.com/patents/WO2003076333A2?cl=en
    Figure 1B – Chemical Structure of cangrelor from Section 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods, Page 10
  - Figure 3 (pg.13) - Section 2.7.3 Summary of Clinical Efficacy, Page 12

- The following tables and figures should have been noted as "created by the FDA":
  - Figure 4 (pg.15)
  - Figure 5 and Table 1 (pg.16)
  - Figure 6 (pg.17)
  - Figure 7 (pg.18)
  - Figure 8 (pg.19)
  - Figure 11 -12 (pg.28)
  - Figure 13 (pg.29)
  - Figure 14 (pg.31)
  - Figure 15 (pg.32)
  - Table 4 (pg.33)

Ethicalness of the Cangrelor Development Program

- The following figure should have been noted as not being created by the FDA
  - Figure 2 (pg.27)

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/s/

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ALISON L BLAUS
01/31/2014

JIALU ZHANG
01/31/2014

SREEDHARAN N SABARINATH
01/31/2014

FORTUNATO F SENATORE
01/31/2014

THOMAS A MARCINIAK
01/31/2014

# CLINICAL REVIEW

| | |
|---|---|
| **Application Type** | **NDA** |
| **Application Number(s)** | **204958** |
| **Priority or Standard** | **Standard** |
| | |
| **Submit Date** | **01 May 2013** |
| **Received Date** | **02 May 2013** |
| **PDUFA Goal Date** | **30 Apr 2014** |
| **Division / Office** | **DCaRP/ODE I** |
| | |
| **Reviewer Names** | **Fred Senatore MD, PhD, FACC** |
| | **B. Nhi Beasley Pharm.D.** |
| **Review Completion Date** | **13 January 2014** |
| | |
| **Established Name** | **To be determined** |
| **(Proposed) Trade Name** | **To be determined** |
| **Therapeutic Class** | **$P2Y_{12}$ receptor antagonist** |
| **Applicant** | **The Medicines Company** |
| | |
| **Formulation(s)** | **intravenous** |

| | |
|---|---|
| **Dosing Regimen** | **A. 30 ug/kg IV bolus, followed by 4 ug/kg/min x 2 hours (PCI)**<br><br>**B. 0.75 ug/kg/min IV infusion for up to 7 days (Bridging)** |
| **Indication(s)** | ***A. Reduction of thrombotic CV events (including stent thrombosis) in patients with CAD undergoing PCI***<br><br>***B. Maintain P2Y12 inhibition in ACS patients or patients with stents who are at increased risk for thrombotic events when oral P2Y12 therapy is interrupted due to surgery*** |
| **Intended Population(s)** | ***A. Patients with CAD undergoing PCI.***<br><br>***B. Patients scheduled to undergo CABG.*** |

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**List of Abbreviations**

| | |
|---|---|
| ACC | American College of Cardiology |
| ACCF | American College of Cardiology Foundation |
| ACUITY | Acute Catheterization and Urgent Intervention Triage Strategy |
| ACS | Acute Coronary Syndrome |
| ADP | Adenosine Di Phosphate |
| AE | Adverse Event |
| AHA | American Heart Association |
| ARC | Academic Research Consortium |
| ARC-ST | ARC-defined ST |
| AUC | Area Under the Curve |
| BARC | Bleeding Academic Research Consortium |
| BMI | Body Mass Index |
| BMS | Bare Metal Stent |
| CABG | Coronary Artery Bypass Graft Surgery |
| CAD | Coronary Artery Disease |
| CAPRIE | Clopidogrel in UA to Prevent Recurrent Ischemic Events |
| CHAMPION | Cangrelor versus standard therapy to achieve optimal management of platelet inhibition |
| CLARITY | Clopidogrel as Adjunctive Reperfusion Therapy |
| CEC | Clinical Events Committee |
| CREDO | Clopidogrel for Reduction of Events During Observation |
| CSR | clinical study report |
| CI | Confidence Interval |
| CTD | Common Technical Document |
| DAPT | Dual Antiplatelet Therapy |
| DES | Drug Eluting Stent |
| EFD | Embryo-Fetal Development |
| Eight(8)-SPT | 8-p-sulophenyl theophylline (non-selective P1-purinoceptor antagonist) |
| FPI | First Patient In (i.e. first patient enrolled) |
| GCP | Good Clinical Practice |
| GPI | Glycoprotein IIb/IIIa Inhibitor |
| HORIZONS-AMI | Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction |
| HR | Hazard ratio |
| HTPR | High On-Treatment Platelet Reactivity |
| IARC | Interim Analysis Review Committee |
| $IC_{50}$ | Concentration resulting in 50% inhibition |
| ICH | Intracranial Hemorrhage |
| $ID_{50}$ | Dose resulting in 50% inhibition |
| IDR | Ischemic-Driven Revascularization |
| IPA | Inhibition of Platelet Aggregation |
| IPST | Intra-Procedural Stent Thrombosis |
| ISE | Integrated Summary of Efficacy |
| ISS | Integrated Summary of Safety |
| ITT | Intention to Treat population |
| IV | Intravenous |
| IVRS | Interactive Voice Response System |
| LAD | Left Anterior Descending Coronary Artery |
| LCX | Left Circumflex Coronary Artery |
| LMWH | Low Molecular Weight Heparin |
| LOE | Level of Evidence |
| LPO | Last Patient Out (i.e. last patient completing the study) |
| LVEF | Left Ventricular Ejection Fraction |
| MACE | Major Adverse Cardiac Event |
| MI | Myocardial Infarction |
| mITT | Modified Intention To Treat population |
| N/A | Not Applicable |
| NDA | New Drug Application |
| NOAEL | No Adverse Event Level |



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| | |
|---|---|
| NPV | Negative Predictive Value |
| NSTEACS | Non-ST segment elevation acute coronary syndrome |
| NSTEMI | Non-ST segment elevation myocardial infarction |
| OR | Odds Ratio |
| P (int) | P value of interaction using Breslow-Day test |
| PAD | Peripheral Arterial Disease |
| PCI | Percutaneous Coronary Intervention |
| PD | Pharmacodynamic |
| PK | Pharmacokinetic |
| PP | Per Protocol population |
| PPI | Percent Platelet Inhibition |
| PPV | Positive Predictive Value |
| PRU | $P2Y_{12}$ or Platelet Reactivity Unit (interchangeable) |
| QC | Quality Control |
| QD | Once a day (i.e. scheduled administration of drug) |
| QWMI | Q-wave Myocardial Infarction |
| RCA | Right Coronary Artery |
| RCT | Randomized Clinical Trial |
| ROC | Receiver Operator Characteristic |
| RPR | Residual Platelet Reactivity |
| RR | Risk Reduction |
| SA | Stable Angina |
| SAP | Statistical Analysis Plan |
| SIHD | Stable Ischemic Heart Disease |
| ST | Stent Thrombosis |
| STEMI | ST segment elevation myocardial infarction |
| TEAE | Treatment-emergent adverse event |
| TIA | Transient Ischemic Attack |
| TIMI | Thrombolysis in Myocardial Infarction |
| TLR | Target Vessel Revascularization |
| TVR | Target Lesion Revascularization |
| UA | Unstable Angina |
| UDMI | Universal Definition Myocardial Infarction |
| URL | Upper Reference Limit |

# 1 Recommendations/Risk Benefit Assessment

## 1.1 Recommendation on Regulatory Action

PCI Indication: We recommend approval of cangrelor for the reduction of death, myocardial infarction, stent thrombosis, and ischemic driven revascularization in patients who have not been recently treated with a thienopyridine and who are undergoing percutaneous coronary intervention.

The basis of this recommendation is:

- The Applicant met the PHOENIX primary efficacy endpoint of Death, MI, IDR and ST for cangrelor vs. clopidogrel (OR 0.79; 95% CI [0.67, 0.93]; p=0.0053). However, the results were driven by ST and MI. There was no difference between the arms for death (OR 0.95, 95%CI 0.51, 1.75) and IDR (OR 0.76, 95%CI 0.47, 1.23). The ST endpoint was a composite of ARC-ST and IPST where IPST drove the results of the ST endpoint. The MI endpoint was a composite of UDMI types where type 4a MI drove the results of the MI component. The adjudication of type 4a and 4b MI required the diagnosis of type 1.The PHOENIX primary efficacy endpoint was carefully crafted following post-hoc analyses of the two previous failed phase 3 trials (PCI and PLATFORM) whose primary efficacy endpoints were all-cause death, MI, and IDR (see section 5.3.3)
- The PHOENIX primary efficacy endpoint remained significant following a sensitivity analysis that removed IPST events from the analysis (OR 0.80; 95% CI [0.67, 0.95]; p=0.0112).
    - The sensitivity analysis was performed because of a concern raised by the post-hoc introduction of the angiographic parameter IPST as a secondary endpoint in a protocol amendment. Although IPST was defined as a secondary endpoint, the Applicant incorporated IPST into the original ST component of the primary endpoint which was defined by the Academic Research Consortium (ARC-ST). This action produced symmetrical contradictions within the amended protocol and SAP as well as hybridizing the ARC-ST, which requires a clinical correlate, with the purely angiographic parameter. This post-hoc action also created a deficiency in the Angiographic Core Lab Charter whereby there was no description of the methodology to diagnosis IPST. Please see section 3.1 for details.
- We recognize that the imbalance in cangrelor treated subjects receiving clopidogrel 600 mg (98%) compared to clopidogrel treated subjects receiving 600 mg (74%) might have played a role in cangrelor achieving its efficacy endpoint. However, the clopidogrel label prescribes 300mg clopidogrel load. The ACCF/AHA 2012 Guidelines have stressed that the optimal clopidogrel loading dose has not been rigorously established and that trials examining the higher



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loading dose versus the standard dose (CURRENT-OASIS 7) have only generated a hypothesis suggesting a greater benefit for the higher dose.

- Although there was evidence of study drug administration after PCI in the CHAMPION programs, including the PHOENIX trial, the ACCF/AHA Guidelines suggested that symptomatic patients with evidence of ischemia referred for PCI might benefit from a clopidogrel load approximately 6-15 hours prior to PCI. However, it was emphasized that the basis of the suggestion was a non-significant trend from a subgroup analysis of the CREDO trial and that no comparison was made between a pre-PCI clopidogrel loading dose vs. a loading dose in the catheterization lab. The label does not specify the optimal timing of load in patients with either UA/NSTEMI or STEMI.
- Demonstrated safety, in particular bleeding risk, across the three large trials in PCI.

Bridge to Surgery Indication: We recommend a Complete Response to the proposed separate indication to maintain $P2Y_{12}$ inhibition in patients with acute coronary syndrome or with stents who are at increased risk for thrombotic events (such as stent thrombosis) when oral $P2Y_{12}$ Inhibitor therapy is interrupted due to surgery.

The basis of the recommendation to provide a Complete Response to a separate Bridging indication is:

- Lack of clinical data from BRIDGE to support the PD effect at the proposed Bridging dose.
- The clinical efficacy observed in the PHOENIX trial is not applicable to the Bridging indication because of the five-fold lower dose used in BRIDGE.
- Literature-based evidence suggesting no relationship between the PD effect from the VerifyNow PRU data and clinical outcome as well as inconsistent and conflicting results regarding pre-CABG $P2Y_{12}$ inhibition therapy.

## 1.2 Risk Benefit Assessment

The risk-benefit assessment was made by evaluating non-CABG bleeding events using various classifications: GUSTO (severe or moderate), TIMI (major or minor), ACUITY Major, and a hybrid bleeding classification (referred to as a “Bad Bleed”). Bad Bleed was defined as any of the following: intracranial hemorrhage, blood transfusion, cardiac tamponade, reoperation for bleeding, any surgical intervention, retroperitoneal bleed, or bleeding events requiring hospitalization or extension of hospitalization. The bleeding events based on the selected criteria were combined with efficacy parameters constructed in hierarchical format: death, death/ST, death/MI, death/MI/ST, and the primary efficacy endpoint (death/MI/ST/IDR) in order to obtain corresponding Risk Reductions and 95% Confidence Intervals.

Five tables shown in the Appendix (see **Section 9.1 Risk benefit tables**) delineate the hierarchical risk-benefit analysis using non-CABG bleeds and the 4 bleeding

classifications described above. In general, the risk-benefit evaluation was equivocal when applying various bleeding classifications to various hierarchical combinations of efficacy parameters. The risk significantly outweighed the benefit for all efficacy combinations for total non-CABG bleeding. The benefit significantly outweighed the risk when MI was combined with GUSTO (severe or moderate) bleed and death. The benefit numerically (non-significantly) outweighed the risk for all efficacy combinations applied to the TIMI (major or minor) bleeding classification except for TIMI bleed and death where the risk significantly outweighed the benefit. Conversely, the risk outweighed the benefit when using the ACUITY major classification in combination with any efficacy parameter (significant for death and death/ST, but non-significant for death/MI, death/MI/ST, and PEP). Similar to GUSTO, MI had an attenuating impact in reducing the risk relative to the benefit when using the ACUITY classification. Finally, the benefit numerically outweighed the risk for all hierarchical efficacy parameter combinations when using the “Bad Bleed” criteria, with the benefit bordering significant.

In summary, the risk-benefit evaluation yielded mixed results. The benefit outweighed the risk using GUSTO, TIMI, and Bad Bleed criteria. One might consider these bleeds to be of greater clinical import. The risk outweighed the benefit in using all non-CABG bleeding and ACUITY major bleed. All non-CABG bleeding captured minor bleeds and a large component of the ACUITY major bleeds included hematomas. Thus, one might consider these bleeds to be of less clinical consequence. In conclusion, there was a marginal benefit over risk for the use of cangrelor in the PCI setting driven by peri-procedural MI.

### 1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

### 1.4 Recommendations for Postmarket Requirements and Commitments

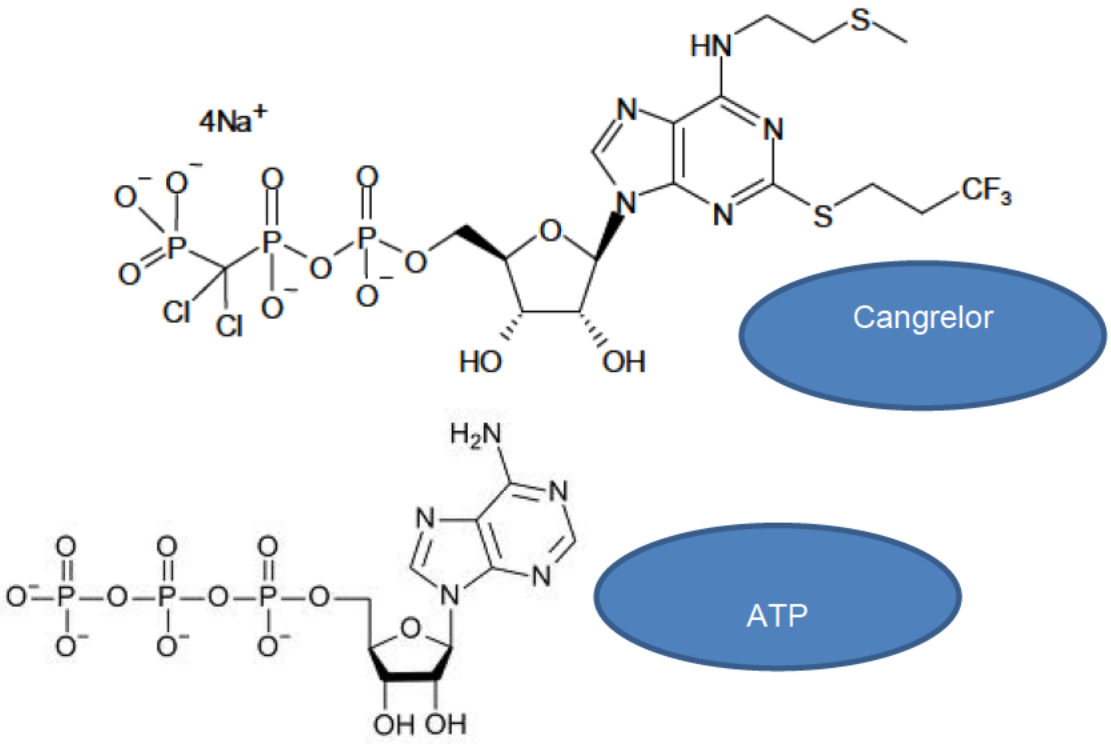
None

## 2 Introduction and Regulatory Background

### 2.1 Product Information

Cangrelor is an intravenous (IV), direct acting, reversible competitive inhibitor of $P2Y_{12}$ receptor that blocks adenosine diphosphate (ADP)-induced platelet activation and aggregation. Cangrelor has been identified as FPL-69931MX, ARL-69931MX, AR-C69931MX, The chemical name of cangrelor is tetrasodium salt of N6-[2-(methylthio) ethyl]-2-[(3, 3, 3 trifluoropropyl) thio]-5’-adenylic acid, monoanhydride with (dichloromethylene) bisphosphonic acid. Cangrelor is an ATP analogue (**Figure 1).**

**Figure 1. Molecular Structure of cangrelor and Corresponding Structure of ATP**




## 2.2 Tables of Currently Available Treatments for Proposed Indications

The five classes of approved anti-platelet drugs are described in **Table 1**. Prasugrel is the only agent which explicitly includes "stent thrombosis" in its indication. There are no drugs approved as a bridge to surgery.

**Table 1: Description of Currently Available Antiplatelet Agents approved in ACS**

| DRUG | Indication | Side Effects | Limitations |
|---|---|---|---|
| | | | |
| Clopidogrel (thienopyridine) | ACS (NSTEACS, NSTEMI, STEMI). Reduce combined endpoint of new ischemic stroke, new MI and other vascular death for patients with recent MI, stroke or established peripheral vascular disease. | Rash, neutropenia, TTP (rare) | Warning: diminished effectiveness in CYP2C19 poor metabolizers. |

| | | | |
|---|---|---|---|
| Prasugrel (thienopyridine) | Reduction of thrombotic CV events (including stent thrombosis) in patients with ACS managed with PCI (NSTEMI, STEMI-primary or delayed PCI). | Warning: enhanced bleeding risk (contraindicated in patients with active pathological bleeding, or history of Transient Ischemic Attack (TIA) or stroke; patients > 75 years, patients to undergo urgent CABG, bleeding diatheses). | More hemorrhagic side effects than clopidogrel. |
| Ticagrelor (nucleoside analogue) | Reduction of rate of thrombotic CV events in patients with ACS (UA, NSTEMI, STEMI). | Warning: contraindicated in patients with history of ICH, active pathological bleeding, severe hepatic impairment, hypersensitivity. | Dyspnea reported more frequently than with clopidogrel. Discontinuation increases the risk of MI, stent thrombosis, and death. |
| | | | |
| Dipyridamole (phosphodiesterase inhibitor) | Adjunctive therapy to coumarin anticoagulants in the prevention of post-operative thromboembolic complications of cardiac valve replacement. | GI toxicity, hypotension and blood pressure lability, flushing, headache, dizziness. | Benefit most evident in combination therapy. |
| Tirofiban (GPI) | In combination with heparin, treatment of patients with ACS, including patients undergoing medical management and PTCA or atherectomy. | Thrombocytopenia | Requires intravenous administration; not indicated for primary PCI. |
| Eptifibatide (GPI) | Prevention of death and MI in patients with UAP or NQWMI. As an adjunct to | Thrombocytopenia | Requires intravenous administration. |

| | | | |
|---|---|---|---|
| | PTCA with or without stent for the prevention of abrupt closure of a treated coronary vessel and related acute ischemic complications. | | |
| Abciximab (GPI) | Adjunct to PCI for the prevention of cardiac ischemic complications in patients undergoing PCI and in patients with UAP not responding to conventional medical therapy when PCI is planned within 24 hours. | Thrombocytopenia | Requires intravenous administration; not indicated for medical management. |

## 2.3 Availability of Proposed Active Ingredient in the United States

N/A

## 2.4 Important Safety Issues with Consideration to Related Drugs

As indicated in Table 1, an over-riding important safety issue with respect to related drugs is bleeding as a consequence of the antiplatelet mechanism of action. Specific safety issues with Thienopyridines are GI toxicity (ticlopidine), neutropenia and rare TTP (ticlopidine and clopidogrel), enhanced bleeding risk for prasugrel (greater risk than that of clopidogrel), and dyspnea for Ticagrelor (greater risk than that of clopidogrel). Common contra-indications for clopidogrel, prasugrel, and ticagrelor include active pathological bleeding and hypersensitivity. Prasugrel retains a contraindication in those with a prior TIA or stroke. Ticagrelor retains a contraindication in those with severe hepatic impairment and a history of intracranial hemorrhage (ICH).

Elinogrel, a $P2Y_{12}$ inhibitor, was being developed for the treatment of acute coronary syndrome and prevention of secondary thrombotic events. Elinogrel showed rapid inhibition of ADP-mediated platelet response and complete reversal within 24 hours of discontinuation. A randomized, double-blind dose ranging Phase 2b trial (Welsh, R, et al., 2012, INNOVATE-PCI) was conducted where 652 subjects received either oral clopidogrel load + maintenance, or IV Elinogrel load plus oral elinogrel maintenance.

TIMI major and minor bleeding was increased with elinogrel compared to clopidogrel (HR 1.98; 95% CI [1.10, 3.57]. There was an increased incidence of dyspnea (elinogrel 50/408 [12.3%] vs. Clopidogrel 8/208 [3.8%]) and liver transaminase elevations (elinogrel 18/408 [4.4%] vs. Clopidogrel 2/208 [1.0%]). The development of elinogrel was terminated by the Applicant, Novartis, in January 2012.

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

There were 8 meetings with the Applicant from 05 AUG 2005 (EOP2 Meeting) to 25 FEB 2013 (PHOENIX Top-line disclosure). The pre-NDA BRIDGE meeting occurred 20 NOV 2012.

Key items of advice, understanding, directive, agreement, or non-resolution between the Division and the Applicant were:

- CHAMPION PHOENIX focused on $P2Y_{12}$ naïve subjects. Patients undergoing PCI should be pretreated with clopidogrel as the standard of care.
- One clinical trial similar to the CHAMPION trials (i.e. PCI, PLATFORM) demonstrating a decrease in death/Q-MI/acute stent thrombosis is likely to be sufficient for a NDA submission.
- A priority review request would require evidence that cangrelor is superior to all available therapies. There is no data comparing cangrelor to either prasugrel or ticagrelor, both of which are superior to clopidogrel.
- BRIDGE and PHOENIX would be viewed as two separate indications.
- CHAMPION studies should be presented as individual trials and analyzed as specified in each protocol.
- The Division understood that neither thrombotic nor bleeding events were adjudicated in BRIDGE and requested the BRIDGE adjudication committee charter, all adjudication packages, and an adjudication data file.
- The Division requested that the Applicant review the value of using Verify-Now results for determining the type and dose of thienopyridine and other platelet $P2Y_{12}$ inhibitors. The Applicant agreed to provide relevant data in the dossier.
- The Division requested the Applicant calculate the actual event rate of stent thrombosis in those patients who discontinued clopidogrel and include information on whether the stent was a drug eluting stent (DES) or bare metal stent (BMS) as well as stent characteristics (diameter, length).
- From the GRAVITAS trial, post-PCI patients randomized to high or standard doses of clopidogrel had identical proportions of patients with death, MI, or stent thrombosis. Furthermore, the proportion of patients with GUSTO severe or major bleeding was higher in the group randomized to the standard dose of clopidogrel which had a higher level of PRU. This suggested that treatment-driven changes in Verify-Now based PRU results may not be useful in predicting the risk of either CV events or bleeding complications.



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- Antiplatelet drug approvals are not ordinarily based solely on antiplatelet activity measured ex-vivo.

### 2.6 Other Relevant Background Information

No other relevant clinical background.

## 3 Ethics and Good Clinical Practices

### 3.1 Submission Quality and Integrity

The submission quality and integrity was generally adequate. An endpoint ambiguity associated with the introduction of IPST and document inconsistencies were noted and communicated to the Applicant in the 74-day letter. The original protocol defined the primary efficacy endpoint as the composite of all-cause mortality, UDMI, IDR, and ST. The term ST was specified as being defined by ARC criteria (i.e. ARC-ST). In a protocol amendment prior to the enrollment of the first subject, the term IPST (i.e. intraprocedural stent thrombosis) was introduced as a secondary endpoint, distinct from ARC-ST. However, in another section of the protocol, ST was redefined as a sub-composite of both ARC-ST and IPST. There was an analogous inconsistency in the definition of the ST component of the primary efficacy endpoint between sections of the SAP. The Angiographic Core Laboratory of the Cardiovascular Research Institute, which evaluated and interpreted all protocol-mediated angiographic procedures, detailed in its charter the event analysis process for pre and post stent deployment. The evaluation of IPST, whose characterization was distinct from pre or post stent deployment, was not described. The Applicant also provided an “expanded glossary” as a supplement to the Angiographic Core Laboratory where IPST was described. The definition of IPST in the CEC Charter (i.e. “any procedural new or worsened thrombus related to the stent”) was considered ambiguous and not readily discriminated from acute ST as per ARC. The original publication describing IPST (Brener, S, et al., 2013) provided a description creating similar ambiguity in distinction from acute ARC-ST. Furthermore, as opposed to ARC-ST, IPST did not appear to require clinical signs or symptoms.

The efficacy results remained statistically significant in favor of the cangrelor arm compared to the clopidogrel arm following removal of the IPST data from the ST component of the primary efficacy endpoint. Consequently, the document inconsistencies and ambiguity concerning the introduction of IPST did not have clinical impact regarding the outcome of the PHOENIX trial.

The term IPST could easily have been perceived as angiographically analogous to acute ARC-ST because thrombotic events after stent deployment while the subject was still in the catheterization laboratory were considered by the Adjudication



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Committee to be an IPST although acute ARC-ST, the diagnosis of which also required clinical signs or symptoms, was defined between times 0 – 24 hours following stent deployment.

## 3.2 Compliance with Good Clinical Practices

OSI performed three foreign and two domestic site inspections. The three foreign inspections found minor recordkeeping discrepancies, as well as minor protocol deviations in one site assessed as unlikely to significantly affect the integrity of the data in support of the indication. No Form FDA 483 was issued and there was no action indicated. The two domestic inspections yielded only very minor discrepancies at one site with no action indicated. The other domestic inspection found several instances of failure to report adverse events (i.e. hemoglobin change greater than protocol allowance-two instances; one instance each of atrial fibrillation, small puncture site hematoma, back pain, small oozing at puncture site, and agitation). These findings were assessed as unlikely to significantly impact the outcome of the study and that in general, the study was conducted well at the site. A Form FDA 483 was issued for failure to report to the Sponsor adverse effects that may be regarded as caused by the investigational drug. Based on the reports from OSI, it was felt that no evidence emerged which suggested non-noncompliance with Good Clinical Practice.

The Informed Consent form (ICF) described the risks of cangrelor and the risks of clopidogrel. There was no mention of alternative therapy (other P2Y12 inhibitors or GPIs). It is not clear whether or not the design of the ICF was based on a restriction to those subjects for whom clopidogrel was the intended regimen. Although the protocol and ICF underwent IRB review and approval, the lack of alternative therapy disclosure is unusual.

## 3.3 Financial Disclosures

The Applicant has certified that there was no financial arrangement with investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). The Applicant also certified that no investigator disclosed any proprietary interest in the drug or significant equity in the Applicant as defined in 21CFR54.2(b), and that no investigator was the recipient of significant payments of other sorts as defined in 21CFR 54.2(f).

# 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

## 4.1 Chemistry Manufacturing and Controls

Based on the ONDQA Review, the recommendation and conclusion on approvability was to “recommend approval from CMC perspective on receipt of an overall acceptable recommendation from CDER Office of Compliance”. The review listed all but one evaluation as adequate. One evaluation assessed as inadequate concluded that the “ability of cangrelor to meet its related substance acceptance criteria while being stored in the diluents has not been demonstrated”. Data will have been requested from the Applicant and this was conveyed to the Applicant on 18 OCT 2013.

Based on this review, there does not appear to be any clinically impactful issues.

## 4.2 Clinical Microbiology

The Applicant stated that cangrelor injection is a preservative free sterile product which is aseptically filtered, filled under sterile nitrogen in a sterile area, and lyophilized in an aseptic environment. The Applicant also stated that the primary container (glass vial and stopper) provides adequate barrier to microbial ingress (CTD section 3.2.P.2.5). Review by Microbiology specified that the conclusions of the growth promotion study are not reflected in product labeling. Product labeling indicates that the drug product diluted in either diluent may be stored at room temperature for 24 hours whereas the growth promotion submitted on 09 October 2013 concluded that product diluted in 5% Dextrose may be stored at room temperature for only 12 hours. The suggested hold period for saline, at 24 hours, was supported by the study and was therefore acceptable.

## 4.3 Preclinical Pharmacology/Toxicology

Salient features from the finalized Pharmacology/toxicology review include the following:

- Cangrelor was evaluated in a series of toxicity studies in-vitro and in dogs and rats which were considered appropriate models for humans due to pharmacological similarity between dogs, rats, and humans. The primary adverse effects of cangrelor in rats and dogs consisted of injury to renal tubules, renal pelvis, and ureter (caused by the parent molecule). Anatomic changes correlated with increased plasma creatinine and urea, and increased albumin and red blood cells in urine. The changes in the kidney tubules and ureter tended to reverse upon cessation of treatment.



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- Based on in-vitro and in-vivo genetic toxicity studies involving bacterial mutagenicity, mouse lymphoma tyrosine kinase, in-vitro human peripheral lymphocyte chromosome aberration, and mouse bone marrow micronucleus assays, there was no evidence of genotoxicity.

- In the rat EFD study, cangrelor produced dose-related fetal growth retardation characterized by incidences of incomplete ossification and ossified hind limb metatarsals. In the rabbit EFD study, cangrelor was associated with increased incidences of abortion and intrauterine losses. There was no additional teratogenicity in either the rat or rabbit EFD studies, respectively.

- The exposure safety margin for the BRIDGE setting at the NOAEL doses in the 1 month toxicity studies ranged from 4 to 5 fold for cangrelor and 3 to 5 fold for the metabolite AE-C69712CXX, and were several-fold higher in regard to exposure at doses that were not associated with histological changes to the kidney and urinary tract.

- The proposed dose of 30 ug/kg followed by 4 ug/kg/min for 2 hours (in the PCI setting) exceeds the NOAEL in dogs ($AUC_{0\text{-}28d}$ 53957 ng*h/ml) by ~8-fold.

## 4.4 Clinical Pharmacology

### 4.4.1 Mechanism of Action

Cangrelor is an intravenous direct-acting $P2Y_{12}$ receptor antagonist that blocks adenosine diphosphate (ADP)-induced platelet activation and aggregation.

### 4.4.2 Pharmacodynamics

Key points in the pharmacodynamic studies as described by the Applicant were:

- Cangrelor is a reversible competitive inhibitor with a half-life of 3-6 minutes.
- Pre-clinical studies showed a concentration-dependent (in-vitro) inhibition of ADP-induced platelet aggregation and a dose-related (in-vivo dog model) inhibition of thrombosis with little effect on bleeding time.
- Based on two clinical studies (SC-931-5058 and SC-931-5129), the Applicant identified the highest infusion tested (4ug/kg/min) as the dose maintaining steady-state lowest platelet reactivity to 3uM ADP within 15-30 minutes of initiating infusion.
- In order to achieve rapid reduction in ADP-mediated platelet reactivity, study TMC-CAN-04-02 was performed and showed that the highest bolus of 30ug/kg antecedent to the highest infusion of 4ug/kg/min produced complete IPA measured by blood impedance aggregometry within 2 minutes.

- The dosing regimen for the BRIDGE indication was based on Stage 1 of the BRIDGE study (0.75ug/kg/min infusion). The Applicant opined that from a population PK/PD model based on several studies (TMC-CAN-05-02-S1, TMC-CAN-05-03-S1, TMC-CAN-08-02 {BRIDGE study}) there was a lower probability of achieving a PRU threshold in the PCI population compared to the BRIDGE population. Therefore, the Applicant felt that the dosing regimen for the PCI population should be higher than that for the BRIDGE population. Based on TMC-CAN-04-02, the selected dosing regimen for the PCI indication was 30ug/kg bolus and 4ug/kg/min infusion.

### 4.4.3 Pharmacokinetics

The plasma pharmacokinetic properties of cangrelor were linear and dose-proportional at a dose range from 4.8 to 60ug/kg/min (Table 2.6.4.3-2 CTD-Pharmacokinetic Written Summary). Steady-state plasma levels of cangrelor were attained 10-60 minutes following initiation of infusion. Elimination was rapid and biphasic with an initial $t_{1/2}$ of 1-2 minutes and a terminal half-life of 1-4 hours. Approximately 90% of the total cangrelor dose was cleared from plasma during the initial elimination phase.

Cangrelor was rapidly inactivated via de-phosphorylation to metabolic byproducts which were eliminated mainly through the biliary route (80% in 48 hours) with 15% of the total dose recovered in the urine within 24-48 hours post-dose.

# 5 Sources of Clinical Data

Cangrelor has been evaluated in 16 clinical trials, including four pivotal trials (**Table 2 and Table 3**). Doses of cangrelor have included a range of IV boluses up to 60ug/kg, and an IV infusion ranging from 0.01 to 8ug/kg/min. The four pivotal trials described in **Table 2** support efficacy and safety: CHAMPION-PCI (TMC-CAN-05-02), CHAMPION-PLATFORM (TMC-CAN-05-03), CHAMPION PHOENIX (TMC-CAN-10-01), and BRIDGE (TMC-CAN-08-02).

## 5.1 Tables of Studies/Clinical Trials

See **Table 2** for a description of the four pivotal trials conducted for the proposed indications.

CHAMPION-PCI and CHAMPION-PLATFORM failed to meet their respective primary endpoints. Post-hoc analyses of PLATFORM and PCI led to the PHOENIX hypothesis and development of new primary endpoints. Therefore, the PHOENIX trial was the sole trial supporting the PCI claim.

The BRIDGE trial is the sole trial for evaluation of the proposed claim to maintain $P2Y_{12}$ inhibition in patients who are at increased risk of thrombotic events (such as stent

thrombosis) when oral $P2Y_{12}$ therapy is interrupted due to surgery. The BRIDGE trial was a PD study evaluating platelet reactivity of cangrelor vs. placebo. The Applicant provided published literature of clinical data designed to demonstrate three key items pursuant to their program hypothesis: 1) high association between platelet reactivity and thrombotic events (POPULAR trial and ADAPT-DES trial); 2) risk of thrombosis if oral $P2Y_{12}$ therapy is discontinued 5-7 days prior to CABG (Dutch Stent Thrombosis Registry Registry); and 3) risk of bleeding if oral $P2Y_{12}$ therapy is discontinued too close to CABG (two meta-analyses and one review article).

In the Dutch Stent Registry Study (Van Werkum, JW, et al., 2009), a total of 21,009 patients were reviewed from which two cohorts were selected. A total of 437 patients with angiographically demonstrated ST and 866 matched control patients were selected for analysis. The control group did not have angiographically demonstrated ST but were matched for PCI indication, same date of index PCI, and same intervention center. The median follow-up time was 30.9 months ($25^{th}$ percentile: 23.6 months; $75^{th}$ percentile 41.9 months).

**Table 2. Pivotal Trials**

| TRIAL | Study Design | ITT Sample Size | Subject Description | Primary objective | Primary End Point |
|---|---|---|---|---|---|
| CHAMPION-**PCI** (TMC-CAN-05-02) | Prospective, randomized (1:1), double-blind, double-dummy, active-control, parallel-group Active control: clopidogrel 600 mg | 8,877<br><br>Cangrelor: 4,433 Clopidogrel: 4,444 | UA/ NSTEACS/ STEMI patients amenable to PCI | To demonstrate that the efficacy of cangrelor was superior to that of clopidogrel 600 mg in patients requiring percutaneous coronary intervention (PCI) as measured by a composite of all-cause mortality, myocardial infarction (MI), and ischemia-driven revascularization (IDR) at 48 hours | Composite of all-cause mortality, MI, and IDR 48 hours after randomization |
| CHAMPION-**PLATFORM** (TMC-CAN-05-03) | Prospective, randomized (1:1), double-blind, double-dummy, placebo-control, parallel-group over standard of care: including clopidogrel 600mg | 5,364<br><br>Cangrelor: 2,695 Placebo: 2,669 | UA/NSTEACS patients amenable to PCI | To demonstrate that the efficacy of cangrelor (combined with usual care) was superior to that of usual care, in subjects requiring percutaneous coronary intervention (PCI) as measured by a composite of all-cause mortality, myocardial infarction (MI), and ischemia-driven revascularization (IDR) | Composite of all-cause mortality, MI, and IDR 48 hours after randomization |
| CHAMPION-**PHOENIX** (TMC-CAN-10-01) | Prospective, randomized (1:1), double-blind, double-dummy, active-control, parallel-group Active control: clopidogrel 300 mg or 600 mg | 11,145<br><br>Cangrelor: 5,581 Clopidogrel: 5,564 | UA/NSTEACS patients amenable to PCI | To demonstrate that in patients requiring percutaneous coronary intervention (PCI), cangrelor provides superior efficacy to clopidogrel standard of care, as measured by a composite of all-cause mortality, myocardial infarction (MI), ischemia-driven revascularization (IDR) and stent thrombosis | Composite of all-cause mortality, MI, IDR and ST 48 hours after randomization:<br><br>MI: as per UDMI<br>ST: as per ARC |
| **BRIDGE** (TMC-CAN-08-02) | Stage 1: Prospective, open label, dose-finding, multi-center. Stage 2: Prospective, double-blind, placebo-controlled, randomized, multi-center. | Stage 1: 11 Stage 2: 207 (n=106 cangrelor; n=101 placebo) | Patients requiring bridging from oral thienopyridine therapy prior to cardiac surgery | To demonstrate that intravenous (IV) cangrelor, compared to standard of care (SOC) provides effective and consistent P2Y12 inhibition below levels known to be associated with a low risk of thrombotic events up to the time of surgery, without increasing surgical bleeding | Stage 1: Maintenance of platelet inhibition > 60% in at least 80% patient samples by VerifyNow $P2Y_{12}$ point of care assay. Stage 2: percentage of patients with PRU < 240 as determined by VerifyNow $P2Y_{12}$ point of care assay measured during study drug infusion pre-surgery. |



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Cangrelor Dose: CHAMPION trials: 30ug/kg IV bolus + 4ug/kg/min IV infusion x 2-4 hours; BRIDGE: Stage 1: 0.5ug/kg/min or 0.75ug/kg/min or 1.0ug/kg/min or 1.5ug/kg/min IV infusion, Stage 2: 0.75ug/kg/min IV infusion 48 hours or more;

**Table 3. Additional 12 trials included in the ISS**

| Trial | Study design | Subjects treated (cangrelor treated) Subject type | Objectives | Cangrelor max infusion (ug/kg/min) | Max duration |
|---|---|---|---|---|---|
| **SC-931-5014** | DB, PC | 40 (28) HV | PK, PD† | 0.0005 – 4 | ≤ 24 h |
| **SC-931-9017** | OL | 4 (4) HV | ADME cangrelor & metabolite | 2 | 2 h |
| **SC-931-5037** | DB, PC, XO | 12 (12) HV | Effects of aspirin, heparin, and nitroglycerin on safety, PK, PD | 2 | 3 h 45 min |
| **SC-931-5036** | DB, PC | 23 (15) HV | PK, PD | 0.1 – 4 | ≤ 24 h |
| **TMC-CAN-04-02** | OL | 42 (42) HV | PK, PD transition to /from clopidogrel | 1.5 – 4.2‡ | 2 h |
| **TMC-CAN-08-01** | DB, PC, moxifloxacin control, XO | 71 (71) HV | cardiac repolarization | 3.7 – 8* | 3 h |
| **SC-931-5109** | OL | 24 (24) HV renal impaired | PK, PD | 1.6 – 3.2 | 5 h |
| **SC-931-5058** | OL, stepped dose titration | 39 (39) UA/NQWMI BRIDGE indication | PK, PD† | 2 - 4 | 72 h |
| **SC-931-5060** | DB, PC | 91 (45) UA/NQWMI BRIDGE indication | PK | 4 | 72 h |
| **SC-931-5129Pt1** | DB, PC | 200 (149) Not STEMI; PCI | PK, PD† | 1 - 4 | 24 h |
| **SC-931-5129Pt2** | OL, abciximab control | 199 (105) Not STEMI; PCI | PD† | 4 | 24 h |
| **SC-931-5135**** | OL, alteplase control | 92 (85) STEMI | Compare coronary artery patency | 0.3 – 5.2 | 72 h |

Reviewer's analysis: exposure\infdose, Applicant datasets: iss disp, isd

ADME=absorption, distribution, metabolism, excretion, DB=double-blind, h=hour, HV=healthy volunteers, OL=open label, PC=placebo-controlled, PD=pharmacodynamics, PK=pharmacokinetic, XO=crossover
† ADP-induced platelet aggregation
‡ 15 or 30 ug/kg IV bolus prior to infusion
* 30 or 60 ug/kg IV bolus prior to infusion
**prematurely terminated because of "reprioritization of drug development candidates by Astra Zeneca"

## 5.2 Review Strategy

Dr. Senatore reviewed efficacy. The review strategy to evaluate efficacy to support the PCI claim focused on the CHAMPION PHOENIX trial as the sole basis of a regulatory recommendation. This strategy was based on the fact that the uniquely crafted PHOENIX primary efficacy endpoint was derived from post-hoc analyses of the previous CHAMPION trials and was distinct from the endpoints of those trials. Key items of the review strategy included:

- Evaluation of the adjudication process leading to the diagnosis of IPST, considered a biomarker and its prognostic significance from the PHOENIX data. This was considered a strategic action item because IPST drove the ST endpoint which subsequently drove the composite primary efficacy endpoint.
- Evaluation of the adjudication process leading to the diagnosis of UDMI type 4a, as opposed to type 4b, the former which was a co-driver of the primary endpoint and the latter which was associated with ST.

The review strategy to evaluate efficacy data to support the Bridge claim associated with surgery included:

- Evaluation of the Verify-Now $P2Y_{12}$ assay as a prognostic indicator for clinical events.
- Evaluation of thrombotic events from BRIDGE and the Dutch Registry.
- Evaluation of $P2Y_{12}$ therapeutic impact on bleeding risk from the meta-analyses and literature review provided by the Applicant which addressed this risk.

Dr. Beasley reviewed safety. The review strategy for safety focused on the primary safety concern, bleeding, in the PHOENIX trial since PHOENIX contained substantive data to support safety; the other CHAMPION trials were stopped for futility, not for safety. Data from the other CHAMPION trials were examined to aid with interpretation of subgroup analyses. Other safety analyses included analyses of the ISS dataset (16 trials) for AEs, SAEs, and clinically significant laboratory findings.

Drs. Senatore and Beasley reviewed the risk benefit. The risk benefit analysis was approached from the perspective of evaluating the degree of benefit relative to the degree of risk. The degree of clinical benefit was small (e.g. driven by subjects with stable angina who were thienopyridine naïve, evidence of effectiveness only in the PCI setting, loss of efficacy beyond 48 hours when subtracting IPST from the primary endpoint). Consequently, there was less tolerance for bleeding. The safety review incorporated many bleed classifications in order to ensure a comprehensive and balanced approach to evaluating safety.

The four pivotal trials are discussed in Section 5.3.

## 5.3 Discussion of Individual Studies/Clinical Trials

### 5.3.1 CHAMPION PCI

The objective of CHAMPION PCI was to demonstrate that the efficacy of cangrelor was superior to that of clopidogrel in subjects requiring PCI as measured by the primary efficacy endpoint: composite of all-cause mortality, MI, and IDR assessed 48 hours after randomization.

CHAMPION PCI was a prospective, randomized (1:1), double-blind, active-control, parallel-group trial that compared cangrelor (30ug/kg bolus plus 4ug/kg/min infusion) to oral clopidogrel 600mg in patients with coronary atherosclerosis requiring PCI. Subjects were randomized to receive an IV bolus / infusion of cangrelor and placebo capsules vs. Clopidogrel capsules (600mg) / IV bolus and infusion of placebo. After infusion of at least 2 hours or the duration of the procedure (whichever was longer), subjects in the IV cangrelor + placebo capsule arm received clopidogrel capsules (600mg), and subjects in the clopidogrel capsule (600mg) +IV placebo arm received placebo capsules. All subjects subsequently received clopidogrel maintenance as per physician discretion. See **Figure 2** for a schematic of the trial design.

The original subject population mirrored that of CHAMPION PLATFORM. Following a protocol amendment on 08 May 2007 (same date as the protocol amendment of CHAMPION PLATFORM), subjects were required to demonstrate one of the two same criteria described in CHAMPION PLATFORM trial.

The sample size was based on the assumption that the primary endpoint in the SA /UA/ NSTEMI population would be 7.0% in the clopidogrel arm and 5.4% in the cangrelor arm (22.9% relative risk reduction). A sample of 4000 subjects in each arm (total 8000) was estimated to provide a power of 82.3% to detect this difference at a two-sided significance level of 0.05. In addition, up to 1000 STEMI subjects were planned to be enrolled, resulting in a total sample size of 9000 SA/UA/NSTEMI/STEMI subjects. The Applicant planned a group sequential method, allowing for the possibility of sample-size re-estimation based on interim data.

The timeline for the CHAMPION PCI trial spanned from FPI March 2006 to LPO (30 days) June 2009. Study enrollment was terminated on 13 May 2009 at 98.7% enrollment following a recommendation from the IARC (i.e. Cyrus Mehta, Christian Hamm, Robert Califf, Carl Pepine, and James Ware) where at a meeting (closed and open session) on 22 September 2008, it was determined that there was a low likelihood of achieving the primary endpoint.



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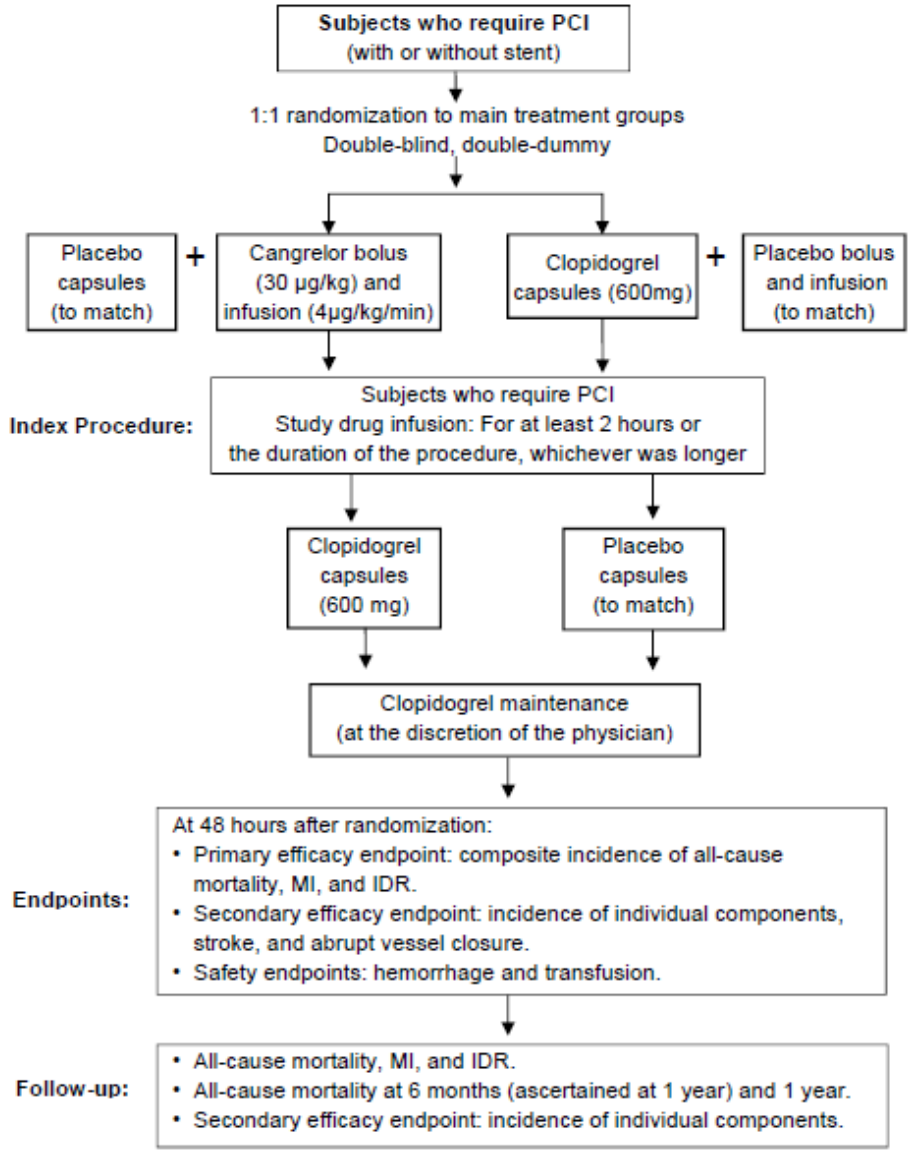
**Figure 2. CHAMPION PCI trial design**




At this IARC meeting and similar to CHAMPION PLATFORM, Dr. Mehta reviewed his steps leading to his determination that the IARC should recommend terminating the trial due to futility. He described the G0 (mITT /ex-STEMI population), G1 (subset of G0 containing only diabetic or baseline cardiac marker positive patients), and G2 (subset of G1 consisting of patients that are clopidogrel-naïve at baseline). He showed that for each population, increasing the sample size to the limit of 15,000 (maximum sample size specified by the Applicant if there was a need to re-estimate sample size in the PCI trial) would not produce sufficient power to detect a treatment effect.

PCI had a planned enrollment of 9000 subjects. At the time of trial termination, 8882 subjects were randomized (4435 to cangrelor; 4447 to clopidogrel 600mg). The incidence of the primary endpoint (composite of all-cause mortality, MI, and IDR at 48 hours after randomization) for the ITT populations was 292/3933 (7.4%) in the cangrelor arm and 277/3924 (7.1%) in the clopidogrel arm (OR 1.06, 95% CI [0.89, 1.25], p=0.5323-Table 5.1.2.1 PCI CSR). The incidence of the all-cause mortality component was 8/3933 (0.2%) in the cangrelor arm and 6/3924 (0.2%) in the clopidogrel arm (OR 1.33, 95% CI [0.46, 3.84], p=0.5969-Table 5.1.2.1 PCI CSR). The incidence of ST was 7/3933 (0.2%) in the cangrelor arm and 11/3924 (0.3%) in the clopidogrel arm (OR 0.63, 95% CI [0.25, 1.64], p=0.3469-Table 5.1.2.1 PCI CSR). The incidence of Acute ST was 5/3933 (0.1%) in the cangrelor arm and 9/3924 (0.2%) in the clopidogrel arm (OR 0.55, 95% CI [0.19, 1.65], p=0.2987-Table 5.1.2.1 PCI CSR). The incidence of adjudicated MI was 278/3933 (7.1%) in the cangrelor arm and 256/3924 (6.5%) in the clopidogrel arm (OR 1.09, 95% CI [0.91, 1.30], p=0.3378). The incidence of adjudicated IDR was 15/3933 (0.4%) in the cangrelor arm and 23/3924 (0.6%) in the clopidogrel arm (OR 0.65, 95% CI [0.34, 1.25], p=0.1943).

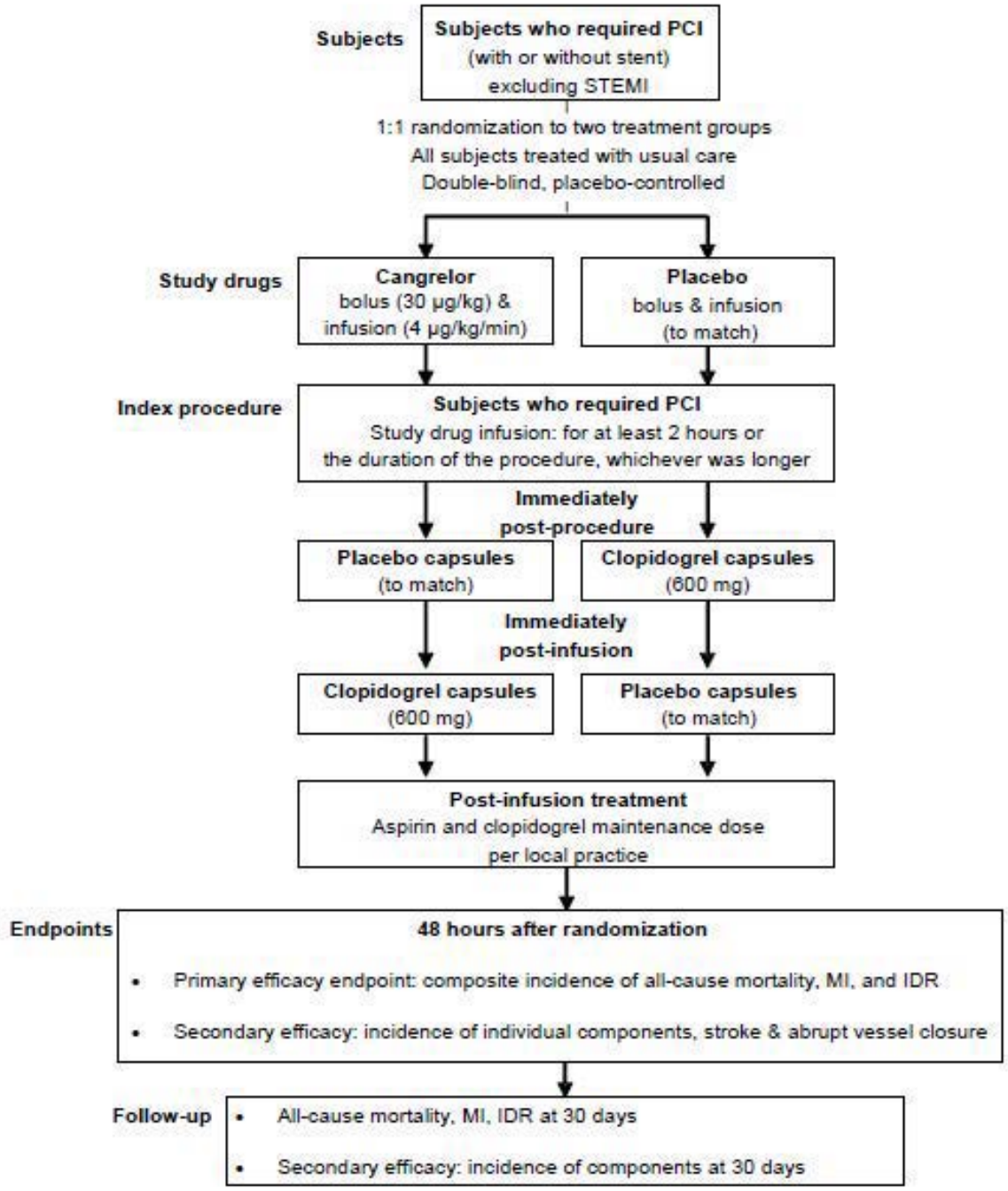
Contrary to the CHAMPION PLATFORM trial, there was no difference between the cangrelor and clopidogrel arm for any of the components of the composite efficacy endpoint. This efficacy issue is discussed in section 6.1.1.10 of this review.

### 5.3.2 CHAMPION PLATFORM

The objective of CHAMPION PLATFORM was to demonstrate that the efficacy of cangrelor (combined with usual care) was superior to that of usual care, in subjects requiring PCI as measured by the primary efficacy endpoint: composite of all-cause mortality, MI, and IDR assessed 48 hours after randomization.

CHAMPION PLATFORM was a prospective, randomized (1:1), double-blind, placebo-control, parallel-group trial that compared IV cangrelor (30ug/kg bolus plus 4ug/kg/min infusion) to IV placebo in patients with coronary atherosclerosis requiring PCI. Subjects were randomized to receive an IV bolus and infusion of study drug (cangrelor or placebo). Immediately post-procedure, subjects in the IV cangrelor arm received placebo capsules, and subjects in the IV placebo arm received clopidogrel capsules (600mg). Immediately following the infusion period of at least 2 hours or the duration of the procedure (whichever was longer), those having received cangrelor infusion and post-procedure placebo capsules were also given clopidogrel capsules (600mg); and those subjects having received placebo infusion and post-procedure clopidogrel capsules (600mg) were also given placebo capsules. Post-infusion maintenance therapy included aspirin and clopidogrel as per local practice (see **Figure 3**).

**Figure 3. CHAMPION PLATFORM trial design**




The original subject population included patients with a diagnostic coronary angiography demonstrating atherosclerosis amenable to treatment by PCI with or without stent implantation regardless of disease severity. Following a protocol amendment (08 May 2007), in addition to the diagnostic coronary angiography demonstrating atherosclerosis amenable to PCI, one of the following criteria was required to be satisfied: NSTEMI

based on troponin I or T or CK-MB> upper limit of normal, or UA defined as ischemic chest discomfort ≥ 10 minutes duration and dynamic ECG changes.

The sample size was based on the assumption that the primary endpoint in the SA /UA/ NSTEMI population would be 7.70% in the placebo arm and 5.78% in the cangrelor arm (25% relative risk reduction). A sample of 3200 subjects in each arm (total 6400) was estimated to provide 85% power to detect this difference at a one-sided significance level of 0.025. The Applicant planned a group sequential method, allowing for the possibility of sample-size re-estimation based on interim data.

The timeline for the CHAMPION PLATFORM trial spanned from FPI October 2006 to LPO (30 days) July 2009. Study enrollment was terminated on 13 May 2009 at 84% enrollment following a recommendation from an Interim Analysis Review Committee (IARC) (i.e. Cyrus Mehta, Christian Hamm, Robert Califf, Carl Pepine, and James Ware) where at a closed meeting on 1 May 2009, it was determined that there was a low likelihood of achieving the primary endpoint.

At this IARC closed meeting, Dr. Mehta reviewed his steps leading to his determination that the IARC should recommend terminating the trial due to futility. He described the G0 (mITT population) and G1 (subset of G0 containing only diabetic or baseline cardiac marker positive patients) and showed that for each population, increasing the sample size to the limit of 15,000 (maximum sample size specified by the Applicant if there was a need to re-estimate sample size in the PLATFORM trial) would not produce sufficient power to detect a treatment effect.

CHAMPION PLATFORM had a planned enrollment of 6400 subjects. At the time of trial termination, 5364 subjects were randomized (2695 to cangrelor→placebo capsules; 2669 to IV placebo→oral clopidogrel 600mg). The incidence of the primary endpoint for the ITT population was 187/2691 (6.9%) in the cangrelor arm and 210/2641 (8.0%) in the clopidogrel arm (OR 0.86, 95% CI [0.70, 1.05], p=0.1456-Table 13 PLATFORM CSR). The incidence of the all-cause mortality component was 8/2691 (0.3%) in the cangrelor arm and 19/2664 (0.7%) in the clopidogrel arm (OR 0.42, 95% CI [0.18, 0.95], p=0.0374-Table 5.1.2.1 PLATFORM CSR). The incidence of ST was 5/2691 (0.2%) in the cangrelor arm and 16/2664 (0.6%) in the clopidogrel arm (OR 0.31, 95% CI [0.11, 0.84], p=0.0217-Table 5.1.2.1 PLATFORM CSR). The ST results were driven by Acute ST: 5/2691 (0.2%) in the cangrelor arm and 14/2664 (0.5%) in the clopidogrel arm (OR 0.35, 95% CI [0.13, 0.98], p=0.0456-Table 5.1.2.1 PLATFORM CSR). There were no differences in the rate of adjudicated MI (cangrelor: 177/2691 (6.6%); clopidogrel: 192/2664 (7.2%); OR 0.91, 95% CI (0.73, 1.12), p=0.3632) or in the rate of adjudicated IDR (cangrelor: 19/2691 (0.7%); clopidogrel: 26/2664 (1.0%); OR 0.72, 95% CI (0.40, 1.31), p=0.2814).

Although there was no difference between the arms of the CHAMPION PLATFORM trial for the primary efficacy endpoint, a significant mortality signal was empirically evident



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against clopidogrel. There was also a significantly higher incidence of acute stent thrombosis in the clopidogrel arm. See section 6.1.1.10 for a review analysis of the results from CHAMPION PLATFORM and CHAMPION PCI – latter shown in section 5.3.1.

### 5.3.3 POOLED ANALYSIS of CHAMPION PCI and CHAMPION PLATFORM

In a post-hoc analysis of the pooled data from CHAMPION PCI and CHAMPION PLATFORM published by White, H, et al., 2012, substitution of the original CEC adjudicated MI with the UDMI type 4a definition of MI resulted in a significant decrease in the incidence of the composite endpoint of death, UDMI-type 4a, and IDR for cangrelor over comparator (placebo or clopidogrel) (OR 0.82, 95%CI [0.68-0.99], p=0.0374). Similarly, cangrelor was observed to have a significantly lower incidence of the post-hoc composite of death, UDMI type 4a, and ARC-ST (OR 0.82, 95%CI [0.67-1.00], p=0.0458) and the composite of death, QWMI and IDR (OR 0.61, 95%CI [0.42-0.88], p=0.0080) over comparator (placebo or clopidogrel).

In a study by Leonardi, S, et al., 2013, substitution of the originally defined CEC-adjudicated MI with the UDMI type 4a, using criteria 5x ULN and 10x ULN but not 3x ULN, into the primary composite endpoint, yielded a significant difference for the revised composite endpoint favoring cangrelor over placebo.

Based on these post-hoc analyses (CHAMPION PLATFORM and pooled analysis of CHAMPION PLATFORM and PCI), CHAMPION PHOENIX was designed for a composite endpoint of all-cause mortality, MI, IDR, and ST assessed at 48 hours after randomization. MI was defined as per UDMI and ST was defined as per ARC.

### 5.3.4 CHAMPION PHOENIX

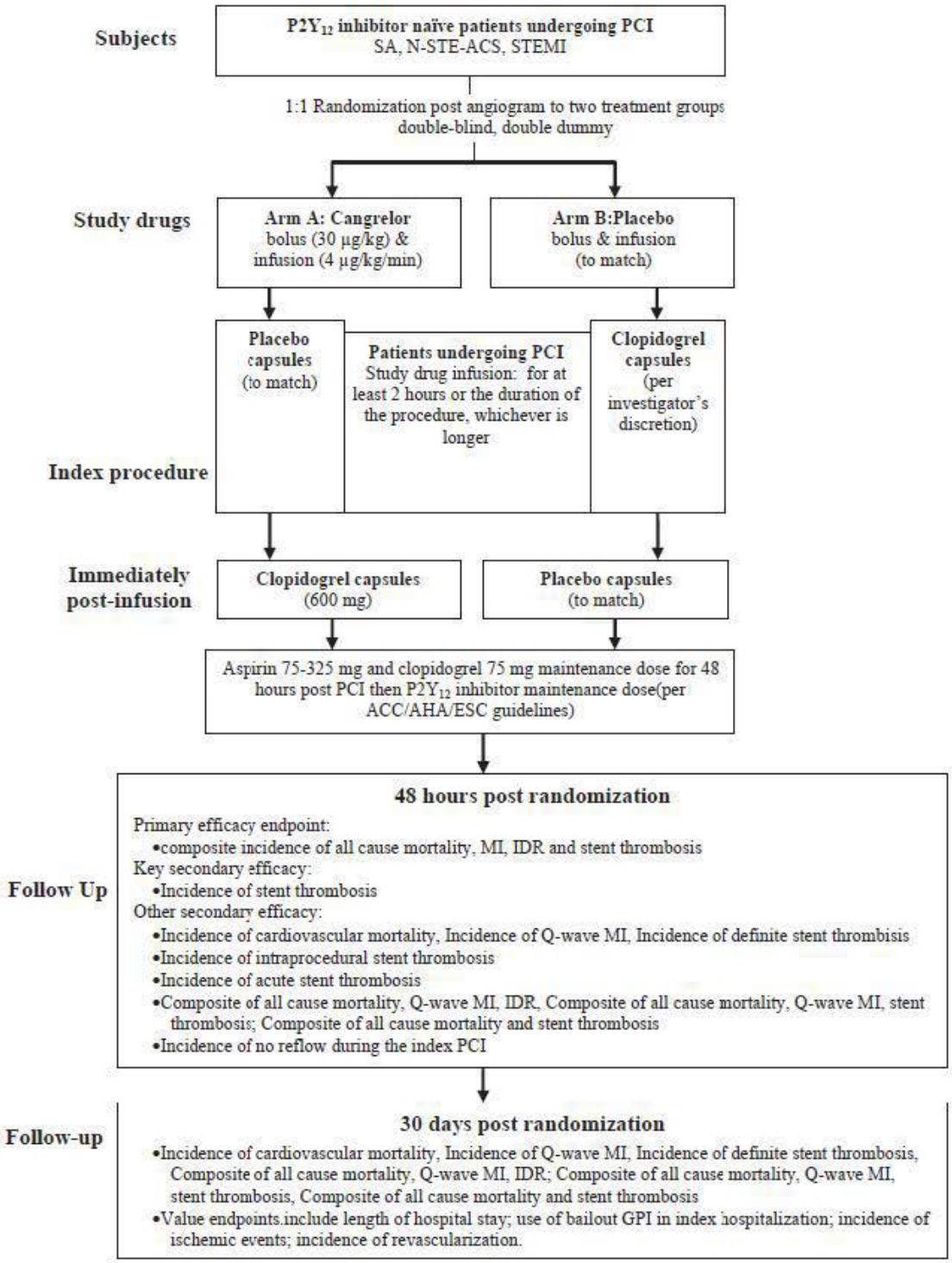
In support of the proposed indication, the Applicant conducted “A clinical trial comparing cangrelor to clopidogrel standard of care therapy in subjects who require percutaneous coronary intervention: CHAMPION PHOENIX (Cangrelor versus standard therapy to achieve optimal management of platelet inhibition)”. An overview of the final protocol (and only amendment which was dated prior to the first patient being enrolled) dated 28 September 2010 is described in this section.

#### 5.3.4.1 Study Design

The CHAMPION PHOENIX trial was a phase III, randomized, double-blind, double-dummy, active comparator, controlled trial comparing cangrelor IV + placebo PO to placebo IV + clopidogrel PO (300mg or 600mg) in patients presenting either with stable angina (SA), non-ST-segment elevation acute coronary syndrome (NSTEACS), or ST-segment elevation myocardial infarction (STEMI) who are planned to undergo either

elective or urgent PCI. The trial design, key efficacy endpoints and follow-up are shown in **Figure 4**.

**Figure 4: CHAMPION PHOENIX Trial Design and Follow-up**



### 5.3.4.2 Study Duration/Dates

The first subject was enrolled on 30 September 2010. The last patient completed on 14 November 2012.

### 5.3.4.3 Study Population

Main inclusion criteria required that subjects be at least 18 years of age with SA, NSTEACS, or STEMI who required PCI and had not previously received a $P2Y_{12}$ inhibitor within 7 days.

Notable exclusion criteria were related to bleeding including ischemic stroke within the last year, any previous hemorrhagic stroke, and trauma or major surgery within the last month.

### 5.3.4.4 Study Procedures

Randomization occurred once eligibility was confirmed and prior to commencement of the index PCI. To be eligible, coronary anatomy and suitability for PCI was assessed via angiography in SA and NSTEACS patients.[1] STEMI patients could be randomized on diagnosis prior to angiography based on ECG (e.g., in the Emergency Room), provided there was no impediment to PCI. Subjects were randomized by IV/WRS with stratification based on site, baseline status[2] and intended clopidogrel loading dose.

*Reviewer comment: The protocol did not provide guidance on clopidogrel loading dose strength. It is unclear what criteria the investigator used to choose the intended clopidogrel loading dose. Moreover, it was also unclear why all subjects randomized to cangrelor received only clopidogrel 600 mg loading dose whereas subjects randomized to clopidogrel could receive either 300 mg or 600 mg. So while the blinded investigator declared an "intended dose" (300 mg or 600 mg), subjects randomized to cangrelor only received clopidogrel 600 mg. The "intended dose" was used in the Applicant's regression analysis of the primary efficacy endpoint.*

Subjects received a study drug kit containing IV drug and two sets of capsules (pink and blue). Intravenous study drug was to be administered as soon as possible following randomization but not more than 30 minutes prior to PCI (defined as time of guidewire

[1] Angiography within 90 days of index PCI for SA patients and within 72 hours prior to randomization for NSTEACS patients.
[2] The CEC classified "baseline status" using troponin levels, ischemic symptoms and ECG changes to designate subjects as "baseline normal" or "baseline abnormal." The purpose was to assess peri-procedural MI at 48 hours.

insertion).[3] In STEMI patients, this would be prior to or immediately after angiography. For others this would be after angiography confirmation of suitability for PCI.

The first set of oral over-encapsulated capsules (pink) was to be ingested as soon as possible following randomization per the investigator's discretion.[4] For subjects randomized to cangrelor, these capsules were placebo. For subjects randomized to clopidogrel, this was clopidogrel at a dose of either 300 mg or 600 mg (at investigator discretion).

The second set of oral over-encapsulated capsules (blue) was the transition dose and was to be taken immediately following infusion cessation. For subjects randomized to cangrelor, these capsules were clopidogrel 600 mg. For subjects randomized to clopidogrel, this was placebo.

Aspirin 75-325 mg and clopidogrel 75 mg were prescribed for 48 hours post PCI then a P2Y12 inhibitor maintenance dose per ACC/AHA/ESC guidelines.

Pertinent tests included the following:

- Within 72 hours prior to randomization: 12-lead ECG, hemoglobin, hematocrit, platelets, PT/INR, Troponin I or T (at least one, ideally two or more).
- Immediately following randomization prior to study drug imitation: Troponin I or T and CK-MB mass
- Following drug infusion cessation through hospital discharge or 48 hours, whichever occurs sooner: 12-lead ECG within 1 hour after the index PCI and on the morning after the procedure (or at hospital discharge, whichever occurs sooner), CK-MB mass every 6 hours post PCI (minimum of 3 samples), Troponin I or T and CK-MB according to hospital standard of care, hemoglobin, hematocrit, and platelet count on the day after the index PCI (or at hospital discharge, whichever occurs first)

*Concomitant medications*

Glycoprotein IIb/IIIa inhibitors were allowed during the index PCI as bailout therapy. Antithrombin therapy (heparin, fondaparinux, and bivalirudin) was also allowed.

CYP2C19 inhibitors (e.g. omeprazole) were prohibited for the first 48 hours post randomization.

[3] In cases where intravascular ultrasound (IVUS) was used during the diagnostic angiogram, study drug infusion was to begin prior to the IVUS catheter crossing the target lesion.
[4] Each capsule contained two clopidogrel 75 mg tablets.

*48 hour follow-up*
All patients were contacted either by telephone (if already discharged from the hospital), evaluated during an office visit, or evaluated as an in-patient for the following assessments:

- Concomitant medications (i.e., ticlopidine, aspirin, clopidogrel, prasugrel)
- Clinical endpoints: Death, MI, IDR, stent thrombosis, no reflow
- Value endpoints: length of hospital stay, use of bailout GPI during index hospitalization, incidence of ischemic events, incidence of revascularization.
- AEs and hemorrhage assessment occurring through 48 hours after randomization

The patient could be contacted up to 72 hours after the 48-hour time point in order to determine patient status at 48 hours (48 hours [+ 72 hours]). If there was a delay of more than 12 hours between time of randomization and start of study drug, AEs were to be collected from time of randomization through 48 hours after study drug initiation.

*Reviewer comment: Concomitant and discharge medications were assessed post procedure/discharge. These did not appear to be assessed on the 48 hour follow-up eCRF.*

*30 day follow-up*
All patients were to be contacted 30 days (+5 days) after randomization for efficacy endpoints. The following was ascertained: occurrence of ischemia, MI, angiography, revascularization, and death. Patients were to be questioned regarding their use of maintenance thienopyridines and aspirin.

*Reviewer comment: Although the protocol specified that subjects would be questioned regarding thienopyridine and aspirin use, the CRF did not collect this information at the 30 day follow-up visit.*

### 5.3.4.5 Efficacy Endpoints

The primary efficacy endpoint was a composite of all-cause mortality, Myocardial Infarction (MI), Ischemic Driven Revascularization (IDR) and Stent Thrombosis (ST) at 48 hours. The MI component was based on the Universal Definition of Myocardial Infarction (UDMI) as part of the Applicant's strategy to re-define this endpoint from the previous CHAMPION studies pursuant to optimizing the probability of a successful PHOENIX trial. The assessment of acute MI followed satisfying at least one of the following diagnostic criteria:
a) Rise and fall of cardiac biomarkers above the 99$^{th}$ percentile of the upper reference limit (URL) with evidence of at least one of the following: ischemic symptoms, ECG changes indicative of new ischemia, development of pathological Q waves in the ECG, imaging evidence of new loss of viable myocardium or new regional wall motion abnormality;



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b) Sudden, unexpected cardiac death involving cardiac arrest with signs or symptoms of myocardial ischemia;
c) For PCI in patients with normal baseline troponin values, elevation of cardiac biomarkers greater than the 99$^{th}$ percentile of the URL is indicative of peri-procedural myocardial necrosis. Conventionally, increases in biomarkers greater than 3 x 99$^{th}$ percentile URL have been designated as defining PCI-related MI;
d) For CABG in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99$^{th}$ percentile URL are indicative of myocardial necrosis. Conventionally, increases of biomarkers greater than 5 x 99$^{th}$ percentile URL plus either new pathological Q waves or new left bundle branch block (LBBB), or angiographically documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium, have been designated as defining CABG-related myocardial infarction;
e) Pathological findings of an acute MI.

The UDMI was classified according to 5 types (**see section 9.2 Universal Definition of Myocardial Infarction**). The Applicant's program objective focused on the re-defined hypothesis, compared to the original CHAMPION program, that the benefit of cangrelor would be made manifest by decreasing the incidence of peri-procedural MI compared to clopidogrel. Therefore, the trial design focused on Type 4a and Type 4b MI where baseline cardiac biomarkers were normal.

The ST component was a combination of Academic Research Consortium (ARC) defined ST (see section **9.3 Stent Thrombosis**) and Intra-Procedural Stent Thrombosis (IPST). ARC defined ST (ARC-ST) was developed in order to harmonize endpoint definitions (see section **6.1.1.5 Analysis of Secondary Endpoints(s)**). ARC-ST was defined by time and by probability. [5] The key feature of ARC-ST was the association of angiographically demonstrated thrombosis and clinical signs or symptoms. IPST was introduced by Brener, S, et al. in 2013 (see section **6.1.1.5 Analysis of Secondary Endpoints(s)**) as a variable postulated to not be included in the ARC definitions of ST. The ARC defined acute ST, which began at time 0 immediately after stent implantation, was argued by Brenner et al. to not consider thrombosis which occur while the stent is being implanted (e.g. a discreet time period prior to "time 0"). Because of the post-hoc derived prognostic significance for major adverse cardiac events, the Applicant included IPST into the ARC-ST component of the primary endpoint. The CEC Charter defined IPST for adjudication purposes and as such, rendered challenging the distinction between IPST and ARC-acute ST. The difference between ARC-acute ST and IPST was the lack of requisite clinical signs or symptoms when adjudicating IPST. As pointed out in section 6.1.1.5, the combination of IPST and ARC-ST in defining ST as a component of the primary efficacy endpoint was analogous to combining a clinically

[5] Time (acute: 0-24 hours after stent implantation; subacute: > 24 hours to 30 days after stent implantation; late: > 30 days to 1 year after stent implantation; very late: > 1 year after stent implantation); probability (definite, probable, possible-see section 9.2).

meaningful angiographic parameter with a biomarker which has not undergone a validation or harmonization process.

IDR (see section **9.4 Ischemic Driven Revascularization**) was defined as repeat PCI or CABG due to signs or symptoms of ischemia. The episode of ischemia leading to repeat PCI or CABG will have been required to have occurred following completion of the index procedure.

A protocol defined key secondary endpoint was ST at 48 hours. Other secondary endpoints were: individual incidences of all-cause mortality, MI, and IDR at 48 hours; cardiovascular mortality at 48 hours and 30 days; QWMI at 48 hours and 30 days; Definite ST at 48 hours; IPST; Acute ST (ARC-defined); the composite of all-cause mortality, QWMI and IDR at 48 hours and 30 days; the composite of all-cause mortality, QWMI, and ST 48 hours and 30 days; the composite of all-cause mortality and ST at 48 hours and 30 days; no-reflow during PCI; and value endpoints (i.e. length of hospital stay, bailout GPI).

### 5.3.4.6 Safety Endpoints and Definitions

The primary safety endpoint was the incidence of GUSTO severe bleeding. This was stated in the SAP which was finalized just prior to the last patient completing the trial. The Applicant chose this bleeding classification because of its common use in coronary artery disease and anti-platelet studies. Other bleeding scales defined in the SAP are shown in Table 4.

*Reviewer comment: The final protocol and SAP did not distinguish between CABG and non-CABG bleeding. However, the synopsis in the original protocol and amended protocol stated that one of the safety endpoints was "the incidence of major/minor non-CABG related hemorrhage by clinically relevant criteria at 48 hours after randomization."*

Bleeding was assessed from the time of randomization through 48 hours after study drug initiation. The protocol specified that the following safety endpoints would be evaluated (although not adjudicated):

- Incidence of hemorrhage by clinically relevant criteria (GUSTO, TIMI, other major bleeding scales) up through 48 hours, and
- The incidence of blood product transfusion up through 48 hours, categorized according to relationship with CABG surgery.

**Table 4. Bleeding definitions in PHOENIX SAP**

| Bleed Classification | Definition |
|---|---|
| GUSTO severe | • Intracranial bleeding or<br>• Resulting in hemodynamic compromise requiring treatment (includes fatal bleeding) |
| GUSTO moderate | • Requiring blood transfusion |
| GUSTO mild | • Other bleeding requiring intervention, but not requiring transfusion or causing hemodynamic compromise |
| TIMI major† | • Intracranial bleeding or<br>• Any bleeding associated with clinically overt signs associated with a drop in hemoglobin of > 5 g/dL (or when hemoglobin is not available, an absolute drop in hematocrit > 15%) |
| TIMI minor† | • Clinically overt sign of bleeding (including observations by imaging techniques) that is associated with a fall in hemoglobin of ≥3 g/dL and ≤5 g/dL (or when hemoglobin is not available, an absolute drop in hematocrit ≥9% and ≤15%) |
| ACUITY major† | • Intracranial bleeding or<br>• Intraocular bleeding or<br>• Retroperitoneal or<br>• Access site hemorrhage requiring intervention or<br>• ≥ 5 cm diameter hematoma or<br>• Reduction in Hg ≥ 4 g/dL without an overt source of bleeding or<br>• Reduction in Hg ≥ 3 g/dL with an overt source of bleeding or<br>• Reoperation for bleeding or<br>• Use of any blood product transfusion |
| ACUITY minor | • All other bleeding not listed as major |
| BARC Type 0 | • No evidence of bleeding |
| BARC Type 1 | • Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional |
| BARC Type 2 | • Clinically overt sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that is actionable but does not meet criteria for type 3, 4, or 5. |
| BARC Type 3 | • Clinical, laboratory, and/or imaging evidence of bleeding with specific healthcare provider responses as listed below: |
| BARC Type 3a† | • Any transfusion with overt bleeding or<br>• Overt bleeding plus hemoglobin drop of ≥3 g/dL to <5 g/dL (provided hemoglobin drop is related to bleeding) |

| Bleed Classification | Definition |
|---|---|
| BARC Type 3b† | • Overt bleeding plus hemoglobin drop ≥5 g/dL (provided hemoglobin drop is related to bleeding) or<br>• Cardiac tamponade or<br>• Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid) or<br>• Bleeding requiring intravenous vasoactive drugs |
| BARC Type 3c | • Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation; does include intraspinal); or<br>• Subcategories confirmed by autopsy, imaging, or lumbar puncture or<br>• Intraocular bleed compromising vision |
| BARC Type 4 | CABG related bleeding:<br>• Perioperative intracranial bleeding within 48 hours or<br>• Reoperation after closure of sternotomy for the purpose of controlling bleeding or<br>• Transfusion of ≥5 U whole blood or packed red blood cells within a 48-hour period (only allogenic transfusions are considered transfusion for CABG-related bleeds)<br>• Chest tube output ≥2 L within a 24-hour period |
| BARC Type 5 | • Fatal bleeding, bleeding that directly causes death with no other explainable cause: |
| BARC Type 5a | • Probable fatal bleeding: clinically suspicious as the cause of death, but the bleeding is not directly observed and there is no autopsy or confirmatory imaging |
| BARC Type 5b | • Definite fatal bleeding: bleeding that is directly observed (by either clinical specimen [blood, emesis, stool, etc.] or imaging) or confirmed on autopsy. |

| Bleed Classification | Definition |
|---|---|
| "clinically overt" or "overt source" | Used for all of the above bleeding classifications:<br>AT LEAST ONE of the following checked on eCRF:<br>• Requiring intervention: health care professional-guided medical treatment or percutaneous intervention<br>• Leading to hospitalization or an increased level of care: prolonged hospitalization or hospital transfer<br>• Prompting evaluation: an unscheduled visit to healthcare professional resulting in diagnostic testing<br>AND ANY of the following checked on eCRF:<br>• Clinically overt bleed<br>• Intracranial hemorrhage<br>• Intraocular<br>• Cardiac tamponade<br>• Retroperitoneal<br>• Access site bleeding requiring radiologic or surgical intervention<br>• Reoperation for bleeding<br>• Hemodynamic compromise<br>• Epistaxis<br>• Gross hematuria<br>• Hematemesis<br>• Hematoma ≥ 5 cm at puncture site |
| Non-CABG related bleeding | Any bleeding, unless it is marked as "associated with CABG" on eCRF |

† Hemoglobin and hematocrit drop adjusted for packed red blood cells or whole blood transfusion based on the following formula:
Δ Hg=baseline Hg – post transfusion Hg + number of units transfused
Δ Hct=baseline Hct – post transfusion Hct + (number of units transfused x 3)
GUSTO= the Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries (The GUSTO Investigators, 1993)
TIMI=Thrombolysis in Myocardial Infarction (Antman et al, 2005)
ACUITY=Acute Catheterization and urgent intervention triage strategy (Stone et al, 2004)
BARC=Bleeding Academic Research Consortium scale (Mehran et al, 2011)

*Reviewer comment: Applicant's definition of GUSTO mild appears different from that published in 1993 which states that GUSTO mild was "other bleeding, not requiring transfusion or causing hemodynamic compromise." See also* **Section 7.1.2** *for how bleeds were classified.*

*The Stone et al 2004 and 2006 publication do not specify a retroperitoneal bleed to be an ACUITY major bleed but it does appear as a subcategory under major bleeding in a table in the 2006 publication.*

Bleeding events were also classified as instrumented (direct result of an invasive procedure) or spontaneous and as access-site or non-access site.

Treatment emergent AEs (TEAE) was defined as an adverse event occurring at or after study drug start up to 48 hours after initiation of study drug administration. All AEs were coded using the dictionary terms from the MedDRA Adverse Reaction Dictionary (version 13.1).

### 5.3.4.7 Statistical Plan

The sample size calculation was based on the observed results from CHAMPION-PCI and CHAMPION-PLATFORM. A composite event rate of 5.1% in the clopidogrel arm and 3.9% in the cangrelor arm (24.5% reduction in odds ratio) was assumed. The sample size of 10,900 (i.e. 5450 subjects per arm) was estimated to provide a power of 85% to detect this difference at the one-sided significance level of 0.025.

The primary and secondary efficacy analyses were to be based on the Modified Intent-to-treat population (MITT), defined as randomized subjects receiving at least one dose of study drug and who underwent the index PCI procedure. Analyses based on the Intent to Treat (ITT) and Per Protocol (PP)[6] were secondary and confirmatory.

The primary endpoint was analyzed using a logistic regression model adjusted for baseline status and *intended* clopidogrel loading dose.[7] The CEC classified "baseline status" using troponin levels, ischemic symptoms and ECG changes to designate subjects as "baseline normal" or "baseline abnormal." The purpose was to assess peri-procedural MI at 48 hours. The results of logistic regression analysis were presented with proportions by treatment group with adjusted odds ratio, p-value and 95% confidence interval.

The SAP was finalized on 25 October 2012, just shortly before the last patient completed the trial on 14 November 2012.

### 5.3.4.8 Adjudication and Core Lab

A centralized CEC adjudicated the cause of death, occurrence of MI, IDR, and stent thrombosis in a blinded fashion. The angiography core lab was to provide independent,

[6] Per Protocol defined as randomized subjects who received the assigned study drug and underwet the index PCI.
[7] The SAP noted that the primary analysis would also be adjust for intended clopidogrel dose if more than 15% of the patient population were observed to receive clopidogrel 300 mg loading dose at the time of randomization. The SAP notes that at the time of writing, the patient population receiving 300 mg clopidogrel loading dose had exceed 15%.

blinded evaluation of stent thrombosis events according to ARC criteria before CEC adjudication.

### 5.3.4.9 Data Safety and Monitoring Board

The DSMB planned to meet after every 2000 subjects were enrolled. An independent Statistical Reporting Organization at Duke Clinical Research Institute (DCRI) provided study data for DSMB review. A planned 70% interim efficacy analysis occurred on June 27, 2012.

### 5.3.5 BRIDGE

The BRIDGE trial was a phase II prospective, two stage study. The primary objective of this trial was to demonstrate that compared to placebo, discontinuation of oral $P2Y_{12}$ inhibitors followed by institution of IV cangrelor provided effective and consistent $P2Y_{12}$ inhibition up to the time of surgery without increasing surgical bleeding. Furthermore, discontinuation of IV cangrelor would result in rapid return of platelet reactivity to baseline and to levels indistinguishable from placebo.

Stage I was a dose-finding open label study (no reference therapy) with the objective of identifying a dose of cangrelor that achieved a level of IPA after discontinuation of oral $P2Y_{12}$, equivalent to that expected to be maintained if oral $P2Y_{12}$ inhibition had not been discontinued. The primary efficacy endpoint for Stage I was the maintenance of IPA during cangrelor infusion at levels above 60% in at least 80% of patient samples as reported by the *VerifyNow* ™ $P2Y_{12}$ point of care assay. This endpoint was selected as an approximation of the antiplatelet effect expected to meet the stated objective.

Cangrelor was administered as an IV infusion to cohorts of 5 subjects in a stepwise fashion at predetermined doses: 0.5ug/kg/min, 0.75ug/kg/min, 1.0ug/kg/min, 1.5ug/kg/min, until the primary endpoint was met. If the primary endpoint were not met, then the dose would have been increased to a maximum of 2.0ug/kg/min. After each dose-specific cohort of open-label subjects completed their treatment, an interim analysis was performed and results were reviewed by an Applicant Executive Committee prior to dose advancement.

Stage II was a double-blind, placebo controlled, randomized study comparing IV cangrelor to IV placebo with the objective of demonstrating that cangrelor, at the dose identified in Stage 1, maintained levels of platelet reactivity below a threshold for the duration of infusion, which was identified to be associated with a low-risk of thrombotic events (PRU < 240) as measured by the Accumetrics *VerifyNow* ™ $P2Y_{12}$ assay. The primary efficacy endpoint for Stage II was the percentage of patients with PRU < 240, as determined by the *VerifyNow* ™ $P2Y_{12}$ point of care assay, measured during study drug infusion pre-surgery. Based on the assumption that 30% of placebo-treated subjects and at least 60% of cangrelor treated subjects would maintain platelet inhibition

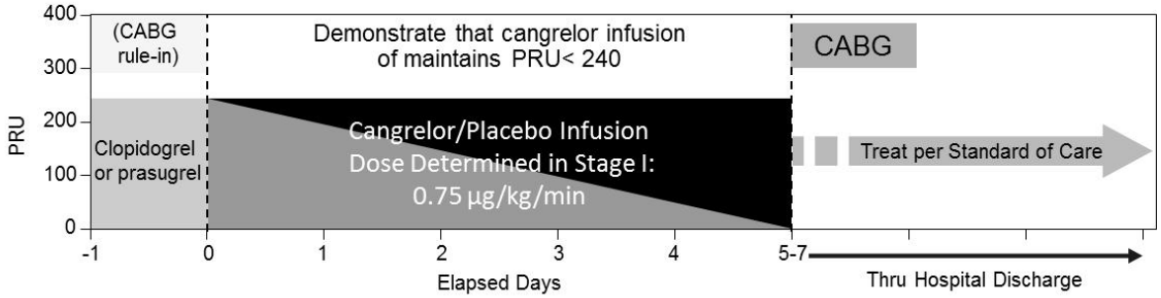
below PRU < 240, a sample size of 106 (53/arm) was calculated to provide 90% power and a significance level of 0.05.

Secondary efficacy endpoints from Stage II included:

- percentage of total patient samples with at least 60% IPA as determined by *VerifyNow* ™ $P2Y_{12}$ point of care assay measured during study drug infusion prior to surgery
- percentage of total patient samples with PRU < 240 as determined by *VerifyNow* ™ $P2Y_{12}$ point of care assay measured during study drug infusion prior to surgery
- percentage of patients with PRU < 240 during their last on-treatment sample prior to surgery
- percentage of patients in whom all PRU evaluations during study drug infusion prior to surgery were less than or equal to baseline PRU
- CABG-related bleeding (i.e. fatal, peri-operative ICH, re-operation after sternotomy closure to control bleeding, transfusion of ≥ 5 units of whole blood or packed red blood cells within a 48 hour period after CABG, chest tube output ≥ 2L within a 24 hour period after CABG), pre-operative bleeding (TIMI, GUSTO, ACUITY).

Approximately 200 subjects (100 subjects per arm) were randomized. The per-protocol population included 70 subjects randomized to the cangrelor arm and 77 subjects randomized to the placebo arm. The trial design of Stage II is illustrated in **Figure 5**.

**Figure 5. BRIDGE Stage II trial design schematics**




Source: BRIDGE CSR, Section 9.1, Figure 1

Subjects included in the BRIDGE trial were those who anticipated non-emergent CABG, either on-pump or off-pump, no sooner than 48 hours from randomization but no longer than 7 days from randomization, with the subject hospitalized until planned CABG. Subjects presented with either ACS or elective PCI with stent deployment where subsequent planned CABG was not based on ACS. Subjects enrolled in the BRIDGE trial received a stent approximately 6 months prior to surgery and were stratified by the

number of days to surgery (< 3 days or > 3 days). Subjects also have received a thienopyridine within 72 hours prior to enrollment for either the treatment of ACS regardless of time from ACS and/or long term preventative therapy following DES or BMS treatment. Study drug infusion (cangrelor or placebo) was initiated immediately after randomization (within 72 hours of the last dose of oral $P2Y_{12}$ inhibitor) and maintained throughout the pre-operative period for a minimum of 48 hours. Infusion durations of up to 7 days were allowed. Sites were instructed to discontinue the infusion 1 to 6 hours prior to surgical incision. Study drug was not administered during or after cardiac surgery. **Figure 6** details the operational schematics applicable to both Stage 1 and Stage 2.

**Figure 6. BRIDGE Schedule of Assessments (Stage I and II)**

| | Screening/Randomization | | Pre-Operative | | Intra-Operative | Post-Operative Through Discharge | | | | Follow-Up |
|---|---|---|---|---|---|---|---|---|---|---|
| Study Assessment | Pretreatment / Screening[a] | Randomization | Days 1-7 | Pre-Surgery | During Surgery[b] | Immediately Post-Surgery[c] | 4 h (± 1 h) Post-Surgery | 24 h (±1 h) Post-Surgery | Discharge | 30-Day (+5 days) |
| Informed consent | X | | | | | | | | | |
| Medical history | X | | | | | | | | | |
| Inclusion/ exclusion criteria | X | | | | | | | | | |
| Pregnancy test (serum or urine), if applicable | X | | | | | | | | | |
| PT/INR | X | | | | | | | | | |
| Previous medications | X | | | | | | | | | |
| Hematology (Hgb, Hct, WBC, platelets) | X | | X[d] | | | | | X | | |
| Serum creatinine and LFTs | X | | | | X[e] | | | | | |
| 12-lead ECG | X | | | | | | | X | | |
| CK, CK-MB | X | | | | | | | | | |
| IVRS randomization | | X[f] | | | | | | | | |
| Verify*Now*™ P2Y12 Assay | | X[g] | X[h] | X[i] | X[j] | X | | X | | |
| Study drug administration | | X | X | X[k] | | | | | | |
| Concomitant medications | | < ---------- X ---------- > | | | | | | | | |
| Clinical endpoint assessments | | < ---------- X ---------- > | | | | | | | | |
| Adverse event reporting | | < ---------- X ---------- > | | | | | | | | |
| Serious adverse event reporting | | <----------X----------> | | | | | | | | |

a Screening period tests were conducted within 24 hours prior to randomization
b Surgery start was defined as time of first incision; surgery stop was defined as last suture placed
c Immediately was defined as within 1 hour post end of CABG surgery unless otherwise defined
d Hematology tests were drawn daily during the infusion period, at approximately the same time each day
e Presurgery serum creatinine and LFTs were drawn following the discontinuation of study drug infusion, but prior to CABG surgery
f IVRS randomization not applicable to Stage I. Patients were enrolled via a manual process
g Verify*Now*™ P2Y12 assay sample was drawn just prior to initiation of study drug
h Verify*Now*™ P2Y12 assay samples were taken daily during infusion period and at approximately the same time each day, in conjunction with daily labs if possible
i Pre-surgery VerifyNow™ P2Y12 assay testing was done before discontinuation of study drug infusion. Patients had to have at least 48 hours on cangrelor infusion before termination. If the last on-infusion VerifyNow™ sample was within 12 hours of study drug discontinuation, an additional sample was not required before cangrelor termination
j Verify*Now*™ P2Y12 assay samples drawn just prior to surgical incision
k Study drug infusion was stopped at no less than 1 and no more than 6 hours prior to anesthesia for surgery
PT = prothrombin time; h = hour(s); INR = International Normalized Ratio; Hgb = hemoglobin; Hct = hematocrit; WBC = white blood cells; LFT = liver function tests; ECG = electrocardiogram; CK = creatine kinase; CK-MB = creatine kinase-myocardial isoenzyme band; IVRS = interactive voice response system

Source: BRIDGE CSR, Section 9.5.1, Table 2

Subjects were enrolled at 35 centers in 5 countries: Austria, Czech Republic, Netherlands, United Kingdom, and USA. The FPI (Stage 1) occurred on 02 January 2009. The FPI (Stage II) occurred 14 October 2009, and the LPO (Stage II) occurred 07 June 2011. The CSR was finalized on 29 March 2013.

# 6 Review of Efficacy

## ***Efficacy Summary***

**CHAMPION-PHOENIX**:

The CHAMPION-PHOENIX trial showed that in the ITT population, including subjects with SA, NSTEACS and STEMI, cangrelor reduced the incidence of the composite primary endpoint of death, MI, IDR, and ST to a greater degree than clopidogrel (OR 0.79, 95%CI [0.67-0.93], p=0.0053) at 48 hours. The results were driven by MI (OR 0.80, 95%CI [0.67-0.97], p=0.0212) and ST (OR 0.62, 95%CI [0.43-0.89], p=0.0098). There was no significant difference between cangrelor and clopidogrel for death (OR 0.95, 95%CI [0.51-1.75], p=0.8702), and IDR (OR 0.76, 95%CI [0.47-1.23], p=0.2663). The MI component of the composite primary endpoint was driven by UDMI-type 4a (i.e. associated with PCI). There were no other significant differences between cangrelor and clopidogrel for other MI definitions (i.e. QWMI, types 1, 2, 3, 4b, and 5). The ST component of the composite primary endpoint was driven by IPST (OR 0.64, 95%CI [0.42-0.99], p=0.0421). There was no difference between cangrelor and clopidogrel for Definite ST (OR 0.54, 95%CI [0.27-1.10], p=0.0847) and Acute ST (OR 0.52, 95%CI [0.25-1.08], p=0.0757). Probable and Possible ST were not evaluated at 48 hours. Results for the composite primary endpoint were similar for the ITT and PP populations.

The incidence of the composite of death, QWMI, and ST was significantly lower in the cangrelor group (69/5573{1.2%}) compared to the clopidogrel group (100/5561{1.8%}), OR 0.68, 95% CI [0.50, 0.93], p=0.0156. The Agency told the Applicant that this composite from PHOENIX would be sufficient for an NDA submission.

At 30 days, the composite endpoint of death, MI, IDR and ST for the ITT population was also significantly reduced in the cangrelor cohort compared to the clopidogrel cohort (OR 0.85, 95%CI [0.73-0.99], p=0.0326). These results were also driven by MI (OR 0.82, 95%CI [0.68-0.98], p=0.0281) and ST (OR 0.68, 95%CI [0.50-0.92], p=0.0122). There was no significant difference between cangrelor and clopidogrel for death (OR 1.10, 95%CI [0.77-1.57], p=0.5980). As the OR indicates, however, there was a numerical increase in the death rate for cangrelor (64/5564: 1.2%) compared to clopidogrel (58/5545: 1.0%). There was no significant difference between cangrelor and clopidogrel in the rate of IDR (OR 0.85, 95%CI [0.59-1.21], p=0.3564). The ST results were driven by IPST (OR 0.64, 95%CI [0.42-0.99], p=0.0415). There was no difference between cangrelor and clopidogrel for Definite ST (OR 0.71, 95%CI [0.43-1.16], p=0.1669), Subacute ST (OR 0.87, 95%CI [0.52-1.45], p=0.5954) and Probable ST (OR 0.80, 95%CI [0.37-1.70], p=0.5572). Possible ST was not evaluated at 30 days. Results for the composite primary endpoint were similar for the ITT and PP populations.

The efficacy endpoint of death, MI, IDR and ARC-ST, devoid of IPST, maintained a significant difference favoring cangrelor over clopidogrel (OR 0.80, 95%CI [0.67-0.95], p=0.0112) at 48 hours, but not at 30 days (OR 0.87, 95%CI [0.75-1.01], p=0.0752).

The overall CEC-adjudicated results were driven by the SA population, as well as those overall subjects (SA, NSTEACS, and STEMI) who did not have an elevated baseline biomarker associated with myocardial injury. There were no regional variations between the US and non-US populations.

Issues supportive of efficacy included:

- The primary endpoint (death, MI, IDR, and ST at 48 hours) was satisfied and sustained for 30 days.
- The primary endpoint following removal of IPST (e.g. death, MI, IDR, and ARC-ST) was still satisfied.

Issues not supportive of efficacy included:

- The primary endpoint following removal of IPST, although satisfied at the pre-specified 48 hour time point, was not sustained at 30 days.
- The endpoints which were used in the CHAMPION PLATFORM and PCI trials (death, MI, and IDR) were not significantly different between the cangrelor and clopidogrel arms of PHOENIX.

**BRIDGE:**

The Stage I (open-label, dose finding) study identified the cangrelor dose of 0.75ug/kg/min as having satisfied the Stage 1 primary efficacy endpoint (i.e.>60% IPA in at least 80% of subject samples) by maintaining platelet inhibition above 60% in 94.4% (17/18) of subject samples. Results for the lower dose of 0.5ug/kg/min showed that platelet inhibition remained above 60% in 76.5% (13/17) of subject samples, thereby not satisfying the primary efficacy endpoint. Doses higher than 0.75ug/kg/min were not evaluated.

The Stage II (double-blind placebo controlled randomized) study showed that cangrelor infusion of 0.75ug/kg/min maintained a PRU < 240 for all time points measured in 98.8% of subjects, compared to 19.9% of placebo subjects (RR 5.2 [95%CI,3.3-8.1] p<0.001). These results satisfied the Stage II primary efficacy endpoint. After discontinuation of the infusion (1-6 hours before surgery), platelet function prior to surgery for subjects in the cangrelor arm was similar to that for subjects in the placebo arm.

Death, MI, stroke, and IDR prior to surgery in Stage II occurred at a rate of 2.8% (3/106) and 4.0% (4/101) in the cangrelor and placebo subjects, respectively. The number of

deaths was numerically lower in the cangrelor group (1) compared to the placebo group (3) during the pre-surgery period. Cangrelor was associated with a numerical increase in non-CABG related bleeding during the 5-day bridge period.

## 6.1 Indication

### 6.1.1 PCI Indication

The Applicant's proposed indication is "Platelex IV is an intravenous $P2Y_{12}$ platelet inhibitor indicated for the reduction of thrombotic events (including stent thrombosis) in patients with coronary artery disease undergoing percutaneous coronary intervention (PCI)."

#### 6.1.1.1 Methods

As described in section 5.3.3, the Applicant's method was to design the CHAMPION PHOENIX trial where the primary efficacy endpoint was based on post-hoc analyses of the CHAMPION PLATFORM and PCI trials. This resulted in the introduction of the UDMI type 4a and ARC-ST as two components of the PHOENIX primary efficacy endpoint.

Pursuant to the review strategy described in section 5.2, the review methodology focused on:

- Evaluating the overall results based on the primary efficacy endpoint from the PHOENIX trial.
- Evaluating components of the composite endpoint and their impact on the primary efficacy analysis.
- Verifying that ARC-defined ST criteria were satisfied by reviewing adjudication packages.
- Determining if the prognostic significance of IPST as outlined by Brener et al. (2013) from the ACUITY and HORIZONS-AMI trials was also evident in the PHOENIX database.
- Evaluating subgroup results by clinical presentation (i.e. STEMI, NSTEACS, and SA), baseline biomarker status, region (US vs. non-US), clopidogrel loading dose in the comparator arm, and other general subgroups.

#### 6.1.1.2 Demographics

**Table 5** and **Table 6** show the CHAMPION PHOENIX subject demographic and baseline characteristics of the ITT population. The mean age was 64 years with equal distribution above and below the mean age. Seventy two percent of the subjects were male and approximately 94% were white, 3% black/African American, 3% Asian. An overall 3.6% were of Hispanic/Latino ethnicity. The approximate average weight was



Reference ID: 3435333

85kg with an average BMI of 29. Approximately 58% of the subjects presented with SA, 27% with NSTEACS, and 16% with STEMI (**Table 7**). Demographic and baseline characteristics were similar between the two arms of the study.

**Table 5. CHAMPION PHOENIX ITT Subject Demographics and Baseline Characteristics-1**

| Parameter, Statistic Category | Cangrelor (N=5581) | Clopidogrel (N=5564) | Overall (N=11,145) |
|---|---|---|---|
| Age, years | | | |
| N | 5581 | 5564 | 11,145 |
| Mean ± SD | 64.0 ± 11.0 | 63.8 ± 11.0 | 63.9 ± 11.0 |
| Median (Q1, Q3) | 64.0 (56, 72) | 64.0 (56, 72) | 64.0 (56, 72) |
| Age group, years | | | |
| <65, n (%) | 2892 (51.8) | 2902 (52.2) | 5794 (52.0) |
| ≥65, n (%) | 2689 (48.2) | 2662 (47.8) | 5351 (48.0) |
| Male, n (%) | 3982 (71.3) | 4042 (72.6) | 8024 (72.0) |
| Race | | | |
| N | 5578 | 5557 | 11,135 |
| White, n (%) | 5231 (93.8) | 5206 (93.7) | 10,437 (93.7) |
| Asian, n (%) | 173 (3.1) | 177 (3.2) | 350 (3.1) |
| Black/African American, n (%) | 156 (2.8) | 152 (2.7) | 308 (2.8) |
| Native Hawaiian/Pacific Islander, n (%) | 13 (0.2) | 16 (0.3) | 29 (0.3) |
| American Indian/Alaskan native, n (%) | 5 (0.1) | 6 (0.1) | 11 (0.1) |
| Ethnicity | | | |
| N | 5581 | 5564 | 11,145 |

**Table 6. CHAMPION PHOENIX ITT Subject Demographics and Baseline Characteristics-2**

| Parameter, Statistic Category | Cangrelor (N=5581) | Clopidogrel (N=5564) | Overall (N=11,145) |
|---|---|---|---|
| Hispanic/Latino, n (%) | 196 (3.5) | 202 (3.6) | 398 (3.6) |
| Weight, kg | | | |
| N | 5580 | 5564 | 11,144 |
| Mean ± SD | 85.2 ± 17.8 | 85.6 ± 17.9 | 85.4 ± 17.8 |
| Median (Q1, Q3) | 84.0 (73, 95) | 84.0 (74, 96) | 84.0 (73, 96) |
| BMI, kg/m$^2$ | | | |
| N | 5577 | 5561 | 11,138 |
| Mean ± SD | 28.96 ± 5.22 | 29.01 ± 5.14 | 28.99 ± 5.18 |
| Median (Q1, Q3) | 28.37 (25.5, 31.8) | 28.37 (25.6, 31.8) | 28.37 (25.6, 31.8) |
| Patient types, n (%) [a] | | | |
| N | 5581 | 5564 | 11,145 |
| SA | 3158 (56.6) | 3059 (55.0) | 6217 (55.8) |
| NSTE-ACS | 1401 (25.1) | 1424 (25.6) | 2825 (25.3) |
| STEMI | 1022 (18.3) | 1081 (19.4) | 2103 (18.9) |
| Cardiac markers >ULN | | | |
| Troponin I/T | 1885/5534 (34.1) | 1947/5520 (35.3) | 3832/11,054 (34.7) |
| CK-MB | 1190/5270 (22.6) | 1230/5280 (23.3) | 2420/10,550 (22.9) |

Source: Section 14.1, Table 1.1, Table 2.1.2.1 and Table 2.2.2.1.
[a] As determined by statistical analysis, taking into account clinical study data available after time of randomization.
Q1 = first quartile; Q3 = third quartile; SD = standard deviation.

**Table 7. Investigator declared patient type**

| | Cangrelor | | Clopidogrel | |
|---|---|---|---|---|
| **Treated** | **N=5581** | **(%)** | **N=5564** | **(%)** |
| Stable Angina | 3220 | (57.7) | 3208 | (57.7) |
| NSTEACS | 1479 | (26.5) | 1435 | (25.8) |
| STEMI | 882 | (15.8) | 921 | (16.6) |

Reviewer's analysis: time\time tx relative. Dataset raw\dem (pttype)

**Table 8** and **Table 9** show the medical history of the ITT population. Approximately 28% had diabetes mellitus of which 71% were non-insulin dependent. Approximately 29% were current smokers, 80% had hypertension, 69% had hyperlipidemia, 5% had a cerebrovascular event, 21% had a previous MI, 10% had congestive heart failure, and

8% had peripheral artery disease. Approximately 24% had a previous PCI and 10% had a previous CABG. Medical histories were similar between the two arms of the study.

**Table 8. CHAMPION PHOENIX ITT Subject Medical History-1**

| | n/N (%) | | |
|---|---|---|---|
| **Parameter Category** | **Cangrelor (N=5581)** | **Clopidogrel (N=5564)** | **Overall (N=11,145)** |
| Diabetes Mellitus | 1546/5571 (27.8) | 1559/5555 (28.1) | 3105/11126 (27.9) |
| Insulin-dependent | 464/5571 (8.3) | 412/5555 (7.4) | 876/11126 (7.9) |
| Non–insulin-dependent | 1040/1504 (69.1) | 1121/1533 (73.1) | 2161/3037 (71.2) |
| Unknown | 42/5571 (0.8) | 25/5555 (0.5) | 67/11126 (0.6) |
| Current smoker within past 30 days | 1533/5444 (28.2) | 1573/5428 (29.0) | 3106/10872 (28.6) |
| Hypertension | 4460/5566 (80.1) | 4406/5546 (79.4) | 8866/11112 (79.8) |
| Hyperlipidemia | 3412/4942 (69.0) | 3380/4908 (68.9) | 6792/9850 (69.0) |

**Table 9. CHAMPION PHOENIX ITT Subject Medical History-2**

| | n/N (%) | | |
|---|---|---|---|
| **Parameter Category** | **Cangrelor (N=5581)** | **Clopidogrel (N=5564)** | **Overall (N=11,145)** |
| Cerebrovascular event | 276/5559 (5.0) | 252/5543 (4.5) | 528/11102 (4.8) |
| Family history of coronary artery disease | 2121/5214 (40.7) | 2108/5195 (40.6) | 4229/10409 (40.6) |
| Previous MI | 1111/5547 (20.0) | 1191/5517 (21.6) | 2302/11064 (20.8) |
| ≤30 days before enrollment | 55/5547 (1.0) | 54/5517 (1.0) | 109/11064 (1.0) |
| Previous PCI | 1281/5569 (23.0) | 1344/5550 (24.2) | 2625/11119 (23.6) |
| ≤30 days before enrollment | 13/5569 (0.2) | 19/5550 (0.3) | 32/11119 (0.3) |
| Previous CABG | 581/5574 (10.4) | 509/5553 (9.2) | 1090/11127 (9.8) |
| ≤30 days before enrollment | 581/5574 (10.4) | 509/5553 (9.2) | 1090/11127 (9.8) |
| Congestive heart failure | 565/5567 (10.1) | 592/5546 (10.7) | 1157/11113 (10.4) |
| Peripheral artery disease | 449/5513 (8.1) | 390/5509 (7.1) | 839/11022 (7.6) |

Source: Section 14.1, Table 2.3.2.1.
CABG = coronary artery bypass graft; MI = myocardial infarction; PCI = percutaneous coronary intervention.

### 6.1.1.3 Subject Disposition

**Table 10** shows the subject disposition. A total of 11,145 ITT subjects were randomized (5581 to the cangrelor arm and 5564 to the clopidogrel arm). A total of 109 subjects in the cangrelor arm and 94 subjects in the clopidogrel arm were reported to either not

have received study drug or not have undergone the index procedure. Of the resulting mITT population (98.0% of the ITT cangrelor arm and 98.3% of the ITT clopidogrel arm), 232 subjects in the cangrelor arm and 225 subjects in the clopidogrel arm had protocol violations, the majority of which were deviations from inclusion/exclusion criteria or incorrect administration of IV or oral study drug. The Applicant also reported that in the ITT population, a total of 341/5581 (6.1%) cangrelor subjects and 319/5564 (5.7%) clopidogrel subjects had a protocol “major deviation” also described as incorrect study drug administration (see CSR Table 7). The per-protocol population included 5240 in the cangrelor arm (93.9% of the ITT cangrelor population) and 5245 in the clopidogrel arm (94.3% off the ITT clopidogrel population). A total of 5498 of the 5581 (98.5%) cangrelor ITT subjects completed the study, and a total of 5482 of the 5564 (98.5%) clopidogrel ITT subjects completed the study. Of the 83 subjects in the cangrelor arm who discontinued from the study, 64 died, 1 had an adverse event leading to discontinuation, 5 withdrew consent, 1 was discontinued as per physician discretion, 10 were lost to follow-up, and 2 were classified as “other”. Of the 82 subjects in the clopidogrel arm who discontinued from the study, 57 died, 0 had an adverse event leading to discontinuation, 7 withdrew consent, 4 were discontinued as per physician discretion, 12 were lost to follow-up, and 2 were classified as “other”.

**Table 11** shows the subject stratification for the ITT population. Approximately 75% of the subjects were administered clopidogrel 600mg (active drug or placebo image) loading dose as specified by the investigator at the time of randomization. Approximately 69% of the subjects were reported to be non-ischemic and 73% of the subjects were reported to not have any ECG changes.

**Table 10. CHAMPION PHOENIX Subject Disposition**

| Category | Stat | Cangrelor | Clopidogrel | Overall |
|---|---|---|---|---|
| Number of Subjects Randomized | N | 5581 | 5564 | 11,145 |
| ITT Population | n/N (%) | 5581/5581(100) | 5564/5564(100) | 11145/11145(100) |
| mITT Population | n/N (%) | 5472/5581(98.0) | 5470/5564(98.3) | 10942/11145(98.2) |
| PP Population | n/N (%) | 5240/5581(93.9) | 5245/5564(94.3) | 10485/11145(94.1) |
| Safety Population | n/N (%) | 5529/5581(99.1) | 5527/5564(99.3) | 11056/11145(99.2) |
| Number of Subjects Completing Study | n/N (%) | 5498/5581(98.5) | 5482/5564(98.5) | 10980/11145(98.5) |
| Number of Subjects Discontinued | n/N (%) | 83/5581 (1.5) | 82/5564(1.5) | 165/11145 (1.5) |
| • Death | n/N (%) | 64/5581 (1.1) | 57/5564 (1.0) | 121/11145 (1.1) |
| • AE | n/N (%) | 1/5581 (0.0) | 0/5564 (0.0) | 1/11145 (0.0) |
| • Withdrew Consent | n/N (%) | 5/5581 (0.1) | 7/5564 (0.1) | 12/11145 (0.1) |
| • Physician Decision | n/N (%) | 1/5581 (0.0) | 4/5564 (0.1) | 5/11145 (0.0) |
| • Lost to Follow-Up | n/N (%) | 10/5581 (0.2) | 12/5564 (0.2) | 22/11145 (0.2) |
| • Other | n/N (%) | 2/5581 (0.0) | 2/5564 (0.0) | 4/11145 (0.0) |

Source: CSR section 14.1.1 (Table 1.0)

**Table 11. CHAMPION PHOENIX ITT Subject Stratification**

| Stratum | Number (%) of patients | | |
|---|---|---|---|
| | Cangrelor (N=5581) | Clopidogrel (N=5564) | Overall (N=11,145) |
| Patient Type [a] | | | |
| Stable angina | 3220 (57.7) | 3208 (57.7) | 6428 (57.7) |
| NSTE-ACS | 1479 (26.5) | 1435 (25.8) | 2914 (26.1) |
| STEMI | 882 (15.8) | 921 (16.6) | 1803 (16.2) |
| Clopidogrel Loading Dose [b] | *(Placebo)* | *(Clopidogrel)* | |
| 600 mg | 4148 (74.3) | 4136 (74.3) | 8284 (74.3) |
| 300 mg | 1433 (25.7) | 1428 (25.7) | 2861 (25.7) |
| NSTE-ACS patients [a] | N=1479 | N=1435 | N=2914 |
| Patient Baseline Status [a] | | | |
| Abnormal | 1994 (35.7) | 2000 (35.9) | 3994 (35.8) |
| Normal | 3587 (64.3) | 3564 (64.1) | 7151 (64.2) |
| Ischemia Status | | | |
| Yes | 467 (31.6) | 439 (30.6) | 906 (31.1) |
| No | 1012 (68.4) | 996 (69.4) | 2008 (68.9) |
| ECG Changes | | | |
| Yes | 408 (27.6) | 374 (26.1) | 782 (26.8) |
| No | 1071 (72.4) | 1061 (73.9) | 2132 (73.2) |

Source: Section 14.1, Table 1.4.2.

[a] As determined by investigator at the time of randomization (does not take into account clinical data available after time of randomization).

[b] As specified by investigator at the time of randomization.

ITT = intent-to-treat; NSTE-ACS = non-ST-segment elevation acute coronary syndrome; STEMI = ST-segment elevation myocardial infarction; ECG = electrocardiogram.

*Reviewer comment: Note that the clopidogrel loading dose in the above table is the investigator "declared/intended" dose at randomization. Nearly all subjects in the cangrelor arm actually received clopidogrel 600 mg as a transition dose.*

### 6.1.1.4 Analysis of Primary Endpoint(s)

**Table 12** shows that the incidence of the primary composite efficacy endpoint of all-cause mortality, MI, IDR and ST at 48 hours was significantly lower in the cohort randomized to cangrelor compared to clopidogrel (RR 0.80, 95%CI [0.68, 0.94]; OR 0.79, 95%CI [0.67, 0.93], p=0.0053) for the ITT population. This result was consistent across the mITT and PP populations. **Table 13** summarizes the results of the trial for the primary composite efficacy endpoint, as well as individual components of the

composite endpoint, for the ITT population. The results favoring cangrelor over clopidogrel were driven by ST (OR 0.62, 95%CI [0.43, 0.89], p=0.0098) and MI (OR 0.80, 95%CI [0.67, 0.97], p=0.0212). There was no difference between cangrelor and clopidogrel for the component endpoints of all-cause mortality, and IDR.

The ST component of the primary composite endpoint was driven by IPST (OR 0.64, 95%CI [0.42, 0.99], p=0.0421). There was no difference between cangrelor and clopidogrel for Definite ST (OR 0.54, 95%CI [0.27-1.10], p=0.0847) and Acute ST (OR 0.52, 95%CI [0.25-1.08], p=0.0757). Probable and Possible ST were not analyzed at 48 hours.

The MI component of the composite primary endpoint was driven by UDMI-type 4a (OR 0.80, 95%CI [0.66, 0.97], p=0.0258). There were no other significant differences between cangrelor and clopidogrel for other MI definitions (i.e. QWMI, types 1, 2, 3, 4b, and 5). Results for the composite primary endpoint were similar in the ITT and PP populations.

The incidence of the composite of death, QWMI, and ST was significantly lower in the cangrelor group (69/5573{1.2%}) compared to the clopidogrel group (100/5561{1.8%}), OR 0.68, 95% CI [0.50, 0.93], p=0.0156. The Agency told the Applicant that this composite from PHOENIX would be sufficient for an NDA submission.

As indicated in section 5.3.3, the sample size estimation was based on a presumed composite event rate of 5.1% in the clopidogrel arm and 3.9% in the cangrelor arm (24.5% reduction in odds ratio). A sample size of 10,900 was estimated to provide 85% power to detect this difference at the one-sided alpha of 0.025. The actual data (n=11,145) showed a clopidogrel event rate of 5.8% and a cangrelor event rate of 4.7%. (21% reduction in odds ratio).

**Figure 7** shows the Kaplan-Meier plot to first occurrence of the primary efficacy endpoint within 48 hours post- randomization (mITT population). The separation between the arms occurred within the initial 2 hours after randomization, after which the difference between the arms remained the same. **Figure 8** shows the Kaplan-Meier plot to first occurrence of ST within 48 hours post- randomization (mITT population). The time course for ST was similar to that for the primary efficacy endpoint.

**Figure 9** shows the results of an exploratory landmark analysis of first occurrence of the composite efficacy endpoint of death, MI, IDR, and ST at 48 hours for the mITT population. The landmark analysis was originally designed to minimize bias in estimating time to event probabilities in each group conditional on the group characteristics at a specific time-point (Dafni, U, 2011). The original premise of the landmark analysis regarding clopidogrel studies was to explore the association of extended clopidogrel use and long-term outcomes of patients receiving DES and BMS for the treatment of CAD.  This analysis was performed by the Applicant in order to

investigate the effect of transitioning from cangrelor to clopidogrel on clinical outcomes between 2 time periods: early treatment (0 →6 hours) and extended treatment (6 →48 hours). The results showed an early protective benefit of cangrelor over clopidogrel in the early treatment time period. After the transition to the extended treatment period, there was no difference in the estimated event rate for the primary endpoint between "clopidogrel and clopidogrel". The data showed that the transition from cangrelor to clopidogrel did not result in a differential benefit for any arm of the study. This suggested no harm due to the transition process. The Applicant's interpretation, considered acceptable in this review, was that there was no gap in the effectiveness of $P2Y_{12}$ inhibitor therapy when transitioning from IV cangrelor to oral clopidogrel.

**Table 12. CHAMPION PHOENIX 48 hour Composite Results in various Populations**

| | n (%) of patients | | | | |
|---|---|---|---|---|---|
| | **Cangrelor** | **Clopidogrel** | **RR and 95% CI** | **OR and 95% CI** | **P-value [a]** |
| **mITT (primary), N** | 5470 | 5469 | | | |
| Death/MI/IDR/ST | 257 (4.7) | 322 (5.9) | 0.80 (0.68, 0.94) | 0.79 (0.67, 0.93) | 0.006 |
| mITT all-subjects [b], N | 5472 | 5470 | | | |
| Death/MI/IDR/ST | 257 (4.7) | 322 (5.9) | 0.80 (0.68,0.94) | 0.79 (0.67,0.93) | 0.005 |
| ITT, N | 5573 | 5561 | | | |
| Death/MI/IDR/ST | 260 (4.7) | 325 (5.8) | 0.80 (0.68,0.94) | 0.79 (0.67,0.93) | 0.005 |
| ITT all-subjects [b], N | 5581 | 5564 | | | |
| Death/MI/IDR/ST | 260 (4.7) | 325 (5.8) | 0.80 (0.68,0.93) | 0.79 (0.67,0.93) | 0.005 |
| PP, N | 5240 | 5245 | | | |
| Death/MI/IDR/ST | 233 (4.4) | 290 (5.5) | 0.80 (0.68,0.95) | 0.80 (0.67,0.95) | 0.011 |
| PP all-subjects [b], N | 5240 | 5245 | | | |
| Death/MI/IDR/ST | 233 (4.4) | 290 (5.5) | 0.80 (0.68,0.95) | 0.80 (0.67,0.95) | 0.011 |

Source: Section 14.1, Table 5.1.1.1, Table 5.1.2.1, Table 5.1.3.1, Table 5.4.1.1, Table 5.4.2.1, Table 5.4.3.1.

[a] P-value for the odds ratio comparing cangrelor versus clopidogrel.

[b] Analysis of the specified population in which patients who did not complete follow-up were counted in the denominator as having had no event.

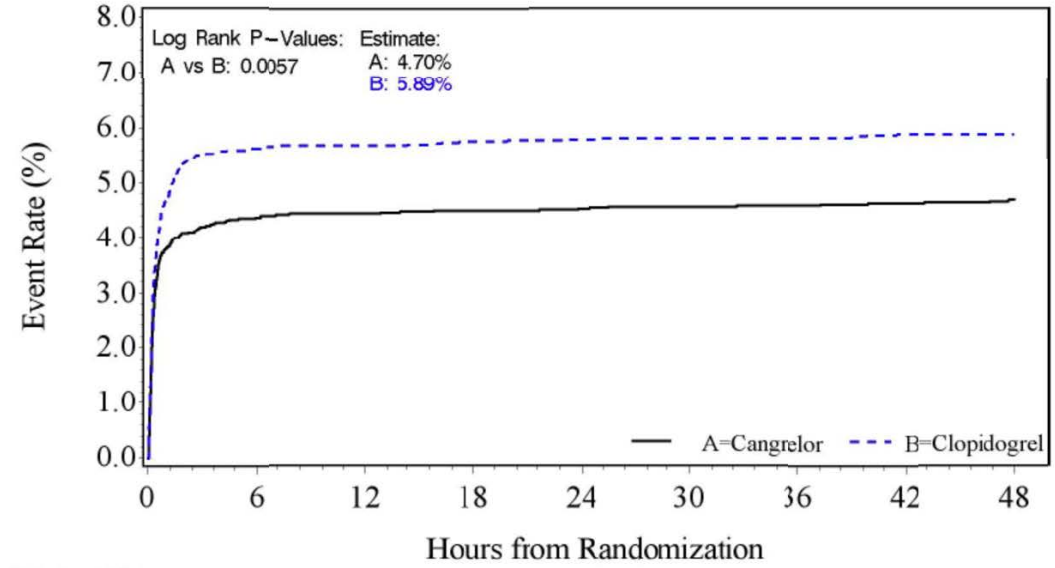
**Table 13. CHAMPION PHOENIX 48 hour CEC Adjudicated Efficacy Endpoint (ITT)**

| | | | Cangrelor vs. Clopidogrel | | |
|---|---|---|---|---|---|
| | Cangrelor (N=5581) | Clopidogrel (N=5564) | RR and 95%CI | OR and 95%CI | P-value for OR |
| 48 hours post randomization | | | | | |
| Death/MI/IDR/ST (primary end point) | 260/5573(4.7%) | 325/5561(5.8%) | 0.80(0.68,0.94) | 0.79(0.67,0.93) | 0.0053 |
| ST | 46/5573(0.8%) | 74/5561(1.3%) | 0.62(0.43,0.89) | 0.62(0.43,0.89) | 0.0098 |
| -IPST | 35/5573(0.6%) | 54/5561(1.0%) | 0.65(0.42,0.99) | 0.64(0.42,0.99) | 0.0421 |
| -Def. ST | 12/5573(0.2%) | 22/5561(0.4%) | 0.54(0.27,1.10) | 0.54(0.27,1.10) | 0.0847 |
| -Prob. ST | 0/5573(0.0%) | 0/5561(0.0%) | -----(-----) | -----(-----) | |
| -Poss. ST | 0/5573(0.0%) | 0/5561(0.0%) | -----(-----) | -----(-----) | |
| Acute ST | 11/5573(0.2%) | 21/5561(0.4%) | 0.52(0.25,1.08) | 0.52(0.25,1.08) | 0.0757 |
| Death | 20/5573(0.4%) | 21/5561(0.4%) | 0.95(0.52,1.75) | 0.95(0.51,1.75) | 0.8702 |
| -CV Death | 20/5573(0.4%) | 21/5561(0.4%) | 0.95(0.52,1.75) | 0.95(0.51,1.75) | 0.8702 |
| MI | 207/5573(3.7%) | 255/5561(4.6%) | 0.81(0.68,0.97) | 0.80(0.67,0.97) | 0.0212 |
| -Q MI | 11/5573(0.2%) | 18/5561(0.3%) | 0.61(0.29,1.29) | 0.61(0.29,1.29) | 0.1911 |
| -Type 1 | 1/5573(0.0%) | 1/5561(0.0%) | 1.00(0.06,15.95) | 1.00(0.06,15.96) | 0.9988 |
| -Type 2 | 0/5573(0.0%) | 0/5561(0.0%) | -----(-----) | -----(-----) | |
| -Type 3 | 3/5573(0.1%) | 0/5561(0.0%) | -----(-----) | -----(-----) | 0.0836 |
| -Type 4a | 194/5573(3.5%) | 239/5561(4.3%) | 0.81(0.67,0.98) | 0.80(0.66,0.97) | 0.0258 |
| -Type 4b | 9/5573(0.2%) | 15/5561(0.3%) | 0.60(0.26,1.37) | 0.60(0.26,1.37) | 0.2182 |
| -Type 5 | 0/5573(0.0%) | 0/5561(0.0%) | -----(-----) | -----(-----) | |
| IDR | 29/5573(0.5%) | 38/5561(0.7%) | 0.76(0.47,1.23) | 0.76(0.47,1.23) | 0.2663 |
| -PCI | 22/5573(0.4%) | 33/5561(0.6%) | 0.67(0.39,1.14) | 0.66(0.39,1.14) | 0.1349 |

| | | | | | |
|---|---|---|---|---|---|
| **-CABG** | 7/5573(0.1%) | 5/5561(0.1%) | 1.40(0.44,4.40) | 1.40(0.44,4.41) | 0.5660 |
| **Death/MI/IDR/ARC-ST** | 233/5573(4.2%) | 289/5561(5.2%) | 0.80(0.68,0.95) | 0.80(0.67,0.95) | 0.0112 |
| **Death/Q MI/ IDR/ST** | 83/5573(1.5%) | 115/5561(2.1%) | 0.72(0.54,0.95) | 0.72(0.54,0.95) | 0.0209 |
| **Death/MI/IDR** | 233/5573(4.2%) | 289/5561(5.2%) | 0.80(0.68,0.95) | 0.80(0.67,0.95) | 0.0112 |
| **Death/Q MI/IDR** | 52/5573(0.9%) | 67/5561(1.2%) | 0.77(0.54,1.11) | 0.77(0.54,1.11) | 0.1632 |
| **Death/MI/ST** | 251/5573(4.5%) | 315/5561(5.7%) | 0.80(0.68,0.93) | 0.79(0.66,0.93) | 0.0053 |
| **Death/MI/ARC-ST** | 224/5573(4.0%) | 279/5561(5.0%) | 0.80(0.67,0.95) | 0.79(0.66,0.95) | 0.0113 |
| **Death/Q MI/ST** | 69/5573(1.2%) | 100/5561(1.8%) | 0.69(0.51,0.93) | 0.68(0.50,0.93) | 0.0156 |
| **Death/MI** | 222/5573(4.0%) | 275/5561(4.9%) | 0.81(0.68,0.96) | 0.80(0.67,0.96) | 0.0140 |
| **Death/Q MI** | 30/5573(0.5%) | 39/5561(0.7%) | 0.77(0.48,1.23) | 0.77(0.48,1.24) | 0.2732 |
| **Death/IDR** | 46/5573(0.8%) | 57/5561(1.0%) | 0.81(0.55,1.19) | 0.80(0.54,1.19) | 0.2714 |
| **Death/ST** | 61/5573(1.1%) | 90/5561(1.6%) | 0.68(0.49,0.93) | 0.67(0.49,0.93) | 0.0169 |

Source: PHOENIX CSR, Table 5.1.2.1, generated by T_ENDPT51.SAS 21MAR13 17:08

**Figure 7. CHAMPION PHOENIX Kaplan-Meier Plot to first occurrence of the primary efficacy endpoint within 48 hours (mITT Population)**

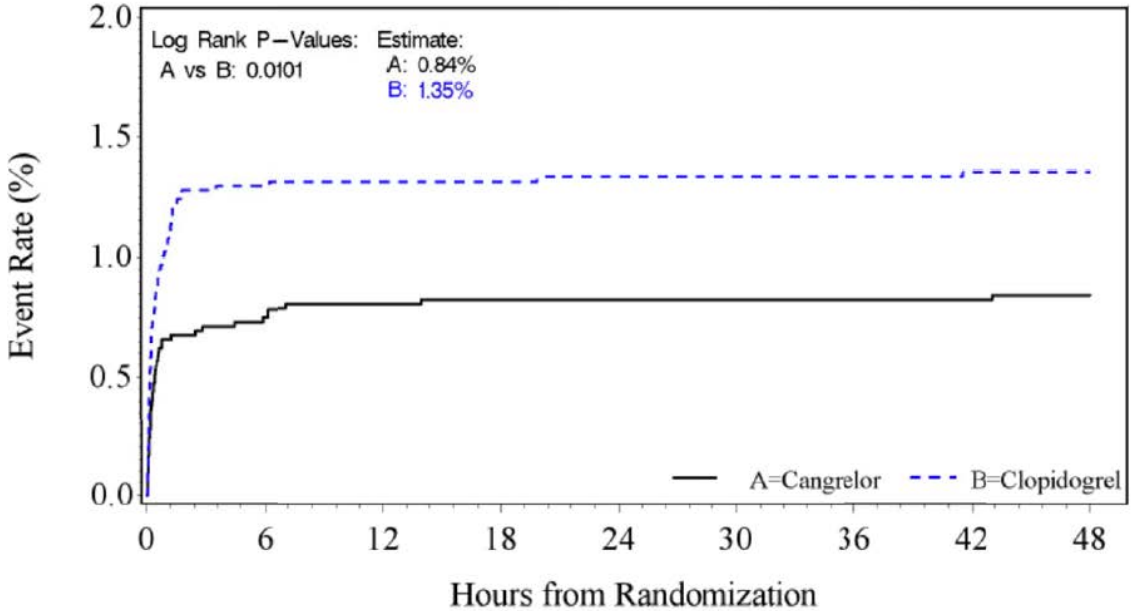



Patients at Risk

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| A: | 5472 | 5233 | 5229 | 5225 | 5223 | 5221 | 5220 | 5217 | 5213 |
| B: | 5470 | 5162 | 5159 | 5155 | 5152 | 5151 | 5151 | 5147 | 5147 |

Source: Section 14.2, Figure 5.11.1.1.

**Figure 8. CHAMPION PHOENIX Kaplan-Meier Plot to first occurrence of ST within 48 hours (mITT Population)**

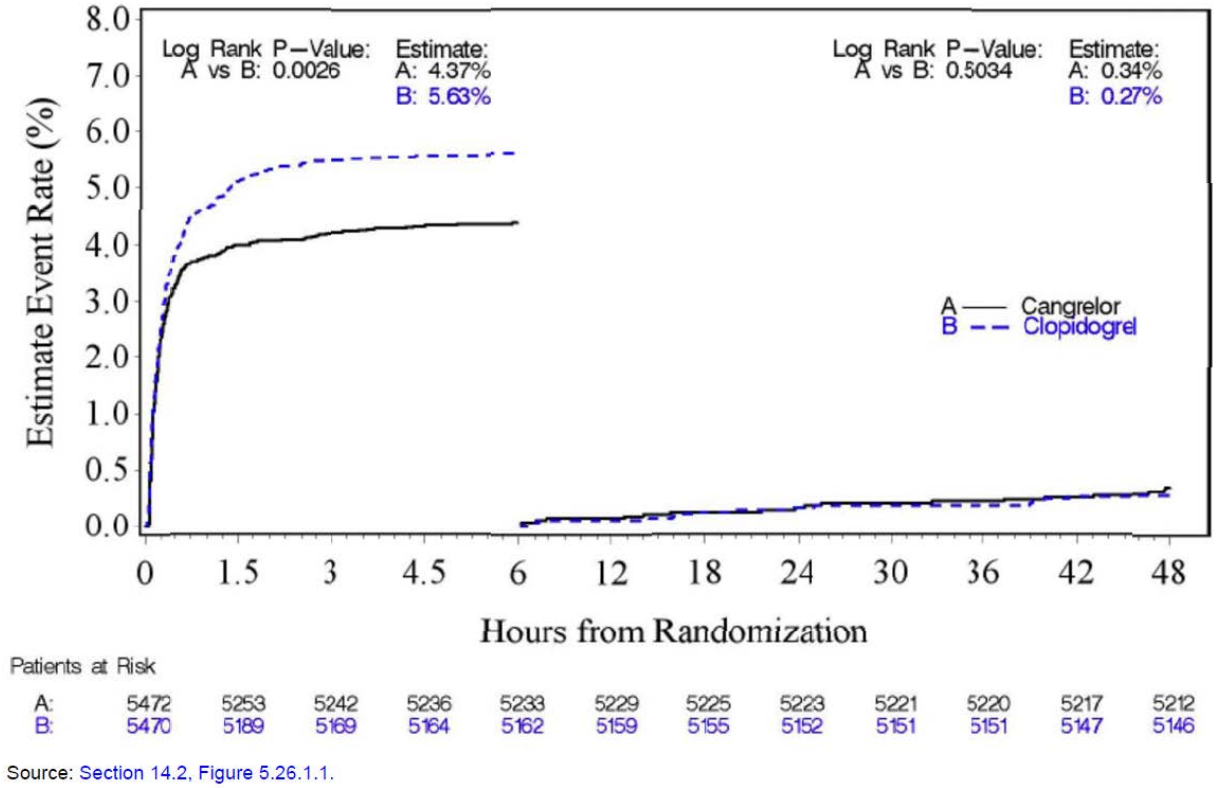



Patients at Risk

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| A: | 5472 | 5426 | 5421 | 5419 | 5419 | 5418 | 5417 | 5416 | 5414 |
| B: | 5470 | 5392 | 5389 | 5388 | 5386 | 5385 | 5385 | 5383 | 5383 |

Source: Section 14.2, Figure 5.51.1.1.

**Figure 9. Landmark analysis of first occurrence of death/MI/IDR/ST in 48 hours (mITT population)**




Source: Section 14.2, Figure 5.26.1.1.

**Table 14** summarizes the 30 day efficacy (composite and components) dataset for the ITT population. The results favored cangrelor over clopidogrel for the composite primary efficacy endpoint (OR 0.85, 95%CI [0.73, 0.99], p=0.0326). As with the 48 hour data, the results at 30 days were driven by ST (OR 0.68, 95%CI [0.50, 0.92], p=0.0112) and MI (OR 0.82, 95%CI [0.68, 0.98], p=0.0281). There was no difference between cangrelor and clopidogrel for the component endpoints of all-cause mortality, and IDR at 30 days.

The ST component of the 30 day composite endpoint was driven by IPST (OR 0.64, 95%CI [0.42, 0.99], p=0.0415). There was no difference between cangrelor and clopidogrel for Definite ST (OR 0.71, 95%CI [0.43-1.16], p=0.1669), Subacute ST (OR 0.87, 95%CI [0.52-1.45], p=0.5954) and Probable ST (OR 0.80, 95%CI [0.37-1.70], p=0.5572). Possible ST was not evaluated at 48 hours.

The MI component of the composite primary endpoint was driven by UDMI-type 4a (OR 0.81, 95%CI [0.66, 0.98], p=0.0285). There were no other significant differences between cangrelor and clopidogrel for other MI definitions (i.e. QWMI, types 1, 2, 4b, and 5). Results for the primary composite endpoint were similar for the ITT and PP populations.

There was a numerical difference in UDMI type 3 disfavoring cangrelor vs. clopidogrel at 30 days (4 events vs. 0 events, p=0.0458) in the mITT and ITT, but not the PP populations where in the latter, there was no difference for UDMI type 3.

The composite endpoint of death, MI, IDR and ARC-ST, devoid of IPST, maintained a significant difference favoring cangrelor over clopidogrel (OR 0.80, 95%CI [0.67-0.95], p=0.0112) at 48 hours (**Table 13**), but not at 30 days (OR 0.87, 95%CI [0.74-1.01], p=0.0752) (**Table 14**).

**Figure 10** shows the Kaplan-Meier plot to first occurrence of death, MI, IDR, or ST within 30 days post randomization (mITT population). Using the time-scale measured in days, the separation between the arms occurred early within the first day, consistent with the initial 2 hours after randomization, after which the difference between the arms remained the same. The Kaplan-Meier plot (**Figure 11**) to first occurrence of ST within 30 days post-randomization (mITT population) showed a similar profile to that of the composite endpoint. These results are consistent with the benefit of cangrelor occurring peri-procedurally.

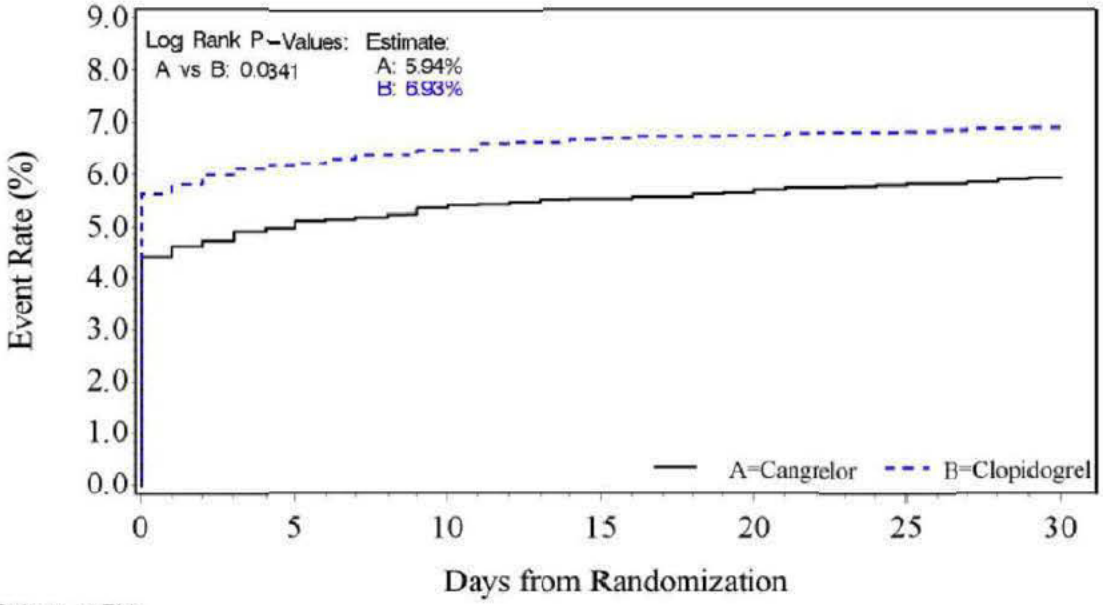
**Table 14. CHAMPION PHOENIX: 30 Day CEC Adjudicated Efficacy Endpoint (ITT)**

| | | | Cangrelor vs. Clopidogrel | | |
|---|---|---|---|---|---|
| | Cangrelor (N=5581) | Clopidogrel (N=5564) | RR and 95%CI | OR and 95%CI | P-value for OR |
| 30 days post randomization | | | | | |
| Death/MI/IDR/ST (primary end point) | 330/5564(5.9%) | 384/5545(6.9%) | 0.86(0.74,0.99) | 0.85(0.73,0.99) | 0.0326 |
| ST | 71/5564(1.3%) | 104/5545(1.9%) | 0.68(0.50,0.92) | 0.68(0.50,0.92) | 0.0112 |
| -IPST | 35/5564(0.6%) | 54/5545(1.0%) | 0.65(0.42,0.99) | 0.64(0.42,0.99) | 0.0415 |
| -Def. ST | 27/5564(0.5%) | 38/5545(0.7%) | 0.71(0.43,1.16) | 0.71(0.43,1.16) | 0.1669 |
| -Prob. ST | 12/5564(0.2%) | 15/5545(0.3%) | 0.80(0.37,1.70) | 0.80(0.37,1.70) | 0.5572 |
| -Poss. ST | 0/5564(0.0%) | 0/5545(0.0%) | -----(-----) | -----(-----) | |
| Subacute ST | 28/5564(0.5%) | 32/5545(0.6%) | 0.87(0.53,1.45) | 0.87(0.52,1.45) | 0.5954 |
| Death | 64/5564(1.2%) | 58/5545(1.0%) | 1.10(0.77,1.57) | 1.10(0.77,1.57) | 0.5980 |
| -CV Death | 51/5564(0.9%) | 49/5545(0.9%) | 1.04(0.70,1.53) | 1.04(0.70,1.54) | 0.8542 |
| MI | 225/5564(4.0%) | 272/5545(4.9%) | 0.82(0.69,0.98) | 0.82(0.68,0.98) | 0.0281 |
| -Q MI | 14/5564(0.3%) | 22/5545(0.4%) | 0.63(0.32,1.24) | 0.63(0.32,1.24) | 0.1784 |
| -Type 1 | 5/5564(0.1%) | 9/5545(0.2%) | 0.55(0.19,1.65) | 0.55(0.19,1.65) | 0.2819 |
| -Type 2 | 0/5564(0.0%) | 1/5545(0.0%) | -----(-----) | -----(-----) | 0.3165 |
| -Type 3 | 4/5564(0.1%) | 0/5545(0.0%) | -----(-----) | -----(-----) | 0.0458 |
| -Type 4a | 195/5564(3.5%) | 239/5545(4.3%) | 0.81(0.68,0.98) | 0.81(0.66,0.98) | 0.0285 |
| -Type 4b | 21/5564(0.4%) | 27/5545(0.5%) | 0.78(0.44,1.37) | 0.77(0.44,1.37) | 0.3790 |
| -Type 5 | 0/5564(0.0%) | 0/5545(0.0%) | -----(-----) | -----(-----) | |
| IDR | 57/5564(1.0%) | 67/5545(1.2%) | 0.85(0.60,1.20) | 0.85(0.59,1.21) | 0.3564 |
| -PCI | 49/5564(0.9%) | 62/5545(1.1%) | 0.79(0.54,1.14) | 0.79(0.54,1.14) | 0.2083 |

| | | | | | |
|---|---|---|---|---|---|
| -CABG | 8/5564(0.1%) | 5/5545(0.1%) | 1.59(0.52,4.87) | 1.60(0.52,4.88) | 0.4086 |
| Death/MI/IDR/ARC-ST | 305/5564(5.5%) | 348/5545(6.3%) | 0.87(0.75,1.01) | 0.87(0.74,1.01) | 0.0752 |
| Death/Q MI/ IDR/ST | 152/5564(2.7%) | 176/5545(3.2%) | 0.86(0.70,1.07) | 0.86(0.69,1.07) | 0.1686 |
| Death/MI/IDR | 304/5564(5.5%) | 346/5545(6.2%) | 0.88(0.75,1.02) | 0.87(0.74,1.02) | 0.0814 |
| Death/Q MI/IDR | 121/5564(2.2%) | 128/5545(2.3%) | 0.94(0.74,1.20) | 0.94(0.73,1.21) | 0.6341 |
| Death/MI/ST | 307/5564(5.5%) | 362/5545(6.5%) | 0.85(0.73,0.98) | 0.84(0.71,0.98) | 0.0251 |
| Death/MI/ARC-ST | 282/5564(5.1%) | 326/5545(5.9%) | 0.86(0.74,1.01) | 0.85(0.73,1.01) | 0.0603 |
| Death/Q MI/ST | 122/5564(2.2%) | 147/5545(2.7%) | 0.83(0.65,1.05) | 0.82(0.65,1.05) | 0.1161 |
| Death/MI | 278/5564(5.0%) | 319/5545(5.8%) | 0.87(0.74,1.02) | 0.86(0.73,1.02) | 0.0771 |
| Death/Q MI | 75/5564(1.3%) | 78/5545(1.4%) | 0.96(0.70,1.31) | 0.96(0.70,1.32) | 0.7906 |
| Death/IDR | 115/5564(2.1%) | 118/5545(2.1%) | 0.97(0.75,1.25) | 0.97(0.75,1.26) | 0.8220 |
| Death/ST | 114/5564(2.0%) | 137/5545(2.5%) | 0.83(0.65,1.06) | 0.83(0.64,1.06) | 0.1347 |

Source: PHOENIX CSR, Table 5.2.1.1, generated by T_ENDPT52.SAS 21MAR13 17:17

**Figure 10. CHAMPION PHOENIX Kaplan-Meier Plot to first occurrence of death, MI, IDR and ST within 30-Days (mITT Population)**

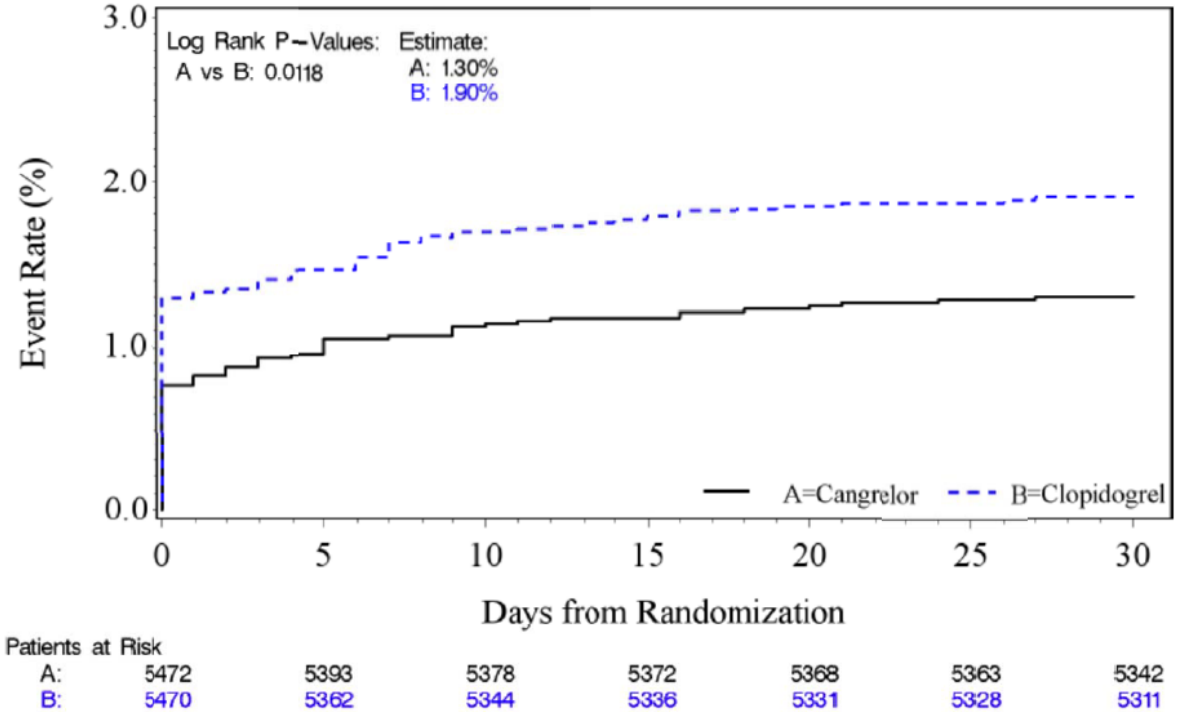



Patients at Risk

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| A: | 5472 | 5189 | 5169 | 5159 | 5153 | 5145 | 5119 |
| B: | 5470 | 5120 | 5103 | 5090 | 5086 | 5082 | 5062 |

Source: Section 14.2, Figure 5.14.1.1.

**Figure 11. CHAMPION PHOENIX Kaplan-Meier Plot to first occurrence of ST within 30-Days (mITT Population)**




Source: Section 14.2, Figure 5.52.1.1.

### 6.1.1.5 Analysis of Secondary Endpoints(s)

**Stent Thrombosis**

ST was developed as a novel tool by the ARC as part of an informal collaborative effort to establish a broad-based consensus on endpoint definitions involving coronary stent clinical trials (Cutlip, D, et al., 2007). Although it was recognized by the ARC that consensus criteria would include some arbitrary features, consistency of endpoints across studies was postulated to facilitate the evaluation of safety and efficacy of stents and therefore foster recognition for regulatory purposes.

The definition of ARC-ST included accompanying clinical signs or symptoms as described in Appendix 9.2. The apparent rationale underlying the definition of ARC-ST was to ensure clinical significance to an angiographically based visual biomarker. The ARC-ST was sub-defined in relation to timing (i.e. Acute ST: 0-24 hours after stent implantation, Subacute ST: > 24 hours-30 days after stent implantation, Late ST: > 30 days-1 year after stent implantation, and Very Late ST: > 1 year after stent implantation) and likelihood of event (i.e. Definite ST, Probable ST, Possible ST).

The Applicant's use of ARC-ST was based on the hypothesis generated from the post-hoc analyses of the CHAMPION PCI and CHAMPION PLATFORM trials. The data from PHOENIX indicated that in the cangrelor arm (n=5472, mITT population), 3061 (55.9%) received a DES and 2308 (42.2%) received a non-DES. Similarly in the clopidogrel arm (n=5470, mITT population), 3020 (55.2%) received a DES and 2344 (42.9%) received a non-DES (see Table 4.2.1.1 CHAMPION PHOENIX CSR). Therefore, 98.1% of the mITT subject population received a stent. As Tables 9 and 10 respectively indicated, the results significantly favoring cangrelor over clopidogrel in the reduction of the primary composite endpoint was driven by ST thereby confirming the Applicant's hypothesis generated by the CHAMPION PCI and PLATFORM post-hoc analyses. The ST results were driven by IPST (see below). The data also suggested no difference in the incidence of the primary composite efficacy endpoint between those subjects given a DES and those given a non-DES (see Figure 6 CHAMPION PHOENIX CSR).

The Applicant's definition of ARC-ST required that the event occurred after the subject will have departed from the catheterization lab. Based on Cutlip, D, et al. (2007), it is this reviewer's opinion that "time 0" occurred immediately after stent deployment, whereby the subject is still located in the catheterization lab. Therefore, events which could have been adjudicated as an acute ARC-ST were adjudicated as an IPST (see next section below on IPST).

A random sampling of cangrelor treated subjects (n=13/122) adjudicated to have sustained an ARC-ST is shown in **Table 15**. Similarly, a sampling of clopidogrel treated subjects (n=13/140) adjudicated to have sustained an ARC-ST is shown in **Table 16**. Under the column titled "Reviewer Comments", the ECG and Ischemia symptoms were defined at baseline. The presence of MI occurred after randomization. Based on the approximate 10% sampling from both arms of the PHOENIX trial, the following features were observed:

- There was a tendency to align the timing of the ARC-ST to the time of chest pain, as per comments from the adjudicators located in the comment field of individual adjudication packages.
- The average time from PCI to ARC-ST was 5.1 days (range 0 days → 21 days) for subjects in the cangrelor arm and 3.7 days (range 0 days → 30 days) for subjects in the clopidogrel arm.
- Of the 13 ARC-ST in the cangrelor arm (**Table 15**), 10 were definite ST and 3 were probable ST. Of the 13 ARC-ST in the clopidogrel arm (**Table 16**), 11 were definite ST and 2 were probable ST.
- In the cangrelor arm, 9 of the 10 definite ST were associated with an MI (usually STEMI), 6 of which had an abnormal baseline ECG and 3 of which had a normal baseline ECG. None of the probable ST subjects were associated with an MI. In the clopidogrel arm, all 11 of the definite ST were associated with an MI (approximately 50% STEMI and 50% NSTEMI), 7 of which had an abnormal baseline ECG and 4 of which had a normal baseline ECG. Both of the probable ST subjects were associated with an MI (ECG



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characteristics not identified due to lack of available ECG at the time of MI in each case).

- In both arms, the timing of the MI and the timing of the definite ST were identical.

Based on the observed features of the randomly sampled subjects who were adjudicated to have sustained an ARC-ST, these events occurred several days post PCI, were associated with an MI, and were similar in characteristics between each arm. The adjudication of ARC-ST was consistent with the analysis description in the CEC Charter.

**Table 15. Cangrelor-treated Subjects Adjudicated to have sustained ARC-ST**

| Cangrelor-treated Subjects Adjudicated to have sustained ARC-ST (random sampling n= 13/122) | | | | | |
|---|---|---|---|---|---|
| **Patient ID** | **Angiography: Date(Time)** | **PCI: Date(Time start, end)** | **ARC-Stent Thrombosis Date(Time)** | **CEC Comments** | **Reviewer Comments** |
| 401001027 | (b) (6) | | Def. ST (b) (6) | Timed to CP | ECG: ABN no criteria entered MI: yes. STEMI (b) (6) Isch: yes |
| 401091342 | | | Prob. ST (b) (6) | Timed by Clinical Scenario not death. Death at (b) (6) | ECG: ABN no criteria applies MI: no Isch: no |
| 401091647 | | | Prob. ST (b) (6) | ----- | ECG: ABN no criteria applies MI: no Isch: yes |
| 407005010 | | | Def. ST (b) (6) | Autopsy report confirmed ST. Death (b) (6) | ECG: ABN STE and ST-dep MI: yes by autopsy report Isch: yes |
| 407007014 | | | Def. ST (b) (6) | ----- | ECG: ABN STE MI: yes (b) (6) not ECG specified Isch: yes |
| 420005054 | | | Prob. ST | Death 20 | ECG: N |

| | | | | |
|---|---|---|---|---|
| | (b) (6) | (b) (6) (-) | days after PCI, unknown cause | MI: no<br>Isch: no |
| 420009271 | | Def. ST<br>(b) (6) | Timed to onset of angina<br>(b) (6) | ECG: N<br>MI: yes, STEMI<br>(b) (6)<br>Isch: yes |
| 439004225 | | Def. ST<br>(b) (6) | ----- | ECG: ABN STE<br>MI: no<br>Isch: yes |
| 448001321 | | Def. ST<br>(b) (6) | ----- | ECG: N<br>MI: yes STEMI<br>(b) (6)<br>Isch: no |
| 448001378 | | Def. ST<br>(b) (6) | Per core lab | ECG: N<br>MI: yes STEMI<br>(b) (6)<br>Isch: no |
| 449005020 | | Def. ST<br>(b) (6) | ----- | ECG: ABN no criteria applies<br>MI: yes STEMI<br>(b) (6)<br>Isch: no |
| 459002020 | | Def. ST<br>(b) (6) | Timed to onset of recurrent symptoms | ECG: ABN no criteria applies<br>MI: yes STEMI<br>(b) (6)<br>)<br>Isch: no |
| 466001076 | | Def. ST<br>(b) (6) | ----- | ECG: ABN STE, new QW<br>MI: yes unknown ECG<br>(b) (6)<br>Isch: yes |

Date and Time: month/day/year; 24-hour clock. CP = Chest Pain; ABN = abnormal; N= Normal; Rem-ABN = Remains abnormal; ECG=electrocardiogram performed at baseline; STE = ST-segment elevation; ST-dep = ST-segment depression; Isch = ischemic symptoms at baseline; TWI = T wave inversion; Def ST = Definite ARC-Stent

Thrombosis; Prob ST – Probable ARC-Stent Thrombosis; MI = Myocardial Infarction; QW= Q-wave

**Table 16. Clopidogrel-treated Subjects Adjudicated to have sustained ARC-ST**

| Clopidogrel-treated Subjects Adjudicated to have sustained ARC-ST (random sampling n= 13/140) | | | | | |
|---|---|---|---|---|---|
| **Patient ID** | **Angiography: Date(Time)** | **PCI: Date(Time start, end)** | **ARC-Stent Thrombosis Date(Time)** | **CEC Comments** | **Reviewer Comments** |
| 401001119 | (b) (6) | | Def.ST (b) (6) | ---- | ECG: N<br>MI: yes<br>STEMI (b) (6)<br>Isch: No |
| 401015011 | | | Def. ST (b) (6) | ----- | ECG: ABN no criteria applies<br>MI: yes<br>STEMI (b) (6)<br>Isch: No |
| 401030335 | | | Prob. ST (b) (6) | ----- | ECG: ABN no criteria applies<br>MI: yes, no ECG (b) (6)<br>Isch: yes |
| 401032015 | | | Def. ST (b) (6) | Core lab assessment confirmed in-stent thrombosis | ECG: N<br>MI: yes<br>STEMI (b) (6)<br>Isch: no |
| 401058008 | | | Def. ST (b) (6) | Symptoms with angio→ST | ECG: ABN no criteria applies<br>MI: yes<br>NSTEMI (b) (6)<br>Isch: not at baseline |
| 401070012 | | | Def. ST (b) (6) | ----- | ECG: ABN no criteria applies<br>MI: yes<br>STEMI (b) (6)<br>Isch: no |
| 401077030 | | | Def. ST (b) (6) | Timed to onset of | ECG: ABN, SB |

| | | | | |
|---|---|---|---|---|
| | (b) (6) | (b) (6) | chest pain after end of index PCI | MI: yes, NSTEMI (b) (6) Isch: yes |
| 401079204 | | Prob. ST (b) (6) | ----- | ECG: ABN no criteria applies MI: yes, no ECG available (b) (6) Isch: no |
| 401084003 | | Def. ST (b) (6) | Timed to recurrence of ischemic symptoms. No source documents available | ECG: ABN, possible septal infarct (b) (6) MI: yes, NSTEMI (b) (6) Isch: yes |
| 401091451 | | Def. ST (b) (6) | New symptoms plus abrupt closure of LAD and some STE | ECG: N MI: yes NSTEMI (b) (6) Isch: no |
| 401109073 | | Def. ST (b) (6) | In stent thrombosis (core lab report) | ECG: N MI: yes STEMI (b) (6) Isch: yes |
| 407005206 | | Def. ST (b) (6) | | ECG: ABN ST-dep and new QW MI: yes STEMI (b) (6) Isch: yes |
| 420009100 | | Def. ST (b) (6) | ----- | ECG: ABN STE MI: yes STEMI (b) (6) Isch: yes |

Date and Time: month/day/year; 24-hour clock. CP = Chest Pain; ABN = abnormal; N= Normal; Rem-ABN = Remains abnormal; ECG=electrocardiogram performed at baseline; STE = ST-segment elevation; ST-dep = ST-segment depression; Isch = ischemic symptoms at baseline; TWI = T wave inversion; Def ST = Definite ARC-Stent

Thrombosis; Prob ST – Probable ARC-Stent Thrombosis; MI = Myocardial Infarction; QW= Q-wave; SB = Sinus Bradycardia

**Intra-Procedural Stent Thrombosis**

A total of 89 subjects in the PHOENIX trial were adjudicated to have sustained an IPST. A random sampling of cangrelor treated subjects (n=13/35) adjudicated to have sustained an IPST is shown in **Table 17**. Similarly, a sampling of clopidogrel treated subjects (n=13/54) adjudicated to have sustained an IPST is shown in **Table 18**. Under the column titled "Reviewer Comments", the ECG and Ischemia symptoms were defined at baseline. The presence of MI occurred after randomization. Based on the approximate 30% sampling from both arms of the PHOENIX trial, the following features were observed:

- The adjudicated timing of the IPST was precisely the same as the adjudicated timing of the start of PCI for each of the sampled subjects.
- Of the 13 IPST in the cangrelor arm, 2 were associated with MI, of which 1 had a baseline abnormal ECG. Of the 11 IPST not associated with an MI, 7 had a baseline abnormal ECG, 3 had a baseline normal ECG, and 1 ECG was not performed.
- Of the 13 IPST in the clopidogrel arm, 3 were associated with MI, of which 2 had a baseline abnormal ECG and 1 had a baseline normal ECG. Of the 10 IPST not associated with an MI, 5 had a baseline abnormal ECG, 4 had a baseline normal ECG, and 1 ECG was not performed.

The precise coincidence of the timing of the adjudicated IPST with the timing of the start of PCI raised a question about whether or not the specified timing in the adjudication package was an arbitrary artifact of "in-cath-lab" thrombosis, which was observed during angiography and which occurred prior to or at the start of PCI. This raised an additional question about whether or not the thrombotic event was truly intra-procedural. Unlike ARC-ST, the event of an IPST was usually not associated with an MI, thereby raising a further question on the clinical significance of this angiographic-driven endpoint based on the PHOENIX data.

Brener, S et al., 2013, postulated that IPST was a rare but serious complication of PCI and that the ARC-ST definition excluded events occurring during PCI. The term Intra-Procedural Stent Thrombosis (IPST) was coined to incorporate stent thrombotic events during stent deployment, compared to after the stent was deployed. In a post-hoc analysis of angiographic data from the ACUITY and HORIZONS-AMI trial, a frame- by-frame review by an independent core laboratory sought to identify patients with the occurrence of an IPST. Patients with versus without IPST were compared to each other in order to identify baseline characteristics associated with IPST and demonstrate the independent association between IPST and adjudicated events at 30 days and 1 year. **Table 19** shows that IPST was associated with baseline STEMI, bailout GPI, TIMI-

grade 0/1 flow, lesions with thrombus treated, bifurcation lesions, and BMS deployment (compared to DES). **Table 20** shows that IPST was also associated with 30 day and 1 year clinical events: death, MI, ARC-ST (definite or probable), ARC-ST definite, TVR, and TIMI Major Bleed (non-CABG). Brenner, S, et al. concluded that IPST was a relatively rare complication of PCI in ACS but was strongly associated with subsequent out-of-lab ST and mortality. It was opined that IPST should be considered as a distinct category of ST and routinely reported, particularly for ACS patients.

Key to the Applicant's application was their position that IPST was an important parameter based on the work of Brener, S, et al., and consequently justified including this parameter as an expansion of the ARC-ST definition. The inclusion of IPST was consistent with the Applicant's program hypothesis of benefit in the peri-procedural domain based on the "fast on—fast off" property of cangrelor.

As a consequence of queries dispatched to the Applicant, the Applicant explored the prognostic significance of IPST from the PHOENIX data. The results at 48 hours shown in **Table 21** and at 30 days shown in **Table 22** revealed a similar pattern to that observed in the ACUITY and HORIZONS-AMI post-hoc analysis by Brener et al., 2013. The presence of an IPST was significantly associated with the composite primary endpoint of death, MI, IDR, and ARC-ST as well as with each component of the composite primary endpoint both at 48 hours and at 30 days. Because this was an exploratory analysis, the Applicant performed a propensity score adjusted analysis in order to evaluate whether or not IPST as a predictor of MACE was independent of potential confounders (i.e. patient type, worst pre-procedure TIMI Score, stent type, bifurcation treatment). Adjustments for these potential confounders demonstrated that the effect of IPST remained an independent predictor of clinical outcomes (OR and 95%CI on death, MI, IDR, ARC-ST: 10.11[6.29, 16.23], $p<0.0001$). The addition of other covariates (i.e. age $\geq$ 65 years, biomarker status, previous PCI, previous CABG, aspirin, PAD, US region, race, weight, smoking, number of vessels, clopidogrel loading dose, infusion duration $\geq$ 129 minutes, previous MI, use of bivalirudin) did not attenuate the independent predictor status of IPST for the composite of death, MI, IDR, ARC-ST (OR and 95% CI: 11.85 [7.08, 19.84], $p<0.0001$). These same adjustments also did not affect the difference between cangrelor and clopidogrel (Applicant response to 74 day letter, appendix 4, Table 5.15.1.1).

It is unclear whether or not Acute ARC-ST, if subjected to a similar post-hoc analysis as was IPST, would have yielded a similar prognostic indication of clinical outcome. The strong correlation between IPST and ARC-ST suggested that the presence of ARC-ST would be of similar prognostic significance for MACE.

The inter-reader variability of IPST was estimated to be Kappa 0.7125. **Table 23** describes the measurement of observer agreement for categorical data (Landis, JR, et al., 1977) and represented this value as "substantial" (i.e. between "moderate" and "almost perfect" which is the highest score). Alternatively, in an expert opinion (Byrt, T,

1996) which challenged this categorical assessment, a revised categorical description was offered and shown in **Table 24**. Under this revision, the estimated Kappa of 0.7125 has been represented as “good” (i.e. above “fair” but below “very good”, which is one level below the highest score of “excellent”). Therefore, scale categories might reflect differences in the confidence of data accuracy. The Applicant has recognized that inter-reader variability by the Angiography Core Lab was “not considered perfect”, and have argued that this level of variability was consistent with that of many diagnostic tests in widespread use, as illustrated in **Table 25**. Based on this evaluation, the inter-reader variability was considered to be acceptable.

Distinguishing IPST from Acute ARC-ST appeared to have been dependent on timing relative to stent deployment. From the definitions (see Appendix 9.2), an ARC-ST would be diagnosed starting from the time immediately after the stent will have been deployed unless other requisite diagnostic criteria (i.e. clinical signs and/or symptoms) were not present. IPST would presumably be diagnosed while the stent was still being deployed (i.e. after crossing the lesion to the deployment of stent). In the index publication by Brener, S, et al. (2013), IPST was defined “as new or increasing (compared with baseline) thrombus within or adjacent to a deployed stent occurring during the index PCI procedure, whether occlusive or non-occlusive. IPST was also deemed present when the baseline level of thrombus was decreasing or resolved after balloon angioplasty or thrombus aspiration but then increased any time after stent implantation (including stent post-dilation)”. This published definition of IPST overlaps with acute ARC-ST from the angiographic perspective. The definitions of IPST as provided by the CEC Charter and the Angiographic Core Laboratory Charter (i.e. ST occurring while the subject is still in the catheterization lab) also overlaps with that of acute ARC-ST from the angiographic perspective. This overlap, in addition to the issues which were raised in section 3.1 (i.e. IPST is a biomarker devoid of associated requisite clinical signs/symptoms), has caused IPST to become a questionable entity.

Based on the efficacy data, IPST drove the primary endpoint whereby its removal from the ST component of the primary endpoint caused loss of sustained benefit for cangrelor at 30 days.

**Table 17. Cangrelor-treated Subjects Adjudicated to have sustained IPST**

| Cangrelor-treated Subjects Adjudicated to have sustained IPST (random sampling n= 13/35) | | | | | |
|---|---|---|---|---|---|
| **Patient ID** | **Angiography: Date(Time)** | **PCI: Date(Time start, end)** | **IPST Date(Time)** | **CEC Comments** | **Reviewer Comments** |
| 401010006 | (b) (6) | | IPST (b) (6) | ----- | ECG: ABN, SB with occasional PVC<br><br>MI: no<br><br>Isch: no |
| 401017066 | | | IPST (b) (6) | Core lab report = IPST | ECG: not done- protocol violation<br><br>MI: no<br><br>Isch: no |
| 401023002 | | | IPST (b) (6) | ----- | ECG: N<br><br>MI: no<br><br>Isch: yes |
| 401029071 | | | IPST (b) (6) | ----- | ECG: ABN no criteria applies<br><br>MI: no<br><br>Isch: no |
| 401079059 | | | IPST (b) (6) | ----- | ECG: ABN no criteria applies<br><br>MI: no<br><br>Isch: no |
| 420009476 | | | IPST (b) (6) | ----- | ECG: N<br>MI: no<br>Isch: yes |
| 420009638 | | | IPST (b) (6) | ----- | ECG: N<br><br>MI: no<br><br>Isch: yes |
| 420019004 | | | IPST (b) (6) | ----- | ECG: ABN, STE, new QW<br><br>MI: no (no entry)<br><br>Isch: yes |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | Note: troponin-I 11.74 |
| 439004216 | | (b) (6) | IPST (b) (6) | ----- | ECG: not done- protocol violation<br><br>MI: yes, NSTEMI, NQWMI, CKMB 22.5, (b) (6)<br><br>Isch: no |
| 448019001 | | | IPST (b) (6) | ----- | ECG: ABN, STE, new QW<br><br>MI: no (no audit trial)<br><br>Isch: yes<br><br>Note: troponin-T 0.148. Patient considered to have had STEMI upon entry. |
| 449001025 | | | IPST (b) (6) | ----- | ECG: ABN, TWI<br><br>MI: no<br><br>Isch: no |
| 495002003 | | | IPST (b) (6) | ----- | ECG: ABN, ST-dep and STE<br><br>MI: no<br><br>Isch: yes |
| 495005595 | | | IPST (b) (6) | Thrombosis detected during, not after PCI | ECG: ABN, old QW<br><br>MI: yes, type 3 associated with death on (b) (6)<br><br>Cardiac |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | markers not increased. No ECG available.<br><br>Isch: no |

Date and Time: month/day/year; 24-hour clock. CP = Chest Pain; ABN = abnormal; N= Normal; ECG=electrocardiogram performed at baseline; SB = Sinus Bradycardia; STE = ST-segment elevation; ST-dep = ST-segment depression; Isch = ischemic symptoms at baseline; TWI = T wave inversion; MI = Myocardial Infarction; QW= Q-wave; ULN = upper limit of normal; PVC = premature ventricular contraction; CKMB ULN 5.09

**Table 18. Clopidogrel-treated Subjects Adjudicated to have sustained IPST**

| Clopidogrel-treated Subjects Adjudicated to have sustained IPST (random sampling n= 13/54) | | | | | |
|---|---|---|---|---|---|
| **Patient ID** | **Angiography: Date(Time)** | **PCI: Date(Time start, end)** | **IPST Date(Time)** | **CEC Comments** | **Reviewer Comments** |
| 401010011 | (b) (6) | | IPST (b) (6) | ----- | ECG: ABN no criteria applies<br><br>MI: no<br><br>Isch: yes |
| 401010092 | | | IPST (b) (6) | No evidence of IPST in catheterization report | ECG: ABN no criteria applies<br><br>MI: yes, NSTEMI, NQWMI, (b) (6)<br><br>Isch: no |
| 401053066 | | | IPST (b) (6) | Per core lab | ECG: ABN no criteria applies<br><br>MI: no<br><br>Isch: no |
| 401073002 | | | IPST (b) (6) | ----- | ECG: not done- protocol violation<br><br>MI: no<br><br>Isch: no |
| 401079061 | | | IPST (b) (6) | ----- | ECG: N<br><br>MI: no<br><br>Isch: no |
| 401091530 | | | IPST (b) (6) | ----- | ECG: ABN no criteria applies<br><br>MI: yes, NSTEMI (b) (6)<br><br>Isch: yes |
| 420009051 | | | IPST (b) (6) | ----- | ECG: N<br><br>MI: no |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | Isch: no |
| 420009318 | (b) (6) | | IPST (b) (6) | Per core lab report | ECG: ABN, ST-dep<br><br>MI: no<br><br>Isch: yes |
| 420009566 | | | IPST (b) (6) | Per core lab report | ECG: N<br><br>MI: no<br><br>Isch: no |
| 420011009 | | | IPST (b) (6) | ----- | ECG: ABN STE, old QW<br><br>MI: no<br><br>Isch: yes-day before but not at baseline |
| 443002362 | | | IPST (b) (6) | Per core labs | ECG: N<br><br>MI: yes STEMI, (b) (6)<br><br>CKMB 17.8<br><br>Isch: no |
| 448001092 | | | IPST (b) (6) | IPST vs. definite ST | ECG: ABN, old LBBB<br><br>MI: no<br><br>Isch: yes |
| 449002020 | | | IPST (b) (6) | Core lab assessment confirmed IPST | ECG: N<br><br>MI: no<br><br>Isch: yes |

Date and Time: month/day/year; 24-hour clock. CP = Chest Pain; ABN = abnormal; N= Normal; ECG=electrocardiogram performed at baseline; SB = Sinus Bradycardia; STE = ST-segment elevation; ST-dep = ST-segment depression; Isch = ischemic symptoms at baseline; TWI = T wave inversion; MI = Myocardial Infarction; QW= Q-wave; ULN = upper limit of normal; CKMB ULN 5.09

**Table 19. Baseline associations with IPST from ACUITY and HORIZONS-AMI**

Table 1. Baseline Clinical and Angiographic Characteristics of Patients With and Without IPST

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(JACC Cardiovasc Interv. 2013;6:36–43)

**Table 20. Clinical Event associations with IPST from ACUITY and HORIZONS-AMI**

Table 2. Clinical Events Through 30-Day and 1-Year Follow-Up

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(JACC Cardiovasc Interv. 2013;6:36–43)

**Table 21. CHAMPION PHOENIX 48 Hour efficacy and safety outcomes in patients with and without IPST during index PCI**

| 48 hour endpoint | IPST | Not IPST | RR (95% CI) | p-value |
|---|---|---|---|---|
| Efficacy (mITT population) | (N=89) | (N=10,850*) | | |
| Death/MI/IDR/ARC-ST | 26 (29.2) | 490 (4.5) | 6.47 (4.63,9.04) | <0.0001 |
| Death | 5 (5.6) | 31 (0.3) | 19.66 (7.83,49.40) | <0.0001 |
| ARC ST | 3 (3.4) | 31 (0.3) | 11.80 (3.67,37.88) | <0.0001 |
| IDR | 4 ( 4.5) | 62 (0.6) | 7.87 (2.92,21.15) | <0.0001 |
| MI | 23 (25.8) | 439 (4.0) | 6.39 (4.44,9.19) | <0.0001 |
| Safety (Safety population) | (N=89) | (N=10,967) | | |
| Any TIMI bleeding | 1 (1.1) | 21 (0.2) | 5.87 (0.80,43.15) | 0.0494 |
| Major | 0 (0.0) | 10 (0.1) | (,) | 0.7756 |
| Minor | 1 (1.1) | 11 (0.1) | 11.20 (1.46,85.85) | 0.0035 |

Source: Appendix 4, Tables 91.5.1.1.1, 91.6.1.4.1

* 3 patients have no efficacy data at 48 h – total mITT population for patients without IPST is N = 10,853

**Table 22. CHAMPION PHOENIX 30-day efficacy outcomes in patients with and without IPST during index PCI**

| 30 day endpoint | IPST | Not IPST | RR (95% CI) | p-value |
|---|---|---|---|---|
| Efficacy (mITT population) | (N=89) | (N=10,830*) | | |
| Death/MI/IDR/ARC-ST | 28 (31.5) | 617 (5.7) | 5.52 (4.03,7.57) | <0.0001 |
| Death | 9 (10.1) | 106 (1.0) | 10.33 (5.41,19.75) | <0.0001 |
| ARC ST | 5 (5.6) | 86 (0.8) | 7.07 (2.94,17.01) | <0.0001 |
| IDR | 5 (5.6) | 117 (1.1) | 5.20 (2.18,12.42) | <0.0001 |
| MI | 24 (27.0) | 473 (4.4) | 6.17 (4.34,8.79) | <0.0001 |

Source: Appendix 4, Table 91.5.2.1.1

* 23 patients have no efficacy data at 30 days – total mITT population for patients without IPST is N = 10,853

**Table 23. Measurement of Observer Agreement for Categorical Data**

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**Landis JR and Koch GG. The Measurement of Observer Agreement for Categorical Data. Biometrics. 1977; 33:159-174.**

**Table 24. Revised quality of Observer Agreement for Categorical Data**

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**Byrt T: How good is that agreement? (Letter to editor) Epidemiology 1996;7:561.**

**Table 25. Score reproducibility and variability in quantitative coronary measurements**

| Test Modality | Kappa value |
|---|---|
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LV indicates left ventricle; CT, computerized tomography; PFO, patent foramen ovale; ACC, American College of Cardiology; and AHA, American Heart Association

Source: Genereux, P, et al., 2011, Circ Cardiovasc Interv, 4:553-561

**MI**

Based on the post-hoc analyses of the CHAMPION PLATFORM and PCI trials, the Applicant hypothesized that evolving MIs prior to PCI masked the beneficial effect of cangrelor in attenuating the rate of peri-procedural events. Therefore, baseline myocardial status was required to be within normal limits at the start of PCI.

A normal baseline in the NSTEACS population was identified as two normal troponin and/or CKMB samples taken 6 hours apart, with no new changes in 12-lead ECG and no ongoing or recent clinical symptoms since the 1st normal biomarker. A normal baseline in the SA population was identified as one normal troponin or CKMB sample, with no new ECG changes and no ACS symptoms. An abnormal baseline was identified as one sample greater than the ULN or two normal samples < 6 hours apart, or new ECG changes, or recent symptoms within the last 6 hours. A “baseline unknown” was defined as no availability of pre-PCI samples.

From the PHOENIX Executive Committee Meeting Minutes of 22 SEPT 2010 (see CSR section 16.1.4.2), the definition of MI for adjudication purposes required a normal baseline followed by CKMB elevation > 3x ULN (troponin could be used if CKMB was not available). Evidence of angiographic, ECG and ischemic symptoms were not required as qualification parameters for the adjudication of an MI. Reinfarction was defined as an abnormal but decreasing baseline or baseline unknown followed by re-elevation of CKMB ≥ 50% above the nadir and 3x ULN from the last sample. This was required to be accompanied by angiographic evidence of re-occlusion, or ischemic symptoms, or new ECG changes. Patients determined to have a baseline STEMI (including patients with normal baseline cardiac markers who were confirmed by the CEC adjudication to have baseline STEMI ECG) were not reviewed by the CEC for peri-procedural MI (from PHOENIX CSR section 9.5.2.3.2).

The UDMI (see Appendix 9.1 and section 5.3.3) was used in the CHAMPION PHOENIX trial. The CEC Adjudication Review Guideline provided the definition and timing of the 5 types of UDMI. Type 1 (spontaneous MI due to plaque-mediated ischemia) and Type 2 (MI due to coronary vasospasm or embolism, anemia, arrhythmia, hypo or hyper tension) were not related to procedures and the timing of the event was defined as time to 1st qualifying criteria (symptoms, first cardiac markers, first ECG). Type 3 MI was related to sudden death and the timing of the event was defined as time of death. Type 4a MI was related to PCI and the timing of the event was defined as start of PCI. Type 4b MI was related to stent thrombosis and the timing of the event was defined as time to 1st qualifying criteria (symptoms, first cardiac markers, first ECG). Type 5 MI was related to CABG and the timing of the event was defined as CABG start-time.

The CHAMPION-PHOENIX results showed that the overall MI rate was significantly lower in the ITT cangrelor group (207/5573: 3.7%) compared to the clopidogrel group (255/5561: 4.6%), (OR 0.80, 95% CI [0.67, 0.97], p=0.0212). This result was driven by



Reference ID: 3435333

UDMI type 4a: 194/5573 (3.5%) in the cangrelor group and 239/5561 (4.3%) in the clopidogrel group (OR 0.80 [0.66, 0.97], p=0.0258). There was only one adjudicated Type 1 MI reported in each group. There was no reported Type 2 MIs. There were 3 reported Type 3 MIs in the cangrelor group and none in the clopidogrel group. There were 9 / 5573 (0.2%) Type 4b MIs in the cangrelor group and 15/5561 (0.3%) Type 4b MIs in the clopidogrel group (OR 0.60, 95% CI [0.26. 1.37], p=0.2182). There was no reported Type 5 MIs.

Type 1 MI was required for an adjudication of Type 4a MI (associated with PCI and aligned with IPST) and Type 4b MI (associated with ST and aligned with ARC-ST). Since the Adjudication Charter restricted multiple assignments of MI (e.g. an MI assigned to type 4a would not be simultaneously assigned to type 1), the paucity of type 1 MI was an artifact of the adjudication process.

The lack of a significant difference between cangrelor and clopidogrel for Type 4b MI in the setting of a significant difference in ST between the cangrelor and clopidogrel had raised a question about how the adjudication process discriminated Type 4a from Type 4b MI. This question was communicated to the Applicant. The Applicant replied that adjudication of a Type 4b MI required spontaneous MI or re-MI in association with an ARC- ST defined by the Applicant as an ST occurring after the subject departed from the catheterization lab. An MI or re-MI in the presence of an IPST, defined as an ST occurring while the subject was still in the catheterization lab, did not qualify a patient for a Type 4b MI and therefore such an MI was adjudicated as a Type 4a. **Table 26** shows the subjects adjudicated to have sustained an MI, subdivided by UDMI Type. The Applicant combined the adjudicated-MI subjects from both groups and re-distributed them in accordance to whether or not they were adjudicated to have an ST or not reported to have an ST. The incidences of adjudicated-ST vs. no-reported ST were further subdivided into adjudicated-IPST vs. no-reported IPST, and adjudicated-ARC-ST vs. no-reported ARC-ST, respectively. Of the 462 ITT (same number mITT) adjudicated MI subjects (207 cangrelor and 255 clopidogrel- see **Table 13**), 46/120 (38.3%) subjects were adjudicated to have an ST, and 416/10,819 (3.8%) subjects were not reported to have an ST. Those ST events in MI subjects adjudicated as IPST were also adjudicated to Type 4a MI, and those ST events in MI subjects adjudicated as ARC-ST were also adjudicated to Type 4b MI. Furthermore, all cases of ST with evidence suggestive of baseline cardiac marker elevation without re-elevation, or MI antecedent to ST, were adjudicated to Type 4a MI. This resulted in a higher number of adjudicated UDMI Type 4a MIs. Also, the low Type 1 MI event rate was attributed to the CEC adjudication process of not assigning more than one type of MI to each adjudication package.

It is the opinion of this reviewer that the incidence of MI favoring cangrelor over clopidogrel was due to the requirement of a normal baseline, thereby confirming the hypothesis generated from the post-hoc analyses of CHAMPION PLATFORM and CHAMPION PCI. The CHAMPION PLATFORM and PCI trials suggested that if the MI adjudications were not filtered to exclude those experiencing an MI prior to PCI, the

results from PHOENIX likely would not have shown a difference between cangrelor and clopidogrel for MI. The higher incidence of Type 4a MI was likely due to an artifact of the adjudication process associated with the nebulous distinction between IPST and Acute ARC-ST as well as the assignment of MI occurring prior to ST as Type 4a.

A random sampling of cangrelor treated subjects (n=25/469) adjudicated to have sustained an MI is shown in **Table 27**. Similarly, a random sampling of clopidogrel treated subjects (n=25/526) adjudicated to have sustained an MI is shown in **Table 28**. Under the column titled "Reviewer Comments", the ECG and Ischemia symptoms were defined at baseline. Based on the approximate 5% sampling from both arms of the PHOENIX trial, the following features were observed:

- The adjudicated MIs were mostly NSTEMIs and assessed as a Type 4a from the UDMI classification. One subject from the sampled cangrelor group and three subjects from the sampled clopidogrel group were assessed as Type 4b MIs.
- In all Type 4a MI adjudications, the adjudicated timing of the event was precisely coincident with the time of the start of PCI. Baseline status in those subjects adjudicated to have sustained a Type 4a MI were classified by the Adjudication Committee as either normal, decreasing and returning to normal.
- In the Type 4b MI diagnoses, the MI was adjudicated to have occurred 2 weeks after the PCI (subject 401030065), 27 minutes after PCI (subject 401001119), 46 minutes after PCI (subject 401070012), and 67 minutes after PCI (401084003).
- The MIs were based on laboratory measurements mostly of CKMB. The average peak CKMB in the cangrelor arm was 31.7, and the average peak CKMB in the clopidogrel arm was 89.7. The reference upper limit of normal was reported to be 5.1.
- An approximate average of 70% of the subjects was adjudicated to have an abnormal ECG at baseline; and 66% of the subjects were adjudicated to have ischemia at baseline.

The respective timing of the adjudicated MI relative to the start of PCI appeared to have guided the Clinical Endpoint Committee in classifying the type of UDMI diagnosis. This was consistent with the analysis description in the Clinical Endpoint Committee Charter. Despite the large number of abnormal baseline ECGs as well as baseline ischemia, the "normal" or "returning to normal" baseline adjudication was focused on laboratory parameters. Additionally, for those baseline ECGs recorded as abnormal, the criteria for such abnormality as specified in the Case Report Form were not met in the majority of cases. The assessment of the ECG abnormalities was based on "no criteria apply".



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**Table 26. CHAMPION PHOENIX Allocation of 48 hour MI by Type in Patients with ST**

| mITT population | ST (N=120) | Not ST (N=10,819*) | RR (95% CI) |
|---|---|---|---|
| MI | 46 (38.3) | 416 (3.8) | 9.97 (7.80,12.75) |
| Type 1 | 0 (0.0) | 2 (0.0) | ( , ) |
| Type 2 | 0 (0.0) | 0 (0.0) | ( , ) |
| Type 3 | 2 (1.7) | 1 (0.0) | 180.32 (16.46,1975.19) |
| Type 4a | 20 (16.7) | 413 (3.8) | 4.37 (2.89,6.59) |
| Type 4b | 24 (20.0) | 0 (0.0) | ( , ) |
| Type 5 | 0 (0.0) | 0 (0.0) | ( , ) |
| **mITT population** | **IPST (N=89)** | **Not IPST (N=10,850**)** | **RR (95% CI)** |
| MI | 23 (25.8) | 439 (4.0) | 6.39 (4.44,9.19) |
| Type 1 | 0 (0.0) | 2 (0.0) | ( , ) |
| Type 2 | 0 (0.0) | 0 (0.0) | ( , ) |
| Type 3 | 2 (2.2) | 1 (0.0) | 243.82 (22.31,2664.59) |
| Type 4a | 20 (22.5) | 413 (3.8) | 5.90 (3.97,8.78) |
| Type 4b | 1 (1.1) | 23 (0.2) | 5.30 (0.72,38.82) |
| Type 5 | 0 (0.0) | 0 (0.0) | ( , ) |
| **mITT population** | **ARC-ST (N=34)** | **Not ARC-ST (N=10,905***)** | **RR (95% CI)** |
| MI | 25 (73.5) | 437 (4.0) | 18.35 (14.70,22.90) |
| Type 1 | 0 (0.0) | 2 (0.0) | ( , ) |
| Type 2 | 0 (0.0) | 0 (0.0) | ( , ) |
| Type 3 | 0 (0.0) | 3 (0.0) | ( , ) |
| Type 4a | 1 (2.9) | 432 (4.0) | 0.74 (0.11,5.13) |
| Type 4b | 24 (70.6) | 0 (0.0) | ( , ) |
| Type 5 | 0 (0.0) | 0 (0.0) | ( , ) |

Source: Appendix 4, Tables 92.5.1.1.1; 91.5.1.1.1; 93.5.1.1.1

* 3 patients have no efficacy data at 48 h – total mITT population for patients without ST is N = 10,822

** 3 patients have no efficacy data at 48 h – total mITT population for patients without IPST is N = 10,853

*** 3 patients have no efficacy data at 48 h – total mITT population for patients without ARC-ST is N = 10,908

**Table 27. Cangrelor-Treated Subjects Adjudicated to have sustained MI**

| Patient ID | MI: Date(Time) | PCI: Date(Time) | Peak CKMB | Peak TPN | ST Class | UDMI Type | If 4a, assess baseline | CEC Comments | Reviewer Comments |
|---|---|---|---|---|---|---|---|---|---|
| 401001005 | | (b) (6) | 19.3 | ----- | NSTEMI | 4a | N/D and Rtn to N | ----- | ECG: N<br>Isch: no |
| 401001137 | | | 17.8 | ----- | NSTEMI | 4a | N/D and | ----- | ECG: N |

| | (b) (6) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Rtn to N | | Isch: yes |
| 401001158 | | 22.0 | ----- | NSTEMI | 4a | N/D and Rtn to N | ----- | ECG: ABN no criteria applies<br><br>Isch: yes |
| 401002034 | | 33.0 | ----- | NSTEMI | 4a | N/D and Rtn to N | ----- | ECG: N<br><br>Isch: no |
| 401010004 | | 39.3 | ----- | NSTEMI | 4a | N/D and Rtn to N | ------ | ECG: ABN LVH cannot r/o septal MI<br><br>Isch: yes |
| 401010067 | | 16 | ----- | NSTEMI | 4a | N/D and Rtn to N | ----- | ECG: ABN no criteria applies<br><br>Isch: no |
| 401015010 | | 20.9 | ----- | NSTEMI | 4a | N/D and Rtn to N | ----- | ECG: ABN no criteria applies<br><br>Isch: no |
| 401024016 | | 27 | ---- | NSTEMI | 4a | N/D and Rtn to N | ----- | ECG: ABN no criteria applies<br><br>Isch: no |
| 401025020 | | 25.8 | ----- | NSTEMI | 4a | N/D and Rtn to N | ----- | ECG: ABN Q-wave, not new<br><br>Isch: yes |
| 401029049 | | 19.5 | ----- | NSTEMI | 4a | N/D and Rtn to N | ----- | ECG: ABN no criteria applies<br><br>Isch: no |
| 401030065 | | ----- | 469.48 | NSTEMI | 4b | ----- | ----- | ECG: ABN atrial pacer, t-wave abn<br><br>Isch: no |
| 401030207 | | 26.0 | ----- | NSTEMI | 4a | N/D and Rtn to N | ----- | ECG: N<br><br>Isch: no |
| 401053011 | | 99.6 | 20.45 (ULN 0.4) | STEMI | 4a | ABN/D Rem-ABN | ----- | ECG: ABN, new QW<br><br>Isch: yes |
| 401055063 | | 15.9 | 7.0 (ULN 0.049) | NSTEMI | 4a | ABN/D Rem-ABN | ABN/D and angio compl. | ECG: N<br><br>Isch: no |
| 401059027 | | 19.0 | ----- | NSTEMI | 4a | N/D and Rtn to N | ----- | ECG: ABN no criteria applies<br><br>Isch: yes |
| 401079223 | | 16.2 | ----- | NSTEMI | 4a | N/D and Rtn to N | ----- | ECG: ABN no criteria applies |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | Isch: no |
| 401091423 | (b) (6) | | 116.2 | ----- | NSTEMI | 4a | N/D and Rtn to N | ----- | ECG: ABN no criteria applies<br><br>Isch: no |
| 401091615 | | | 43.6 | | NSTEMI | 4a | N/D and Rtn to N | CEC: SA patient with normal baseline; MB increasing | ECG: N<br><br>Isch: yes |
| 401093046 | | | 19.5 | ----- | NSTEMI | 4a | N/D and Rtn to N | Stable Angina: 1 sample sufficient to assess baseline | ECG: N<br><br>Isch: no |
| 420001052 | | | 23.5 (ULN 6.3) | 6.17 (ULN 0.03) | Un-known | 4a | N/D and Rtn to N | CEC: BBB on ECG; MB increased > 3x ULN with normal baseline | ECG: ABN, old LBBB<br><br>Isch: no |
| 420003007 | | | 62.2 | ----- | STEMI | 4a | N/D and Rtn to N | CEC: no baseline but post PCI ECG with stent elevated that decreased on L/V ECG | ECG: ABN no criteria applies<br><br>Isch: no |
| 420003070 | | | 18.9 | ----- | NSTEMI | 4a | N/D and Rtn to N | CEC: partial LBBB. SA with normal baseline | ECG: ABN, old LBBB<br><br>Isch: no |
| 420003144 | | | 15.9 | ----- | NSTEMI | 4a | N/D and Rtn to N | ----- | ECG: N<br><br>Isch: no |
| 420003191 | | | 16.9 | ----- | NSTEMI | 4a | N/D and Rtn to N | CEC: baseline abnormal, decreasing and returned to normal; post PCI CKMB > 3 x ULN | ECG: ABN; ST dep in at least 2 contiguous leads and TWI<br><br>Isch: yes |
| 420009187 | | | 27.0 | ----- | NSTEMI | 4a | N/D and Rtn to N | ----- | ECG: N<br><br>Isch: yes |

Date and Time: month/day/year; 24-hour clock. N=Normal; D=decreasing; Rtn to N= return to normal; ABN = abnormal; Rem-ABN = Remains abnormal; ECG=electrocardiogram performed at baseline; STE = ST-segment elevation; ST-dep = ST-segment depression; CKMB upper limit of normal = 5.09; Troponin-I upper limit of normal = 0.06; compl = complications; Isch = ischemic symptoms at baseline; TWI = T wave inversion

**Table 28. Clopidogrel-treated Subjects Adjudicated to have sustained MI**

| Patient ID | MI: Date(Time) | PCI Date (Time) | Peak CKMB | Peak TPN | ST Class | UDMI | If 4a, assess baseline | CEC Comments | Reviewer Comments |
|---|---|---|---|---|---|---|---|---|---|
| 401001002 | [redacted] | (b) (6) | 16.0 | ---- | NSTEMI | 4a | N/D and Rtn to N | ----- | ECG: N<br><br>Isch: no |
| 401001031 | [redacted] | [redacted] | 241.2 | ---- | STEMI | 4a | ABN/D and Rem-ABN | Abnormal decreasing with angiographic complication | ECG: ABN with STE<br><br>Isch: yes |
| 401001119 | [redacted] | [redacted] | 82.4 | ----- | STEMI | 4b | ----- | Non QW STEMI | ECG: N<br><br>Isch: no |
| 401001152 | [redacted] | [redacted] | 15.6 | ----- | NSTEMI | 4a | N/D and Rtn to N | ----- | ECG: ABN no criteria applies<br><br>Isch: yes |
| 401003047 | [redacted] | [redacted] | 17.8 | ----- | Un-known | 4a | N/D and Rtn to N | ----- | ECG: ABN no criteria applies<br><br>Isch: no |
| 401008026 | [redacted] | [redacted] | 28.1 | ----- | NSTEMI | 4a | N/D and Rtn to N | ----- | ECG: ABN no criteria applies<br><br>Isch: no |
| 401010033 | [redacted] | [redacted] | 17.8 | ----- | NSTEMI | 4a | N/D and Rtn to N | ----- | ECG: N<br><br>Isch: no |
| 401010066 | [redacted] | [redacted] | 46.0 | ----- | NSTEMI | 4a | N/D and Rtn to N | ----- | ECG: ABN no criteria applies<br><br>Isch: no |
| 401010117 | [redacted] | [redacted] | 17.9 | ----- | NSTEMI | 4a | N/D and Rtn to N | ----- | ECG: ABN no criteria applies<br><br>Isch: no |
| 401010229 | [redacted] | [redacted] | 139.5 | ----- | NSTEMI | 4a | N/D and Rtn to N | 4 troponin pre-PCI nl. MB all slightly abn. PCI complications with sig MB post PCI. | ECG: ABN no criteria applies<br><br>Isch: yes |
| 401011070 | [redacted] | [redacted] | 437.7 | ----- | STEMI | 4a | N/D and Rtn to N | ----- | ECG: not done-protocol violation<br><br>Isch: no |
| 401012108 | [redacted] | [redacted] | 70.7 | ----- | NSTEMI | 4a | N/D and Rtn to N | No new QW | ECG: not done-protocol violation<br><br>Isch: no |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 401019008 | (b) (6) | 43.5 | ----- | NSTEMI | 4a | N/D and Rtn to N | ----- | ECG: ABN no criteria applies<br><br>Isch: yes |
| 401024036 | | 17.2 | ----- | NSTEMI | 4a | N/D and Rtn to N | ----- | ECG: ABN no criteria applies<br><br>Isch: yes |
| 401025016 | | 298.3 | ----- | NSTEMI | 4a | N/D and Rtn to N | MB increasing at 0100, significant increase in MB at 0700 post IDR sx at 0933. Still calling index PCI MI. | ECG: ABN no criteria applies<br><br>Isch: no |
| 401027083 | | 168.9 | ----- | NSTEMI | 4a | N/D and Rtn to N | ----- | ECG: ABN no criteria applies<br><br>Isch: yes |
| 401028004 | | 69.5 | 10.26 (ULN 0.1) | STEMI | 4a | N/D and Rtn to N | ECG post PCI with >2mm STE MI, also had IPST and dissection | ECG: N<br><br>Isch: yes |
| 401030137 | | 21.8 | ----- | NSTEMI | 4a | N/D and Rtn to N | ----- | ECG: ABN TWA<br><br>Isch: no |
| 401045005 | | 21.6 | 1.51 | NSTEMI | 4a | N/D and Rtn to N | Baseline normal | ECG: ABN no criteria applies<br><br>Isch: no |
| 401058029 | | 85.6 | 16.36 (ULN 0.29) | NSTEMI | 4a | N/D and Rtn to N | ----- | ECG: ABN no criteria applies<br><br>Isch: no |
| 401070012 | | 73.0 | ----- | STEMI | 4b | ----- | ----- | ECG: ABN no criteria applies<br><br>Isch: no |
| 401077048 | | 94.2 | ----- | NSTEMI | 4a | N/D and Rtn to N | ----- | ECG: ABN no criteria applies<br><br>Isch: yes |
| 401079002 | | 16.0 | 2.638 (ULN 0.19) | NSTEMI | 4a | N/D and Rtn to N | ----- | ECG: ABN no criteria applies<br><br>Isch: no |
| 401084003 | | 185.6 | 4.86 (ULN 0.03) | NSTEMI | 4b | ----- | ----- | ECG: ABN possible septal infarct<br><br>Isch: no |
| 401091432 | | 16.1 | ----- | NSTEMI | 4a | N/D and Rtn to N | ----- | ECG: ABN no criteria |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | (b) (6) | | | | | | | applies<br><br>Isch: no |

Date and Time: month/day/year; 24-hour clock. Normal=N; D=decreasing; Rtn to N= return to normal; ABN = abnormal; Rem-ABN = Remains abnormal; ECG=electrocardiogram performed at baseline; STE = ST-segment elevation; ST-dep = ST-segment depression; CKMB upper limit of normal = 5.09; Troponin-I upper limit of normal = 0.06; compl = complications; Isch = ischemic symptoms at baseline; TWI = T wave inversion; TWA = T wave abnormality

### 6.1.1.6 Other Endpoints

No other endpoints.

### 6.1.1.7 Subpopulations

**Subpopulation Summary**

Subpopulations of interest included:

- Clinical presentation
- Timing of Study Drug Treatment
- Subjects with normal baseline biomarkers
- US .vs. non-US subjects
- Age
- Gender
- Body Weight
- Use of GPI Therapy
- General subgroup analyses

Analysis of subpopulations suggested that compared to clopidogrel, cangrelor significantly reduced the incidence of the primary efficacy endpoint in the SA population. There was no significant difference in efficacy between the $P2Y_{12}$ inhibitors for the NSTEACS and STEMI populations. These results could have been due to lack of adequate power to evaluate individual cohorts, or to a hypothetical pathophysiology-treatment-time profile. The results of the trial were also driven by those subjects who did not have a baseline elevation of biomarkers associated with myocardial injury. There were no empirical confounding effects based on regional differences between the US and non-US populations, age, gender, body weight, concomitant disease, procedures (e.g. type of stent, location of arterial access) or medications with the exception of those subjects presenting with PAD. In the PAD cohort, there was an outlying OR in favor of cangrelor.

## Clinical Presentation

In the PLATFORM trial, there was no difference in the primary efficacy endpoint (all-cause mortality, MI, and IDR at 48 hours) between the cangrelor and clopidogrel cohorts for the SA population and for the UA/NSTEMI population, respectively (see Figure 7 in the CSR for the PLATFORM trial). In PLATFORM, clopidogrel therapy was delayed with respect to cangrelor therapy. In the PCI trial, where both study drugs were given at the same time, there was no difference in the composite of all-cause mortality, UDMI, and ST (not the pre-specified endpoint in PCI) at 48 hours between cangrelor and clopidogrel for any of the subgroups (SA, UA/NSTEMI, STEMI). However, the point estimates favored clopidogrel in the STEMI population, was neutral (i.e. was on the 1.0 line) in the UA/NSTEMI population, and favored cangrelor in the SA population (see Figure 11 in the CSR for the PCI trial). In the ISE which combined all the CHAMPION trials(see Figure 9, ISE), the results favored cangrelor over clopidogrel in the SA and NSTEACS populations, but did not show a significant difference between the two study drugs in the STEMI population.

The possible differential results empirically observed between the SA population and the ACS population (NSTEACS and STEMI) in the PHOENIX may have been due to chance based on lack of power for individual subgroups. However, this raises a hypothesis on the efficacy of cangrelor versus an active comparator control as a function of state of inflammation.

## Timing and Load of Study Drug Treatment

Subjects randomized to clopidogrel started active treatment later than subjects randomized to cangrelor (**Table 29.** Time (minutes) from PCI to start of active treatment by patient type**, and Figure 12**). The timing of active drug was more similar between treatments in STEMI patients than in SA or NSTEACS patients (**Figure 13**).

**Table 29. Time (minutes) from PCI to start of active treatment by patient type**

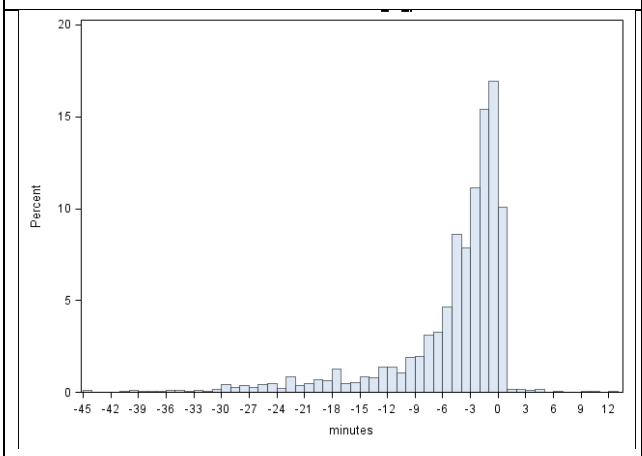
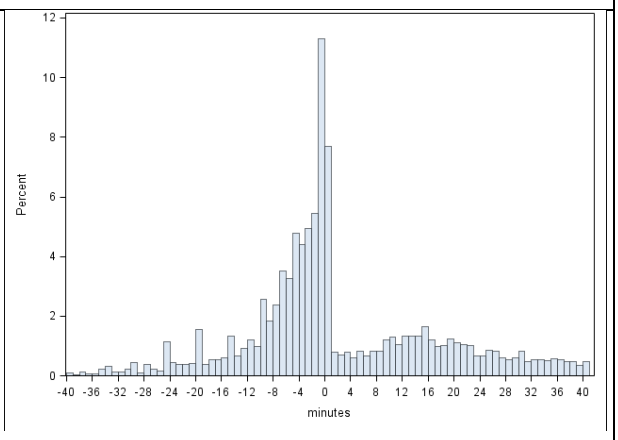
| | Cangrelor Median | Cangrelor (Q1, Q3) | Clopidogrel Median | Clopidogrel (Q1, Q3) |
|---|---|---|---|---|
| All Subjects | -3 | (-6, -1) | -1 | (-6, 14) |
| Stable angina | -3 | (-6, -1) | 0 | (-5, 17) |
| NSTEACS | -3 | (-7, -1) | -2 | (-7, 7) |
| STEMI | -4 | (-17, -1) | -4 | (-16, -1) |

Investigator declared patient type. PCI is time 0. A negative number means the subject started drug before PCI. A positive number means the subject started drug after PCI.
Reviewer's analysis: time\time active drug pci, Dataset isd osd dem



Reference ID: 3435333

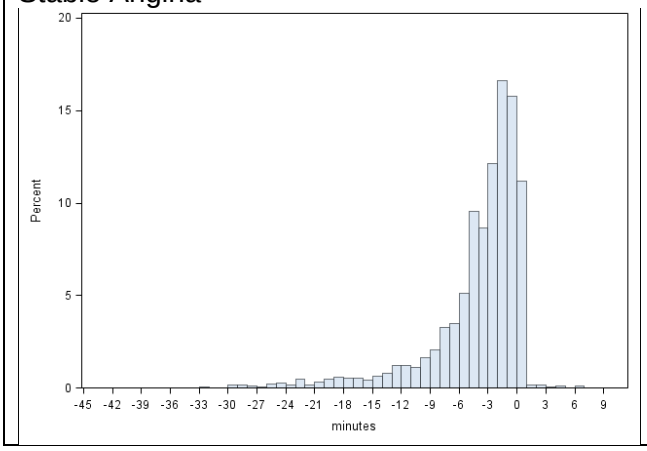
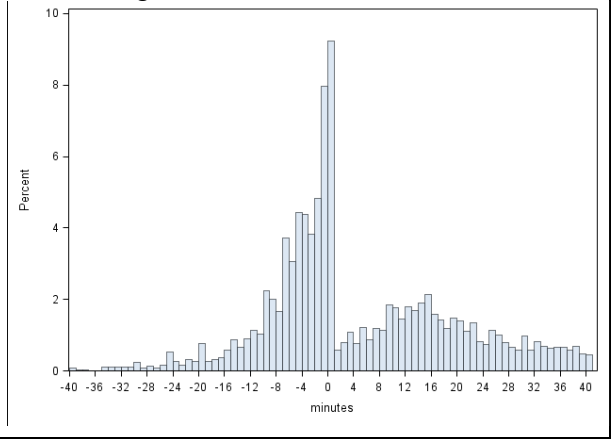
**Figure 12. Start of active drug relative to PCI**

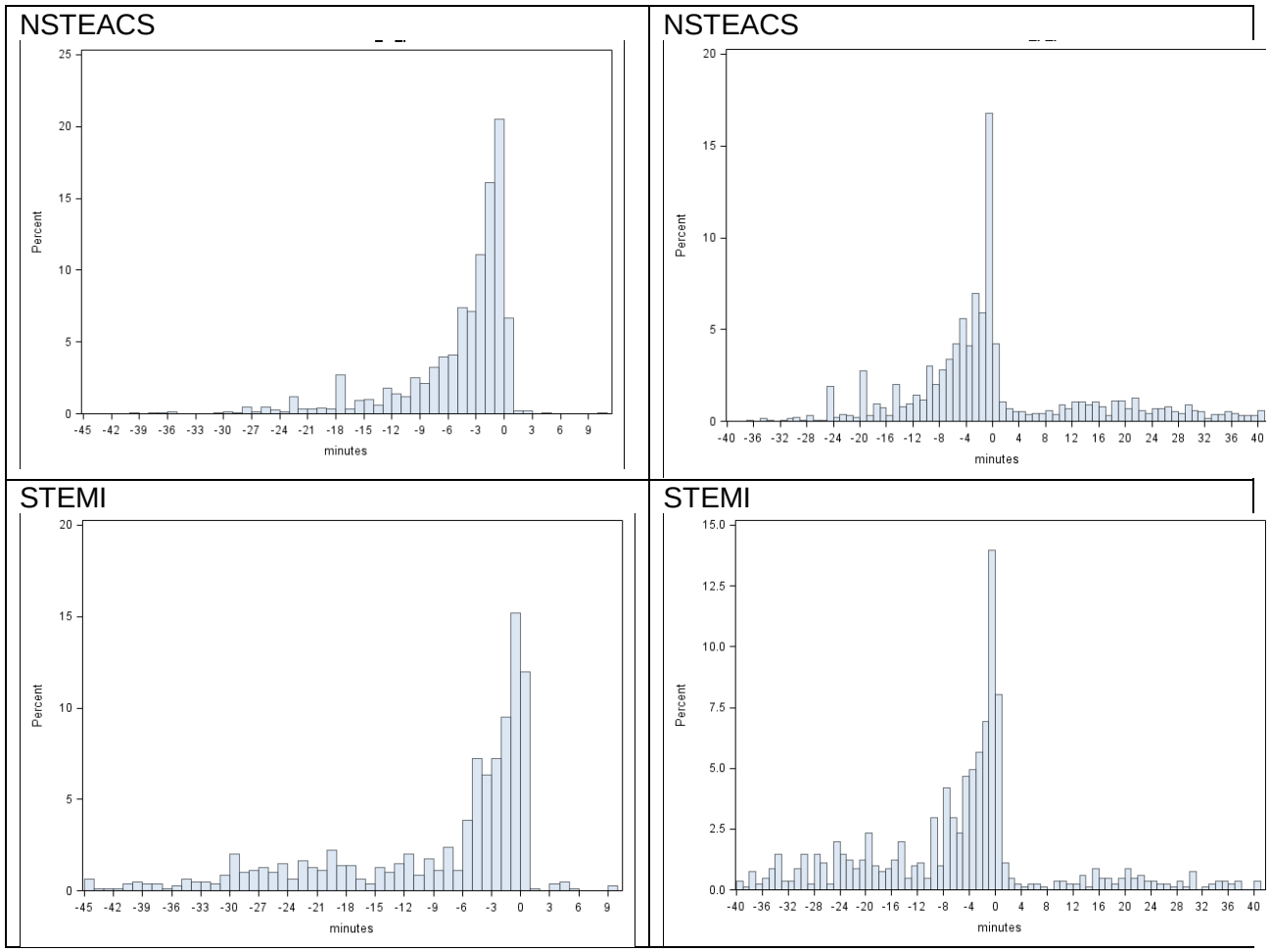
| A.Timing of cangrelor infusion start relative to PCI | B. Timing of clopidogrel dose relative to PCI |
|---|---|
|  |  |



PCI is at time 0. A negative number means subject received drug before PCI.
Reviewer's analysis: time\time active drug pci, Dataset isd osd dem. X-axis truncated.

**Figure 13. Start of active drug relative to PCI by patient type**

| A.Timing of cangrelor infusion start relative to PCI | B. Timing of clopidogrel dose relative to PCI |
|---|---|
| Stable Angina  | Stable Angina  |




Investigator declared patient type. PCI is time 0. A negative number means subject received drug before PCI. Reviewer's analysis: time\time active drug pci, Dataset isd osd dem. X-axis truncated.

*Reviewer comment: In the SA population a substantial number of subjects received clopidogrel after the procedure compared to the NSTEACS and STEMI populations, respectively (**Figure 13**). While the guidelines (**page 105**) for P2Y12 inhibitors (clopidogrel, ticagrelor, and prasugrel) are a Class I, Level A for PCI/stent they do not specify the precise timing of these agents relative to the start of PCI. However, practice patterns generally provide for administration before start of PCI. The primary efficacy endpoint favoring cangrelor was driven by the SA population. The data above raises speculation that the delay in clopidogrel in the SA population might have contributed to the positive results of the trial.*

**Table 30** shows the difference between actual clopidogrel loading dose and the investigator declared clopidogrel loading dose. Nearly all subjects in the cangrelor arm received clopidogrel 600 mg as a transition dose, whereas only 74% of subjects in the clopidogrel arm received 600 mg. It is unknown how the investigators determined which

dose to give. Analyses to determine the effect of the lower dose on endpoints was limited because few subjects in the cangrelor arm received clopidogrel 300 mg.

**Table 30. Intended versus actual clopidogrel loading dose**

| | Cangrelor | | Clopidogrel | |
|---|---|---|---|---|
| | N=5529 | (%) | N=5527 | (%) |
| Intended clopidogrel load of 300 mg | 1428 | (25.8) | 1425 | (25.8) |
| Intended clopidogrel load of 600 mg | 4101 | (74.2) | 4102 | (74.2) |
| | | | | |
| Actual clopidogrel load of 300 mg | 3 | (0.1) | 1427 | (25.8) |
| Actual clopidogrel load of 600 mg | 5442 | (98.4) | 4061 | (73.5) |

Reviewer's analysis: dose\loaddose. Dataset: raw\osd, analysis\disp

*Reviewer comment: Note that the numbers reported by Bhatt et al in the New England Journal of Medicine are the intended dose and not the actual clopidogrel loading dose received.*

**Subjects with normal baseline biomarkers**

The Applicant's program hypothesis was that subjects with pre-procedural MIs as indicated by elevated baseline biomarkers might have obscured the efficacy of cangrelor in the PCI setting. Post-hoc analysis of the CHAMPION PCI and PLATFORM trials engendered this hypothesis on which the PHOENIX trial was based.

**Table 31** and **Table 32** show the PHOENIX outcome data in those mITT subjects who had normal baseline cardiac biomarkers at 48 hours and at 30 days, respectively. The incidence of the primary efficacy endpoint at 48 hours (death, MI, IDR, ST) was significantly lower in the cangrelor arm vs. the clopidogrel arm (OR 0.80, 95%CI [0.66, 0.96], p=0.0199). These results were driven by IPST and MI where no specific component of MI (i.e. QWMI, type 1, 2, 3, 4a, 4b, 5) reached statistical significance. Similar results were obtained when IPST was removed from the ST component of the composite endpoint: death, MI, IDR, ARC-ST (OR 0.82, 95%CI [0.67, 0.99], p=0.0431). The outcome at 30 days for subjects with normal baseline biomarkers was similar to that at 48 hours for the efficacy endpoint of death, MI, IDR, and ST (OR 0.81, 95%CI [0.68, 0.98], p=0.0262). The results were driven by IPST and MI where no specific component of MI (i.e. QWMI, type 1, 2, 3, 4a, 4b, 5) reached statistical significance. When IPST was removed from the ST component of the composite endpoint, the 30-day benefit of cangrelor was lost (OR 0.83, 95%CI [0.69, 1.00], p=0.0537).

**Table 33** shows the PHOENIX 48 hour outcome data in those mITT subjects who had abnormal baseline cardiac biomarkers. The incidence of the 48 hour primary efficacy

endpoint of death, MI, IDR and ST for cangrelor (57/1921: 3.0%) did not show a significant difference from clopidogrel (76/1945:3.9%): OR 0.75, 95%CI [0.53, 1.07], p=0.1088. When IPST was removed from the ST component of the composite endpoint, the results were similar: cangrelor 36/1921 (1.9%); clopidogrel 53/1945: (2.7%); OR 0.68, 95%CI [0.44, 1.05], p=0.0778). Similarly, there was no difference between cangrelor and clopidogrel at 30 days for the efficacy endpoint in the subgroup of subjects who had abnormal baseline cardiac markers (see table 5.2.1.7 of PHOENIX CSR).

The data suggested that the beneficial effect of cangrelor over clopidogrel appeared to have been focused on the SA population without pre-PCI myocardial injury.



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**Table 31. CHAMPION PHOENIX 48 hour efficacy data in subjects with normal baseline biomarkers (mITT)**

| | | | Cangrelor vs. Clopidogrel | | |
|---|---|---|---|---|---|
| | Cangrelor (N=3550) | Clopidogrel (N=3525) | RR and 95%CI | OR and 95%CI | P-value for OR |
| 48 hours post randomization | | | | | |
| Death/MI/IDR/ST (primary end point) | 200/3549(5.6%) | 246/3524(7.0%) | 0.81(0.67,0.97) | 0.80(0.66,0.96) | 0.0199 |
| ST | 17/3549(0.5%) | 34/3524(1.0%) | 0.50(0.28,0.89) | 0.49(0.28,0.89) | 0.0158 |
| -IPST | 11/3549(0.3%) | 23/3524(0.7%) | 0.47(0.23,0.97) | 0.47(0.23,0.97) | 0.0372 |
| -Def. ST | 7/3549(0.2%) | 12/3524(0.3%) | 0.58(0.23,1.47) | 0.58(0.23,1.47) | 0.2444 |
| -Prob. ST | 0/3549(0.0%) | 0/3524(0.0%) | -----(-----) | -----(-----) | |
| -Poss. ST | 0/3549(0.0%) | 0/3524(0.0%) | -----(-----) | -----(-----) | |
| Acute ST | 6/3549(0.2%) | 12/3524(0.3%) | 0.50(0.19,1.32) | 0.50(0.19,1.32) | 0.1524 |
| Death | 5/3549(0.1%) | 2/3524(0.1%) | 2.48(0.48,12.79) | 2.48(0.48,12.81) | 0.2605 |
| -CV Death | 5/3549(0.1%) | 2/3524(0.1%) | 2.48(0.48,12.79) | 2.48(0.48,12.81) | 0.2605 |
| MI | 187/3549(5.3%) | 226/3524(6.4%) | 0.82(0.68,0.98) | 0.81(0.66,0.99) | 0.0402 |
| -Q MI | 6/3549(0.2%) | 12/3524(0.3%) | 0.50(0.19,1.32) | 0.50(0.19,1.32) | 0.1524 |
| -Type 1 | 0/3549(0.0%) | 0/3524(0.0%) | -----(-----) | -----(-----) | |
| -Type 2 | 0/3549(0.0%) | 0/3524(0.0%) | -----(-----) | -----(-----) | |
| -Type 3 | 2/3549(0.1%) | 0/3524(0.0%) | -----(-----) | -----(-----) | 0.1587 |
| -Type 4a | 180/3549(5.1%) | 216/3524(6.1%) | 0.83(0.68,1.00) | 0.82(0.67,1.00) | 0.0531 |
| -Type 4b | 5/3549(0.1%) | 10/3524(0.3%) | 0.50(0.17,1.45) | 0.50(0.17,1.45) | 0.1915 |
| -Type 5 | 0/3549(0.0%) | 0/3524(0.0%) | -----(-----) | -----(-----) | |
| IDR | 19/3549(0.5%) | 20/3524(0.6%) | 0.94(0.50,1.76) | 0.94(0.50,1.77) | 0.8550 |
| -PCI | 15/3549(0.4%) | 18/3524(0.5%) | 0.83(0.42,1.64) | 0.83(0.42,1.64) | 0.5866 |

| | | | | | |
|---|---|---|---|---|---|
| -CABG | 4/3549(0.1%) | 2/3524(0.1%) | 1.99(0.36,10.84) | 1.99(0.36,10.86) | 0.4190 |
| Death/MI/IDR/ARC-ST | 194/3549(5.5%) | 233/3524(6.6%) | 0.83(0.69,0.99) | 0.82(0.67,0.99) | 0.0431 |
| Death/Q MI/ IDR/ST | 32/3549(0.9%) | 50/3524(1.4%) | 0.64(0.41,0.99) | 0.63(0.40,0.99) | 0.0422 |
| Death/MI/IDR | 194/3549(5.5%) | 233/3524(6.6%) | 0.83(0.69,0.99) | 0.82(0.67,0.99) | 0.0431 |
| Death/Q MI/IDR | 23/3549(0.6%) | 30/3524(0.9%) | 0.76(0.44,1.31) | 0.76(0.44,1.31) | 0.3217 |
| Death/MI/ST | 196/3549(5.5%) | 242/3524(6.9%) | 0.80(0.67,0.97) | 0.79(0.65,0.96) | 0.0190 |
| Death/MI/ARC-ST | 190/3549(5.4%) | 229/3524(6.5%) | 0.82(0.68,0.99) | 0.81(0.67,0.99) | 0.0415 |
| Death/Q MI/ST | 23/3549(0.6%) | 42/3524(1.2%) | 0.54(0.33,0.90) | 0.54(0.32,0.90) | 0.0166 |
| Death/MI | 189/3549(5.3%) | 228/3524(6.5%) | 0.82(0.68,0.99) | 0.81(0.67,0.99) | 0.0410 |
| Death/Q MI | 10/3549(0.3%) | 14/3524(0.4%) | 0.71(0.32,1.59) | 0.71(0.31,1.60) | 0.4036 |
| Death/IDR | 22/3549(0.6%) | 22/3524(0.6%) | 0.99(0.55,1.79) | 0.99(0.55,1.80) | 0.9812 |
| Death/ST | 20/3549(0.6%) | 35/3524(2.5%) | 0.57(0.33,0.98) | 0.56(0.33,0.98) | 0.0397 |

Source: Table 5.1.1.6 PHOENIX CSR



Reference ID: 3435333

**Table 32. CHAMPION PHOENIX 30 day efficacy data in subjects with normal baseline biomarkers (mITT)**

| | | | Cangrelor vs. Clopidogrel | | |
|---|---|---|---|---|---|
| | Cangrelor (N=3550) | Clopidogrel (N=3525) | RR and 95%CI | OR and 95%CI | P-value for OR |
| 30 days post randomization | | | | | |
| Death/MI/IDR/ST (primary end point) | 226/3544(6.4%) | 272/3518(7.7%) | 0.82(0.70,0.98) | 0.81(0.68,0.98) | 0.0262 |
| ST | 26/3544(0.7%) | 49/3518(1.4%) | 0.53(0.33,0.85) | 0.52(0.32,0.84) | 0.0069 |
| -IPST | 11/3544(0.3%) | 23/3518(0.7%) | 0.47(0.23,0.97) | 0.47(0.23,0.97) | 0.0371 |
| -Def. ST | 13/3544(0.4%) | 20/3518(0.6%) | 0.65(0.32,1.30) | 0.64(0.32,1.30) | 0.2140 |
| -Prob. ST | 3/3544(0.1%) | 8/3518(0.2%) | 0.37(0.10,1.40) | 0.37(0.10,1.40) | 0.1283 |
| -Poss. ST | 0/3544(0.0%) | 0/3518(0.0%) | -----(-----) | -----(-----) | |
| Subacute ST | 10/3544(0.3%) | 16/3518(0.5%) | 0.62(0.28,1.37) | 0.62(0.28,1.37) | 0.2310 |
| Death | 17/3544(0.5%) | 17/3518(0.5%) | 0.99(0.51,1.94) | 0.99(0.51,1.95) | 0.9828 |
| -CV Death | 14/3544(0.4%) | 11/3518(0.3%) | 1.26(0.57,2.78) | 1.26(0.57,2.79) | 0.5601 |
| MI | 194/3544(5.5%) | 236/3518(6.7%) | 0.82(0.68,0.98) | 0.81(0.66,0.98) | 0.0301 |
| -Q MI | 8/3544(0.2%) | 14/3518(0.4%) | 0.57(0.24,1.35) | 0.57(0.24,1.35) | 0.1941 |
| -Type 1 | 1/3544(0.0%) | 6/3518(0.2%) | 0.17(0.02,1.37) | 0.17(0.02,1.37) | 0.0574 |
| -Type 2 | 0/3544(0.0%) | 1/3518(0.0%) | -----(-----) | -----(-----) | 0.3155 |
| -Type 3 | 2/3544(0.1%) | 0/3518(0.0%) | -----(-----) | -----(-----) | 0.1588 |
| -Type 4a | 181/3544(5.1%) | 216/3518(6.1%) | 0.83(0.69,1.01) | 0.82(0.67,1.01) | 0.0596 |
| -Type 4b | 10/3544(0.3%) | 15/3518(0.4%) | 0.66(0.30,1.47) | 0.66(0.30,1.47) | 0.3076 |
| -Type 5 | 0/3544(0.0%) | 0/3518(0.0%) | -----(-----) | -----(-----) | |
| IDR | 34/3544(1.0%) | 34/3518(1.0%) | 0.99(0.62,1.59) | 0.99(0.62,1.60) | 0.9757 |
| -PCI | 30/3544(0.8%) | 32/3518(0.9%) | 0.93(0.57,1.53) | 0.93(0.56,1.53) | 0.7762 |

| | | | | | |
|---|---|---|---|---|---|
| -CABG | 4/3544(0.1%) | 2/3518(0.1%) | 1.99(0.36,10.83) | 1.99(0.36,10.85) | 0.4192 |
| Death/MI/IDR/ARC-ST | 220/3544(6.2%) | 259/3518(7.4%) | 0.84(0.71,1.00) | 0.83(0.69,1.00) | 0.0537 |
| Death/Q MI/ IDR/ST | 59/3544(1.7%) | 77/3518(2.2%) | 0.76(0.54,1.06) | 0.76(0.54,1.07) | 0.1092 |
| Death/MI/IDR | 219/3544(6.2%) | 258/3518(7.3%) | 0.84(0.71,1.00) | 0.83(0.69,1.00) | 0.0533 |
| Death/Q MI/IDR | 49/3544(1.4%) | 56/3518(1.6%) | 0.87(0.59,1.27) | 0.87(0.59,1.28) | 0.4677 |
| Death/MI/ST | 213/3544(6.0%) | 264/3518(7.5%) | 0.80(0.67,0.95) | 0.79(0.65,0.95) | 0.0124 |
| Death/MI/ARC-ST | 207/3544(5.8%) | 251/3518(7.1%) | 0.82(0.69,0.98) | 0.81(0.67,0.98) | 0.0273 |
| Death/Q MI/ST | 40/3544(1.1%) | 64/3518(1.8%) | 0.62(0.42,0.92) | 0.62(0.41,0.92) | 0.0160 |
| Death/MI | 205/3544(5.8%) | 248/3518(7.0%) | 0.82(0.69,0.98) | 0.81(0.67,0.98) | 0.0301 |
| Death/Q MI | 23/3544(0.6%) | 30/3518(0.9%) | 0.76(0.44,1.31) | 0.76(0.44,1.31) | 0.3212 |
| Death/IDR | 48/3544(1.4%) | 48/3518(1.4%) | 0.99(0.67,1.48) | 0.99(0.66,1.48) | 0.9710 |
| Death/ST | 37/3544(1.0%) | 57/3518(1.6%) | 0.64(0.43,0.97) | 0.64(0.42,0.97) | 0.0346 |

Source: Table 5.2.1.6 PHOENIX CSR

**Table 33. CHAMPION PHOENIX 48 hour efficacy data in subjects with abnormal baseline biomarkers (mITT)**

| | | | Cangrelor vs. Clopidogrel | | |
|---|---|---|---|---|---|
| | Cangrelor (N=1922) | Clopidogrel (N=1945) | RR and 95%CI | OR and 95%CI | P-value for OR |
| 48 hours post randomization | | | | | |
| Death/MI/IDR/ST (primary end point) | 57/1921(3.0%) | 76/1945(3.9%) | 0.76(0.54,1.06) | 0.75(0.53,1.07) | 0.1088 |
| ST | 29/1921(1.5%) | 40/1945(2.1%) | 0.73(0.46,1.18) | 0.73(0.45,1.18) | 0.1991 |
| -IPST | 24/1921(1.2%) | 31/1945(1.6%) | 0.78(0.46,1.33) | 0.78(0.46,1.34) | 0.3658 |
| -Def. ST | 5/1921(0.3%) | 10/1945(0.5%) | 0.51(0.17,1.48) | 0.50(0.17,1.48) | 0.2043 |
| -Prob. ST | 0/1921(0.0%) | 0/1945(0.0%) | -----(-----) | -----(-----) | |
| -Poss. ST | 0/1921(0.0%) | 0/1945(0.0%) | -----(-----) | -----(-----) | |
| Acute ST | 5/1921(0.3%) | 9/1945(0.5%) | 0.56(0.19,1.68) | 0.56(0.19,1.68) | 0.2948 |
| Death | 13/1921(0.7%) | 16/1945(0.8%) | 0.82(0.40,1.71) | 0.82(0.39,1.71) | 0.5991 |
| -CV Death | 13/1921(0.7%) | 16/1945(0.8%) | 0.82(0.40,1.71) | 0.82(0.39,1.71) | 0.5991 |
| MI | 20/1921(1.0%) | 29/1945(1.5%) | 0.70(0.40,1.23) | 0.70(0.39,1.23) | 0.2112 |
| -Q MI | 5/1921(0.3%) | 6/1945(0.3%) | 0.84(0.26,2.76) | 0.84(0.26,2.77) | 0.7785 |
| -Type 1 | 1/1921(0.1%) | 1/1945(0.1%) | 1.01(0.06,16.18) | 1.01(0.06,16.20) | 0.9930 |
| -Type 2 | 0/1921(0.0%) | 0/1945(0.0%) | -----(-----) | -----(-----) | |
| -Type 3 | 1/1921(0.1%) | 0/1945(0.0%) | -----(-----) | -----(-----) | 0.3142 |
| -Type 4a | 14/1921(0.7%) | 23/1945(1.2%) | 0.62(0.32,1.19) | 0.61(0.31,1.20) | 0.1474 |
| -Type 4b | 4/1921(0.2%) | 5/1945(0.3%) | 0.81(0.22,3.01) | 0.81(0.22,3.02) | 0.7527 |
| -Type 5 | 0/1921(0.0%) | 0/1945(0.0%) | -----(-----) | -----(-----) | |
| IDR | 9/1921(0.5%) | 18/1945(0.9%) | 0.51(0.23,1.12) | 0.50(0.23,1.12) | 0.0880 |
| -PCI | 6/1921(0.3%) | 15/1945(0.8%) | 0.40(0.16,1.04) | 0.40(0.16,1.04) | 0.0523 |

| | | | | | |
|---|---|---|---|---|---|
| -CABG | 3/1921(0.2%) | 3/1945(0.2%) | 1.01(0.20,5.01) | 1.01(0.20,5.02) | 0.9879 |
| Death/MI/IDR/ARC-ST | 36/1921(1.9%) | 53/1945(2.7%) | 0.69(0.45,1.05) | 0.68(0.44,1.05) | 0.0778 |
| Death/Q MI/ IDR/ST | 48/1921(2.5%) | 62/1945(3.2%) | 0.78(0.54,1.14) | 0.78(0.53,1.14) | 0.1977 |
| Death/MI/IDR | 36/1921(1.9%) | 53/1945(2.7%) | 0.69(0.45,1.05) | 0.68(0.44,1.05) | 0.0778 |
| Death/Q MI/IDR | 26/1921(1.4%) | 34/1945(1.7%) | 0.77(0.47,1.29) | 0.77(0.46,1.29) | 0.3210 |
| Death/MI/ST | 53/1921(2.8%) | 70/1945(3.6%) | 0.77(0.54,1.09) | 0.76(0.53,1.09) | 0.1368 |
| Death/MI/ARC-ST | 32/1921(1.7%) | 47/1945(2.4%) | 0.69(0.44,1.08) | 0.68(0.43,1.08) | 0.0991 |
| Death/Q MI/ST | 44/1921(2.3%) | 55/1945(2.8%) | 0.81(0.55,1.20) | 0.81(0.54,1.20) | 0.2903 |
| Death/MI | 31/1921(1.6%) | 44/1945(2.3%) | 0.71(0.45,1.12) | 0.71(0.45,1.13) | 0.1438 |
| Death/Q MI | 18/1921(0.9%) | 22/1945(1.1%) | 0.83(0.45,1.54) | 0.83(0.44,1.55) | 0.5510 |
| Death/IDR | 21/1921(1.1%) | 32/1945(1.6%) | 0.66(0.38,1.15) | 0.66(0.38,1.15) | 0.1400 |
| Death/ST | 39/1921(2.0%) | 52/1945(2.7%) | 0.76(0.50,1.14) | 0.75(0.50,1.15) | 0.1871 |

Source: Table 5.1.1.7 PHOENIX CSR

**US .vs. non-US subjects**

There were 4097 mITT subjects in the US and 6842 mITT subjects in the rest of the world (**Table 34**). Cangrelor-treated subjects had a significantly lower incidence of the 48-hour primary efficacy endpoint compared to clopidogrel-treated subjects in the US population [cangrelor 93/2048{4.7%}, clopidogrel 131/2049{6.4%}; OR 0.70, 95%CI (0.53, 0.92)], and trended in favor of cangrelor in the rest of the world [cangrelor 164/3422{4.8%}, clopidogrel 191/3420{5.6%}; OR 0.85, 95%CI (0.69, 1.05)]. The regional subgroup analysis suggested no difference in the primary endpoint (P [Int] = 0.258). It was not clear how the SA, NSTEACS and STEMI populations were regionally distributed.

**Age**

Age was stratified (see **Table 34**) into subjects < 75 years (n=8931) and subjects ≥ 75 years (n=2008). In the older subgroup, there was a trend favoring the cangrelor-treated subjects for the primary efficacy endpoint: 55/1021 (5.4%) for cangrelor and 73/987 (7.4%) for clopidogrel (OR 0.71, 95% CI [0.50, 1.02]). In the younger cohort, there was a significant difference in the incidence of the primary efficacy endpoint favoring cangrelor (OR 0.81, 95% CI [0.67, 0.98]). For the ITT population (n= 11,145), the mean age of the subjects in the PHOENIX trial was 63.9 ± 11.0 years with a median of 64.0

years (1st quartile 56 years, 3rd quartile 72 years) (see CSR Table 8). The Applicant's choice of stratifying age at 75 years was very likely due to the enhanced bleeding risk in patients receiving anticoagulation or antiplatelet agents who are above age 75. The age subgroup analysis suggested no difference in the primary endpoint as a function of age (P [Int] = 0.546).

**Gender**

Of the ITT population, there were 8024 (72.0%) males and 3121 (28.0%) females (see CSR Table 8). The Applicant reported that in the mITT population (see **Table 34**), the incidence of the primary efficacy endpoint in males was 183/3913 (4.7%) in the cangrelor treated group and 219/3976 (5.5%) in the clopidogrel treated group (OR 0.84, 95% CI [0.69, 1.03]). The incidence of the primary efficacy endpoint in females was 74/1557 (4.8%) in the cangrelor treated group and 103/1493 (6.9%) in the clopidogrel treated group (OR 0.67, 95% CI [0.50, 0.92]). The gender subgroup analysis suggested no gender difference regarding efficacy of cangrelor for the primary endpoint (P [Int] = 0.234).

**Body Weight**

In the ITT population, the mean weight was 85.4 ± 17.8kg with a median of 84.0kg (1st quartile 73kg, 3rd quartile 96kg) (see CSR Table 8). This corresponded to a mean BMI (kg/m$^2$) 28.99 ±5.18 with a median of 28.37 (1st quartile 25.6, 3rd quartile 31.8). The Applicant performed a subgroup analysis based on weight, stratified by subjects < 60kg (n =583) and ≥ 60kg (n =10,356) in the mITT population (see **Table 34**). Of those subjects < 60kg, 18/315 subjects in the cangrelor arm and 20/268 subjects in the clopidogrel arm experienced a primary efficacy endpoint (OR 0.75, 95% CI [0.39, 1.45]). Of those subjects ≥ 60kg, 239/5155 (4.6%) subjects in the cangrelor arm and 302/5201 (5.8%) subjects in the clopidogrel arm experienced a primary efficacy endpoint (OR 0.79, 95% CI [0.66, 0.94]). This subgroup analysis suggested no difference in efficacy of cangrelor vs. Clopidogrel between two subgroups stratified by weight. It is not clear why 60kg was chosen as the boundary condition for weight stratification (P [Int] = 0.890).

**Use of GPI Therapy**

The use of GPI therapy: eptifibatide and tirofiban within 12 hours preceding randomization, or abciximab within 7 days preceding randomization were exclusion criteria (#2, #3 respectively) for subject selection into PHOENIX. The use of GPI, however, was permitted per protocol as bailout therapy defined when there was a new or persistent thrombus formation, slow or no reflow, side branch compromise, dissection, or distal embolization (CSR 9.4.7.2; 10.4.3).

In the cangrelor arm, 129/5581 ITT subjects (2.3%) were reportedly administered GPI as bailout. Of these 129 subjects, 76 (59%) were STEMI patients. In the clopidogrel



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arm, 194/5564 (3.5%) were reportedly administered GPI as bailout, of which 102 (53%) were STEMI patients (CSR section 14.1, Table 3.4.2.1, 3.4.2.2).

Of those subjects receiving GPI inhibitors as bailout, abciximab was used in 63/5581 (1.1%) in the cangrelor arm and 62/5564 (1.1%) in the clopidogrel arm. Eptifibatide was used in 57/5581 (1.0%) subjects in the cangrelor arm and 112/5564 (2.0%) subjects in the clopidogrel arm. Tirofiban was sparingly used (8/5581 {0.1%} in the cangrelor arm and 18/5564 {0.3%} in the clopidogrel arm).

In addition to those subjects administered GPI for bailout, the Applicant reported that among the mITT patients, 26 cangrelor-treated subjects and 35 clopidogrel-treated subjects were reported by study investigators to have received GPI for reasons specified to not be bailout.

The 26 mITT cangrelor subjects administered GPI for reasons other than bailout were identified: 401009005, 401055128, 407005040, 407005041, 407005057, 407005185, 407012075, 420019004, 439001068, 439004169, 439004183, 439004186, 439004218, 439004247, 439008031, 439008037, 443002007, 443002022, 443002066, 443002234, 443002504, 448015030, 449001020, 455005005, 455005015, and 466001006. The ITT subjects included the above 26 subjects in addition to 401012030, 401012069, and 401012104.

The 35 mITT clopidogrel subjects administered GPI for reasons other than bailout were identified: 401055033, 401091247, 401091729, 401091735, 401104003, 407005012, 407005044, 407005184, 420001017, 420001084, 420005002, 420009998, 420019046, 439001014, 439004111, 439004124, 439004168, 439004175, 439004185, 439004239, 443002005, 443002010, 443002021, 443002031, 443002056, 443002186, 443002223, 443002491, 443002492, 449001009, 449003002, 449014041, 459002015, 459002017, and 459007057. The ITT subjects included the above 35 subjects in addition to subject 407005086.

The Applicant reviewed these subjects and concluded that the reasons provided by the investigators for administering GPI were not clearly distinguishable from bailout. The Applicant therefore did not classify these subjects as protocol violations. An independent review of these cases revealed that the average reason for GPI administration were “thrombus”, “continued ST elevation” (i.e. ECG ST interval), “keeping the blood fluid”, “physician discretion”, “ESC guidelines”, “in-stent thrombus”. This confirmed the Applicant’s opinion that GPI administration for reasons other than bailout were similar to bailout.

From **Table 34,** concomitant use of peri-procedural GPI attenuated the benefit of cangrelor over clopidogrel even though the point-estimate still favored cangrelor. This might have been attributed to either a masking effect of GPI, or the relatively small sample size of those subjects receiving GPI, or a greater severity of illness in those

subjects requiring GPI which attenuated the effect of cangrelor therapy for the duration of treatment in this trial.

The use of GPI has been recognized as valuable therapeutic regimen and can serve as an alternative therapy to $P2Y_{12}$ platelet inhibitor therapy. Several guidelines (Anderson, J, et al., 2013; O'Gara, P, et al., 2013; Hillis, L, D, et al., 2011; Levine, G, et al., 2011) have described recommendations for GPI use in terms of a class of precision (C) and level of evidence (LOE) in various settings: C I, LOE (A) for UA/STEMI in both PCI and Medical Management; C IIa, LOE (A-B) in STEMI / primary PCI; C IIb, LOE (B) in stable ischemic heart disease (SIHD). The class and LOE is strong favoring GPI therapy in the absence of clopidogrel pre-treatment. In the setting of clopidogrel pre-treatment, the class and LOE for GPI administration is slightly weaker (C IIa, LOE (B-C)). $P2Y_{12}$ therapy (clopidogrel, Ticagrelor, prasugrel) generally received a C I, LOE (A) recommendation in the PCI/stent setting. Prasugrel, however, received a C III (i.e. harm), LOE (B) recommendation in patients with prior TIA / stroke.

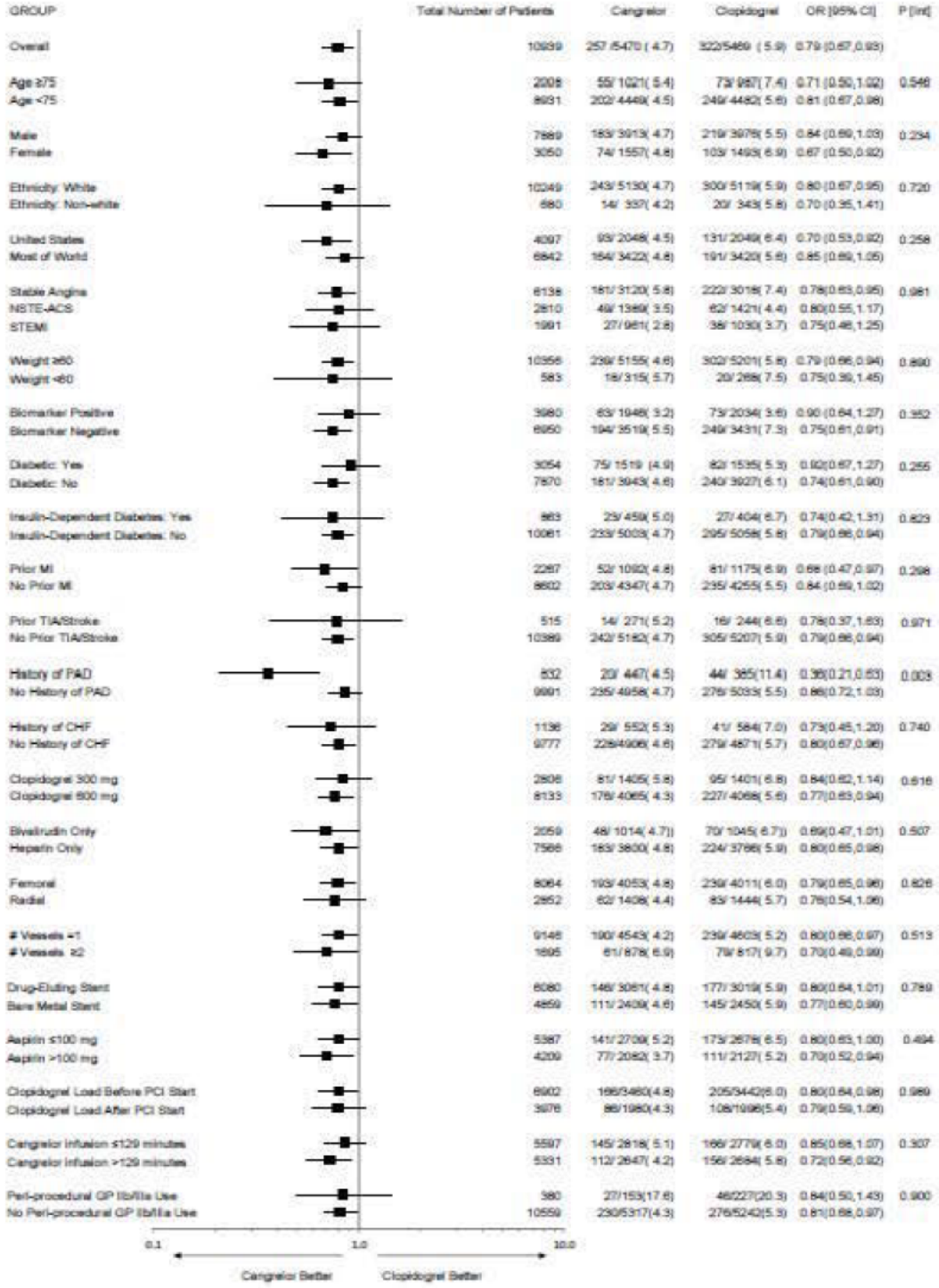
## General subgroup analyses

**Table 34** shows the results of various subgroup analyses for the 48 hour primary efficacy endpoint of death, MI, IDR, and ST in the mITT population.

Subjects stratified by medical histories, concomitant illnesses, concomitant medications, and protocol-based procedures (e.g. type of stent, location of arterial access) did not affect the results and generally showed point estimates either significantly favoring or trending in favor of cangrelor over clopidogrel. One outlying subgroup showed that subjects with a history of PAD significantly benefited from cangrelor over clopidogrel (cangrelor 20/447:4.5%, clopidogrel 44/385:11.4%, OR 0.36, 95%CI [0.21, 0.63]) compared to those subjects without a history of PAD (cangrelor 235/4958:4.7%, 276/5033:5.5% clopidogrel, OR 0.86, 95%CI [0.72, 1.03]), p (int) =0.003. The benefit of cangrelor over clopidogrel became significant when cangrelor infusion exceeded 129 minutes. The higher loading dose of clopidogrel (600mg) provided in the IV placebo arm during the initial 2-4 hours of the trial paradoxically favored cangrelor.

There were no subgroup cohorts favoring clopidogrel, thereby voiding concern about efficacy of cangrelor in a unique subgroup. The preponderance of the results might have been impacted by the timing of drug initiation where clopidogrel, having been initiated after the index PCI in a large number of subjects, might not have had sufficient time to manifest a clinical benefit (see section 6.1.1.10).

**Table 34. CHAMPION PHOENIX general subgroup analyses for 48-hour composite primary efficacy endpoint (mITT)**

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Source: PHOENIX CSR, Section 11.2.5.2, Figure 8

### 6.1.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Dosing recommendation was based on bolus and maintenance infusion doses used in the CHAMPION PHOENIX trial.

### 6.1.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

No additional discussion.

### 6.1.1.10 Additional Efficacy Issues/Analyses

Timing of clopidogrel Administration relative to cangrelor

As shown in sections 5.3.1 and 5.3.2, the CHAMPION PLATFORM trial demonstrated a significantly higher mortality rate and acute ST rate in the clopidogrel group compared to the cangrelor group. The mortality rate was 8/2691 (0.3%) in the cangrelor group and 19/2664 (0.7%) in the clopidogrel group (OR 0.42, 95% CI [0.18, 0.95], p=0.0374). The rate of acute ST was 5/2691 (0.2%) in the cangrelor group and 14/2664 (0.5%) in the clopidogrel group (OR 0.35, 95% CI [0.13, 0.98], p=0.0456). The Interim Analysis Review Committee (IARC) attributed these differences to a cangrelor benefit. In the CHAMPION PCI trial, however, there was no difference between cangrelor and clopidogrel in the incidence of death or acute ST.

**Table 35** shows a comparison of the composite primary efficacy endpoints in CHAMPION PLATFORM (death, MI, IDR at 48 hours), CHAMPION PCI (death, MI, IDR at 48 hours) and CHAMPION PHOENIX (death, UDMI, IDR, and ST at 48 hours), as well as the respective components in each of the composite primary efficacy endpoints. For comparison, the incidence of ST and acute ST were included in the table for PLATFORM and PCI although the ST variable did not comprise a component of the primary endpoint in these two trials.

In the CHAMPION PLATFORM trial, while cangrelor was initiated at the time of PCI, clopidogrel was initiated at least 2 hours after PCI. In the CHAMPION PCI trial, cangrelor and clopidogrel were both initiated at the time of PCI. The significant mortality and ST signals disfavoring clopidogrel in PLATFORM were not apparent in PCI.

*Reviewer comment: This reviewer hypothesizes that the mortality and acute ST signals in PLATFORM were not due to a cangrelor efficacy benefit, as inferred by the IARC, but rather due to delayed clopidogrel therapy. There are no rigorous guidelines regarding the optimal timing of clopidogrel loading. Although the optimal timing of administration of the clopidogrel loading dose in the PCI setting could not be determined with certainty from the PCI-CURE trial, the ACCF/AHA Guidelines suggested that symptomatic patients with evidence of ischemia referred for PCI might benefit from clopidogrel load*

*approximately 6-15 hours prior to PCI. However, it was emphasized that the basis of the suggestion was a non-significant trend from a subgroup analysis of the CREDO trial and that no explicit comparison was made between a pre-PCI loading dose vs. a loading dose in the catheterization lab (Anderson, J, et al, 2013). The current clopidogrel label does not specify the optimal timing of load in patients with either UA/NSTEMI or STEMI.*

**Table 35. Comparison of efficacy endpoints from PLATFORM, PCI, and PHOENIX**

| CHAMPION TRIALS | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | PLATFORM | | PCI | | PHOENIX | | | |
| | Cangrelor | Clopidogrel | Cangrelor | Clopidogrel | Cangrelor (pre PCI) | Clopidogrel (pre PCI) | Cangrelor (post PCI) | Clopidogrel (post PCI) |
| Primary End Point | 187.2961 (6.9%) | 213/2664 (8.0%) | 292/3993 (7.4%) | 277/3924 (7.1%) | 90/2105 (4.3%) | 113/2090 (5.4%) | 81/1931 (4.2%) | 105/1947 (5.4%) |
| Mortality | 8/2961 (0.2%) | 19/2664 (0.7%) | 8/3993 (0.2%) | 6/3924 (0.2%) | 4/2105 (0.3%) | 7/2090 (0.3%) | 2/1931 (0.2%) | 1/1947 (0.1%) |
| ST | 5/2961 (0.2%) | 16/2664 (0.6%) | 7/3933 (0.2%) | 11/3924 (0.3%) | 18/2105 (0.9%) | 31/2090 (1.5%) | 12/1931 (0.6%) | 19/1947 (1.0%) |
| Acute ST | 5/2691 (0.2%) | 14/2664 (0.5%) | 5/3933 (0.1%) | 9/3924 (0.2%) | _____ | _____ | _____ | _____ |
| MI | 177/2691 (6.6%) | 192/2664 (7.2%) | 278/3993 (7.1%) | 256/3924 (6.5%) | 74/2105 (3.5%) | 86/2090 (4.1%) | 69/1931 (3.6%) | 94/1947 (4.8%) |
| IDR | 19/2691 (0.7%) | 26/2664 (1.0%) | 15/3933 (0.4%) | 23/3924 (0.6%) | 13/2105 (0.6%) | 10/2090 (0.5%) | 7/1931 (0.4%) | 14/1947 (0.7%) |

Source: PLATFORM: Table 5.1.2.1 CSR; PCI: Table 5.1.2.1 CSR; PHOENIX (pre-PCI administration of study drug): Table 9.106.1.1 CSR; PHOENIX (post-PCI administration of study drug): Table 9.107.1.1 CSR.
Primary Efficacy Endpoint: PLATFORM (All-Cause Mortality, MI, IDR); PCI (All-Cause Mortality, MI, IDR); PHOENIX (All-Cause Mortality, UDMI, IDR, and ST). Population: ITT (PLATFORM, PCI); mITT (PHOENIX)

Dosing of clopidogrel

The PHOENIX study permitted either 300mg or 600mg clopidogrel loading dose in the clopidogrel arm during the double-dummy double-blinded infusion period. Following infusion period, subjects in the cangrelor arm received a protocol mandated 600mg clopidogrel loading dose; subjects in the clopidogrel arm received matching placebo. Approximately 26% of the subjects in the clopidogrel arm received the 300mg clopidogrel loading dose.

*Reviewer Comment: The PHOENIX trial can be construed as a comparison between cangrelor + clopidogrel (600mg loading dose + 75mg daily maintenance) vs. clopidogrel (300mg or 600mg loading dose + 75mg daily maintenance). Statistical review and evaluation suggested that the imbalance in the clopidogrel loading dose between the arms of PHOENIX yielded the favorable effect of cangrelor compared to clopidogrel. If all subjects in each arm received clopidogrel 600mg loading dose, the treatment effect would not be statistically significant anymore in the PHOENIX trial. The clopidogrel label specifies a loading dose of 300mg followed by 75mg once daily for patients with ACS (CURE trial). A maintenance dose of 75mg is prescribed in the label for STEMI (COMMIT trial), recent MI or recent stroke or established peripheral arterial disease (CAPRIE trial), and prevention of ischemic events in patients with vascular disease or multiple risk factors for atherosclerosis (CHARISMA trial). The optimal loading dose with clopidogrel has not been rigorously established (Anderson, J, et al, 2013). Higher loading doses have been evaluated (600mg to 900mg) but the database for such higher doses is not sufficiently robust to formulate definitive recommendations (Anderson, J, et al., 2013). The CURRENT-OASIS 7 trial randomized 25,086 patients with ACS who were intended for PCI and who were not considered to be at high risk for bleeding. They received either a higher dose clopidogrel (600mg load and 150mg maintenance for 6 days followed by 75mg daily thereafter) vs. a standard dose of clopidogrel (300mg load and 75mg daily). The primary endpoint was the composite of cardiovascular death, myocardial (re)infarction or stroke at 30 days. The overall trial failed, but a PCI subgroup generated a hypothesis suggesting a significant benefit for the higher dose offset by increased major bleeding.*

### 6.1.2 Bridge Indication

"Platelex IV is indicated to maintain $P2Y_{12}$ inhibition in acute coronary syndromes (ACS) patients or patients with stents who are at increased risk for thrombotic events (such as stent thrombosis) when oral $P2Y_{12}$ therapy is interrupted due to surgery."

#### 6.1.2.1 Methods

The Applicant submitted the Phase II BRIDGE trial results (Stage 1 dose-finding, Stage 2 dose confirmation) to support their proposed indication. The trial focused on platelet reactivity as a prognostic indicator for attenuating both the incidence of thrombotic events pre-CABG and incidence of bleeding during CABG.

The Applicant opined that a treatment dilemma currently exists in patients receiving oral platelet $P2Y_{12}$ inhibitors for coronary artery disease who require CABG. Product labeling and treatment guidelines for all oral $P2Y_{12}$ inhibitors (clopidogrel, prasugrel, and ticagrelor) include the warning that premature discontinuation of oral $P2Y_{12}$ platelet inhibitors confers a high risk for thrombotic cardiac events, such as ST, MI, and death. Complicating matters further, product labeling and treatment guidelines also recommend discontinuation of these agents at least five to seven days prior to any surgery to avoid the high risk of surgical bleeding known to be associated with oral $P2Y_{12}$ inhibitors when taken at the time of surgery.

The Applicant's treatment-dilemma reconciliation strategy was to optimize the timing of $P2Y_{12}$ discontinuation prior to CABG in order to minimize both thrombotic and bleeding events by utilizing the fast on—fast off PD effect of cangrelor as measured by the Verify Now assay. In the absence of clinical data from the Applicant's BRIDGE trial to support the PD effect, the Applicant's tactical approach was refer to data from published literature to demonstrate the following: validity of the VerifyNow PRU assay, the risk of thrombosis upon premature termination of oral $P2Y_{12}$ inhibitors, and the risk of bleeding upon continued therapy with oral $P2Y_{12}$ inhibitors in the peri-CABG period given the current standard of care. The Applicant utilized the Dutch Stent Thrombosis Registry (van Werkum, JW, et al., 2009) of 21,009 patients in order to demonstrate the risk of ST due to discontinuation of clopidogrel after PCI/stent placement. The Applicant also referenced 2 meta-analyses and a literature review to demonstrate the bleeding risk of continued therapy with oral $P2Y_{12}$ inhibitors during the peri-CABG period.

The review methodology, pursuant to the review strategy described in section 5.2, focused on endpoint validation:

- Evaluating BRIDGE endpoint data and validity of the Verify Now Assay as a prognostic indicator of clinical events.
- Evaluating the risk of ST from the Dutch Registry and Bleeding Risk from the literature review provided by the Applicant which addressed these risks.

### 6.1.2.2 Demographics

**Table 36** displays the subject demographics for the BRIDGE trial. The average age was approximately 64 years, predominately white male with an average weight of 89 kg.

**Table 36. BRIDGE Safety Patient Demographics**

| | Stage I | | Stage II | |
|---|---|---|---|---|
| | Cohort I (N=5) | Cohort II (N=6) | Cangrelor (N=106) | Placebo (N=101) |
| Age, years | | | | |
| Mean ± SD | 64.6 ± 6.1 | 62.3 ± 12.0 | 64.8 ± 10.4 | 63.1 ± 11.1 |
| Median (Q1, Q3) | 64.0 (62, 70) | 64.5 (52, 70) | 65.0 (57, 73) | 62.0 (55, 71) |
| Age ≥65 years, n/N (%) | 2/5 (40.0) | 3/6 (50.0) | 54/106 (50.9) | 42/101 (41.6) |
| Age ≥75 years, n/N (%) | 0/5 (0.0) | 1/6 (16.7) | 20/106 (18.9) | 16/101 (15.8) |
| Male, n/N (%) | 5/5 (100) | 4/6 (66.7) | 80/106 (75.5) | 74/101 (73.3) |
| Ethnicity, n/N (%) | | | | |
| Asian | 0/5 (0.0) | 0/6 (0.0) | 3/106 (2.8) | 0/101 (0.0) |
| Black or African American | 0/5 (0.0) | 1/6 (16.7) | 6/106 (5.7) | 5/101 (5.0) |
| Hispanic or Latino | 2/5 (40.0) | 1/6 (16.7) | 4/106 (3.8) | 2/101 (2.0) |
| White | 3/5 (60.0) | 4/6 (66.7) | 93/106 (87.7) | 94/101 (93.1) |
| Weight, kg | | | | |
| Mean ± SD | 90.8 ± 16.9 | 88.7 ± 10.4 | 88.8 ± 16.2 | 86.1 ± 19.0 |
| Median (Q1, Q3) | 93.7 (77, 99) | 89.6 (86, 98) | 88.0 (79, 97) | 85.0 (73, 98) |

Source: Section 14.1, Table 2.1.3
SD = standard deviation

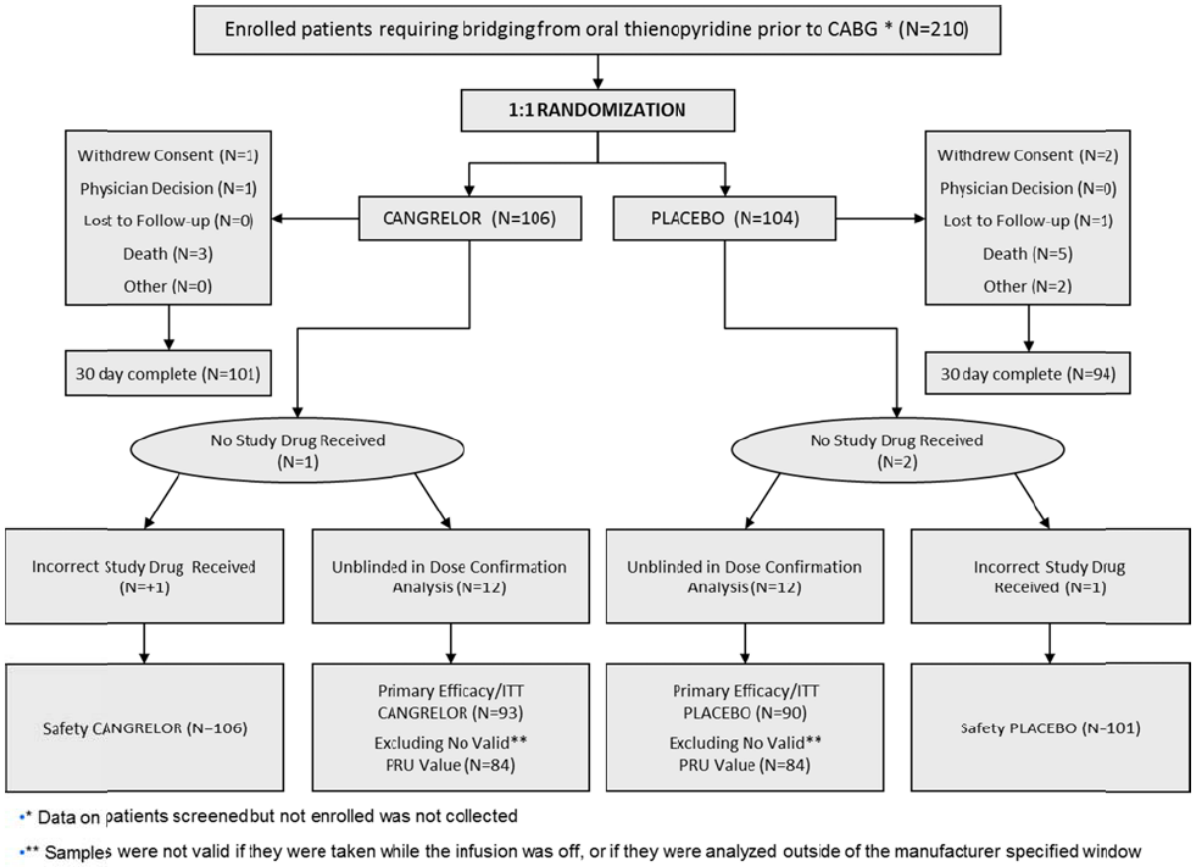
### 6.1.2.3 Subject Disposition

A total of 11 subjects from 4 US sites participated in Stage I. Of these, 10 subjects had evaluable VerifyNow data for dose assessment; 5 subjects completed the 1st cohort at a dose of 0.5ug/kg/min, and 5 subjects completed the 2nd cohort at a dose of 0.75ug/kg/min. All 11 subjects completed Stage 1 and were considered part of the safety population.

A total of 210 subjects (106 cangrelor, 104 placebo) from 35 global sites (Australia, Czech Republic, Netherlands, UK, US) participated in Stage II. **Figure 14** illustrates the BRIDGE trial Stage II subject disposition. One subject in the cangrelor arm and 2 in the placebo arm did not receive study medication. One subject in the placebo arm was erroneously given active medication. This subject was consequently added to the cangrelor arm. Therefore, a total of 106 subjects in the cangrelor arm and 101 subjects

in the placebo arm were respectively included in the safety population. Of the 106 cangrelor subjects, 1 subject withdrew consent, 1 was withdrawn as per physician discretion, and 3 died. Of the 104 placebo subjects, 2 subjects withdrew consent, 1 was lost to follow-up, 5 died, and 2 were listed as “other”. A total of 101 subjects in the cangrelor arm and 94 subjects in the placebo arm completed the study. The DSMB conducted a pre-specified unblinded review of the initial 24 subjects (12 per group) randomized in Stage II, in order to confirm the dose identified in Stage I. These subjects were excluded from the ITT population and the primary efficacy analysis. Therefore, the “primary efficacy / ITT population” was composed of 93 cangrelor and 90 placebo subjects.

**Figure 14. BRIDGE Subject disposition (Stage 2)**




Source: BRIDGE CSR, Section 10.1, Figure 2

### 6.1.2.4 Analysis of Primary Endpoint(s)

**Stage I**

**Table 37** shows the results from Stage I of the BRIDGE trial. In Cohort 1 (0.5ug/kg/min), platelet inhibition was maintained above 60% in 76.5% (13/17) of subject samples. This result was shy of the primary endpoint of 80% of the subject samples, thereby initiating Cohort II (0.75ug/kg/min). Cangrelor at the dose of 0.75ug/kg/min maintained platelet inhibition above 60% in 94.4% (17/18) of subject samples, thereby meeting the Stage I primary endpoint. A total of 80% (n=4/5) of subjects in Cohort I and 100% (n=6/6) of subjects in Cohort II had all of the cangrelor on-infusion samples < 240 PRU. Based on these results, the dose of 0.75ug/kg/min was selected for advancement to Stage II.

**Table 37. BRIDGE Primary Efficacy Result (Stage I)**

| | | Stage I | |
|---|---|---|---|
| **During Infusion** | **Statistic** | **Cohort I (N=5)** | **Cohort II (N=6)** |
| Analysis by patient sample | | | |
| Primary endpoint: Samples with >60 PPI | n (%) | 13 (76.5) | 17 (94.4) |
| Samples <240 PRU | n (%) | 16/17 (94.1) | 18/18 (100.0) |
| Analysis by patient | | | |
| Patients with all samples <240 PRU | n (%) | 4 (80.0) | 6 (100.0) |

Source: Section 14.1, Table 5.3.3.1
PPI = percent platelet inhibition; PRU = $P2Y_{12}$ Reaction Unit(s)

**Stage II**

The original $P2Y_{12}$ inhibitor therapy was discontinued for approximately 29 hours in cangrelor arm and 30 hours in the placebo arm prior to randomization (CSR Table 7). Of the 106 subjects in the cangrelor arm, 105 were previously on clopidogrel (n: last dose = 88:75mg; 1:150mg; 4:300mg; 12:600mg) and 1 was previously on prasugrel (n: last dose = 1:10mg). Of the 101 subjects in the placebo arm, 93 were previously on clopidogrel (n: last dose = 65:75mg; 2:150mg; 12:300mg; 13:600mg; 1:900mg) and 8 were previously on prasugrel (n: last dose = 6:10mg; 1:60mg; 1:75mg).

**Table 38** shows the stratification data by days to surgery. The number of subjects administered study drug for less than or equal to 3 days prior to surgery, and for greater than 3 days prior to surgery, were equally distributed.

**Table 38. BRIDGE Subject Stratification by days to surgery (Stage II)**

| | Number (%) of patients | | |
|---|---|---|---|
| **Stratum** | **Cangrelor** | **Clopidogrel** | **Overall** |
| Safety population | N=106 | N=101 | N=207 |
| ≤ 3 days to surgery | 55 | 52 | 107 |
| > 3 days to surgery | 51 | 49 | 100 |
| ITT population | N=93 | N=90 | N=183 |
| ≤ 3 days to surgery | 49 | 48 | 97 |
| > 3 days to surgery | 44 | 42 | 86 |

Source: Section 14.1, Table 5.1.1.3 and Table 5.1.3.3
ITT = Intent to treat.
As determined by investigator at the time of randomization.

The duration of infusion for the cangrelor group was 75.8 ± 34.6 hours (mean) and 67.0 hours (median) with a minimum of 1 hour and a maximum of 162 hours. Similarly, the duration of infusion for the placebo group was 90.4 ± 45.7 hours (mean) and 82.7 hours (median) with a minimum of 2 hours and a maximum of 306 hours (see CSR Table 21).

**Table 39** shows the results from Stage II of the BRIDGE trial. The primary efficacy endpoint was achieved with 98.8% of cangrelor treated subjects maintaining target levels of PRU < 240 for all on-infusion timepoints measured over the bridging period compared to 19.0% of placebo subjects (OR 353 [95% CI 45.6, 2728], p<0.0001; ref: page 63 of BRIDGE CSR). The results were unchanged when analyzed using logistic regression adjusted by the stratification variable of expected days to surgery (either ≤ 3 days or >3 days), (OR 473 [95% CI 56.3, 3974], p=0.001; ref: page 63 of BRIDGE CSR).

**Table 39. BRIDGE Primary Efficacy Result (Stage II)**

| | Stage II | | | |
|---|---|---|---|---|
| **During Infusion Statistic** | **Cangrelor (N=93) n/N (%)** | **Placebo (N=90)** | **P-value** | **RR (95% CI)** |
| Patients with all samples PRU <240 [a] | 83/84 (98.8) | 16/84 (19.0) | <0.0001 CH<br>0.0000 LR | 5.19 (3.34, 8.07)<br>5.15 (3.32, 8.00) |

Source: Section 14.1, Table 5.1.1.1
[a] Primary efficacy analysis
CH = Chi-square test; CI = confidence interval; ITT = intent-to-treat; LR = Logistic regression adjusting for stratification factor, expected CABG ≤3 versus >3 days; OR = odds ratio; PRU = $P2Y_{12}$ Reaction Unit(s).

The efficacy results remained significant when sensitivity analyses were conducted for the following patient populations (see CSR Table 20, source Table 99.5.1):

- All ITT patients with missing data counted as non-response.
- All randomized subjects (including the 12 subjects in each arm that were unblinded for the dose-confirmation analysis and consequently excluded from the primary efficacy analysis) for whom valid PRU data was available.
- All randomized patients with missing data counted as non-response.
- Safety population with missing data counted as non-response.

#### 6.1.2.5 Analysis of Secondary Endpoint(s)

**Table 40** shows the secondary efficacy endpoint results, with analyses performed by patient and by patient samples, respectively. All secondary efficacy endpoints were significantly in favor of cangrelor over placebo.

**Table 41** provides an analysis of PRU data in the ITT population before, during, and after study drug infusion. The pre-study drug infusion PRU data shows that approximately 62% of the cangrelor subjects and 52% of the placebo subjects had a PRU level < 240. This was interpreted as residual activity of recently discontinued $P2Y_{12}$ inhibitor. The post-study drug infusion PRU data showed a platelet reactivity rebound effect such that there was no difference between cangrelor (PRU 280) and placebo (PRU 298).

**Table 40. BRIDGE Secondary Efficacy Result (Stage II)**

| Endpoint | Cangrelor (N=93) %(n/N) | Placebo (N=90) %(n/N) | RR (95% CI) | P value |
|---|---|---|---|---|
| **During Study Drug Infusion (Analyses by patient)** | | | | |
| Patients with last sample during infusion with platelet reactivity < 240 PRU | 98.8% (83/84) | 31.0% (26/84) | 3.19 (2.32,4.40) | <0.001 |
| All samples ≤ baseline PRU value | 92.1% (70/76) | 12.3% (10/81) | 7.46 (4.16, 13.4) | < 0.001 |
| **During Study Drug Infusion (Analyses by patient sample)** | | | | |
| Samples with platelet reactivity < 240 | 99.6% (258/259) | 33.3% (98/294) | 2.99(2.54, 3.51) | <0.001 |
| Total samples that maintained > 60% platelet inhibition (primary efficacy endpoint Stage 1) | 83.8% (217/259) | 3.7% (11/294) | 22.4(12.5, 40.1) | <0.001 |

Source: CSR Section 14.1, Table 5.1.1.1 and Table 5.3.1.1

**Table 41. BRIDGE Analysis of Platelet Reactivity (ITT population)**

| Endpoint | Statistic | Cangrelor (N=93) | Placebo (N=90) | P value |
|---|---|---|---|---|
| **Prior to Study Drug Infusion (washout period from oral P2Y12 inhibition)** | | | | |
| Patients with platelet reactivity < 240 PRU | %<br>(n/N) | 62.4%<br>(53/85) | 52.3%<br>(45/86) | 0.185 |
| PRU Values | Mean ± SD | 210.9±94.0 | 214.1±85.9 | 0.817 |
| **During Study Drug Infusion** | | | | |
| Patients with platelet reactivity < 240 PRU and throughout entire infusion period (primary endpoint) | %<br>(n/N) | 98.8%<br>(83/84) | 19.0%<br>(16/84) | <0.001<br><0.001 |
| Patients with last sample during infusion with platelet reactivity < 240 PRU | %<br>(n/N) | 98.8%<br>(83/84) | 31.0%<br>(26/84) | <0.001 |
| PRU values last sample during infusion | Mean ± SD | 68.9±67.8 | 263.7±68.3 | <0.001 |
| **Following Discontinuation of Study Drug Infusion** | | | | |
| Patients with Platelet Reactivity < 240 PRU | %<br>(n/N) | 26.9%<br>(21/78) | 20.0%<br>(15/75) | 0.313 |
| PRU Values | Mean ± SD | 279.7±106.5 | 297.8±67.3 | 0.212 |

Source: CSR Section 14.1, Table 5.1.1.1 and Table 5.2.1.1

Bleeding was listed as a secondary efficacy endpoint pursuant to the program hypothesis of reducing bleeding during CABG as well as reducing thrombotic events

during the bridging period prior to CABG. There was no difference between cangrelor and placebo for CABG related bleeding events (CSR section 14.3, Tables 4.2.3; 6.1.3.1; 6.1.3.2; and 6.4.3). Regarding non-CABG bleeding during the 5-day bridging period, there were numerical increases in mild (8 vs. 5) and moderate (10 vs.4) GUSTO bleeding in the cangrelor subjects vs. the placebo subjects, respectively. There was also a numerical increase in Major ACUITY bleed (12 cangrelor vs. 5 placebo subjects) (source: CSR section 14.3, Table 6.2.3). The Applicant claimed that these numerical differences were based on 3 cangrelor subjects (201018001; 201018003; and 201018007). As will be elucidated in the safety section, the Applicant had attributed bleeding events in these 3 subjects to other interventional procedures and therefore they were not spontaneous. It is not clear what the PRU levels were during these adverse events.

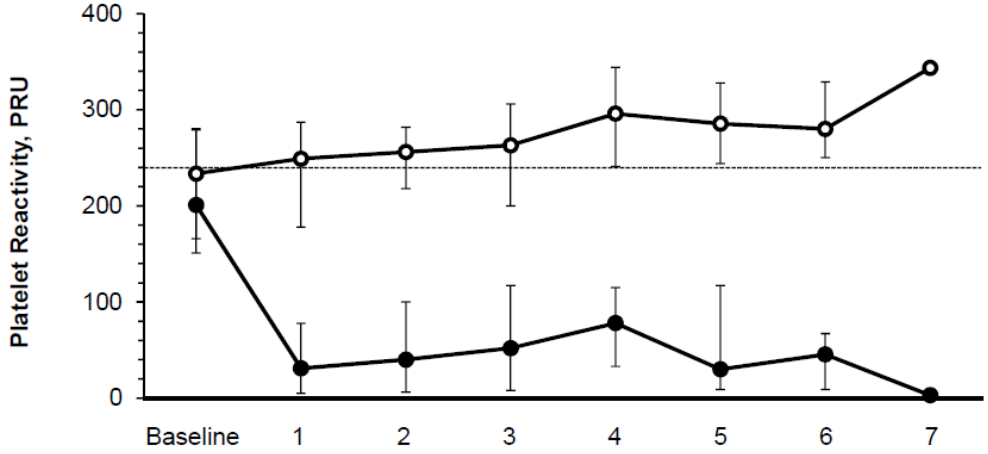
### 6.1.2.6 Other Endpoints

**PRU-Time Dependency**

**Figure 15** shows the PRU time-course in subjects randomized to cangrelor (closed circles) vs. placebo (open circles) during the infusion period. The data showed a consistent decrease of PRU for the infusion period in the cangrelor arm compared to placebo. The boundary condition of 240 PRU has been opined by the Applicant as the value below which thrombotic events were attenuated (see section 6.1.2.8 in this review).

**Figure 16** shows the PRU time-course in subjects randomized to cangrelor (closed circles) vs. placebo (open circles) following discontinuation of study drug. The figure showed that when cangrelor was discontinued, PRU rebounded to a level consistent with placebo. The duration of time for this rebound, although not specified in the Applicant's figure, was reported in the CSR to be a median of 4.2 hours from the last sample taken during the infusion to the pre-CABG sample. The median time from the termination of the infusion until the start of CABG was 3.1 hours (see CSR 11.2.2.1.3).

**Figure 15. BRIDGE PRU time-course during infusion period**

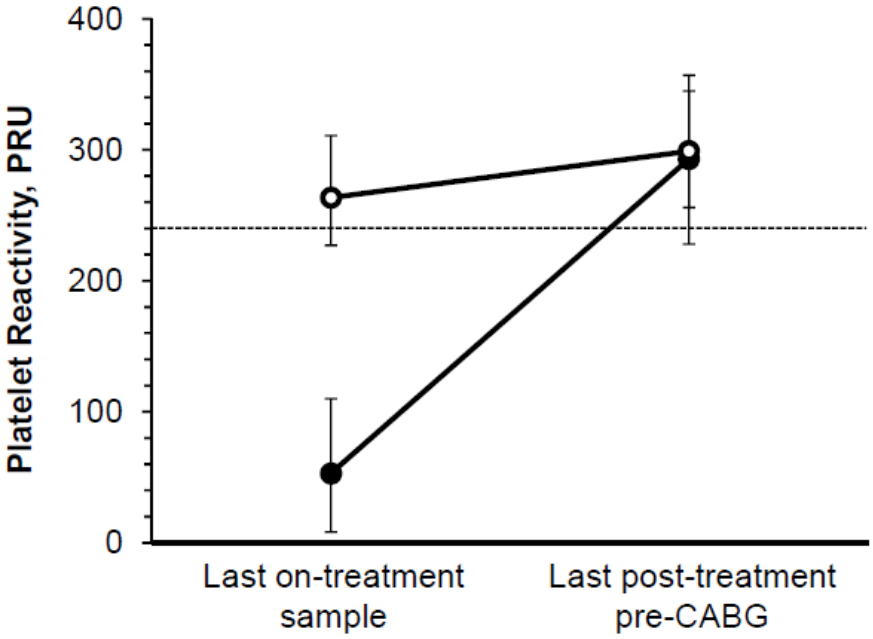



| No. of patients with valid sample in the ITT population | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Placebo/clopidogrel | 86 | 76 | 73 | 57 | 34 | 24 | 14 | 2 |
| Cangrelor+clopidogrel | 85 | 80 | 70 | 55 | 33 | 7 | 6 | 1 |

Source: Section 14.1, Table 5.2.1.1

Open circle: placebo; closed circle: cangrelor

**Figure 16. BRIDGE PRU time-course post-study drug infusion**




| No. of patients with valid sample in the ITT population | | |
|---|---|---|
| Placebo/clopidogrel | 84 | 75 |
| Cangrelor+clopidogrel | 84 | 78 |

Source: Section 14.1, Table 5.2.1.1

Open circle: placebo; closed circle: cangrelor

### 6.1.2.7 Subpopulations

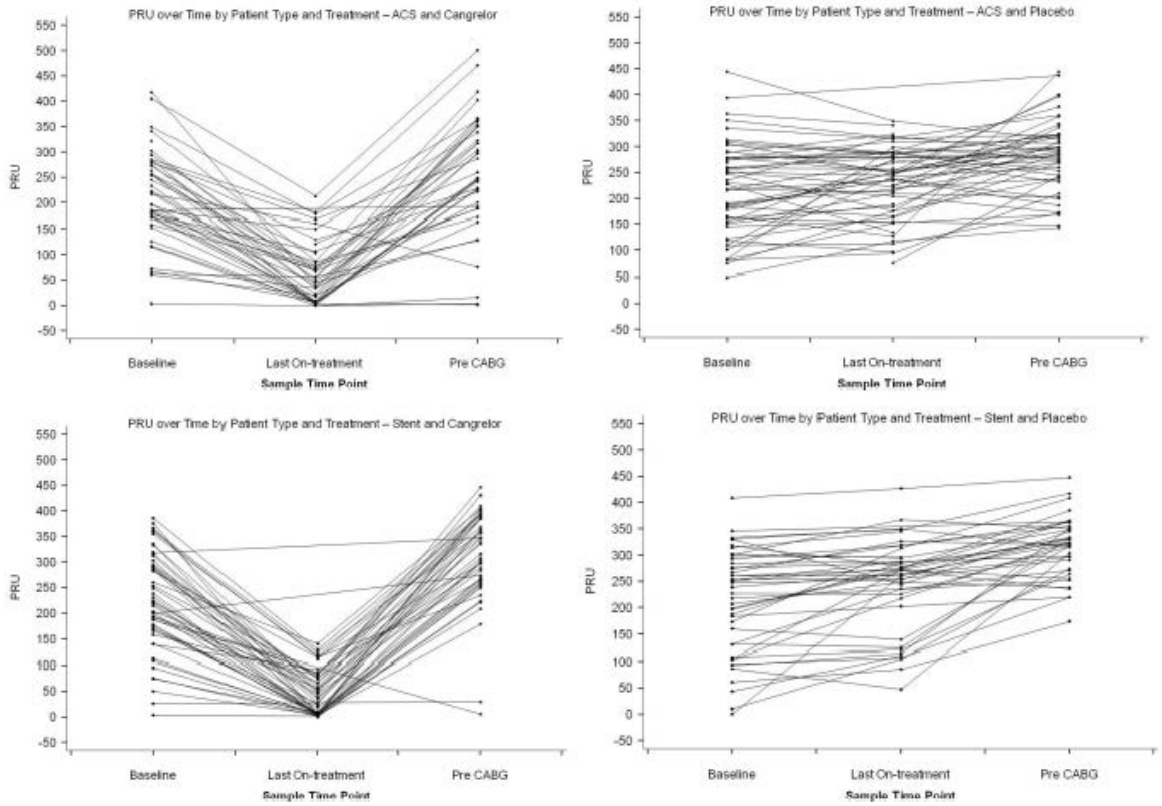
**ACS and Stent**

Two subpopulations in the BRIDGE trial were those presenting with ACS referred for CABG and those with a history of stent deployment where planned CABG was not based on ACS. **Figure 17** shows PRU over time by subject type for individual subjects (ACS: cangrelor vs. placebo –top half of figure; Stent: cangrelor vs. placebo –lower half of figure). Variability in the baseline PRU levels was attributed to an attenuating effect of recently discontinued oral $P2Y_{12}$ inhibition. The baseline levels of PRU were not different between subjects treated with cangrelor vs. placebo (p=0.916) or subjects bridging to surgery with a stent or with ACS (p=0.532) (see CSR 11.2.2.1.3.2, page 68).

The characteristic V-shaped profiles for the individual subjects in the cangrelor treated group (both ACS and PCI/stent) showed decreased PRU below 240 during cangrelor infusion and rebound of PRU to baseline levels upon discontinuation of cangrelor. On-

treatment PRU was significantly lower in the cangrelor group (median PRU 59) vs. the placebo group (median PRU 264), p<0.001 (see CSR 11.2.2.1.3.2, page 68).

**Figure 17. PRU values over time by subject type (ACS vs. stent) and treatment (cangrelor vs. Placebo)**




Upper left: ACS and cangrelor. Upper right: ACS and placebo. Lower left: stent and cangrelor. Lower right: stent and placebo.

Source: Section 14.2, Figure 99.1.1.1, Figure 99.1.2.1, Figure 99.1.3.1 and Figure. 99.1.4.1

Note: Some on-treatment samples are missing.

## Variations in Subject Characteristics

The subjects were stratified by expected time to CABG (3 days or less vs. greater than 3 days) in order to avoid potential bias. The Applicant performed an analysis adjusting for variations in subject characteristics (i.e. subjects with all samples PRU < 240; Baseline PRU < 240 vs. ≥ 240; ACS vs. stent; cardiac markers greater than vs. less than or equal to upper limit of normal; duration of infusion <48 hours vs. ≥ 48 hours or < 72 hours, 72-96 hours, > 96 hours) and confirmed that the primary efficacy results did not change (see CSR Table 19).

#### 6.1.2.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The dose-selection strategy pursuant to the BRIDGE indication was based on the Accumetrics VerifyNow Assay which was developed to provide a rapid and easy method to measure an individual's response to antiplatelet agents. This assay measures the amount of ADP-mediated platelet aggregation as an increase in light transmittance in whole blood. Light transmittance increases due to binding of activated platelets onto fibrinogen-coated beads. This assay is specific to the platelet $P2Y_{12}$ receptor and is expressed as PRU ($P2Y_{12}$ Reaction Unit). A higher PRU reflects greater ADP-mediated platelet reactivity.

Bonello, L, et al. (2010) studied the relationship of PRU during clopidogrel treatment to both peri-procedural and long-term ischemic risk, resulting in the conclusion that there was continued controversy regarding the optimal method to quantify PRU and identify a threshold value for clinical correlation. Based on reviewing a series of studies linking high on-treatment ADP-mediated platelet reactivity with clinical outcome, it was suggested that the level of on-treatment platelet reactivity might be a superior predictor of risk compared with the difference between baseline and post-treatment platelet reactivity. This was because platelet reactivity to ADP was variable prior to clopidogrel treatment in patients on aspirin therapy. In using the VerifyNow assay, a cut-off value of 240 PRU was identified where values above this cutoff appeared to be prognostic for subsequent thrombotic events (i.e. cardiovascular death and ST, or cardiovascular death and nonfatal MI and ST). However, the authors stated that there was limited data showing that alteration of therapy as a response to PRU measurement improved clinical outcome. Furthermore, the observed cut-off PRU value had a poor positive predictive value for thrombotic ischemic events despite a high negative predictive value. Finally, the authors have opined that it is unknown whether on-treatment platelet reactivity cut points associated with peri-procedural events are the same as those associated with long-term risk.

Breet, N, et al. (2010) evaluated the capability of multiple platelet function tests to predict clinical outcome. The authors designed a prospective, observational, single-center cohort study of 1069 consecutive patients who were administered clopidogrel and underwent elective coronary stent implantation between December 2005 and December 2007. The primary efficacy endpoint was the 1-year composite of all-cause death, nonfatal acute MI, ST, and ischemic stroke. Each platelet function test (i.e. light transmittance aggregometry at 5umol/L ADP, light transmittance aggregometry at 20umol/L ADP, Verify Now, Plateletworks, IMPACT-R, Dade PFA collagen/ADP, and Innovance PFA P2Y) was evaluated for predicting the occurrence of the primary efficacy endpoint as a function of cut-off values for high on-treatment platelet reactivity established by ROC curve analysis for each respective function test. The light transmittance aggregometry at 5umol/L ADP, light transmittance aggregometry at 20umol/L ADP, Verify Now, and Plateletworks showed an association between the

occurrence of the primary endpoint and the ROC-based platelet reactivity cutoff values for these respective function tests, as shown in **Table 42**.The IMPACT-R, Dade PFA collagen/ADP, and Innovance PFA P2Y function tests were reportedly unable to discriminate between patients with and without the primary end point. For the VerifyNow assay, the ROC analysis resulted in a cutoff value of 236 PRU. There were 646 patients with PRU below 236, and 406 patients with PRU greater than or equal to 236. The primary endpoint occurred more frequently in patients with high on-treatment platelet reactivity (i.e. above the cutoff): 13.3% vs. 5.7%; OR 2.53 (95% CI 1.63, 3.91), $p < 0.001$. Similar results were achieved with the other function tests shown in **Table 42**. The authors opined that the predictive accuracy of these tests was modest for those tests showing associations between platelet reactivity and clinical outcome. However, none of them provided accurate prognostic information to identify low-risk patients at higher risk of bleeding following stent implantation.

**Table 42. Clinical Outcome Based on Different Platelet Tests (Breet, N, et al., 2010)**

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Source: Breet, N, et al., 2010, JAMA, 303(8):754-762

Marcucci, R, et al. (2009), in a prospective study, used the VerifyNow assay to determine Residual Platelet Reactivity (RPR) to ADP during clopidogrel therapy and whether or not this predicted adverse clinical events in 683 ACS patients undergoing PCI with either BMS or DES. The primary endpoint was the composite of cardiovascular

death, nonfatal MI, and TVR at 12 months. There were 51 ischemic events (24 cardiovascular deaths [3.5%], 27 non-fatal MIs [3.9%]), and 40 TVRs [5.8%]. ROC analysis identified a PRU of ≥ 240 (defined as high RPR) as a significant and independent predictor of 12 month cardiovascular death (HR 2.55, 95% CI [1.08, 6.07], p = 0.034) and nonfatal MI (HR 3.36, 95% CI [1.49, 7.58], p = 0.004). There was no association found between a high RPR and TVR.

In the ADAPT-DES prospective registry study involving 10, 000 patients (Stone, GW, et al., 2013), platelet reactivity and clinical outcomes after coronary artery implantation of drug-eluting stents were evaluated. The results showed that high on-treatment platelet reactivity (HTPR) (PRU > 208 with clopidogrel as the treatment agent) was strongly related to ARC-ST and MI, inversely related to bleeding, and not related to mortality. However, the authors emphasized that the sensitivity, specificity, and diagnostic accuracy of HTPR with clopidogrel for subsequent ST were poor-to-fair.

Price, M, et al. (2011) described the results of the GRAVITAS (i.e. **G**auging **R**esponsiveness with **A V**erifyNow assay-**I**mpact on **T**hrombosis **A**nd **S**afety) RCT. This trial was designed to evaluate the effect of a high-dose clopidogrel regimen compared to a standard dose of clopidogrel in patients with a high on-treatment VerifyNow measured baseline PRU 12-24 hours after PCI with DES deployment. High on-treatment platelet reactivity was defined as PRU ≥ 230. A total of 2214 patients were enrolled (n = 1109 to the high dose clopidogrel regimen, median PRU 282; n = 1105 to the standard dose of clopidogrel, median PRU 283). The high dose clopidogrel was 600mg load + 150mg QD, and the standard dose clopidogrel was no load + 75mg QD. The primary efficacy endpoint was the 6 month incidence of cardiovascular death, nonfatal MI, and ST. The key safety endpoint was moderate or severe GUSTO bleeding. A key PD endpoint was the rate of persistently high on-treatment reactivity at 30 days. The study was powered with an assumed primary efficacy endpoint event rate of 5% in patients with high on-treatment PRU treated with the standard clopidogrel dose, where 1100 patients in each group would provide 80% power to detect a 50% relative risk reduction in the rate of the primary efficacy endpoint. The primary efficacy endpoint occurred in 25 of 1109 (2.3%) patients receiving high dose clopidogrel, and in 25/1105 (2.3%) patients receiving the standard dose clopidogrel. Moderate or severe GUSTO bleeding was not increased with the high dose clopidogrel. Compared to the standard dose clopidogrel, the high dose clopidogrel provided a 22% (95% CI 18%--26%) absolute reduction in the rate of high on-treatment reactivity at 30 days (62%, 95% CI 59%--65%, vs. 40%, 95% CI 37%--43%; p < 0.001). The decreased PRU for the high dose clopidogrel vs. the standard dose clopidogrel was not reflected in corresponding differences in clinical events, including bleeding events between the arms of the study. The study might have been underpowered due to the lower than expected event rate in the standard clopidogrel dose arm. This study did not impute missing data and patient lost to follow-up were censored at the date of last contact (only 2 patients in the high dose clopidogrel arm).

Gurbel, P, et al. (2009) wrote an editorial on the GRAVITAS trial where several questions were posed to address the discrepancy between PRU results and clinical outcome. One of the suggestions was that PRU is a biomarker which does not modify the level of risk. The sentiment expressed in this editorial appeared to be consistent with those expressed by Bonello, L, et al. (2010) where it was stated that there was limited data showing that alteration of therapy as a response to PRU measurement improved clinical outcome.

TRIGGER-PCI (Trenk, D, et al., 2012) was a randomized double-blind active comparator control trial designed to investigate the efficacy, safety, and antiplatelet effect of prasugrel compared to clopidogrel in patients who present with stable CAD and HTPR (PRU > 208) after elective PCI with DES. The primary efficacy endpoint was the incidence of CV-death or MI at 6 months. The primary safety endpoint was non-CABG related TIMI Major Bleed. Sample size calculations were based on the following assumptions: 1) an incidence of the primary efficacy endpoint of 4.7% for the clopidogrel-treated population; 2) patients with PRU>208 represented the upper tertile of the entire population with respect to on-clopidogrel platelet reactivity; and 3) the incidence of the primary efficacy endpoint in patients on clopidogrel with PRU>208 was increased 2-fold as compared with patients whose PRU $\leq$ 208. Based on these assumptions, it was anticipated that 1,075 subjects would need to be randomized to each group: α, β not mentioned. In 212 subjects randomized to prasugrel, PRU decreased from 245 (median 225, interquartile range 273) at baseline to 80 (median 42, interquartile range 124). In 211 subjects randomized to clopidogrel, PRU decreased from 249 (median 225, interquartile range 277) to 241(median 194, interquartile range 275) ($p<0.001$ vs. prasugrel). The primary efficacy endpoint occurred in nobody on prasugrel vs. 1 subject in clopidogrel. TIMI Major bleed occurred in 3 subjects (1.4%) on prasugrel vs. 1 (0.5%) on clopidogrel. The relationship between PRU and clinical outcome was not demonstrated in TRIGGER-PCI.

ARCTIC (Collet, J-P, et al., 2012) was a randomized open label study comparing bedside platelet function monitoring with treatment adjustment in subjects who had a poor response to antiplatelet therapy, vs. a conventional strategy (no monitoring and no treatment adjustment). Subjects who were enrolled presented with stable CAD or NSTEACS undergoing DES placement. The primary efficacy endpoint was the incidence of death, MI, ST, stroke, or urgent revascularization at 1 year. The authors hypothesized that the annual event rate would be 15% among subjects with a poor response to antiplatelet therapy (PRU $\geq$235 with thienopyridine; PRU $\geq$550 on aspirin, or 15% less IPA) and 6% among those with a good response. The authors expected that 33% of the subjects would have a poor response. Assuming an annual risk of 9% in the control group (66% of the subjects at an event rate of 6% and 33% of the subjects at an event rate of 15%) for the primary endpoint, and expecting a 33% reduction in relative risk in the monitoring group (two-sided α 5% and β of 20%), it was estimated that 2500 subjects would be required. In the monitored group, high platelet reactivity in



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subjects taking clopidogrel (34.5% of the subjects) or aspirin (7.6% of the subjects) led to the administration of an additional bolus of clopidogrel, prasugrel, or aspirin along with GPI during the PCI. If HTPR observed 14-30 days post-PCI, the subjects were switched to prasugrel or to an increased maintenance dose of clopidogrel. The primary efficacy endpoint occurred in 34.6% in the monitored group compared to 31.1% in the conventional group. The study showed that PRU monitoring and subsequent dose adjustment was ineffectual.

The Applicant has argued that these negative trials (i.e. GRAVITAS, TRIGGER-PCI, ARCTIC) were underpowered, focused on low-risk, and demonstrated that individualization strategies are not effective. The Applicant has further argued that an individualization strategy was not the focus of their BRIDGE hypothesis, but rather ensuring the minimization of peri-CABG thrombotic and bleeding risks through management of PRU with cangrelor based on the association of PRU and clinical events. In the opinion of this reviewer, the powering of the failed trials was based on their reasonable apriori statistical assumptions. The end-result was a paucity of data which has created a validation requirement to justify the Bridge indication. Furthermore, the management of PRU during cangrelor treatment in the peri-CABG setting, even in using an “on-off” approach, was analogous to an individualization strategy as it attempted to use PRU to affect a clinical outcome. Although the BRIDGE hypothesis is meritorious, the level of evidence required to support an indication has not been met by the data provided in the Applicant’s NDA.

The salient features of the published data suggested that HTPR is associated with MACE but the observed caveats as expressed by the authors were:

- Limited data showing that alteration of therapy in response to PRU measurement improves clinical outcome.
- Observed cut-off PRU values have a poor predictive value for thrombotic ischemic events.
- No evidence that HTPR cut points with risk for long term risks are the same as those for peri-procedural events.
- No correlation between PRU and clinical outcome.
- Sensitivity, specificity, and diagnostic accuracy for subsequent ST were poor-to-fair.

The data at this point of clinical investigation regarding PRU and clinical outcome is suggestive but inconclusive. In addition to the opinion that PRU may be a biomarker which does not alter the level of risk (Gurbel, P, et al., 2009), it was also opined that platelet function testing “continues to hold promise as a tool to tailor therapy, but the verdict is out on whether this will prove clinically useful or lead to meaningful treatment strategies” (Reed, G, and Cannon, C, 2011).



Reference ID: 3435333

### 6.1.2.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

There is no data on persistence of efficacy and /or tolerance effects.

### 6.1.2.10 Additional Efficacy Issues/Analyses

The Dutch registry identified several predictors of ST in patients having undergone PCI with either a BMS or DES. As shown in **Figure 18**, the strongest predictors of ST in descending order were discontinuation of clopidogrel, followed by stent under-sizing, malignancy, CAD proximal of culprit lesion, TIMI flow < 3 post-PCI, dissection, bifurcation stenting, LVEF < 30%, PAD, CAD distal to culprit lesion, lack of aspirin, any DES, and diabetes mellitus. **Figure 19** shows the independent risk factors for ST as a function of patient presentation (SA in the **Figure 19-A**, and ACS in **Figure 19-B**). **Figure 20** shows the independent risk factors for ST as a function of time from PCI: early (≤ 30 days, Fig 18-A) and late (> 30 days, Fig 18-B). Notwithstanding some variations, the data showed a similar set of independent risk factors for patient presentation and time of ST from PCI, respectively (i.e. stent under-sizing, CAD > 50% proximal to the culprit lesion, post PCI TIMI flow < 3). The authors of the Registry emphasized that the time-varying "cessation of clopidogrel" was not included in these multivariate models.

**Table 43** shows the number of patients with ST distributed over time from index PCI observed in the Dutch Stent Thrombosis Registry. The table also shows the number of patients who were not on clopidogrel for each type of time-dependent ST (i.e. acute, subacute, late, very late). The median time off clopidogrel for each type of time-dependent ST was also delineated. Of the 437 patients with ST selected for this analysis (436 in the publication analysis), 140 patients had acute ST, 179 patients had subacute ST, 58 patients had a late ST, and 59 patients had a very late ST. Therefore, 319 patients (approx. 73%) had a ST within 30 days from the index PCI. Of these, 39 (approx. 12%) were off clopidogrel at the time of ST. Of the total of 437 selected patients with an ST, approximately 31% were not on clopidogrel (presumably not on any other P2Y12 inhibitor). Of the 58 patients with late thrombosis (> 30 days—1 year from index PCI), 39 (approx. 67%) were not on clopidogrel for a median of 13 days (interquartile range 7-61 days).

**Table 44** shows the influence of clopidogrel on ST as extracted from the Dutch Stent Thrombosis Registry publication. Hazard Ratios are shown for two variables: "lack of clopidogrel therapy at time of ST", and "cessation of clopidogrel within 14 days before ST", as a function of three temporal groups representing time of ST from index PCI: < 30 days, 30 days—6 months, > 6 months. The former variable was observed to be a significant predictor of ST for all three temporal groups. The latter variable was introduced by the authors based on their hypothesis that it would reveal the temporal relationship between the discontinuation of clopidogrel and ST in the setting where clopidogrel irreversibly inhibits human platelets throughout their lifespan (10-12 days).

This time-varying covariate was observed to be a significant predictor of ST for the temporal groups of < 30 days (HR: 36.9, 95% CI: 7.9 to 173.3) and 30 days—6months (HR: 21, 95% CI: 2.2 to 198.3), but not for > 6 months from the index PCI. In the latter temporal group, the authors concluded that the number of events were too low to reliably estimate the impact of this time-varying covariate on the event of ST in that timeframe. The authors noted that a significantly higher percentage of patients with ST did not use aspirin at the time of the PCI compared to their matched controls (13.1% vs. 4.5%, $p < 0.0001$). The predominant reason for no aspirin therapy was Coumadin use and aspirin allergy. Multivariate logistic regression analysis identified the absence of aspirin as a strong predictor of ST (HR 1.91, 95% CI 1.01 to 3.88, $p = 0.0052$).

In the Bridge study, 50% of the subjects (53/106) in the clopidogrel arm and 45.5% of the subjects (46/101) in the placebo had a stent deployment. Of these, 67.9% (36/53) of subjects in the cangrelor arm and 56.5% (26/46) in the placebo arm had received a stent > 6 months from planned CABG. The majority of stented subjects in the BRIDGE trial have therefore been placed within the timeframe where there has been no data from the Dutch Stent Thrombosis Registry to demonstrate risk of ST consequent to clopidogrel discontinuation. Therefore, there appears to be risk-stratification mismatch between the BRIDGE population and the ST Registry based on the original authors' time-varying covariate analysis.

The Applicant reported to have been provided with the original stent thrombosis registry database from which they performed additional analyses not shown in the original publication. This led the Applicant to conclude that the cessation of clopidogrel led to a ST within 7 days independent of the duration of time from the index PCI (see abbreviated CSR of the stent thrombosis registry, section 11.6.5, Figure 11). This contradicts the assessment from the original publication that the number of events beyond the 6-month time frame after stent implantation was too small to reliably assess the impact of "cessation of clopidogrel within 14 days before ST" on the occurrence of ST in this subcategory of patients. The Applicant's analysis appeared to have involved grouping the data into three temporal categories: $\leq$ 30 days from index PCI; $\leq$ 180 days from index PCI, and $\leq$ 365 days from index PCI. Since the majority of patients with ST sustained the ST within 30 days from index PCI (73%), incorporation of these patients into the $\leq$ 365 day temporal group probably skewed the results toward resembling the data in the $\leq$ 30 day temporal group. In order to perform an independent analysis, the Applicant was requested to provide the start-stop dates of clopidogrel as well as date of PCI and date of ST from the registry database they were provided. The clopidogrel dates were not available and the Applicant is currently requesting such data at the time of this writing.

In order to confirm the results from the Dutch Stent Registry with another study, the Paris 1-Year (Mehran, R, TCT2012) study was evaluated. This was a multicenter, multinational, observational study designed to determine if discontinuation of dual antiplatelet therapy (DAPT- $P2Y_{12}$ inhibitor and aspirin) after PCI, secondary to bleeding



Reference ID: 3435333

or other events (i.e. non-cardiac surgery), led to subsequent ischemic events. The primary efficacy endpoint was MACE (death, TLR, spontaneous MI, and definite/probable ST). The study enrolled 5,033 subjects at 15 centers in 5 countries (France, Germany, Greece, Italy, and the USA). The association between DAPT cessation and non-adherence (defined as interruption-due to need for surgery with DAPT reinstitution within 14 days, or disruption-due to bleeding, including lowering dose) were entered as time-varying covariates. Additional covariates were generated to further assess the impact of DAPT cessation at different time points (0-7 days, 8-30 days and > 30 days).The results showed that DAPT cessation within 1 year was associated with an increase in MACE, strongest in the first 0-7 days from PCI and attenuated at 8-30 days from PCI. Beyond 30 days, the HR subtended unity (p=0.34). Increased risk was attributable only to non-adherent subjects, whereas adherent subjects (defined as any subject remaining on DAPT at 1 year or those stopping DAPT due to physician-guided recommendations) did not have an increase in MACE.

Both the Stent Thrombosis Registry and the PARIS-1Year study were in alignment regarding loss of association between cessation of antiplatelet therapy and MACE beyond 30 days from index PCI (Paris-1 Year) or between cessation clopidogrel therapy and ST within 14 days of cessation 6 months from index PCI. The preponderance of the published data do not support a BRIDGE indication with the population studied in the BRIDGE trial pending validation of the Applicant’s analysis of the stent thrombosis registry dataset.

**Figure 18. Predictors of Stent Thrombosis derived from Dutch Stent Registry**

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**Figure 1** **Independent Risk Factors for ST**

A comparison of the total group of patients with stent thrombosis (ST) with all matched-control subjects. Represented by hazard ratio (HR) and 95% confidence interval (CI). ASA = acetyl salicylic acid; CAD = coronary artery disease; DES = drug-eluting stent(s); DM = diabetes mellitus; LVEF = left ventricular ejection fraction; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; TIMI = Thrombolysis in Myocardial Infarction.

Source: van Werkum, J, et al., 2009, Predictors of Coronary Stent Thrombosis: Dutch Stent Thrombosis Registry, JACC, 53(16):944-954

**Figure 19. Independent Risk Factors for ST: A) SA; B) ACS**

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**Figure 2** **Independent Risk Factors for ST for the Different Indications of Index Stent Implantation**

**(A)** Cases and matched controls with stable angina as indications for index PCI. **(B)** Cases and matched controls with acute coronary syndrome as indication for index PCI. Represented by odds ratio (OR) and 95% CI. GP = glycoprotein; LAD = left anterior descending; other abbreviations as in Figure 1.

Source: van Werkum, J, et al., 2009, Predictors of Coronary Stent Thrombosis: Dutch Stent Thrombosis Registry, JACC, 53(16):944-954

**Figure 20. Independent Risk Factors for ST: A) Early (≤ 30 days); B) Late (>30 days)**

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**Figure 3** Independent Risk Factors for Early (≤30 Days) and Late (>30 Days) ST

**(A)** Predicators of early (≤30 days) stent thrombosis. **(B)** Predicators of late (>30 days) stent thrombosis. Represented by OR and 95% CI. Abbreviations as in Figures 1 and 2.

Source: van Werkum, J, et al., 2009, Predictors of Coronary Stent Thrombosis: Dutch Stent Thrombosis Registry, JACC, 53(16):944-954

**Table 43: Dutch Stent Thrombosis Registry-distribution of ST over time from index PCI**

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Source: van Werkum, J et al, 2009, Predictors of Coronary Stent Thrombosis, Dutch Stent Thrombosis Registry, JACC, 53:1399-1409). N (%) =number and percent

**Table 44: Dutch Stent Thrombosis Registry-influence of clopidogrel on ST**

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Source: van Werkum, J et al, 2009, Predictors of Coronary Stent Thrombosis, Dutch Stent Thrombosis Registry, JACC, 53:1399-1409).

In support of the argument that there is an increased risk of bleeding and mortality after surgery when oral $P2Y_{12}$ receptor inhibitor therapy is continued during the operative period, the Applicant referred to two meta-analyses (Biancari, F, et al., 2012; Nijjer, S, et al., 2011) and a systematic literature review (Au, A, et al., 2012).

Biancari, F, et al. (2012) performed a meta-analysis of studies evaluating the use of clopidogrel before CABG, taken from the Cochrane Handbook for Systematic Reviews. This yielded 3 prospective randomized trials (i.e. CLARITY, CREDO, and CAPRIE) and 17 observational studies. A meta-analysis of post-hoc studies from the 3 prospective

randomized trials showed a non-significant reduced risk of the 30-day post-operative composite endpoint of death, MI, or stroke in the clopidogrel group vs. control (RR 0.77, 95% CI [0.58, 1.04]). Data from the CREDO and CLARITY trials showed a reduction in the risk of death (RR 0.81, 95% CI [0.20, 3.37]) and MI (RR 0.58, 95% CI [0.25, 1.33]), and an increase in the risk of TIMI Major Bleed (RR 1.48, 95% CI [0.72, 3.04]) for clopidogrel vs. control. In contrast, meta-analysis of the observational studies showed that pre-operative exposure to clopidogrel, compared to control, was associated with an increased risk of death (RR 1.30, 95% CI [1.02, 1.67]), re-operation for bleeding (RR 1.88, 95% CI [1.37, 2.58]), blood loss (mean difference 157.8 ml, 95% CI [61.9, 253.6]), and need for packed red blood cells (RR 1.23, 95% CI [1.10, 1.37]). However, consistent with CREDO and CLARITY, the meta-analysis of observational studies showed a significantly reduced risk of post-operative MI among patients taking clopidogrel (RR 0.63, 95% CI [0.48, 0.82]). Based on the preponderance of the data from the Biancari study, there was a conflict between the meta-analysis of data from randomized trials, which supported the benefit of pre-operative clopidogrel in the post-operative setting, and the meta-analysis of data from observation studies, which detracted from the benefit of pre-operative clopidogrel in the post-operative setting. Both meta-analyses pointed to an increased risk of post-operative bleeding and a decreased risk of post-operative MI. The increased risk of bleeding resulted in an empirical net blood volume loss of 158 ml. The risk-benefit profile of continued clopidogrel therapy based on the Biancari review showing conflicting data did not support the Applicant's unequivocal position that maintaining clopidogrel therapy during surgery was overwhelmingly harmful necessitating a new treatment paradigm.

Nijjer, S, et al. (2011) performed a meta-analysis of 22,584 patients from 34 studies evaluating the risk of CABG in ACS patients while continuing clopidogrel during the 5-7 days prior to CABG. The authors have opined that the studies were "small, non-randomized, retrospective limited subgroup analyses from RCTs". Furthermore, the bleeding and transfusion data were "heterogeneous and with potential for treatment and ascertainment bias". The authors reported that only 4 of the 34 reviewed studies were RCTs that met the criteria for freedom from bias. The remainder of the studies scored poorly on the bias analysis. Although mortality was increased in those patients with a recent exposure to clopidogrel compared to those who were not recently exposed (OR 1.6, 95% CI [1.30, 1.96], $p < 0.00001$), it was influenced by ACS status and urgency for surgery when reviewing studies whose ACS patient population exceeded 50% of the total population. Ironically, in studies which recruited only ACS patients, there was no significant difference in mortality (OR 1.44, 95% CI [0.97, 2.1], $p = 0.07$), in postoperative MI (OR 0.57, 95% CI [0.31, 1.07], $p = 0.08$), and in stroke (OR 1.23, 95% CI [0.66, 2.29], $p = 0.52$). Combined MACE (i.e. stroke, MI, death) were not different between the recent-exposure to clopidogrel group vs. the not-recent-exposure to clopidogrel group (OR 1.10, 95% CI [0.87, 1.41], $p = 0.43$). Although re-operation rates were elevated in the recent-exposure to clopidogrel group, such rates were reduced over time and not different from the not-recent-exposure to clopidogrel group in ACS patients (OR 1.5, 95% CI [0.88, 2.54], $p = 0.13$). The authors have concluded that

"many patients have undergone CABG safely with recent clopidogrel exposure and this practice can continue in expert hands in ACS patients who need to continue clopidogrel".

Au, A, et al. (2012) systematically reviewed 37 studies involving clopidogrel (31 cardiac and 6 non cardiac where 3 were RCTs and 34 were observational studies) in order to address the hypothesis that pre-operative thienopyridine administration influences postoperative outcome up to 30 days post-surgery. The authors reported that exposure to clopidogrel in the 5 days preceding surgery (compared to no exposure) was not associated with a reduction in postoperative MI (23 studies, 12,872 patients, 3.4% vs. 3.0%, OR 0.98, 95% CI [0.72, 1.34]). However, exposure to clopidogrel vs. no exposure in the 5 days preceding surgery was associated with increased risks of stroke (16 studies, 10,265 patients, 1.9% vs. 1.4%, OR 1.54, 95% CI [1.08, 2.20]), reoperation for bleeding (32 studies, 19,423 patients, 4.3% vs. 1.8%, OR 2.62, 95% CI [1.96, 3.49]), and all-cause mortality (28 studies, 22,990 patients, 3.7% vs. 2.6%, OR 1.38, 95% CI [1.13, 1.69]). The authors concluded that the data supported withholding thienopyridine therapy 5 days before cardiac surgery. There was insufficient evidence to make a definitive recommendation for elective non-cardiac surgery although the direction and magnitude of the associations were similar.

The preponderance of the evidence from published literature was based on 1) a registry with author-recognized liabilities, and 2) meta-analyses which included post-hoc data from retrospective subgroup analyses of randomized trials and from small underpowered non-randomized observational studies. The authors of these meta-analyses recognized the liabilities of these analyzes. The summarizing conclusions based on the published data were:

- Cessation of clopidogrel within the first 6 months following stent deployment, especially in the absence of aspirin, significantly raised the risk of ST within 14 days of clopidogrel termination. However, there was insufficient data, based on the authors' comments, to draw this conclusion beyond 6 months.
- The effect of pre-CABG maintenance of clopidogrel treatment on post-operative complications was not clear. However, there was a consistent trend in reduction of post-op MI and an increase in post-op bleeding.
- The current practice of withholding clopidogrel for 5 days prior to CABG was supported by systematic review of published data.
- Recent clopidogrel exposure prior to CABG in ACS patients was safe and can continue.

The Applicant's position that a treatment dilemma exists in patients requiring surgery (i.e. thrombotic events if $P2Y_{12}$ inhibitors are discontinued; and bleeding events with increased morbidity and mortality if $P2Y_{12}$ inhibitors are continued) was not unequivocally supported by the preponderance of the evidence.

Given that the PHOENIX trial's carefully crafted primary endpoint was met in favor of cangrelor vs. clopidogrel with a dose 5.3-fold that which was studied in Bridge and in a different population, it is reasonable to assume that the PRU data from BRIDGE portends efficacy in the BRIDGE population. However, a clinical evaluation of the benefit/risk in the BRIDGE setting was attenuated by the conflicting published data on the relationship between PD and outcome, data paucity in the CABG population where a stent was placed greater than 6 months from the planned CABG, conflicting data on the risk of maintaining $P2Y_{12}$ inhibitor treatment during the peri-CABG period, and lack of clinical data from the Applicant on cangrelor to support their separate BRIDGE indication. It is therefore challenging to recommend a BRIDGE indication based solely on the Applicant's PD data. It is reasonable to describe the BRIDGE trial in section 12.2 of the label in lieu of an indication.

# 7 Review of Safety

***Safety Summary***

Cangrelor is a $P2Y_{12}$ inhibitor that has been studied in active controlled trials primarily at a dosing regimen of 30 ug/kg bolus followed by a continuous infusion of 2 ug/kg/min for ~ 2 hours during PCI. A total of 12,565 subjects received a dose of cangrelor in the CHAMPION trials (n=5529 in CHAMPION PHOENIX). The BRIDGE trial provides the longest duration of data (~72 hours), albeit at ~¼ the usual dose (n=117 subjects treated with cangrelor) in subjects who underwent cardiac surgery.

The demographics of subjects in the Integrated Summary of Safety (ISS) were balanced between cangrelor and control. In the cangrelor arm the mean age was 63 years, 75% were male, and 86% were White. (See also **Figure 22-24**)

The safety review focused on the PHOENIX trial. In the PHOENIX trial the primary safety endpoint (not adjudicated) was the incidence of non-CABG GUSTO severe bleed at 48 hours after randomization. The number of subjects with GUSTO severe bleed was small, but numerically greater in cangrelor treated subjects (10, 0.2%) compared to clopidogrel treated subjects (6, 0.1%). The difference was not significant [RR, 95% CI: 1.64 (0.60, 4.52)].

The reviewer and the Applicant classified bleeds (by CABG and non-CABG related) as GUSTO, TIMI, ACUITY, and BARC. In PHOENIX the incidence of total non-CABG related bleed was ~42% greater in cangrelor treated subjects (857/5529, 15.5%) compared to clopidogrel treated subjects (601/5527, 10.9%), [RR 1.42 (1.29, 1.56)]. There were very few CABG related bleeds (4, cangrelor and 3, clopidogrel). The incidence of non-CABG GUSTO severe, GUSTO moderate, and TIMI major bleeds was low, and there was not a significant difference between treatment arms. Generally, the risk of bleeding was significantly greater on cangrelor for the "lesser" bleeds, i.e.,

GUSTO mild, ACUITY major (which was largely classified as such because of hematomas). However, these bleeds are unlikely to have detrimental clinical consequences/sequelae.

In attempts to find subjects with clinically bad bleeds, the reviewer categorized a “bad bleed” as any of the following: ICH, transfused, cardiac tamponade, reoperation for bleeding, surgical intervention, retroperitoneal, requiring or extending hospitalization. In PHOENIX there were 61 (1.1%) bad bleeds in the cangrelor arm and 41 (0.7%) in the clopidogrel arm. The risk of bad bleed was nearly significant [RR, 95% CI, 1.46 (0.99, 2.17)].

According to the death CRF, there were no fatal bleeds in PHOENIX. However, there were four subjects who had a bleed and died within 48 hours of drug initiation. All four subjects received cangrelor.

From the BRIDGE trial, the incidence of excessive CABG related bleeding was balanced between cangrelor (11.8%) and placebo (10.4%), suggesting that cangrelor can be safely used in the CABG setting.

The incidence of transfusion was another safety endpoint in PHOENIX. More subjects treated with cangrelor (25) than clopidogrel (17) received a transfusion, but the difference was not significant.

A total of 88 (1.6%) subjects treated with cangrelor and 66 (1.2%) subjects treated with clopidogrel had nonfatal SAEs in PHOENIX. These were generally balanced (by %) between arms because the number of subjects with events was low.

Adverse events of interest included dyspnea, renal function effects, and hypersensitivity. Dyspnea was a common adverse event that occurred at greater frequency than control (1.2% in cangrelor treated subjects vs. 0.3% in clopidogrel treated subjects in PHOENIX). Dyspnea was also a common reason for cangrelor discontinuation in the CHAMPION trials. The overall incidence of dyspnea in the ISS was low, 1.3% in cangrelor treated subjects compared to 0.4% of control subjects. There was not a clear safety signal with respect to acute renal failure or rise in serum creatinine in the ISS, despite evidence of renal toxicity from pre-clinical studies. CHAMPION-PCI had a greater numerical increase in renal adverse events as renal function declined in the cangrelor arm compared to clopidogrel, but CHAMPION-PLATFORM did not. Hypersensitivity was balanced between cangrelor (0.7%) and control (0.6%) in the ISS, however SAEs were greater in cangrelor treated subjects compared to control (7 vs. 2).

In sum, the most important safety finding is the risk of bleeding. The incidence of a “severe” bleed was low (< 1%) in both treatment arms. Although bleeds were generally numerically higher in the cangrelor arm compared to clopidogrel, the difference was



Reference ID: 3435333

only significant for the "lesser" severity bleeds (e.g., GUSTO mild). These types of bleeds are less likely to have sequelae/clinical consequences. The PHOENIX data and the BRIDGE data suggest that cangrelor can be safely used in the PCI and CABG setting.

## 7.1 Methods

### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The reviewer focused on the safety data in PHOENIX since the single trial was substantive to support safety. Any discussions that are not of the PHOENIX trial are explicitly stated. The ISS (includes CHAMPION PCI, CHAMPION PLATFORM, and BRIDGE among the trials) was used for analyses of AEs, SAEs and laboratory findings. See **Table 2 and Table 3** in section 5.1 for a description of the 16 trials found in the Integrated Summary of Safety (ISS).

In PHOENIX the last patient completed the trial on 14 November 2012. The database was initially locked on 04 January 2013. Shortly afterwards it was noted that some subjects did not receive an anticoagulant prior to or during the PCI procedure. The Applicant thought that this was due to confusion in collecting these data on the eCRF. The database was unlocked on 01 February 2013 to confirm whether any procedural anticoagulant was administered to subjects in whom no data were entered in the eCRF and to edit the data if necessary. A total of 553 subjects from 84 sites were affected. In addition, a date error was fixed for an MI adjudicated result for one subject. Site investigators reviewed chart information and returned the affected eCRF page. The database was re-locked on 18 February 2013.

### 7.1.2 Categorization of Adverse Events and Bleeding

in **Section 5.3.4.6 Safety Endpoints and Definitions** defines the various bleed classifications reported in the Applicant's CSR for all three CHAMPION trials. Bleeding was not an adjudicated endpoint in PHOENIX. In PHOENIX, the Applicant classified bleeding based on the checked fields on the bleed eCRF.

*Reviewer comment: The bleed CRF was generally well designed to collect the components of the various bleeding classifications. However, it was difficult to determine how uniformly investigators completed subjective fields. Some subjective items such as "hemodynamic compromise" were not checked for what might have been a bleed causing hemodynamic compromise. The reviewer did not reclassify subjective fields.*

The reviewer used the bleed CRF (including text fields in the CRF) as well as the serious adverse event CRF[8], narratives and ISS laboratory dataset to identify and classify subjects that bled. For the reviewer's analysis, within a major classification of bleeding, the sub-classifications were mutually exclusive. **Table 45** highlights differences between the bleed definitions and how the Applicant and reviewer classified bleeds.

**Table 45. Differences between bleed definitions/what was used for classification**

| Term | What was used for classification |
|---|---|
| Clinically overt or overt bleeding | The reviewer defined this as any sign of bleeding (including bleeding seen on imaging). This differs from the Applicant's definition which attempted to assign a severity (see **Table** 4**).** This likely affected the counts for TIMI, ACUITY, and BARC. |
| Drop in hemoglobin or hematocrit | The reviewer noted that this field was sometimes incorrectly marked or not marked on the eCRF, so the reviewer used the ISS lab dataset to obtain the adjusted Hg data for all definitions (TIMI, ACUITY, and BARC) that included a drop in hemoglobin. The Applicant used the field as marked in the eCRF. |
| BARC | Part of the definition includes a Hg drop of < 5 g/dL and ≥ 5 g/dL.<br>The reviewer and the Applicant used ≤ 5 g/dL and > 5 g/dL. |
| Intervention | If the investigator took action to stop the bleed, then the reviewer marked it as an intervention. This might have contributed to differences between the reviewer's and Applicant's BARC3b and ACUITY major. |
| GUSTO mild | The reviewer classified all bleeds that were not GUSTO severe or moderate as mild. The Applicant required that at least one of the following on the CRF also be marked:<br>requiring intervention…<br>leading to hospitalization…<br>prompting evaluation…<br>access site bleeding… |

Adverse events for any pooled analyses were coded using MedDRA version 13.1.

### 7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The Applicant pooled the data into six different sets: all studies, patient studies, controlled studies, placebo-controlled studies, active controlled studies, and CHAMPION trials. From a safety perspective, this approach was reasonable. In general, analyzing all three CHAMPION trials together is sensible since they all used the same dosing scheme in the setting of subjects that required PCI.

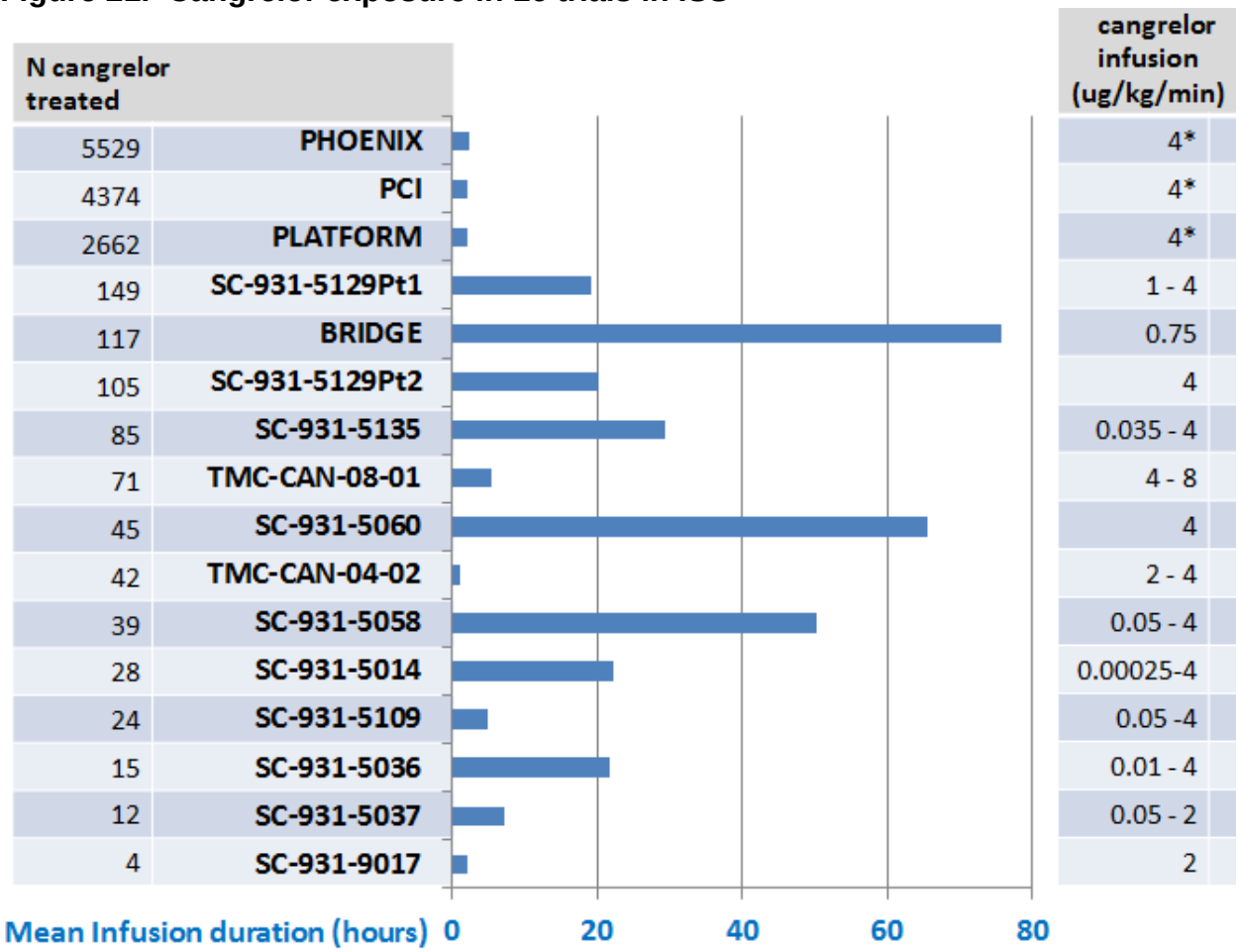
[8] Bleeding was supposed to be captured on the bleed CRF, however the reviewer found a subject treated with cangrelor who had cardiac tamponade (reported as an SAE) and died. The event was not recorded on a bleed CRF.

## 7.2 Adequacy of Safety Assessments

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The majority of the exposure data are found in the CHAMPION trials **(Figure 21)**. In all three CHAMPION trials, subjects randomized to cangrelor received a 30 ug/kg/min IV bolus followed by a continuous infusion of 4 ug/kg/min. The mean infusion duration in each CHAMPION trial was 2.2 hours.[9]

**Figure 21. Cangrelor exposure in 16 trials in ISS**

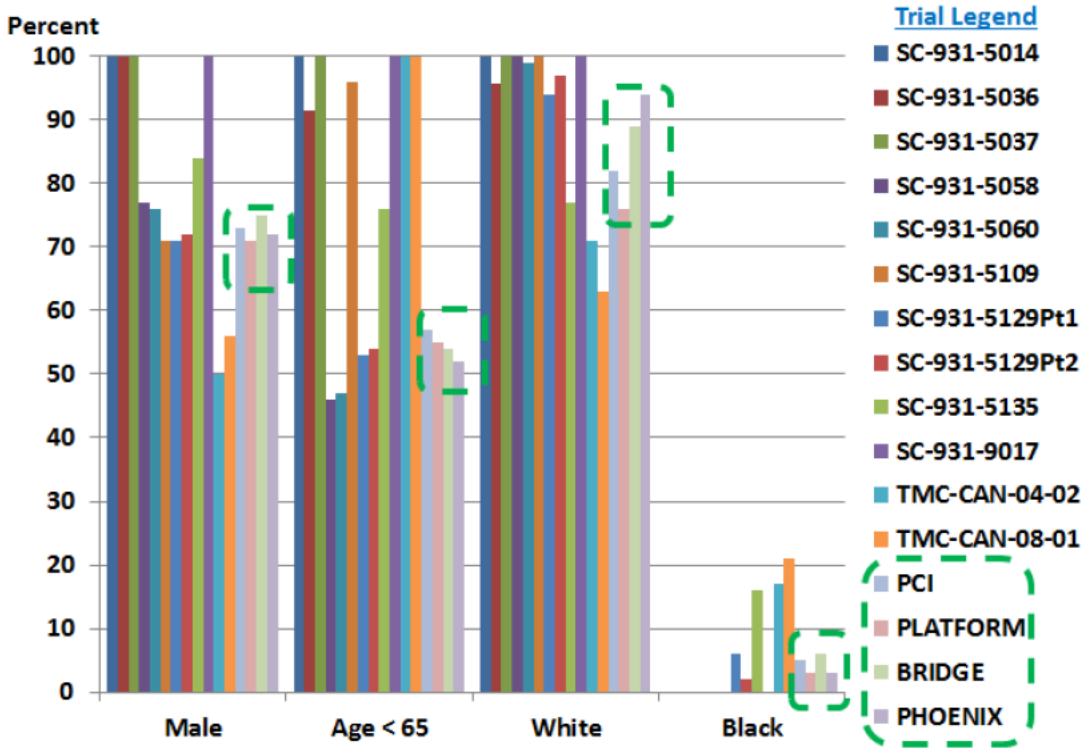



*infusion preceded by bolus
Infusion duration excludes temporary interruptions. Reviewer's analysis \exposure\infdose. Dataset iss\isd

The demographics were balanced between cangrelor and active control or placebo. **Figure 22** shows the demographics for subjects treated with cangrelor in the ISS. There were a low percentage of treated Black subjects.

[9] Infusion time excludes interruptions. Reviewer's analysis: exposure\study exp. Dataset: ISS\isd

**Figure 22. Cangrelor subjects' demographics in trials in ISS**




Reviewer's analysis: \disp\disp_dem. Dataset iss\disp

**Figure 23 Medical history of treated subjects**

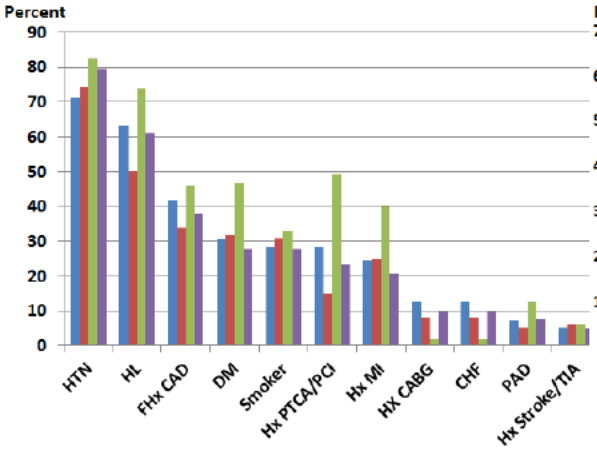
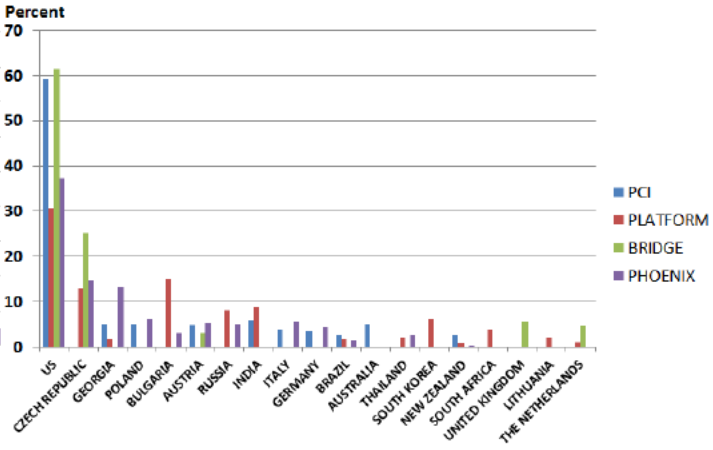



**Figure 24. Country of treated subjects**




Reviewer's analysis: \disp\disp_dem. Dataset iss\disp

Patient demographics were well balanced between arms in the CHAMPION trials also. The mean age was 63 years, 72% of subjects were male, 86% were White, 8% were Asian, and 3% were Black. See also **Table 46**.

**Table 46. CHAMPION trials: Age and patient type**

| | CHAMPION (N=25,107) | |
|---|---|---|
| | Cangrelor N=12565 | Clopidogrel N=12542 |
| **Treated** | **(%)** | **(%)** |
| Age (years) | 15.6 | 10.9 |
| < 55 | 23.5 | 24.0 |
| 55 to < 65 | 30.8 | 30.8 |
| 65 to < 75 | 28.7 | 28.3 |
| ≥ 75 | 17.0 | 16.9 |
| Derived patient type | | |
| STEMI | 11.7 | 12.3 |
| NSTEMI† | 88.3 | 87.7 |

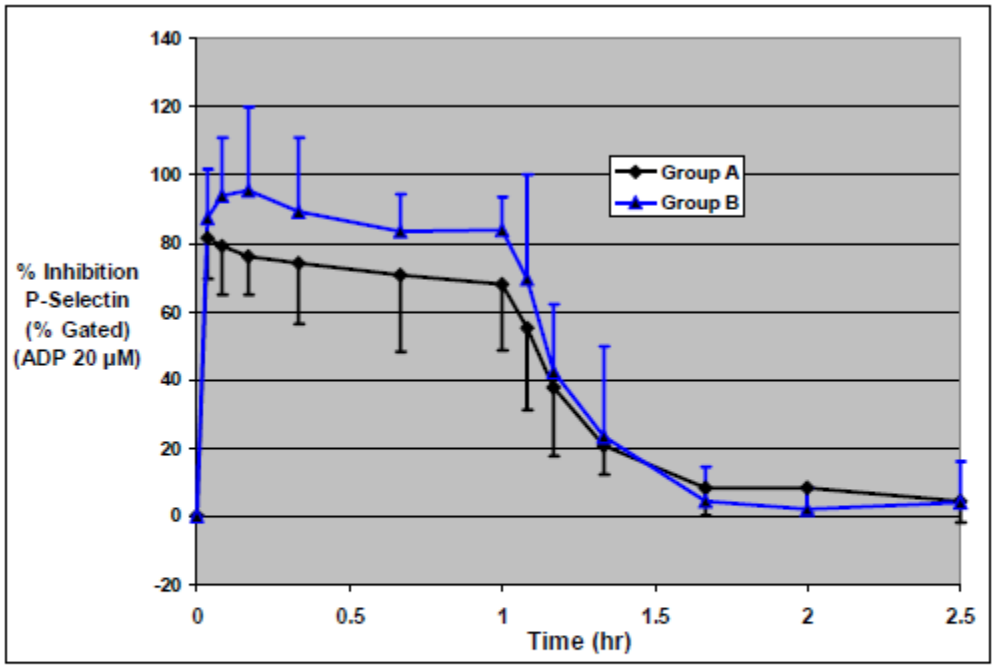
† CAD patients with SA, UA, or NSTEMI
Source: SCS, Table 5.

### 7.2.2 Explorations for Dose Response

See **Figure 21** for dose and duration information. The Applicant evaluated various dosing regimens (infusion alone, bolus followed by an infusion). The Clinical Pharmacology Reviewers concluded that after the start of cangrelor infusion, complete platelet inhibition is achieved in about ~30 minutes. To eliminate this delay the Applicant explored a bolus followed by infusion regimen. The reviewers estimate that a bolus of only ~4.4 fold higher than the target infusion rate of 4 ug/kg/min is needed to achieve platelet inhibition. Thus the 30 ug/kg bolus dose is more than necessary. However, the dose should equilibrate quickly, given its effective half-life of 3-6 minutes.

The Applicant compared 15 mg/kg bolus followed by 2 ug/kg/min to 30 mg/kg bolus followed by 4 ug/kg/min and found that greater inhibition was maintained with the higher continuous infusion **(Figure 25)**. Thus, a 30 ug/kg bolus followed by 4 ug/kg/min was selected as the dose to carry forward into Phase 3.

**Figure 25. Percent inhibition of platelet response**




ADP = adenosine diphosphate
Group A: Cangrelor 15 µg/kg IV bolus + 2 µg/kg/min x 1 hour
Group B: Cangrelor 30 µg/kg IV bolus + 4 µg/kg/min x 1 hour
Data presented are mean ± standard deviation
Source: Section 14.3.2, Figure 3

Source: TMC-CAN-04-02, CSR Figure 6

### 7.2.3 Special Animal and/or In Vitro Testing

According to the finalized Pharmacology/toxicology review the nonclinical testing was adequate to assess the safety of cangrelor.

### 7.2.4 Routine Clinical Testing

Assessments for safety and adverse events in PHOENIX were limited to 48 hours after the start of the infusion. The mean duration of infusion was 2.2 hours. Based on pharmacokinetics, this was a reasonable duration to collect information. PHOENIX only collected hematocrit, hemoglobin, platelets. Serum creatinine, liver, WBC laboratory data are in CHAMPION PCI, PLATFORM, and BRIDGE.

### 7.2.5 Metabolic, Clearance, and Interaction Workup

*In vitro* studies indicate that cangrelor and its metabolite have minimal potential to inhibit or induce CYP enzymes at therapeutic concentrations. The PK of cangrelor and its

metabolite did not alter significantly when co-administered with a combination of aspirin, heparin, and glyceryl trinitrate. See also **4.4.3 Pharmacokinetics**.

### 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The Applicant's assessment for adverse events in PHOENIX was generally adequate. See **Section 7.2.4.** If the investigator was notified of an SAE occurring after 48 hours from randomization and the investigator suspected it to be causally related to study drug, then the event was to be recorded. At the 30 day follow-up contact, only efficacy endpoints were assessed (MI, ischemic symptoms, angiographies, revascularization and death). Non-clinical data showed a reversible effect on renal function, yet PHOENIX did not report serum creatinine values. However, these data were available for CHAMPION PCI, PLATFORM, and BRIDGE (See Section 7.4.2. Laboratory Findings).

## 7.3 Major Safety Results

### 7.3.1 Deaths

Since death was an efficacy endpoint, refer to Section 6, review of efficacy for more information.

Based on the death CRF, there were no fatal bleeds in PHOENIX. This information was not collected on the bleed CRF. However, there were four subjects who had a bleed and died within 48 hours of drug initiation. All four subjects received cangrelor.

Subject 401029051 (cangrelor, stable angina) had cardiac tamponade (reported as an SAE, not in the bleed CRF) and died ~ 1 hour after the start of PCI.[10]

Subject 407005141 (cangrelor, STEMI) had cardiac tamponade and died ~1 hour after the start of PCI.

Subject 401012052 (cangrelor, STEMI) had PCI without complications, but was noted to have a GI bleed (coffee ground emesis) at some time after the PCI. She had a cardiac arrest and died ~ 23 hours after the last dose of study drug.

Subject 466001077 (cangrelor, STEMI) had PCI without complications. She had a GI bleed (gross hematuria) ~ 2.5 hours after the start of study drug. Approximately

[10] Subject 401029051 was not counted in the Applicant's report of subjects with bleed since no bleed CRF was filled out for him. The reviewer counted this subject as a nonCABG GUSTO severe bleed, TIMI major and BARC 3b. Only baseline Hg/Hct were available for him.

~26 hours after the last dose of study drug she experienced a cardiac arrest, subsequent acute renal failure and died shortly thereafter.

Two more subjects identified through the reviewer's search of text fields in the bleed CRF and SAE CRF had bad bleeds and died after 48 hours.

Subject 407005033 (cangrelor, STEMI) experienced cardiogenic shock 15 minutes after the end of the infusion. She had a retroperitoneal bleed and died 4 days after the start of study drug.

Subject 401009010 (clopidogrel, stable angina) had a GUSTO severe bleed (hemodynamic compromise) ~ 2 hours after the start of PCI. He died approximately 7 weeks after surgery, however his cause of death was adjudicated as cardiovascular and a peri-procedural PCI MI was noted in a comment field.

**Table 47** shows that deaths overall were balanced between arms in PHOENIX. So while there were numerically more deaths in subjects that bled on cangrelor, the numbers are too small to make definitive conclusions regarding the risk of death from bleeds caused by cangrelor.

**Table 47. Deaths within 48 hours, by preferred terms (PHOENIX safety population)**

| | Number (%) of patients | |
|---|---|---|
| Preferred Term | Cangrelor (N=5529) | Clopidogrel (N=5527) |
| **Any deaths within 48 hours** | **18 (0.3)** | **20 (0.4)** |
| Cardiogenic shock | 4 (0.1) | 2 (0.0) |
| Acute myocardial infarction | 3 (0.1) | 2 (0.0) |
| Thrombosis in device | 3 (0.1) | 3 (0.1) |
| Myocardial infarction | 2 (0.0) | 0 (0.0) |
| Cardiac arrest | 1 (0.0) | 2 (0.0) |
| Cardiac failure | 1 (0.0) | 1 (0.0) |
| Coronary artery dissection | 1 (0.0) | 0 (0.0) |
| Renal failure acute | 1 (0.0) | 0 (0.0) |
| Aortic dissection | 1 (0.0) | 0 (0.0) |
| Aspiration | 1 (0.0) | 0 (0.0) |
| Cardiac failure congestive | 0 (0.0) | 1 (0.0) |
| Coronary artery disease | 0 (0.0) | 1 (0.0) |
| Coronary artery occlusion | 0 (0.0) | 2 (0.0) |
| Myocardial rupture | 0 (0.0) | 3 (0.1) |
| Pulmonary oedema | 0 (0.0) | 1 (0.0) |
| Ventricular asystole | 0 (0.0) | 1 (0.0) |
| Ventricular fibrillation | 0 (0.0) | 1 (0.0) |

Source: Section 14.1, Table 8.9.4.1.
PHOENIX CSR, Table 48

In the total pooled ISS dataset fatal bleeding was also balanced between arms. Although the numbers are small, there were numerically more bleed related deaths in the nervous system disorder SOC in the cangrelor arm compared to control (4 vs. 1).

**Table 48. Summary of fatal bleeding related deaths by dosing start, ISS**

| | Bleeding-Related Deaths within 30 Days from Dosing Start | | Bleeding-Related Deaths after 30 Days from Dosing Start | |
|---|---|---|---|---|
| System Organ Class/Preferred Term | Cangrelor (N=13301) n (%) | Control (N=12861) n (%) | Cangrelor (N=13301) n (%) | Control (N=12861) n (%) |
| Patients died | 8 (0.1) | 9 (0.1) | 5 (0.0) | 6 (0.0) |
| Cardiac disorders | 3 (0.0) | 4 ( 0.0) | 2 (0.0) | 0 (0.0) |
| Cardiac tamponade | 1 (0.0) | 0 ( 0.0) | 1 (0.0) | 0 ( 0.0) |
| Myocardial rupture | 1 (0.0) | 4 ( 0.0) | 1 (0.0) | 0 ( 0.0) |
| Ventricle rupture | 1 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Gastrointestinal disorders | 1 (0.0) | 2 ( 0.0) | 1 (0.0) | 1 ( 0.0) |
| Gastrointestinal haemorrhage | 0 (0.0) | 2 ( 0.0) | 1 (0.0) | 1 ( 0.0) |
| Retroperitoneal haemorrhage | 1 (0.0) | 0 ( 0.0) | 0 (0.0) | 0 (0.0) |
| Injury, poisoning and procedural complications | 0 (0.0) | 0 (0.0) | 1 (0.0) | 1 ( 0.0) |
| Subdural haematoma | 0 (0.0) | 0 (0.0) | 1 (0.0) | 1 ( 0.0) |
| Neoplasms benign, malignant and unspecified (including cysts and polyps) | 0 (0.0) | 1 ( 0.0) | 0 (0.0) | 0 (0.0) |
| Tumour haemorrhage | 0 (0.0) | 1 ( 0.0) | 0 (0.0) | 0 (0.0) |
| Nervous system disorders | 4 (0.0) | 1 ( 0.0) | 1 (0.0) | 3 (0.0) |
| Cerebral haemorrhage | 1 (0.0) | 0 ( 0.0) | 1 (0.0) | 0 (0.0) |
| Haemorrhage intracranial | 2 (0.0) | 0 ( 0.0) | 0 (0.0) | 1 (0.0) |
| Haemorrhagic stroke | 1 (0.0) | 1 ( 0.0) | 0 (0.0) | 2 (0.0) |
| Respiratory, thoracic and mediastinal disorders | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.0) |
| Pulmonary alveolar haemorrhage | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.0) |
| Vascular disorders | 0 (0.0) | 11 (0.0) | 0 (0.0) | 0 (0.0) |
| Shock haemorrhagic | 0 (0.0) | 1 ( 0.0) | 0 (0.0) | 0 (0.0) |

Source: Section 2.7.4.8.2, Table 11.6.23.4.1 and Table 11.6.23.4.2.
Note: Zero percentages associated with non-zero patient numbers are due to rounding.
AE = adverse event; SOC = system organ class.

Applicant's SCS, Table 34

### 7.3.2 Nonfatal Serious Adverse Events

There were a total of 88 (1.6%) subjects treated with cangrelor and 66 (1.2%) subjects treated with clopidogrel with nonfatal SAEs. **Table 49** shows the SOC for these subjects and lists the Preferred Terms where the relative risk was greater than 5. In general the number of subjects with events is too low to make any decisive conclusions that there are greater SAEs with cangrelor than clopidogrel. However it should be noted that there were anaphylactic reaction and anaphylactic shock reported in three subjects

treated with cangrelor (none in clopidogrel). Two subjects on clopidogrel had "hypersensitivity" SAEs.

**Table 49. Nonfatal SAE occurring in more cangrelor subjects than clopidogrel**

| | Cangrelor | | Clopidogrel | |
|---|---|---|---|---|
| **SOC**<br>**Preferred Term** | **N=5529** | **(%)** | **N=5527** | **(%)** |
| Cardiac disorders | 44 | (0.8) | 36 | (0.7) |
| Cardiogenic shock | 12 | (0.2) | 6 | (0.1) |
| Coronary artery dissection | 9 | (0.2) | 6 | (0.1) |
| Interventricular septum rupture | 2 | (0.0) | 0 | (0.0) |
| Respiratory, thoracic, mediastinal disorders | 11 | (0.2) | 2 | (0.0) |
| Respiratory failure | 2 | (0.0) | 0 | (0.0) |
| Pulmonary embolism | 2 | (0.0) | 0 | (0.0) |
| Vascular disorders | 9 | (0.2) | 5 | (0.1) |
| Renal and urinary disorders | 6 | (0.1) | 5 | (0.1) |
| General disorders and administration site | 4 | (0.1) | 2 | (0.0) |
| Immune system disorders | 3 | (0.0) | 2 | (0.0) |
| Anaphylactic reaction | 2 | (0.0) | 0 | (0.0) |
| Infections and manifestations | 3 | (0.0) | 2 | (0.0) |

Shown are subjects with nonfatal SAE SOCs occurring with greater number in the cangrelor arm compared to clopidogrel. Note that SOC terms do not include fatal SAEs, but the PT might. Reviewer's analysis sae\sae create. Dataset SDTM\AE.

*Reviewer's comment: Analyses including subjects whose SAE result in death produces similar numbers to the SAE tables in the Applicant's PHOENIX report. The general conclusions are the same.*

### 7.3.3 Dropouts and/or Discontinuations

**Table 10** shows the subject disposition in PHOENIX. Only one subject (cangrelor) is reported to have discontinued the study because of an AE. Error! Reference source not found. shows subjects who were reported to have discontinued treatment because of an AE. Although the numbers are greater in the cangrelor arm, the numbers are too small to show a difference between cangrelor and clopidogrel for any SOC. Of note are the 4 subjects with dyspnea that discontinued cangrelor.

**Table 50. Subjects that discontinued treatment because of an AE: PHOENIX**

| | Cangrelor | | Clopidogrel | |
|---|---|---|---|---|
| **SOC** | **N=5529** | **(%)** | **N=5527** | **(%)** |
| Subjects that discontinued treatment | 31 | (0.6) | 21 | (0.4) |
| Cardiac disorders | 18 | (0.3) | 15 | (0.3) |
| Respiratory and thoracic disorders (PT: Dyspnea) | 4 | (0.1) | 0 | (0.0) |
| Gastrointestinal disorders | 3 | (0.1) | 0 | (0.0) |
| Nervous system disorders | 2 | (0.0) | 1 | (0.0) |
| Eye disorders | 1 | (0.0) | 0 | (0.0) |
| Psychiatric disorders | 1 | (0.0) | 0 | (0.0) |
| Skin and subcutaneous tissue disorders | 1 | (0.0) | 0 | (0.0) |
| General disorders and administration site conditions | 1 | (0.0) | 1 | (0.0) |
| Immune system disorders | 2 | (0.0) | 2 | (0.0) |
| Vascular disorders | 3 | (0.1) | 5 | (0.1) |

Reviewer's analysis ae\aedc. Dataset analysis\ae

The AEs leading to discontinuation in the CHAMPION studies is similar to PHOENIX. **Table 51**. Dyspnea was a common reason for cangrelor discontinuation.

**Table 51. AEs leading to discontinuation in CHAMPION trials**

| Preferred Term (≥ 2 events) | Cangrelor (N=13301) n (%) | Control (N=12861) n (%) |
|---|---|---|
| Coronary artery perforation | 14 (0.1) | 7 (0.1) |
| Coronary artery dissection | 12 (0.1) | 9 (0.1) |
| Dyspnoea | 10 (0.1) | 1 (0.0) |
| Hypotension | 8 (0.1) | 8 (0.1) |

Source: SCS, Table 41. Only frequency of ≥ 0.1% shown

## 7.3.4 Significant Adverse Events/Adverse Events of Special Interest

### 7.3.4.1 Dyspnea

In the summary of clinical safety, the Applicant reports that the overall incidence of dyspnea was low, but consistent with cangrelor pharmacology the incidence was greater in the cangrelor arm (179/13301, 1.3%) compared to control (54/12861, 0.4%). Most reports were of just "dyspnea"; dyspnea exertional was reported in 8 subjects on cangrelor and 2 subjects on control. The majority of cases were nonserious (98%); only 3 cases were severe and none led to death. The median time of onset was 2

hours. Of subjects that discontinued cangrelor, 10/179 did so because of dyspnea in the ISS.

### 7.3.4.2 Renal function effects

Following the adverse renal and urinary findings in rat and dog pharmacology /toxicology studies, the Applicant increased monitoring for renal/urinary effects in Study SC-931-5060 (cangrelor dose 4 ug/kg/min or placebo for 72 hours in 94 subjects), but found no effect on renal function, urinary parameters, blood urea, serum creatinine levels, urine dipstick, urine cytology and SDS-PAGE.

The Applicant's Acute renal failure SMQ of the ISS showed a low frequency and similar pattern of AE between cangrelor and control, however there were numerically higher events in the cangrelor arm compared to control **(Table 56)**.

**Table 52. Summary of renal AEs of interest by SOC and PT in ISS**

| SMQ or System Organ Class | Preferred Term | Cangrelor (N=13301) n (%) | Control (N=12861) n (%) |
|---|---|---|---|
| Renal Function Effect (SMQ) | | 93 (0.7) | 64 (0.5) |
| Investigations | Blood creatinine increased | 30 (0.2) | 14 (0.1) |
| | Urine output decreased | 5 (0.0) | 5 (0.0) |
| | Blood urea increased | 4 (0.0) | 2 (0.0) |
| | Protein urine present | 2 (0.0) | 1 (0.0) |
| | Glomerular filtration rate decreased | 1 (0.0) | 0 (0.0) |
| Renal and urinary disorders | Renal failure acute | 19 (0.1) | 16 (0.1) |
| | Proteinuria | 12 (0.1) | 9 (0.1) |
| | Renal failure | 15 (0.1) | 7 (0.1) |
| | Nephropathy toxic | 4 (0.0) | 5 (0.0) |
| | Renal impairment | 2 (0.0) | 4 (0.0) |
| | Oliguria | 3 (0.0) | 3 (0.0) |
| | Renal tubular necrosis | 0 (0.0) | 1 (0.0) |
| | Anuria | 1 (0.0) | 0 (0.0) |
| | Azotaemia | 2 (0.0) | 0 (0.0) |

Source: 2.7.4.8.2, Table 11.6.24.4.1.
Note: Zero percentages associated with non-zero patient numbers are due to rounding.
AE = adverse event; SOC = system organ class; SMQ = standardized MedDRA query.
Source: Applicant's SCS, Table 25, PT=preferred term

The Applicant also examined adverse events by baseline glomerular filtration rate (GFR) in CHAMPION PCI (**Table 53**)and CHAMPION-PLATFORM (**Table 54**). CHAMPION-PCI had a greater numerical increase in renal adverse events as renal function declined in the cangrelor arm compared to clopidogrel, but CHAMPION-PLATFORM did not.

**Table 53. Adverse events of SMQ by baseline renal function in CHAMPION PCI**

| | Baseline Glomerular Filtration Rate | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Severe (<30 mL/min/1.73 $m^2$) | | Moderate (30-<60 mL/min/1.73 $m^2$) | | Mild (60-90 mL/min/1.73 $m^2$) | | Normal (>=90 mL/min/1.73 $m^2$) | |
| Preferred term | Cangrelor N=165 n (%) | Clopidogrel N=162 n (%) | Cangrelor N=1332 n (%) | Clopidogrel N=1302 n (%) | Cangrelor N=1823 n (%) | Clopidogrel N=1800 n (%) | Cangrelor N=902 n (% | Clopidogrel N=956 n (%) |
| Patients with at least 1 SMQ event | 8 (4.8) | 3 (1.9) | 19(1.4) | 10 (0.8) | 5 (0.3) | 9 (0.5) | 1 (0.1) | 0 (0.0) |
| Oliguria | | | 1 (0.1) | 0 (0.0) | | | | |
| Blood creatinine increased | 3 (1.8) | 1 (0.6) | 8 (0.6) | 3 (0.2) | 2 (0.1) | 2 (0.1) | 1 (0.1) | 0 (0.0) |
| Renal failure | 0 (0.0) | 1 (0.6) | 3 (0.2) | 0 (0.0) | 3 (0.2) | 1 (0.1) | | |
| Renal failure acute | 5 (3.0) | 1 (0.6) | 7 (0.5) | 5 (0.4) | 0 (0.0) | 2 (0.2) | | |
| Renal impairment | | | 0 (0.0) | 2 (0.2) | 0 (0.0) | 1 (0.1) | | |
| Renal tubular necrosis | | | | | 0 (0.0) | 1 (0.1) | | |
| Protein urine present | | | | | 0 (0.0) | 1 (0.1) | | |
| Urine output decreased | | | | | 0 (0.0) | 1 (0.1) | | |

Sources: Section 2.7.4.8.2, Table 16.6.24.4.10, Table 16.6.24.4.11, Table 16.6.24.4.12 and Table 16.6.24.4.13.

Source: Applicant's SCS, Table 28

**Table 54. Adverse events of SMQ by baseline renal function in CHAMPION PLATFORM**

| | Baseline Glomerular Filtration Rate | | | | | |
|---|---|---|---|---|---|---|
| | Severe (<30 mL/min/1.73 m²) | | Moderate (30-<60 mL/min/1.73 m²) | | Mild (60-90 mL/min/1.73 m²) | |
| Preferred terms | Cangrelor N=116 n (%) | Clopidogrel N=120 n (%) | Cangrelor N=865 n (%) | Clopidogrel N=857 n (%) | Cangrelor N=986 n (%) | Clopidogrel N=990 n (%) |
| Patients with at least 1 SMQ event | 2 (1.7) | 2 (1.7) | 6 (0.7) | 4 (0.5) | 0 (0.0) | 2 (0.2) |
| Blood creatinine increased | 1 (0.9) | 1 (0.8) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 2 (0.2) |
| Proteinuria | | | 0 (0.0) | 1 (0.1) | | |
| Renal failure | 1 (0.9) | 1 (0.8) | 2 (0.2 | 1 (0.1) | | |
| Renal failure acute | | | 1 (0.1) | 1 (0.1) | | |
| Renal impairment | | | 0 (0.0) | 1 (0.1) | | |
| Nephropathy toxic | | | 2 (0.2 | 1 (0.1) | | |
| Urine output decreased | | | | | 0 (0.0) | 1 (0.1) |

Sources: Section 2.7.4.8.2, Table 16.6.24.4.14, Table 16.6.24.4.15, Table 16.6.24.4.16.
AE = adverse event; SMQ = standardized MedDRA query.

Source: Applicant's SCS, Table 29

Serum creatinine in placebo or active controlled trials was reported in CHAMPION PCI, CHAMPION PLATFORM, and BRIDGE. **Table 55** shows that the subjects with potentially clinically significant changes in serum creatinine were balanced.

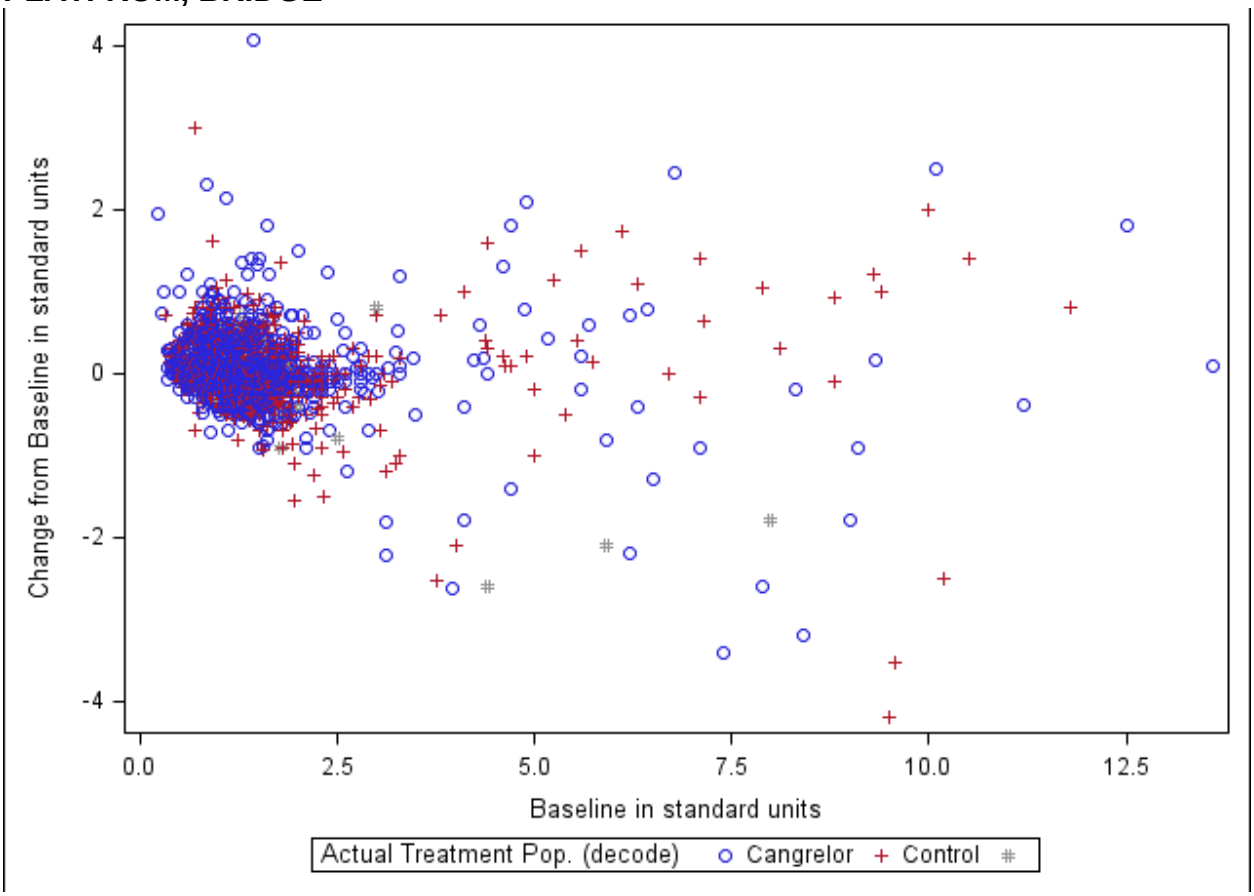
**Table 55. Subjects with potentially clinically significant serum creatinine†**

| | Cangrelor, n/N (%) | Clopidogrel , n/N (%) |
|---|---|---|
| TMC-CAN-05-02 PCI | 78/4063 (1.9) | 73/4073 (1.8) |
| TMC-CAN-05-03 PLATFORM | 65/2500 (2.6) | 61/2464 (2.5) |
| TMC-CAN-08-02 BRIDGE | 2/107 (1.9) | 1/91 (1.1) |

† on treatment values ≥ 2 mg/dL
N is the number of subjects with Scr measured at baseline and on treatment
Reviewers' analysis: lab\scr. Dataset ISS\lab (lbpcsaf lbstres)

**Figure 26** of baseline serum creatinine versus change from baseline does not show a clear pattern of risk.

**Figure 26. Baseline serum creatinine versus change in serum creatinine in PCI, PLATFROM, BRIDGE**




Reviewer's analysis: lab\scr. Dataset iss\lab (lbchgblo)

The Applicant concludes, and the reviewer agrees, that there are no clear safety issues related to renal function. There were small increases in acute renal adverse events that may be worth noting.

### 7.3.4.3 Hypersensitivity

The Applicant did a modified SMQ search of Angioedema and Anaphylactic reactions and identified 93 (0.7%) subjects on cangrelor with hypersensitivity and 75 (0.6%) on control. The most common events were rash, pruritus, urticarial, and wheezing (all nonserious). The majority of the events were mild or moderate in intensity and non-serious. None were fatal. There were 7 subjects with SAEs treated with cangrelor compared to 2 treated with control. These subjects also received multiple drugs, including contrast agents. Although uncommon, hypersensitivity should also be described.

**Table 56. AEs of hypersensitivity in ISS**

| Preferred Term | Cangrelor (N=13301) n (%) | Control (N=12861) n (%) |
|---|---|---|
| Patients with at least one AE of Hypersensitivity | 93 (0.7) | 75 (0.6) |
| Rash [a] | 34 (0.3) | 33 (0.3) |
| Pruritus [b] | 15 (0.1) | 14 (0.1) |
| Urticaria | 13 (0.1) | 9 (0.1) |
| Wheezing | 12 (0.1) | 5 (0.0) |
| Bronchospasm | 5 (0.0) | 2 (0.0) |
| Hypersensitivity | 4 (0.0) | 6 (0.0) |
| Throat tightness | 4 (0.0) | 3 (0.0) |
| Anaphylactic reaction | 2 (0.0) | 1 (0.0) |
| Angioedema | 2 (0.0) | 0 (0.0) |
| Tongue oedema | 1 (0.0) | 0 (0.0) |
| Drug hypersensitivity | 1 (0.0) | 2 (0.0) |
| Anaphylactic shock | 1 (0.0) | 0 (0.0) |
| Laryngeal oedema | 1 (0.0) | 1 (0.0) |
| Pharyngeal oedema | 1 (0.0) | 0 (0.0) |
| Stridor | 1 (0.0) | 0 (0.0) |
| Swelling face | 1 (0.0) | 0 (0.0) |
| Shock | 1 (0.0) | 1 (0.0) |

Source: Section 2.7.4.8.2, Table 11.6.24.4.2.
[a] Includes the terms rash, rash erythematous, rash generalized, rash pruritic.
[b] Includes the terms pruritus and pruritus generalized.
Note: Zero percentages associated with non-zero patient numbers are due to rounding.

Applicant's SCS. Table 23

### 7.3.5 Submission Specific Primary Safety Concerns: Bleeding

The primary safety endpoint in PHOENIX was the incidence of GUSTO severe bleeding at 48 hours. The incidence of blood product transfusion up to 48 hours, categorized according to relationship with CABG surgery was another key safety endpoint.

*Reviewer comment: As stated in* ***Section 5.3.4.6 Safety Endpoints and Definitions*** *the final protocol and SAP did not distinguish between CABG and non-CABG bleeding for the primary safety endpoint. Nevertheless, the Applicant's bleeding results in the main CSR is primarily of non-CABG bleeding. This is not to say that this is unreasonable, it just was not clearly stated in the protocol or SAP. Because of the small number of CABG related bleeds in PHOENIX, the reviewer also presents most of the bleeding data by non-CABG related bleeding.*

Overall bleeding was 42% greater in cangrelor treated subjects compared to clopidogrel treated subjects **(Table 57)**. Most bleeds were non-CABG related.

**Table 57. Total subjects with bleed in PHOENIX**

| | Cangrelor | | Clopidogrel | | Cangrelor vs. Clopidogrel | | Cangrelor vs. Clopidogrel | |
|---|---|---|---|---|---|---|---|---|
| | N=5529 | (%) | N=5527 | (%) | RR | (95% CI) | OR | (95% CI) |
| Any Bleed | 863 | (15.61) | 605 | (11.0) | 1.42 | (1.29, 1.56) | 1.50 | (1.34, 1.68) |
| Any Bleed at 48 hours | 860 | (15.55) | 604 | (10.9) | 1.42 | (1.29, 1.56) | 1.49 | (1.34, 1.67) |
| Non CABG bleeds | 857 | (15.5) | 601 | (10.9) | 1.42 | (1.29, 1.56) | 1.50 | (1.34, 1.67) |
| CABG bleed | 4[†] | (0.1) | 3 | (0.1) | 1.34 | (0.30, 5.99) | 1.34 | (0.30, 6.00) |

Reviewer's analysis: bleed\summary\bleed total. (PTSTATUS and GENDER factors in logistic regression)
Datasets: r_bl.c_rev created with raw\bld, iss lab.
[†]Subject 401079027 had both a nonCABG and a CABG bleed within 48 hours

*Reviewer comment: Although bleed at any time is reported in the **Table 57,** AEs (including bleeding) were only required to be collected up to 48 hours after randomization (or after study drug start if study drug administration delayed). The reviewer reports an additional subject (ID 401029051, cangrelor) with a bleed that the Applicant did not report. This subject was found because of how the reviewer identified bleeds (as discussed in **Section 7.1.2 Categorization of Adverse Events and Bleeding**). The Applicant reports 856 vs. 601 on cangrelor and clopidogrel, respectively.*

CABG

The number of subjects with CABG in PHOENIX was low (see **Table 58**), but interestingly the numbers between treatment arms was imbalanced. The only urgent CABGs were in treated subjects. Of these one out of seven subjects in the cangrelor arm had a bleed associated with CABG, whereas three out of five subjects treated with clopidogrel had bleeding associated with CABG.

**Table 58. CABG and bleeding in PHOENIX**

| | Cangrelor | Clopidogrel |
|---|---|---|
| Randomized population | 45 | 29 |
| CABG as index procedure | 19 | 9 |
| CABG within 48 hours from randomization | 29 | 15 |
| Bleeding not associated with CABG | 5 | 0 |
| Bleeding associated with CABG | 6 | 3 |
| | | |
| CABG from > 48 hours to < 30 days | 16 | 14 |
| Bleeding not associated with CABG | 1 | 3 |
| Bleeding associated with CABG | 0 | 0 |
| | | |
| Treated population | 31 | 25 |
| CABG within 48 hours from treatment start | 20 | 11 |
| Bleeding associated with CABG | 4 | 3 |
| Bleeding not associated with CABG | 4 | 0 |
| Urgent CABG | 7 | 5 |
| Bleeding associated with CABG | 1 | 3 |
| CABG from > 48 hours to < 30 days | 11 | 14 |
| Bleeding not associated with CABG | 1 | 3 |
| Bleeding not associated with CABG | 5 | 3 |

Reviewer's analysis: cabg\cabg. Datasets raw\idr, cabg

The primary safety endpoint in the BRIDGE trial was excessive CABG related bleeding; there were 12/102 (11.8%) in the cangrelor arm and 10/96 (10.4%) in the placebo arm. In total, the data suggest that cangrelor can be used safely in the CABG setting.

Bleed Classifications and Primary Safety Endpoint, Non-CABG Bleeding

More subjects treated with cangrelor than clopidogrel had a GUSTO severe bleed (primary safety endpoint), but the numbers were low (0.2% on cangrelor) and the difference was not significant (**Table 59**).[11] **Table 59** shows the reviewer's and Applicant's (denoted by an asterisk *) number of subjects with bleeds of various classifications. Reasons for differences between the reviewer and the Applicant's counts were described in **Section 7.1.2 Categorization of Adverse Events and Bleeding**. In addition, the reviewer's analysis shown in the table used a logistic regression model adjusting for baseline status[12] and gender. Analyses conducted without baseline status and gender as factors show minor differences in the estimates.

[11] There were no CABG related GUSTO severe bleeds.
[12] Baseline status (variable PTSTATUS) was adjudicated by the CEC as "normal" or "abnormal" based on troponin level, ischemic symptoms and ECG changes. This factor was in the model because the Applicant used it for their primary efficacy analysis and this model was used for the reviewer's risk benefit analysis.

In general, the bleeds that showed significant differences between treatment arms were bleeds that are generally unlikely to have extensive clinical consequences (GUSTO mild, TIMI minor). There was a ~67% higher risk of ACUITY major bleed in cangrelor treated subjects compared to clopidogrel. A large number of subjects in this category were because of hematoma ≥ 5 cm.

In attempts to identify a bad bleed, the reviewer classified subjects with any of the following into a “Bad” category: ICH, transfused, cardiac tamponade, reoperation for bleeding, surgical intervention, retroperitoneal, requiring or extending hospitalization. With this classification, the risk was ~46% higher on cangrelor and it approached significance.
.



Reference ID: 3435333

**Table 59. Non CABG Bleeding Classification Risk at 48 hours in PHOENIX**

| | Cangrelor | | Clopidogrel | | Cangrelor vs. Clopidogrel | | Cangrelor vs. Clopidogrel | |
|---|---|---|---|---|---|---|---|---|
| | N=5529 | (%) | N=5527 | (%) | RR | (95% CI) | OR | (95% CI) |
| Non CABG bleeds | 857† | (15.5) | 601 | (10.9) | 1.42 | (1.29, 1.56) | 1.50 | (1.34, 1.67) |
| | | | | | | | | |
| GUSTO severe or moderate | 32 | (0.6) | 20 | (0.4) | 1.57 | (0.90, 2.74) | 1.57 | (0.90, 2.75) |
| GUSTO severe | 10 | (0.2) | 6 | (0.1) | 1.64 | (0.60, 4.52) | 1.64 | (0.60, 4.53) |
| GUSTO severe* | 9 | (0.2) | 6 | (0.1) | 1.50 | (0.53, 4.21) | 1.50 | (0.53, 4.22) |
| GUSTO moderate | 22 | (0.4) | 14 | (0.6) | 1.54 | (0.79, 3.00) | 1.54 | (0.79, 3.01) |
| GUSTO moderate* | 22 | (0.4) | 13 | (0.2) | 1.69 | (0.85, 3.35) | 1.69 | (0.85, 3.37) |
| GUSTO mild | 825 | (14.9) | 581 | (10.5) | 1.41 | (1.28, 1.56) | 1.49 | (1.33, 1.67) |
| GUSTO mild* | 150 | (2.7) | 88 | (1.6) | 1.70 | (1.31, 2.21) | 1.72 | (1.32, 2.25) |
| TIMI Major or Minor | 38 | (0.7) | 12 | (0.2) | 3.14 | (1.64, 6.00) | 3.15 | (1.65, 6.04) |
| TIMI Major | 9 | (0.2) | 3 | (0.1) | 3.00 | (0.81, 11.09) | 3.01 | (0.81, 11.11) |
| TIMI Major* | 5 | (0.1) | 5 | (0.1) | 1.00 | (0.29, 3.45) | 1.00 | (0.29, 3.45) |
| TIMI Minor | 29 | (0.5) | 9 | (0.2) | 3.18 | (1.51, 6.71) | 3.19 | (1.51, 6.75) |
| TIMI Minor* | 9 | (0.2) | 3 | (0.1) | 3.00 | (0.81, 11.07) | 3.00 | (0.81, 11.10) |
| Acuity Major | 242 | (4.4) | 143 | (2.6) | 1.67 | (1.36, 2.05) | 1.71 | (1.39, 2.11) |
| Barc2 | 111 | (2.0) | 66 | (1.2) | 1.67 | (1.23, 2.26) | 1.68 | (1.24, 2.29) |
| Barc3a | 41 | (0.7) | 14 | (0.3) | 2.88 | (1.57, 5.27) | 2.90 | (1.58, 5.32) |
| Barc3b | 15 | (0.3) | 7 | (0.1) | 2.11 | (0.86, 5.16) | 2.11 | (0.86, 5.18) |
| Barc3c | 3 | (0.1) | 1 | (0.0) | 2.98 | (0.31, 28.63) | 2.98 | (0.31, 28.68) |
| Bad‡ | 61 | (1.1) | 41 | (0.7) | 1.46 | (0.99, 2.17) | 1.47 | (0.99, 2.19) |

* Applicant's classification and analysis
† Reviewer identified an extra bleed (CSUBJECT 401029051) based on SAE report (no BLD CRF page so subject was excluded from Applicant's report). Classified as GUSTO severe, TIMI major and BARC 3b.
‡ Bad defined as any of the following: ICH, transfused, cardiac tamponade, reoperation for bleeding, surgical intervention, retroperitoneal, requiring or extending hospitalization
Reviewer's analysis with factors patient status, gender. Reviewer code: bleed\primary safety ptstatus gender final. Datasets: raw\bld, iss\fda_bld, iss lab.

**Table 60. Bleeding type at 48 hours (non-CABG)**

| | n (%) of patients | |
|---|---|---|
| | Cangrelor (N=5529) | Clopidogrel (N=5527) |
| PCI-related bleeding | 737 (13.3) | 502 (9.1) |
| Hematoma | 461 (8.3) | 312 (5.6) |
| Oozing at puncture site | 236 (4.3) | 158 (2.9) |
| Ecchymosis | 200 (3.6) | 118 (2.1) |
| Transfusion | 25 (0.5) | 16 (0.3) |
| Gastrointestinal bleeding | 16 (0.3) | 9 (0.2) |
| Epistaxis | 15 (0.3) | 15 (0.3) |
| Gross hematuria | 11 (0.2) | 6 (0.1) |
| Access site bleeding requiring radiologic or surgical intervention | 10 (0.2) | 7 (0.1) |
| Genitourinary bleeding | 10 (0.2) | 5 (0.1) |
| Bleeding leading to hemodynamic compromise | 7 (0.1) | 5 (0.1) |
| Retroperitoneal | 7 (0.1) | 3 (0.1) |
| Cardiac tamponade | 7 (0.1) | 1 (0.0) |
| Hematemesis | 4 (0.1) | 3 (0.1) |
| Intracranial hemorrhage | 3 (0.1) | 1 (0.0) |
| Thrombocytopenia | 2 (0.0) | 5 (0.1) |
| Pulmonary bleeding | 2 (0.0) | 1 (0.0) |
| Hemorrhoidal bleeding | 1 (0.0) | 0 (0.0) |
| Reoperation for bleeding | 0 (0.0) | 1 (0.0) |
| Chest tube output ≥2 liters within a 24 hour period | 0 (0.0) | 0 (0.0) |
| Intraocular bleeding | 0 (0.0) | 0 (0.0) |

Source: Section 14.1, Table 6.2.4.1.

NOTE: Not all categories from source table are represented, including some with frequencies >0.1% and Other. For more detail on the Other category from source Table 6.2.4.1, see Appendix 16.2, Listing 6.3.4.4.

Source: PHOENIX CSR, Table 38. Table based on eCRF fields checked by investigator.

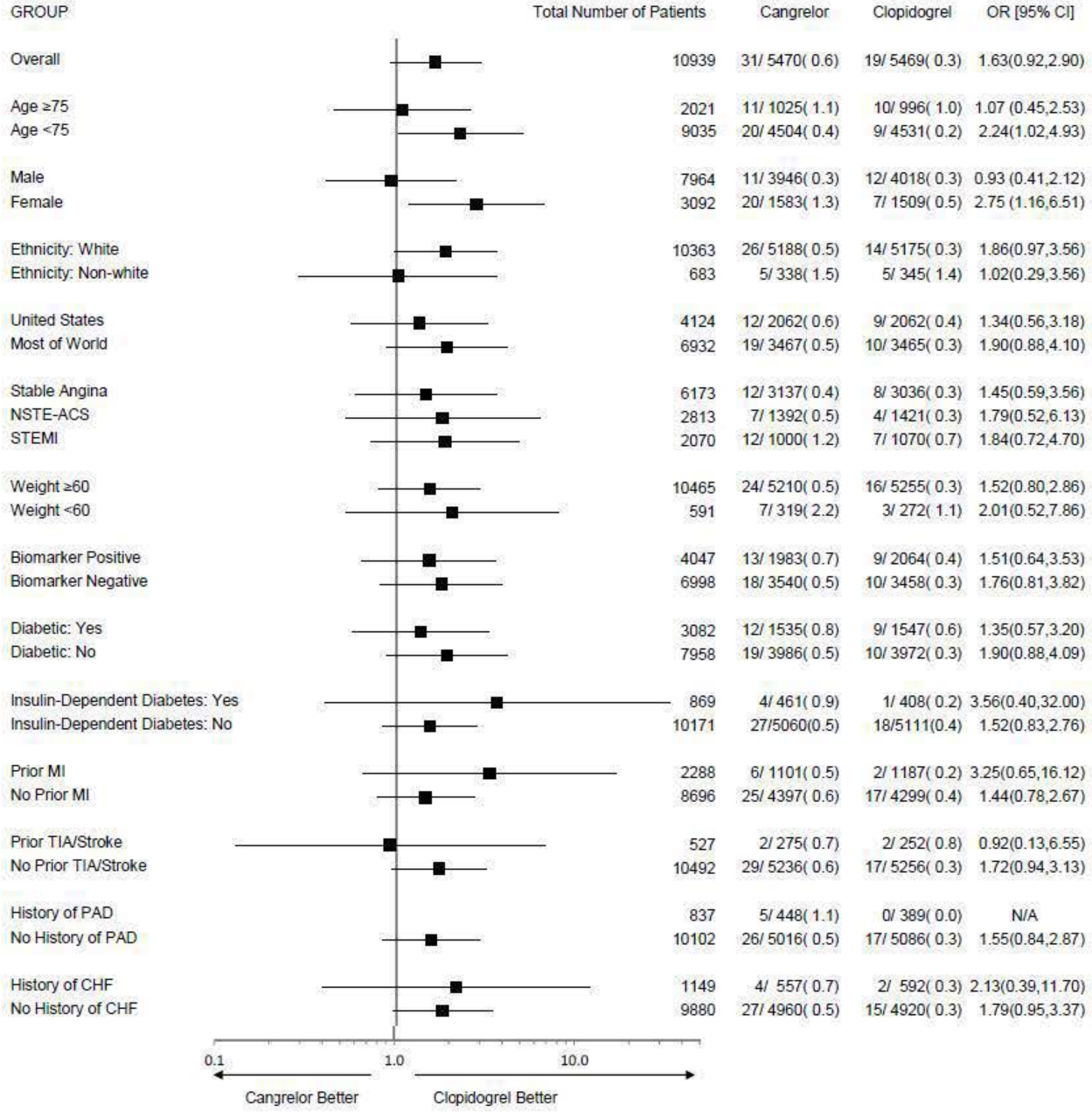
Transfusion

There were more subjects treated with cangrelor that received transfusions, but the difference was not significant (25 vs. 17, respectively).

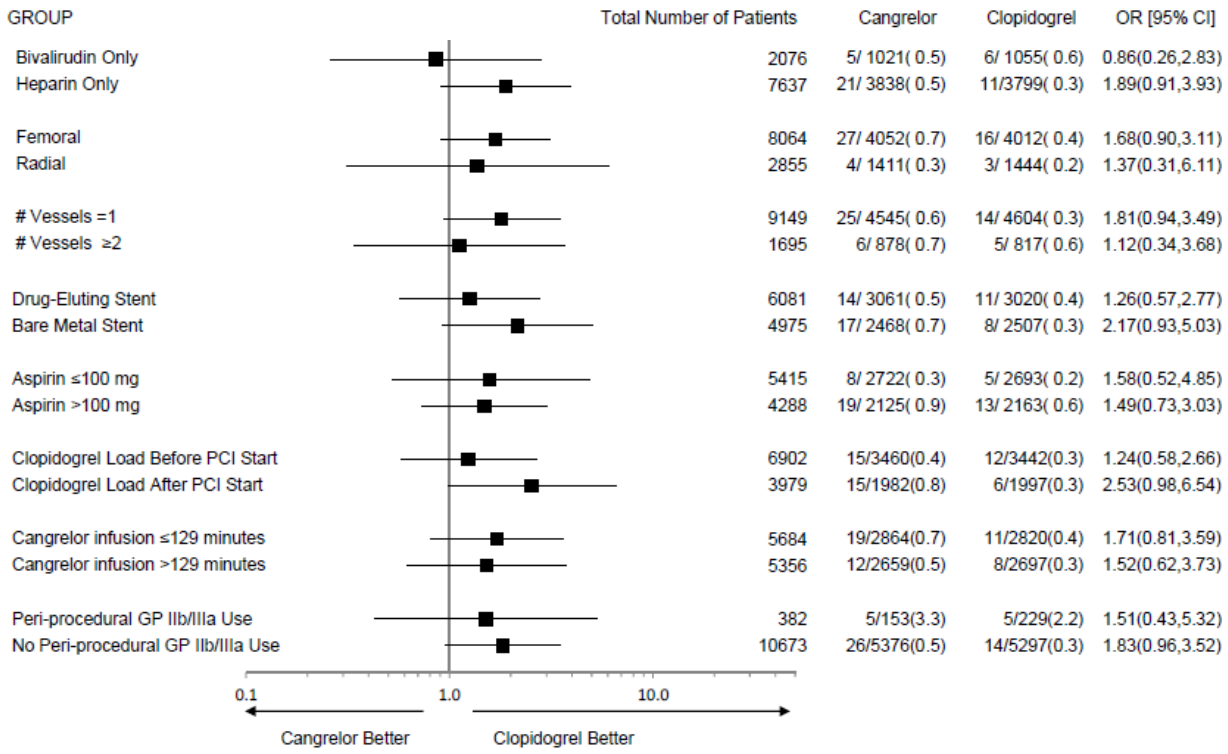
Subgroups

The Applicant combined GUSTO moderate and severe bleeds to do exploratory subgroup analyses. They did not find a difference in GUSTO moderate/severe bleeds for any subgroup.

**Figure 27. Applicant's subgroup analysis of GUSTO moderate/severe bleed**



(continued)




Source: PHOENIX CSR, Figure 11

## Concomitant medications

Post procedural concomitant medications were balanced between treatment arms.

**Table 61. Post procedural concomitant medications (ITT population)**

| Parameter Category | n/N (%) Cangrelor (N=5581) | Clopidogrel (N=5564) |
|---|---|---|
| After index procedure | | |
| Clopidogrel (per protocol) [a] | 5423/5581 (97.2) | 5416/5564 (97.3) |
| Aspirin | 4408/5576 (79.1) | 4403/5557 (79.2) |
| Prasugrel (10 mg) | 17/5581 (0.3) | 20/5564 (0.4) |
| Prasugrel (60 mg) | 11/5581 (0.2) | 7/5564 (0.1) |
| Ticagrelor (90 mg) | 1/5581 (0.0) | 2/5564 (0.0) |
| Ticagrelor (180 mg) | 1/5581 (0.0) | 0/5564 (0.0) |
| At hospital discharge | | |
| Aspirin | 5525/5576 (99.1) | 5498/5557 (98.9) |
| Clopidogrel | 5332/5581 (95.5) | 5323/5564 (95.7) |
| Prasugrel | 86/5581 (1.5) | 88/5564 (1.6) |
| Ticagrelor | 24/5581 (0.4) | 23/5564 (0.4) |

Source: Section 14.1, Table 3.5.2.1 and Table 3.6.2.1.
[a] For post-procedural clopidogrel, administration per protocol was 75 mg for 48 hours after index PCI.
ITT = intent-to-treat.

PHOENIX CSR, Table 14

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

Approximately 20% of subjects in each arm had an AE. The most commonly reported AEs (≥ 2% of subjects in each arm) were balanced between treatment arms (**Table 62**). There was a higher incidence of dyspnea in subjects treated with cangrelor (1.2%) then clopidogrel (0.3%). Most dyspnea events were mild (n=46) in severity; 18 were moderate, 1 was severe (likely an allergic reaction to cangrelor).

**Table 62. AEs reported by ≥ 1% of subjects**

| | Number (%) of patients | |
|---|---|---|
| Preferred Term | Cangrelor (N=5529) | Clopidogrel (N=5527) |
| **Patients with at least one AE** | **1125 (20.3)** | **1064 (19.3)** |
| Back pain | 147 (2.7) | 155 (2.8) |
| Nausea | 117 (2.1) | 107 (1.9) |
| Vessel puncture site pain | 114 (2.1) | 102 (1.8) |
| Hypertension | 112 (2.0) | 93 (1.7) |
| Headache | 101 (1.8) | 110 (2.0) |
| Vomiting | 70 (1.3) | 53 (1.0) |
| Dyspnea | 65 (1.2) | 18 (0.3) |
| Hypotension | 63 (1.1) | 48 (0.9) |
| Chest pain | 55 (1.0) | 94 (1.7) |

Source: PHOENIX CSR, Table 43

The number of subjects with TEAEs was balanced between treatment arms. More subjects on cangrelor had dyspnea. More subjects on clopidogrel had nausea.

**Table 63. Treatment emergent AE**

| | Number (%) of patients | |
|---|---|---|
| Preferred Term | Cangrelor (N=5529) | Clopidogrel (N=5527) |
| **Patients with any AE related to study drug** | **64 (1.2)** | **61 (1.1)** |
| Dyspnea | 13 (0.2) | 1 (0.0) |
| Vomiting | 12 (0.2) | 12 (0.2) |
| Nausea | 8 (0.1) | 18 (0.3) |
| Headache | 6 (0.1) | 3 (0.1) |
| Hypotension | 5 (0.1) | 1 (0.0) |
| Vessel puncture site pain | 4 (0.1) | 2 (0.0) |
| Rash | 2 (0.0) | 4 (0.1) |
| Dyspepsia | 1 (0.0) | 3 (0.1) |
| Pruritus | 1 (0.0) | 3 (0.1) |
| Hypersensitivity | 0 (0.0) | 3 (0.1) |

Source: PHOENIX CSR, Table 46

### 7.4.2 Laboratory Findings

The only reported labs were ALT, AST, alkaline phosphatase, total bilirubin, creatinine, GFR, hematocrit, hemoglobin, platelets, and WBCs. Hemoglobin and hematocrit were analyzed as part of the bleeding analysis. See section **7.3.4.2 Renal function effects** for analysis of serum creatinine.

Liver (**Table 64**), platelets, and WBCs values (**Table 65**) were balanced between arms in the CHAMPION trials. Thrombocytopenia was reported in 2 subjects on cangrelor and 6 subjects on clopidogrel.[13]

**Table 64. Post baseline changes >1x upper limit of normal in CHAMPION and placebo controlled studies**

| | CHAMPION Program | | Placebo controlled | |
|---|---|---|---|---|
| Post baseline changes >1×ULN | Cangrelor n/N (%) | Clopidogrel n/N (%) | Cangrelor n/N (%) | Control n/N (%) |
| Creatinine (mg/dL) >1×ULN | 307/5346 (5.7) | 257/5374 (4.8) | 11/273 (4.0) | 6/174 (3.4) |
| ALT (U/L) >1×ULN | 325/4909 (6.6) | 336/4916 (6.8) | 21/232 (9.1) | 17/143 (11.9) |
| AST (U/L) >1×ULN | 725/4153 (17.5) | 725/4134 (17.5) | 34/203 (16.7) | 12/128 (9.4) |
| Total bilirubin (mg/dL) >1×ULN | 392/5191 (7.6) | 365/5154 (7.1) | 6/273 (2.2) | 3/169 (1.8) |
| Alkaline phosphatase (U/L) >1×ULN | 71/5162 (1.4) | 64/5072 (1.3) | 2/272 (0.7) | 0/180 (0.0) |

Source: Section 2.7.4.8.2, Table 16.6.7.4.1 and Table 14.6.7.4.1.
ULN = upper limit of normal.

Source: SCS, Table 54

[13] PHOENIX, CSR, Table 6.2.4.1

**Table 65. Potentially clinical significant tests, platelets and WBC in CHAMPION and placebo-controlled studies**

| | CHAMPION | | Placebo Controlled | |
|---|---|---|---|---|
| Hematology Parameters | Cangrelor (N=12565) n/N (%) | Clopidogrel (N=12542) n/N (%) | Cangrelor (N=354) n/N (%) | Control (N=218) n/N (%) |
| Platelets ≥700 k/µL | 3/11914 (0.0) | 1/11889 (0.0) | 0/340 (0.0) | 0/213 (0.0) |
| Platelets ≤75 k/µL | 16/11914 (0.1) | 18/11889 (0.2) | 11/340 (3.2) | 6/213 (2.8) |
| WBC [a] ≥16 k/µL | 113/6268 (1.8) | 106/6290 (1.7) | 37/342 (10.8) | 29/211 (13.7) |
| WBC [a] ≤2.8 k/µL | 4/6268 (0.1) | 1/6290 (0.0) | 0/342 (0.0) | 0/211 (0.0) |

Source: Section 2.7.4.8.2, Table 16.6.6.4.1 and Table 14.6.6.4.1.
[a] WBC was not provided in the TMC-CAN-10-01 CHAMPION PHOENIX study.
Note: Zero percentages associated with non-zero patient numbers are due to rounding.
LLN = lower limit of normal.
Source: SCS, Table 52

### 7.4.3 Vital Signs

Vital signs were not collected in PHOENIX. CHAMPION PCI and PLATFORM collected vital signs. No significant differences in blood pressure or heart rate were observed.

### 7.4.4 Electrocardiograms (ECGs)

In the dedicated thorough QT study TMC CAN 08-01 the QT IRT group and the Applicant concluded that cangrelor does not affect cardiac repolarization at a dose of 60 ug/kg bolus followed by 8 ug/kg/min for 3 hours.

### 7.4.5 Special Safety Studies/Clinical Trials

None.

### 7.4.6 Immunogenicity

N/A

## 7.5 Other Safety Explorations

### 7.5.1 Dose Dependency for Adverse Events

Only one dose was explored in the pivotal trials.

### 7.5.2 Time Dependency for Adverse Events

Cangrelor is given as a short infusion (median time 2.2 hours). Time dependency for AEs was not examined.

### 7.5.3 Drug-Demographic Interactions

Gender had a significant effect on bleeding when added as a factor in the regression.

### 7.5.4 Drug-Disease Interactions

A study in subjects with renal impairment showed that impairment of renal function did not significantly alter cangrelor PK . Hepatic impairment is not expected to affect cangrelor because cangrelor is biotransformed by nucleotidases in systemic circulation.

### 7.5.5 Drug-Drug Interactions

Pharmacokinetic interactions are unlikely for reasons already discussed in the Clinical Pharmacology Section.

## 7.6 Additional Safety Evaluations

### 7.6.1 Human Carcinogenicity

N/A.

### 7.6.2 Human Reproduction and Pregnancy Data

There are no controlled studies in women. See **Section 4.3 Preclinical Pharmacology/Toxicology.**

### 7.6.3 Pediatrics and Assessment of Effects on Growth

N/A.

### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

In the CHAMPION trials 24 subjects (12 at US sites) received cangrelor infusions between 5.5 – 13.8 ug/kg/min. [14] The majority of the dosing errors were because the weight recorded in pounds was used as the dosing weight, thus subjects received more than twice the correct dose. Another common reason for the dosing errors was because of incorrect solution preparation.

[14] Reviewer's analysis: ae\ae od check. Datasets: iss\isd, iss\fda_bld

Most of these subjects did not have reports of bleeding related AEs; only one subject had a bleeding report (in CHAMPION PCI, GUSTO mild).[15] There was also no correlation with other AEs.

Six subjects had other AEs of interest noted (hyperbilirubinemia, dyspnea, back pain, visual impairment, dysphagia, and acute renal failure). All were moderate or less in intensity and did not result the infusion being stopped. Subject 401021001 had a reduction in hemoglobin and platelets and a note of dysphagia occurring after 48 hours (not reported as an AE since it occurred after 48 hours, thus investigators were not required to report). No other information was provided on this subject. Subject 449001032 had an AE of acute renal failure of mild intensity reported on the same day as drug start. No time of onset was recorded, but the investigator assessed the event as unrelated to study drug and did not change the dose based on this AE.

In studies that measured pre and post infusion platelet aggregation there was no evidence of increased (rebound) platelet reactivity following cessation of cangrelor infusion at doses up to 4 ug/kg/min.

### 7.7 Additional Submissions / Safety Issues

None.

# 8 Postmarket Experience

N/A

# 9 Appendices

## 9.1 Risk benefit tables

**Table 66. Non-CABG bleed / benefit**

| Endpoint | Cangrelor | Clopidogrel | Cangrelor vs. Clopidogrel | |
|---|---|---|---|---|
| | N=5529 | N=5527 | RR | 95% CI |
| Non-CABG Bleed (NCB) | 857 | 601 | 1.42 | (1.29, 1.56) |
| NCB +D | 871 | 621 | 1.40 | (1.27, 1.54) |
| NCB+D+ST | 905 | 677 | 1.33 | (1.21, 1.46) |
| NCB+D+MI | 1037 | 841 | 1.23 | (1.13, 1.33) |
| NCB+D+MI+ST | 1059 | 877 | 1.20 | (1.11, 1.31) |
| NCB+PEP | 1065 | 885 | 1.20 | (1.11, 1.30) |

[15] TMC-CAN-05-02-043007-001

D= all cause death; ST=stent thrombosis=ARC-ST+IPST; MI= all adjudicated MI (type 1, 2, 3, 4a, 4b, 5); PEP=primary efficacy endpoint=composite of D, ST, MI, IDR; IDR=Ischemic Driven Revascularization

**Table 67. GUSTO severe/moderate bleed / benefit**

| Endpoint | Cangrelor | Clopidogrel | Cangrelor vs. Clopidogrel | |
|---|---|---|---|---|
| | N=5529 | N=5527 | RR | 95% CI |
| GUSTO (severe or moderate)(G) | 32 | 20 | 1.57 | (0.90, 2.74) |
| G +D | 48 | 40 | 1.18 | (0.78, 1.79) |
| G+D+ST | 88 | 109 | 0.80 | (0.61, 1.05) |
| G+D+MI | 248 | 293 | 0.84 | (0.71, 0.99) |
| G+D+MI+ST | 276 | 333 | 0.83 | (0.71, 0.96) |
| G+PEP | 285 | 343 | 0.83 | (0.71, 0.96) |

D= all cause death; ST=stent thrombosis=ARC-ST+IPST; MI= all adjudicated MI (type 1, 2, 3, 4a, 4b, 5); PEP=primary efficacy endpoint=composite of D, ST, MI, IDR; IDR=Ischemic Driven Revascularization

**Table 68. TIMI major/minor bleed / benefit**

| Endpoint | Cangrelor | Clopidogrel | Cangrelor vs. Clopidogrel | |
|---|---|---|---|---|
| | N=5529 | N=5527 | RR | 95% CI |
| TIMI (major or minor)(T) | 38 | 12 | 3.14 | (1.64, 6.00) |
| T +D | 55 | 32 | 1.70 | (1.10, 2.62) |
| T+D+ST | 96 | 100 | 0.95 | (0.72, 1.26) |
| T+D+MI | 255 | 284 | 0.89 | (0.76, 1.05) |
| T+D+MI+ST | 284 | 324 | 0.87 | (0.75, 1.02) |
| T+PEP | 293 | 334 | 0.87 | (0.75, 1.02) |

D= all cause death; ST=stent thrombosis=ARC-ST+IPST; MI= all adjudicated MI (type 1, 2, 3, 4a, 4b, 5); PEP=primary efficacy endpoint=composite of D, ST, MI, IDR; IDR=Ischemic Driven Revascularization

**Table 69. ACUITY major bleed / benefit**

| Endpoint | Cangrelor | Clopidogrel | Cangrelor vs. Clopidogrel | |
|---|---|---|---|---|
| | N=5529 | N=5527 | RR | 95% CI |
| ACUITY Major (A) | 242 | 143 | 1.67 | (1.36, 2.05) |
| A +D | 260 | 163 | 1.57 | (1.30, 1.91) |
| A+D+ST | 297 | 227 | 1.29 | (1.09, 1.53) |
| A+D+MI | 449 | 406 | 1.10 | (0.97, 1.25) |
| A+D+MI+ST | 474 | 445 | 1.06 | (0.94, 1.20) |

| | | | | |
|---|---|---|---|---|
| A+PEP | 483 | 455 | 1.06 | (0.93, 1.19) |

D= all cause death; ST=stent thrombosis=ARC-ST+IPST; MI= all adjudicated MI (type 1, 2, 3, 4a, 4b, 5); PEP=primary efficacy endpoint=composite of D, ST, MI, IDR; IDR=Ischemic Driven Revascularization

**Table 70. Bad bleed / benefit**

| Endpoint | Cangrelor | Clopidogrel | Cangrelor vs. Clopidogrel | |
|---|---|---|---|---|
| | N=5529 | N=5527 | RR | 95% CI |
| Bad Bleed (BB) | 61 | 41 | 1.46 | (0.99, 2.17) |
| BB +D | 76 | 61 | 1.22 | (0.88, 1.71) |
| BB+D+ST | 116 | 127 | 0.90 | (0.70, 1.16) |
| BB+D+MI | 273 | 309 | 0.88 | (0.75, 1.03) |
| BB+D+MI+ST | 301 | 349 | 0.86 | (0.74, 1.00) |
| BB+PEP | 310 | 359 | 0.86 | (0.74, 1.00) |

D= all cause death; ST=stent thrombosis=ARC-ST+IPST; MI= all adjudicated MI (type 1, 2, 3, 4a, 4b, 5); PEP=primary efficacy endpoint=composite of D, ST, MI, IDR; IDR=Ischemic Driven Revascularization; Bad Bleed=any of the following: intracranial hemorrhage, blood transfusion, cardiac tamponade, reoperation for bleeding, any surgical intervention, retroperitoneal bleed, or bleeding events requiring hospitalization or extension of hospitalization

## 9.2 Universal Definition of Myocardial Infarction

As per Thygesen et al. (2007), the criteria for diagnosing acute myocardial infarction and the clinical classifications of different types of myocardial infarction based on UDMI are delineated herewith.

**Definition of myocardial infarction**

## Criteria for acute myocardial infarction

The term myocardial infarction should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischaemia. Under these conditions any one of the following criteria meets the diagnosis for myocardial infarction:

- Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischaemia with at least one of the following:
  - Symptoms of ischaemia;
  - ECG changes indicative of new ischaemia [new ST-T changes or new left bundle branch block (LBBB)];
  - Development of pathological Q waves in the ECG;
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
- Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischaemia, and accompanied by presumably new ST elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.
- For percutaneous coronary interventions (PCI) in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers greater than 3 × 99th percentile URL have been designated as defining PCI-related myocardial infarction. A subtype related to a documented stent thrombosis is recognized.
- For coronary artery bypass grafting (CABG) in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers greater than 5 × 99th percentile URL plus either new pathological Q waves or new LBBB, or angiographically documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium have been designated as defining CABG-related myocardial infarction.
- Pathological findings of an acute myocardial infarction.

## Criteria for prior myocardial infarction

Any one of the following criteria meets the diagnosis for prior myocardial infarction:

- Development of new pathological Q waves with or without symptoms.
- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischaemic cause.
- Pathological findings of a healed or healing myocardial infarction.

**Table 1** Clinical classification of different types of myocardial infarction

**Type 1**
Spontaneous myocardial infarction related to ischaemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection

**Type 2**
Myocardial infarction secondary to ischaemia due to either increased oxygen demand or decreased supply, e.g. coronary artery spasm, coronary embolism, anaemia, arrhythmias, hypertension, or hypotension

**Type 3**
Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischaemia, accompanied by presumably new ST elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood

**Type 4a**
Myocardial infarction associated with PCI

**Type 4b**
Myocardial infarction associated with stent thrombosis as documented by angiography or at autopsy

**Type 5**
Myocardial infarction associated with CABG

| Endpoint Definition | Baseline MI status | Angiographic evidence[2]; ECG[3]; ischemic symptoms[4] | CKMB[1] mass (core lab) |
|---|---|---|---|
| MI | Baseline normal NSTE-ACS | *Not required to qualify MI* | elevation ≥3x ULN |
| | Baseline normal SA/ elective | *Not required to qualify MI* | elevation ≥3x ULN |
| Reinfarction | Baseline decreasing & returns to normal and no intervening event from elevated sample to PCI | *Not required to qualify MI* | elevation ≥3x ULN |
| | Baseline decreasing & remains abnormal and no intervening event from elevated sample to PCI | *(1 of 3):* Angiographic complication Or Ischemic Symptoms Or New ECG changes | AND: Re-elevation of CKMB ≥3xULN & ≥ 50% from the NADIR (lowest previous sample prior to the peak) |
| | Baseline abnormal increasing | (2 of 2): Angiographic complication AND new ECG changes[5] | AND: Re-elevation of CKMB ≥3x ULN & ≥ 50% from the NADIR (lowest previous sample prior to the peak) |
| | Baseline unknown | (2 of 2): Angiographic complication AND new ECG changes[5] | AND: Elevation of CKMB ≥3xULN |
| Not adjudicated | STEMI patients | Patient too early in presentation to assess post PCI events | Patient too early in presentation to assess post PCI cardiac markers |

[1]**CKMB collection post PCI**: 6 hourly collection through 24 hours (minimum of 3 samples required). Core lab values take priority; hospital labs may be used if core lab not available (CKMB priority but troponin may be used)

[2]**Angiographic evidence of complication** (assessed by the angiographic core laboratory):

- New onset of vessel closure or compromise defined as TIMI 0/1 flow after baseline TIMI 2/3 flow (also termed acute closure or no reflow) or
- TIMI 2 flow after baseline TIMI 3 flow (also termed slow reflow)or
- Sustained distal embolization; or
- Sustained side-branch closure of a vessel ≥ 2mm in diameter or

Intra-Procedural Thrombotic Event (IPTE): new or worsening thrombus formation at anytime during the procedure. The occurrence of IPTE can be a stent related or not stent related complication phenomena or intra procedural stent thrombosis (IPST) new or worsening thrombus related to the stent or abrupt closure due to thrombosis. Abrupt closure due to non-thrombotic causes, including major dissections, perforation, or other etiologies, will not be considered IPST. If a non-thrombotic cause of abrupt stent closure can not be definitively determined, the cause will be considered IPST. IPST may present as either acute thrombotic stent closure after a stent was implanted in a patient with a patent vessel beforehand, or new thrombus formation within or adjacent to a stent in a vessel in which thrombus either was not present or had diminished or resolved before the stent was implanted.

[3]**ECG changes**: ST segment elevation/ depression > 0.1mV (>1mm) in at least 2 contiguous leads; new LBBB; new Q wave (greater than 0.03 seconds). ECG collection post PCI: within 1 hour after PCI; pre-discharge



Reference ID: 3435333

## 9.3 Stent Thrombosis

ST was defined according to ARC (Cutlip, D, et al., 2007) taking into account acute (≤ 24 hours post-procedure) and subacute stent thrombosis (>24 hours and ≤30 days), and discriminating Definite from Probable ST. All occurrences of ST were adjudicated by the CEC. ST timing and ST ARC definitions are respectively described in this appendix.

IPST (Brener, S, et al., 2013) was defined as a new or increasing thrombus (compared with baseline) within or adjacent to a deployed stent occurring during the index procedure, whether occlusive or non-occlusive. IPST was also deemed present when the baseline level thrombus was decreasing or resolved after balloon angioplasty or thrombus aspiration but then increased any time after stent implantation (including stent post-dilation). IPST was a secondary endpoint identified in a protocol amendment.

**TABLE 6. Stent Thrombosis: Timing**

| | |
|---|---|
| Acute stent thrombosis* | 0 to 24 hours after stent implantation |
| Subacute stent thrombosis* | >24 hours to 30 days after stent implantation |
| Late stent thrombosis† | >30 days to 1 year after stent implantation |
| Very late stent thrombosis† | >1 year after stent implantation |

Stent thrombosis should be reported as a cumulative value over time and at the various individual time points specified above. Time 0 is defined as the time point after the guiding catheter has been removed and the patient has left the catheter laboratory.

*Acute or subacute can also be replaced by the term early stent thrombosis. Early stent thrombosis (0 to 30 days) will be used in the remainder of this document.

†Includes primary as well as secondary late stent thrombosis; secondary late stent thrombosis is a stent thrombosis after a target lesion revascularization.

**TABLE 7. Definite,* Probable, and Possible Stent Thrombosis**

- Definite stent thrombosis
  - Angiographic confirmation of stent thrombosis†
    - The presence of a thrombus‡ that originates in the stent or in the segment 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 ECG changes that suggest acute ischemia
      - Typical rise and fall in cardiac biomarkers (refer to definition of spontaneous MI)
      - Nonocclusive thrombus
        - Intracoronary thrombus is defined as a (spheric, ovoid, or irregular) noncalcified filling defect or lucency surrounded by contrast material (on 3 sides or within a coronary stenosis) seen in multiple projections, or persistence of contrast material within the lumen, or a visible embolization of intraluminal material downstream.
      - Occlusive thrombus
        - TIMI 0 or TIMI 1 intrastent or proximal to a stent up to the most adjacent proximal side branch or main branch (if originates from the side branch).
  - 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 acute 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 trial follow-up.

*Definite stent thrombosis is considered to have occurred by either angiographic or pathological confirmation.

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

‡Intracoronary thrombus.[36]

§For studies with ST-elevation MI population, one may consider the exclusion of unexplained death within 30 days as evidence of probable stent thrombosis.

## 9.4 Ischemic Driven Revascularization

IDR was defined as any refractory ischemia-driven repeat PCI or CABG surgery involving any native coronary or pre-existing bypass graft vessel. In the absence of pain, new St-segment changes indicative of ischemia, acute pulmonary edema, ventricular arrhythmias, or hemodynamic instability presumed to be ischemic in origin, constituted sufficient evidence of ischemia. The episode of ischemia leading to repeat PCI or CABG must have occurred following completion of the index procedure.

## 9.5 Literature Review/References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## 9.6 Labeling Recommendations

Deferred until further discussions.

## 9.7 Advisory Committee Meeting

An AC meeting is scheduled on February 12, 2014.

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/s/

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BACH N BEASLEY
01/14/2014

FORTUNATO F SENATORE
01/14/2014

THOMAS A MARCINIAK
01/14/2014

Please see also my review dated January 10, 2014, regarding the ethicalness of the cangrelor development program and my review dated January 13, 2014, regarding the risk-benefit of cangrelor.

# 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: January 13, 2014

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

NDA: 204-958
Drug: cangrelor

Indication: For the reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with coronary artery disease undergoing percutaneous coronary intervention (PCI)

Subject: Benefit-risk of cangrelor

## Summary and Recommendation

Cangrelor is an intravenously (IV) administered $P2Y_{12}$ platelet inhibitor studied in three large clinical outcomes trial in patients undergoing percutaneous coronary intervention (PCI). (The sponsor has also submitted a pharmacokinetic/pharmacodynamic study for an indication in transitioning patients on oral $P2Y_{12}$ platelet inhibitors to discontinuation prior to CABG, but I do not address that indication in this review.) The two earlier trials, PCI and PLATFORM, failed to show superiority of a cangrelor regimen to a clopidogrel regimen.[1] The sponsor alleges that the failure of these latter two trials was the result of problems with adjudicating new myocardial infarctions (MIs) in patients having baseline biomarker elevations. A third trial, PHOENIX, allegedly corrected this flaw and demonstrated superiority of the cangrelor regimen to a clopidogrel regimen.

I conclude that the CHAMPION trials did not show superiority or noninferiority of a cangrelor regimen to a clopidogrel regimen or to standard of care for the following reasons:

[1] In this review for brevity I refer to the "cangrelor" regimen or arm and the "clopidogrel" regimen or arm. The more complete references are the "cangrelor infusion followed by clopidogrel" regimen or arm and the "clopidogrel alone" regimen or arm.



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- Clopidogrel administration was delayed inappropriately in all of the trials. The trials themselves provide evidence that earlier administration of clopidogrel was better both by cross-trial comparisons and by logistic regressions of the PHOENIX data. Clopidogrel was never consistently administered early enough such that we can not even conclude that cangrelor is noninferior to clopidogrel.

- The cangrelor regimen was only statistically significantly superior for the sponsor's primary endpoint including predominantly "chemical" MIs. The difference in site-reported events has a higher odds ratio and is not statistically significant.

- In PHOENIX use of a 300 mg loading dose was only allowed in the clopidogrel arm. The exclusive use of the 600 mg loading dose in the cangrelor arm may explain some of the "superiority" of that arm.

- The "superiority" is only statistically significant in the stable angina subgroup. Yet stable angina is the condition for which cangrelor offers minimal advantages if any: We can easily load clopidogrel in stable angina patients at any desired interval before PCI and we can delay CABG for days to washout the clopidogrel effects if the anatomy elucidated at angiography is unsuitable for PCI and CABG is preferred.

- The data suggest the possibility of harm with cangrelor for ST segment elevation MI (STEMI) patients.

- While the trials did not demonstrate convincingly superiority of cangrelor for efficacy, they do demonstrate an increased risk of bleeding with it.

There are other reasons for rejecting approval besides uncertain noninferiority to clopidogrel. Both prasugrel and ticagrelor have demonstrated superior efficacy to clopidogrel. We do not know whether cangrelor affects this superiority so we do not know whether to use cangrelor with or instead of prasugrel and ticagrelor—or prasugrel or ticagrelor instead of cangrelor. Because the superiority involves irreversible harm, i.e., deaths and MIs, we should understand the tradeoffs among these agents.

Finally, I document in a parallel review that the CHAMPION trials were conducted unethically. (Marciniak 2014) We can refuse approval of cangrelor based on that fact alone.

I recommend not approving cangrelor at this time for the PCI indication. I recommend not approving cangrelor until another trial succeeds in correcting the flaws that I have documented in this review and in my parallel review on the ethicalness of the cangrelor development program.



Reference ID: 3435320

## Background

Cangrelor is a new platelet inhibitor studied for use with PCI for the treatment of stable angina or acute coronary syndromes (ACS, or myocardial infarction (MI) and unstable angina (UA)). Cangrelor is a platelet $P2Y_{12}$ receptor inhibitor like clopidogrel, the first approved $P2Y_{12}$ inhibitor. Cangrelor, unlike orally-administered clopidogrel, is administered intravenously and is a reversible rather than an irreversible inhibitor. Cangrelor has a quick onset and offset and short half-life compared to clopidogrel and other approved $P2Y_{12}$ inhibitors, potentially making it very useful in situations in which these qualities are desirable, such as recent onset ACS.

The PHOENIX trial was a randomized, double-blind, active-controlled trial comparing a bolus and infusion of cangrelor followed by clopidogrel 600 mg to clopidogrel 300 or 600 mg alone. (Bhatt, Stone et al. 2013) The trial was conducted from September 30, 2010, to October 3, 2012, in 11,145 patients who were undergoing either urgent or elective PCI, i.e., in both stable angina and ACS patients, and who did not receive pretreatment with platelet inhibitors (except aspirin). The trial was an international trial conducted in the US, Europe (including Austria, Germany, and the Czech Republic), Brazil, New Zealand, and Thailand. The primary endpoint was the composite of death, MI, ischemia-driven revascularization, or stent thrombosis at 48 hours. The rate of this endpoint was significantly lower in the cangrelor group than in the clopidogrel group[2] (4.7% vs. 5.9%; odds ratio [OR], 0.78; 95% confidence interval [CI] 0.66 to 0.93; P = 0.005) in the sponsor's "modified ITT" subgroup. The sponsor in its integrated summary of efficacy introduces the PHOENIX results as follows: "Data from the CHAMPION PHOENIX (N=11,145 mITT) [TMC-CAN-10-01] trial are presented to demonstrate that cangrelor significantly reduces thrombotic events (including death/MI/IDR/ST and ST) superior to clopidogrel in patients who require PCI."

PHOENIX was not the first clinical outcomes trial of cangrelor. Two similar trials preceded it: CHAMPION PCI and CHAMPION PLATFORM. (Bhatt, Lincoff et al. 2009; Harrington, Stone et al. 2009) Both were conducted in patients undergoing PCI, both used clopidogrel with a 600 mg loading dose, and both had a primary endpoint of death, MI, or ischemia-driven revascularization at 48 hours. The major difference was that in CHAMPION PCI clopidogrel was given prior to the PCI (but after angiography except early use was allowed in STEMI) while in PLATFORM clopidogrel administration was delayed until after the PCI. CHAMPION PCI included ST segment elevation MI (STEMI) patients while PLATFORM excluded them; both included 5-15% stable angina. At second planned interim analyses (at 70% enrollment) the sponsor terminated both trials early allegedly because the estimated conditional power to demonstrate superiority was low, i.e., for futility. I summarize relevant results in Table 1.

[2] In this review for brevity I refer to the "cangrelor group" and the "clopidogrel group". The more complete references are the "cangrelor infusion followed by clopidogrel group" and the "clopidogrel alone" group.



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**Table 1: Cangrelor CHAMPION Trials Results at 48 Hours**

| | | PCI | PLATFORM |
|---|---|---|---|
| N | | 8877 | 5301 |
| clopidogrel within 5 days | | 34% | 0% |
| study clopidogrel timing | | immediately prior to PCI | after PCI |
| primary endpoint | cangrelor | 7.5% | 7.0% |
| | clopidogrel | 7.1% | 8.0% |
| efficacy OR* | | 1.05 NS† | 0.87 NS† |
| deaths | cangrelor | 0.2% | 0.2% |
| | clopidogrel | 0.1% | 0.7% |
| death OR* | | 1.59 NS† | 0.33 (p=0.02) |
| stent thrombosis | cangrelor | 0.2% | 0.2% |
| | clopidogrel | 0.3% | 0.6% |
| stent thrombosis OR* | | 0.63 NS† | 0.31 (p=0.02) |
| bleeding ORs* | | 1.2-1.4 | 1.3-1.6 |

* OR = odds ratio cangrelor:clopidogrel; †NS = not significant

For all three CV endpoints the rate that is substantially higher than those in the other three arms is the one in the clopidogrel arm of PLATFORM. In that latter arm clopidogrel initiation was delayed until after PCI. For the PCI trial in which clopidogrel was given earlier—although still not optimally—the point estimates for the primary endpoint and death actually favor clopidogrel. The CHAMPION trials confirmed that delaying clopidogrel initiation is bad.

# Is the PHOENIX Cangrelor Regimen Superior to Delayed Clopidogrel?

## *ITT vs. "Modified ITT"*

As I noted above, PHOENIX was successful for the sponsor's primary adjudicated endpoint of death, MI, ischemia-driven revascularization, or stent thrombosis at 48 hours, with an OR of 0.78 (95% CI 0.66 to 0.93, p = 0.005) in the sponsor's "modified ITT" subgroup. For "modified ITT" the sponsor excluded 203 (94 clopidogrel and 109 cangrelor) patients who were not treated or did not undergo a PCI. I assert that true ITT analyses that preserve the randomization are the appropriate ones for valid statistics. Hence I will use true ITT analyses for the rest of this review. The true ITT analyses are very slightly less favorable for cangrelor than the sponsor's "modified ITT". For the sponsor's primary endpoint at 48 hours there is little difference: the true ITT OR is 0.79 (95% CI 0.67 to 0.93, p = 0.005). I explore the robustness of these results below.

## *Sponsor's Endpoint Rates at 48 Hours by Index Event Type*

Examining the sponsor's endpoint results by the type of index event (stable angina, unstable angina (UA)/NSTEMI, STEMI) suggests a potential problem with the sponsor's definition of endpoints. I show the sponsor's endpoint rates at 48 hours by index event type in Table 2.



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**Table 2: Sponsor's Endpoint Rates at 48 Hours by Index Event Type in PHOENIX**

| index event | primary endpoint | | adjudicated MI | | death | |
|---|---|---|---|---|---|---|
| | clopidogrel | cangrelor | clopidogrel | cangrelor | clopidogrel | cangrelor |
| stable angina | 6.8% | 5.7% | 6.3% | 5.3% | 0.0% | 0.2% |
| UA/NSTEMI | 5.7% | 3.6% | 3.3% | 2.4% | 0.7% | 0.3% |
| STEMI | 2.8% | 2.8% | 0.4% | 0.1% | 1.2% | 1.3% |
| all | 5.8% | 4.7% | 4.6% | 3.7% | 0.4% | 0.4% |

Note that the primary endpoint and adjudicated MI rates in the stable angina patients (58% of randomized subjects) are about 6%, higher for clopidogrel than for cangrelor. On the other hand, there appears to be little benefit in the STEMI subgroup and no overall benefit regarding mortality.

*COMMENT: Event rates of 6% in stable angina patients at 48 hours seem high. The endpoints counted by the sponsor must not be clinically overt events but biomarker rises, e.g., "chemical" MIs, associated with the PCIs. The sponsor has explained the lower rates of MI endpoints in the UA/NSTEMI and particularly in the STEMI subgroups as the result of the difficulties of adjudicating MIs in these patients because of problems with establishing stable or falling biomarkers pre-randomization and with distinguishing new biomarker increases from the biomarker rises from the index event. I believe examining the site-reported events should be informative regarding the real benefit or detriment of cangrelor..*

## *Site-Reported Event Rates at 48 Hours by Index Event Type*

The CRFs for the 48-hour and 30-day follow-ups included a MI CRF with a yes/no checkbox labeled "Did patient experience an MI?" I counted the yes responses from these checkboxes as site-reported MIs. There was a similar CRF checkbox for revascularizations and an additional CRF for indicating whether the revascularization was planned; I counted unplanned revascularizations. I show the site-reported event rates at 48 hours by index event type in PHOENIX in Table 3.

**Table 3: Site-Reported Event Rates at 48 Hours by Index Event Type in PHOENIX**

| index event | primary endpoint | | MI event | |
|---|---|---|---|---|
| | clopidogrel | cangrelor | clopidogrel | cangrelor |
| angina | 2.1% | 1.8% | 1.7% | 1.2% |
| UA/NSTEMI | 2.6% | 2.2% | 1.3% | 1.3% |
| STEMI | 2.3% | 2.8% | 1.2% | 0.5% |
| all | 2.3% | 2.1% | 1.5% | 1.1% |

The site-reported event rates for stable angina are more believable than the sponsor's, although they still seem high for stable angina. One possible explanation is that sites may not have recorded index events accurately because about 4.4% of "stable angina" patients had an elevated CKMB on the baseline measurement (drawn between randomization and study drug administration.) Regardless, overall the cangrelor regimen was not statistically significantly better than the clopidogrel regimen in PHOENIX for a site-reported primary endpoint event rate, with OR 0.91 (95% CI 0.7 to 1.2, $p = 0.5$).



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The point estimates for the site-reported primary endpoint results in STEMI favor clopidogrel, as did the point estimates for all cause mortality. However, the site-reported new MI point estimates favor cangrelor. None of the interactions between treatment and STEMI are statistically significant.

*COMMENT: The site-reported results at 48 hours suggest that the adjudicated results are not robust, particularly in STEMI patients. There are other analyses that should help to clarify the robustness or lack thereof. One is whether the difference in clopidogrel dosing in the two PHOENIX arms (the sponsor forced clopidogrel dosing to 600 mg in the cangrelor arm) affected the results. A second is whether the speed with which PCI was done represents optimal practice. However, the greatest limitation precluding concluding that cangrelor is superior to, or even as effective as, clopidogrel is the fact that the sponsor delayed clopidogrel dosing in PHOENIX. I present data elucidating all of these factors below.*

## *Event Rates by Clopidogrel Loading Dose*

The NEJM article (Bhatt, Stone et al. 2013) has the following tabulation for the "loading dose" of clopidogrel:

Table 1. (Continued.)

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The Results section presents the following subgroup analysis regarding the "loading dose":

> "Similarly, there was no significant difference in the effect of cangrelor on the primary end point between patients who received a 600-mg loading dose of clopidogrel (74.4% of the population) and those who received a 300-mg loading dose (25.6% of the population): the odds ratio for the primary end point with cangrelor was 0.77 (95% CI, 0.63 to 0.94) with the 600-mg loading dose and 0.84 (95% CI, 0.62 to 1.14) with the 300-mg loading dose (P = 0.62 for interaction)."

The Discussion section alleges the following:

> "There are some limitations of the current study. A 600-mg loading dose of clopidogrel is known to be superior to a 300-mg dose in some, though not all, patients undergoing PCI. However, the results of the CHAMPION PHOENIX trial were similar after adjustment for loading dose and in each loading-dose subgroup."

The PHOENIX study report has a corresponding table for results by "loading dose":



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**Table 25: 48-hour composite efficacy endpoint based on CEC-adjudicated results, by clopidogrel loading dose (mITT)**

| | n (%) of patients | | | |
|---|---|---|---|---|
| | Cangrelor (N=5472) | Clopidogrel (N=5470) | OR and 95% CI | P value [a] |
| Death/MI/IDR/ST by assigned clopidogrel loading dose | *(Placebo)* | | | |
| 600 mg | 176/4065 (4.3) | 227/4068 (5.6) | 0.77 (0.63, 0.94) | 0.009 |
| 300 mg | 81/1405 (5.8) | 95/1401 (6.8) | 0.84 (0.62,1.14) | 0.267 |

*COMMENT: The above results are incorrect and misleading. About 26% of patients in each arm did not receive a 300 mg loading dose of clopidogrel. Recall that, by protocol, ALL patients in the cangrelor arm were to receive a 600 mg loading dose. As I document below, adherence to this protocol specification was virtually 100%. The analyses presented are not for the "loading dose" but for the "intended loading dose"—only valid for the clopidogrel arm. Given the protocol specification summarized in the NEJM article's Methods Study Treatment section regarding the 600 mg loading dose in the cangrelor group, the NEJM reviewers and editors should have caught this blatant misrepresentation.*

By the study drug administration records 26% of the patients in the clopidogrel arm received two capsules (clopidogrel 300 mg) and all but 6 of the rest received four capsules (clopidogrel 600 mg) at the first oral study drug administration immediately following randomization. About 26% of the patients in the cangrelor arm also received two clopidogrel dummy capsules at the first oral study drug administration. At the second oral study drug administration after completion of the cangrelor or dummy infusion 99.85% of the patients in the cangrelor arm received four capsules (clopidogrel 600 mg) and 99.71% of patients in the clopidogrel arm received four capsules (dummy).

Clopidogrel dosing in the clopidogrel arm was highly consistent by site. I show the counts of sites and numbers of patients studied by clopidogrel dosing in Table 4.

**Table 4: Loading Doses in Clopidogrel Arm by Site in PHOENIX**

| loading dose | # of sites | patients | % of study |
|---|---|---|---|
| 300 mg only | 5 | 1,170 | 10.5% |
| 600 mg only | 113 | 4,269 | 38.3% |
| both | 35 | 5,706 | 51.2% |

While the majority of the sites used only a 600 mg loading dose, the 35 sites using both randomized the majority of patients. Because only patients at these latter sites had the opportunity for receiving either loading dose, I analyzed the patients at these sites by loading dose used. I show the endpoint and bleed rates at 48 hours by loading dose at these latter sites in Table 5.



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**Table 5: Endpoint Rates at 48 Hours by Loading Dose at Sites Using Both Loading Doses in PHOENIX**

| arm | sponsor's endpoint | | site-reported endpoint | | any GUSTO bleed | | deaths | |
|---|---|---|---|---|---|---|---|---|
| | 300 mg | 600 mg | 300 mg | 600 mg | 300 mg | 600 mg | 300 mg | 600 mg |
| clopidogrel | 7.1% | 4.8% | 2.6% | 1.5% | 0.6% | 1.3% | 0.95% | 0.25% |
| cangrelor | | 4.5% | | 1.9% | | 1.9% | | 0.35% |

The rates in Table 5 suggest that both efficacy and bleeding are higher with the higher loading dose in the clopidogrel arm while bleeding, but not efficacy, is higher in the cangrelor arm compared to the clopidogrel patients loaded with 600 mg. Site-reported primary endpoints and deaths were greater in the cangrelor arm than for patients in the clopidogrel arm loaded with 600 mg.

Because clopidogrel loading did not vary in the cangrelor arm and at some sites, we should only test the effects of the loading dose in the clopidogrel arm at the sites using both loading doses. I show the endpoint odds ratios comparing 600 mg to 300 mg loading in the clopidogrel arm at those sites in Table 6.

**Table 6: Endpoint Odds Ratios at 48 Hours Comparing 600 mg to 300 mg Loading in the Clopidogrel Arm of PHOENIX at Sites Using Both Loading Doses**

| endpoint | OR | 95% LCL | 95% UCL | P |
|---|---|---|---|---|
| sponsor's endpoint | 0.66 | 0.47 | 0.92 | 0.014 |
| site-reported endpoint | 0.57 | 0.33 | 0.99 | 0.047 |
| any GUSTO bleed | 2.2 | 0.84 | 5.8 | 0.105 |
| deaths | 0.26 | 0.09 | 0.80 | 0.019 |

OR = odds ratio 600mg/300mg; LCL = lower confidence limit (of OR)
UCL = upper confidence limit; P = P value

The 600 mg loading dose appears to be more effective perhaps at the expense of more bleeding. However, patients were not randomized to the 300 mg or 600 mg loading dose and we do not know how the dosages were selected. Examining baseline characteristics may help elucidate how loading doses were determined so I show selected baseline characteristics in Table 7.

**Table 7: Baseline Characteristics by Loading Dose at Sites Using Both Loading Doses in PHOENIX**

| arm | mean age | | diabetic | | stable angina | | minutes to PCI* | |
|---|---|---|---|---|---|---|---|---|
| | 300 mg | 600 mg | 300 mg | 600 mg | 300 mg | 600 mg | 300 mg | 600 mg |
| clopidogrel | 61.8 | 64.1 | 17.8% | 28.7% | 40.8% | 60.2% | 10.8 | -6.3 |
| cangrelor | | 63.6 | | 24.0% | | 54.5% | | -1.4 |

*mean minutes from loading dose to PCI start; negative values indicate loading dose after PCI start

While older diabetic patients, i.e., higher risk, more frequently received a 600 mg loading dose, the patients loaded with 600 mg more frequently had an index event of stable angina. The major factor determining loading dose may have been the clopidogrel



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loading timing relative to the PCI start, with the 600 mg dose used more frequently when the oral study drug was to be administered after PCI start. This greater delayed administration of the 600 mg loading dose should favor the 300 mg loading dose regarding outcomes. Loading dose remains a significant predictor of outcomes after adjustment for these factors as I show in Table 8 with a logistic regression of the sponsor's primary endpoint at 48 hours.

**Table 8: Logistic Regression of Sponsor's Primary Endpoint at 48 Hours in the Clopidogrel Arm of PHOENIX at Sites Using Both Loading Doses**

```
Logistic regression                               Number of obs   =       2788
                                                  LR chi2(5)      =      25.39
                                                  Prob > chi2     =     0.0001
Log likelihood = -582.97334                       Pseudo R2       =     0.0213

------------------------------------------------------------------------------
      pep48h | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
 600 mg load |    .485656   .0924904    -3.79   0.000     .3343662    .7053995
         age |   1.014637   .0077365     1.91   0.057     .9995861    1.029914
    diabetes |   .8780803   .1746731    -0.65   0.513     .5945769    1.296762
      angina |   1.617155   .2927221     2.66   0.008     1.134162    2.305834
  hrs to PCI |   .5881325    .164602    -1.90   0.058     .3398189    1.017895
       _cons |   .0281376   .0144412    -6.96   0.000     .0102901      .07694
------------------------------------------------------------------------------
```

The use of the 600 mg loading dose is the most significant predictor of outcome. The timing of clopidogrel (hrs to PCI) is almost a significant predictor and it is (p = 0.012) if angina is omitted from the analysis (and see the next section below.)

Loading dose may also have an effect upon bleeding as shown by the logistic regression of any GUSTO bleed by 48 hours in Table 9.

**Table 9: Logistic Regression of Any GUSTO Bleed by 48 Hours in the Clopidogrel Arm of PHOENIX at Sites Using Both Loading Doses**

```
Logistic regression                               Number of obs   =       2788
                                                  LR chi2(5)      =       7.07
                                                  Prob > chi2     =     0.2157
Log likelihood = -162.26119                       Pseudo R2       =     0.0213

------------------------------------------------------------------------------
any GUSTO bld| Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
 600 mg load |   2.772517    1.57514     1.79   0.073     .9105088    8.442367
         age |     1.0233   .0179589     1.31   0.189        .9887    1.059111
        male |   1.354659   .6023627     0.68   0.495      .566676    3.238361
      weight |   .9927052   .0121671    -0.60   0.550     .9691423    1.016841
  hrs to PCI |   1.275293    .853462     0.36   0.716     .3435281    4.734324
       _cons |   .0016133   .0028174    -3.68   0.000     .0000526    .0494567
------------------------------------------------------------------------------
```

While higher loading dose may be a risk factor for bleeding, the timing of clopidogrel appears to be unimportant, at least within the timings in PHOENIX.

The second largest subgroup by loading dose used is the subgroup of sites that used only a 600 mg loading dose. For this subgroup efficacy was greater in the cangrelor arm for



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the sponsor's primary endpoint, OR 0.69 (95% CI 0.52 to 0.90, p = 0.007). The timing of clopidogrel administration was also later and more variable in this subgroup (mean about 9 minutes after PCI start, 41% after completion of PCI) than in the subgroup of sites using both loading doses.

*COMMENT: The results in the subgroup of sites using both loading doses suggest that the 600 mg clopidogrel loading dose was more effective than the 300 mg loading dose, at least with the delayed administration of clopidogrel forced in PHOENIX. In this subgroup cangrelor appears less effective and less safe than delayed clopidogrel. The results in the subgroup of sites using the 600 mg dose suggest that the cangrelor regimen was more effective than a delayed 600 mg loading dose. A limitation of all of these analyses of sites by loading doses is that they are non-randomized subgroup analyses that we must interpret cautiously.*

## *Event Rates by Timing of Clopidogrel*

The timing of clopidogrel varied by the index event as I show in Table 10.

**Table 10: Minutes from Clopidogrel Administration to PCI by Index Event in the Clopidogrel Arm of PHOENIX**

| index event | mean | SD* | median | IQR† |
|---|---|---|---|---|
| stable angina | -6.1 | 40.3 | 0 | -17, 5 |
| UA/NSTEMI | -1.8 | 19.6 | 2 | -7, 7 |
| STEMI | 6.0 | 20.7 | 4 | 1,16 |

*SD = standard deviation; †IQR = interquartile range

The timings in Table 10 are for the clopidogrel arm only, although the timings for dummy clopidogrel administration in the cangrelor arm are virtually identical. The greatest variability for clopidogrel timing is in the patients with stable angina.

*COMMENT: While there was variability in clopidogrel timing, it is less than what we would want to resolve definitively how clopidogrel timing affects efficacy: Clopidogrel requires about two hours to achieve near maximal pharmacodynamic effects and the European guidelines suggest that efficacy is improved by administration six to 24 hours prior to PCI. The variability in clopidogrel timing in PHOENIX is measured in minutes rather than hours. Also, we do not know the reasons for the variability, although I attempt to explore some reasons below.*

*Note also that clopidogrel was administered minutes before PCI in the patients presenting with STEMI. This delayed administration does not appear consistent with the protocol specification to allow immediate administration without waiting for angiography and with the concept that "time is myocardium" in STEMI patients. That care for STEMI patients may not have been optimal in PHOENIX I discuss in the next section.*

Timing of clopidogrel also varied by the site loading doses as I show in Table 11.



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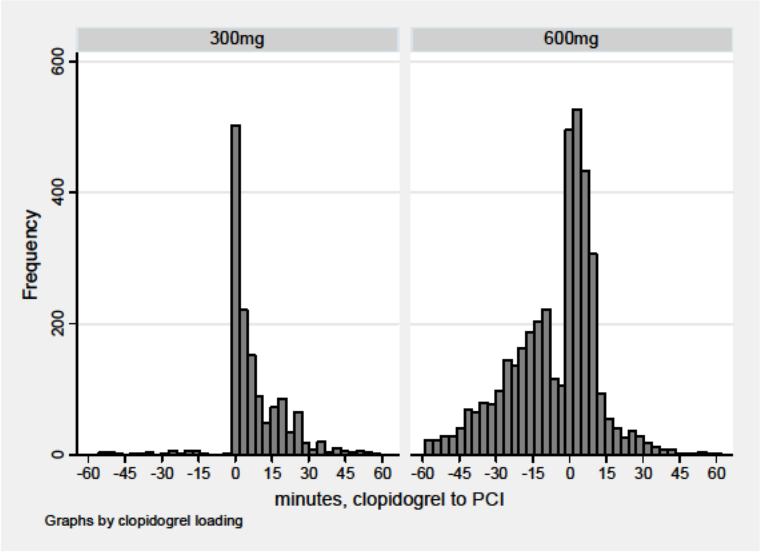
**Table 11: Minutes from Clopidogrel Administration to PCI by Index Event and Site Loading Dose in the Clopidogrel Arm of PHOENIX**

| site loading dose: | 300 mg only | | 600 mg only | | both | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | 300 mg | | 600 mg | |
| index event | mean | SD* | mean | SD* | mean | SD* | mean | SD* |
| stable angina | 22.8 | 121.7 | -10.8 | 30.0 | 5.5 | 12.4 | -9.1 | 16.5 |
| UA/NSTEMI | 3.0 | 13.5 | -9.4 | 23.0 | 11.7 | 10.8 | -4.7 | 17.5 |
| STEMI | 2.0 | 5.0 | 3.6 | 25.0 | 18.5 | 22.6 | 1.6 | 17.3 |

*SD = standard deviation

As shown in Table 11, the 300 mg loading dose was typically administered prior to PCI. The distributions of clopidogrel timings varied by loading dose as I show in Figure 1.

**Figure 1: Timing of Clopidogrel Administration by Loading Dose in the Clopidogrel Arm of PHOENIX**




(outliers <-60 and >60 minutes not shown)

While the 300 mg loading dose was predominantly administered prior to PCI, the 600 mg loading dose has a bimodal distribution with modes both prior to start and after the PCI end. For about 32% of the patients the first oral study drug was administered after the completion of the PCI.

*COMMENT: Given the PLATFORM results, I find it very disturbing that PHOENIX sites delayed clopidogrel administration until after PCI in a substantial number of patients.*

Because of the associations of clopidogrel timing with the index event and loading doses and likely other factors, sorting out timing effects from other effects is difficult. A multivariate analysis seems appropriate. Hence I show the results of a logistic regression of the sponsor's primary endpoint at 48 hours in the clopidogrel arm of PHOENIX in Table 12.



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**Table 12: Logistic Regression of the Sponsor's Primary Endpoint at 48 Hours in the Clopidogrel Arm of PHOENIX**

```
Logistic regression                               Number of obs   =       5440
                                                  LR chi2(5)      =      35.17
                                                  Prob > chi2     =     0.0000
Log likelihood = -1179.9515                       Pseudo R2       =     0.0147

------------------------------------------------------------------------------
      pep48h | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
 600 mg load |   .6272858    .086665    -3.38   0.001     .4784808    .8223682
         age |   1.012741   .0055211     2.32   0.020     1.001977     1.02362
    diabetes |   .8068125   .1090964    -1.59   0.112     .6189763     1.05165
      angina |   1.615914   .2090219     3.71   0.000     1.254046    2.082202
  hrs to PCI |   .6894119   .1077956    -2.38   0.017     .5074414    .9366378
       _cons |   .0287312   .0106205    -9.60   0.000     .0139222    .0592926
------------------------------------------------------------------------------
```

Both the use of a 600 mg loading dose and earlier timing of clopidogrel administration are associated with better outcomes, although the association is stronger for the 600 mg loading dose.

*COMMENT: Because the loading doses and their timing were not randomized it is difficult to sort out their effects from whatever investigator decision factors motivated them. However, the data do suggest that both the 600 mg loading dose and earlier timing are associated with better outcomes. We can not assume that any benefit shown by the cangrelor arm in PHOENIX is the result of a simple superiority of cangrelor over clopidogrel—the regimen (including delayed clopidogrel dosing, differential clopidogrel loading dose between the arms) likely plays a role. Both the delayed clopidogrel dosing and the differential clopidogrel loading dose between the arms could easily have—and should have—been avoided for ethical reasons and to enable PHOENIX to demonstrate the comparability of a cangrelor regimen to standard clopidogrel use.*

## *Timing in STEMI Patients and Quality of Care*

The NEJM article does not present statistics on symptom-to-balloon (PCI) times or door-to-balloon times for the STEMI patients. The sponsor's study report makes this claim:

> "Patient arrival at the catherization laboratory was fast, with a median time from hospital admission to PCI of 4.4 hours for both cangrelor and clopidogrel treatment groups. In the STEMI subgroup, the median time from admission to PCI was faster, at 1.3 hours for both treatment groups."

What the sponsor fails to mention is that the hospital admission time was AFTER the PCI time for 1128 patients. The sites apparently did not collect a "door" time but some or all must have collected an administrative hospital admission time.

*COMMENT: The statistics based on hospital admission time are worthless. The statistics most informative regarding timing in STEMI patients are the times from symptom onset to PCI and the times from clopidogrel administration to angiography and to PCI, which I present below.*



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About 5% of the STEMI patients did not have an initial ischemia onset time recorded and another 5% lack a PCI time. For the STEMI patients with both recorded the median time from symptom onset to PCI was 4.9 hours and the mean time was 10.1 hours. If we assume the intent was primary PCI for patients who went to PCI within the first 24 hours, then the median time was 4.5 hours and the mean time was 6.2 hours. Fewer than 8% of STEMI patients had a PCI within 2 hours of symptom onset and about 58% had a PCI within 6 hours of symptom onset.

*COMMENT: These statistics are substantially worse than the ideal of performing primary PCI in STEMI patients within 2 hours of symptom onset. Whether the study requirements affected the speed of angioplasty is impossible to determine.*

While when the first angiography was done varied widely by the index event, the mean and median timings of administration of oral study drug relative to PCI varied little in PHOENIX as I show in Table 13.

**Table 13: Minutes from Oral Study Drug Administration to Angiography and PCI by Intended Loading Dose in PHOENIX**

| index event | 300mg intended loading dose | | | | 600mg intended loading dose | | | |
|---|---|---|---|---|---|---|---|---|
| | oral to angio | | oral to PCI | | oral to angio | | oral to PCI | |
| | mean | median | mean | median | mean | median | mean | median |
| angina | -2350 | -27 | 11.4 | 3 | -1506 | -41 | -9.7 | -6 |
| UA/NSTEMI | -350 | -25 | 7.3 | 2 | -152 | -37 | -7.3 | 1 |
| STEMI | -34 | -2 | 12.7 | 8 | -44 | -17 | 1.4 | 4 |

The times above are for both arms but they differ minimally for each arm. In the STEMI subgroup oral study drug was administered after angiography in the majority of patients, i.e., about 68%.

*COMMENT: Despite the clinical concept that "time is myocardium" in STEMI, administration of study drug was typically delayed until after angiography. I question whether this is the standard of care at the sites or whether some sites tended to treat all study patients similarly, administering study drug after angiography regardless of index event.*

## *Event Rates at Days 3 to 30 by Index Event Type*

Event rates from days 3 to 30 did not vary greatly between the two arms as I show in Table 14 and Table 15.

**Table 14: Sponsor's Endpoint Rates Days 3 to 30 by Index Event Type in PHOENIX**

| index event | primary endpoint | | adjudicated MI | | death | |
|---|---|---|---|---|---|---|
| | clopidogrel | cangrelor | clopidogrel | cangrelor | clopidogrel | cangrelor |
| stable angina | 1.2% | 1.1% | 0.3% | 0.1% | 0.4% | 0.3% |
| UA/NSTEMI | 2.2% | 2.4% | 0.3% | 0.7% | 1.0% | 1.0% |
| STEMI | 2.3% | 2.9% | 0.2% | 0.5% | 1.0% | 2.2% |



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| index event | primary endpoint | | adjudicated MI | | death | |
|---|---|---|---|---|---|---|
| | clopidogrel | cangrelor | clopidogrel | cangrelor | clopidogrel | cangrelor |
| all | 1.6% | 1.7% | 0.3% | 0.3% | 0.7% | 0.8% |

**Table 15: Site-Reported Event Rates Days 3 to 30 by Index Event Type in PHOENIX**

| index event | primary endpoint | | MI event | |
|---|---|---|---|---|
| | clopidogrel | cangrelor | clopidogrel | cangrelor |
| stable angina | 1.7% | 1.4% | 0.3% | 0.1% |
| UA/NSTEMI | 2.7% | 2.4% | 0.6% | 0.9% |
| STEMI | 3.6% | 4.6% | 0.4% | 0.8% |
| all | 2.3% | 2.2% | 0.4% | 0.4% |

*COMMENT: The one noteworthy variation is that STEMI patients fared slightly, but not usually statistically significantly, worse on cangrelor for days 3 to 30. For deaths days 3 to 30 the difference is nominally statistically significant (19 vs. 9, p = 0.043). While this may be a random subgroup variation, it seems strange to me that the group with the greatest need for good antiplatelet effect has the worst outcomes on cangrelor. Furthermore, for short term outcomes this variation is also true for another reversible $P2Y_{12}$ inhibitor, ticagrelor. I question whether there is a biological explanation for this variation.*

*The event rates from days 3 to 30 seemed low to me, so another issue regarding them is whether the reporting at day 30 was complete in this study. I address that issue next.*

I show the MI and death rates from days 3 to 30 for the control arms of recent ACS trials for the UA/NSTEMI subgroups in Table 16 and for the STEMI subgroups in Table 17.

**Table 16: MI and Death Rates from Days 3 to 30 for the UA/NSTEMI Subgroups in the Control Arms of Recent $P2Y_{12}$ Inhibitor ACS Trials**

| study | mean age | adjudicated MI | site-reported MI | deaths |
|---|---|---|---|---|
| PHOENIX | 63.2 | 0.3% | 0.6% | 1.0% |
| PCI | 62.1 | 0.6% | 0.8% | 0.6% |
| PLATO invasive | 63.2 | 1.9% | 1.1% | 1.5% |
| TRITON | 61.3 | 1.0% | 0.8% | 0.6% |

**Table 17: MI and Death Rates from Days 3 to 30 for the STEMI Subgroups in the Control Arms of Recent $P2Y_{12}$ Inhibitor ACS Trials**

| study | mean age | adjudicated MI | site-reported MI | deaths |
|---|---|---|---|---|
| PHOENIX | 60.8 | 0.2% | 0.4% | 1.0% |
| PCI | 61.0 | 1.2% | 2.0% | 1.8% |
| PLATO invasive | 59.3 | 1.6% | 1.7% | 1.7% |
| TRITON | 59.7 | 1.9% | 1.3% | 1.9% |

For the ticagrelor PLATO trial I have included only the statistics for the subgroup of patients who were managed invasively. In the prasugrel TRITON trial all patients were to



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undergo PCI as in the CHAMPION trials. I have included the mean ages to show that there is good consistency among the trials at least for that demographic statistic. While deaths and site-reported MIs in the UA/NSTEMI group of PHOENIX appear comparable to those in the other studies, the rest of the endpoints are substantially lower in PHOENIX.

*COMMENT: There appears to be underreporting of events at 30 days in PHOENIX. The underreporting is present in both arms, so per se it is not evidence of bias. However, it does raise questions about the quality of conduct of PHOENIX. I am also concerned that the negative lean in events in the STEMI subgroup for cangrelor may be worse than reported and may be associated with worse outcomes with cangrelor in the other subgroups if reporting was complete.*

# CHAMPION Study Comparisons

## *Reasons for Not Pooling CHAMPION Studies*

The CHAMPION Investigators recently published in Lancet a pooled analysis of all three of the CHAMPION studies (PCI, PLATFORM, and PHOENIX). (Steg, Bhatt et al. 2013) The sponsor's integrated summary of efficacy also includes such a pooled analysis. I assert that such a traditional pooled analysis of all three studies is inappropriate because the administration of clopidogrel in the control arm of PLATFORM was consistently by protocol inappropriately delayed until after the completion of PCI. I document the problems with PLATFORM in a parallel review regarding the ethicalness of the cangrelor development program. (Marciniak 2014) I will not repeat the descriptions of the many problems and my analyses of PLATFORM from that review in this review.

*COMMENT: PLATFORM had nominally statistically significantly greater rates of deaths and stent thromboses at 48 hours in its clopidogrel arm. (See Table 1 above.) Its DSMB was considering stopping the trial for these findings when the sponsor convened another committee that recommended stopping the trial for futility. PLATFORM demonstrated that delaying clopidogrel administration until after PCI is inappropriate and hazardous to the patient.*

PHOENIX and PCI are more similar such that we might consider combining them. However, there were five major differences in their design and conduct:

1. PHOENIX allowed a clopidogrel 300 mg loading dose in the clopidogrel arm while the PCI protocol specified a 600 mg loading dose in both arms.

2. The PCI protocol was more explicit regarding administering oral study drug after angiography so oral dosing was typically earlier in PCI than in PHOENIX (median 5 minutes to 1 minute). For example, about 11% of PCI patients received oral study drug after PCI completion compared to 32% of PHOENIX patients. I show the distribution of timing of clopidogrel administration in the clopidogrel arm of PCI in Figure 2.



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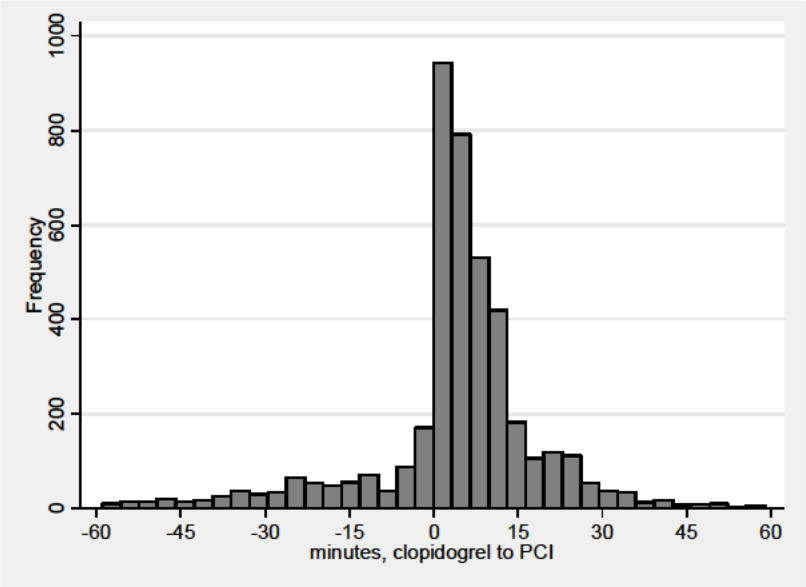
**Figure 2: Timing of Clopidogrel Administration in the Clopidogrel Arm of PCI**




(outliers <-60 and >60 minutes not shown)

PCI does not show the bimodality of the distribution seen with the 600 mg loading dose in PHOENIX.

3. PCI enrolled patients already taking a thienopyridine while PHOENIX excluded such patients.

4. The endpoint definition was different in PCI than in PHOENIX. The pre-specified primary endpoint for PCI did not include stent thrombosis. The sponsor also alleges that in PCI and PLATFORM "The protocol definition of MI was not specific enough to differentiate between evolving pre-procedural biomarker MIs (especially as only one baseline biomarker sample was collected) and MI events that developed during PCI, when the study drug could have an effect."

5. The index event distributions were substantially different. PHOENIX was predominantly stable angina (58%) while PCI was predominantly UA/NSTEMI (74%). The STEMI subgroup in PCI is small enough (996 patients in both arms) that any inferences based on STEMI results from PCI alone are uncertain.

*COMMENT: I judge that there are sufficient differences between PCI and PHOENIX such that we should not combine their results in a traditional pooled analysis. Two of the major differences between PCI and PHOENIX (the allowance of the 300 mg loading dose and the greater delay in clopidogrel timing in PHOENIX) were discretionary changes that would be expected to increase the likelihood that the cangrelor regimen appears superior to the clopidogrel regimen—although not because of any superiority of cangrelor itself. The delay in clopidogrel loading is inappropriate particularly in view of the PLATFORM results.*



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*While I would not combine the studies in a traditional meta-analysis, there are two special topics for which cross-study comparisons are informative (effects by index event type and by delay in clopidogrel loading) and another unique to the PCI study (effects in patients already taking clopidogrel.) I address these three topics below.*

## Comparison of the CHAMPION Studies by Index Event Type

I show the odds ratios for the primary endpoints in the three CHAMPION studies by index event type in Table 18.

**Table 18: Odds Ratios (cangrelor/clopidogrel) for the Primary Endpoints in the CHAMPION Studies by Index Event Type**

| | stable angina | UA/NSTEMI | STEMI |
|---|---|---|---|
| PLATFORM | 0.60 | 0.88 | |
| PHOENIX | 0.83 | 0.61-0.84* | 1.00 |
| PCI | 0.88 | 1.09 | 1.05 |

*0.84 for the site-reported primary endpoint

*COMMENT: With the exception of the low odds ratio for the sponsor's UA/NSTEMI group of PHOENIX—which is not low for the site-reported primary endpoint—there is a pattern to the odds ratios. The odds ratios for the stable angina group are the most favorable. They sort in the same order as the speed of clopidogrel administration, with the lowest odds ratio in PLATFORM with the greatest delay. The odds ratios are neutral to unfavorable for the STEMI subgroups. As I mentioned earlier, ticagrelor showed unfavorable short term results for the STEMI subgroup of PLATO, so I wonder whether there is a biological explanation rather than a chance subgroup variation.*

## Comparison of the CHAMPION Studies by Clopidogrel Timing

As I mentioned earlier, the sponsor has alleged that efficacy endpoint determinations were problematic in PLATFORM and PCI in the ACS subgroups. Hence the most valid cross-trial comparisons for efficacy should be for the stable angina subgroups. For bleeding the type of index event should be unimportant and, because moderate and severe bleeding events were less frequent than the efficacy endpoints, restricting to the stable angina groups is not necessary. I show a scatter plot of the odds ratios of the primary endpoints in the stable angina groups of the three trials vs. the median minutes from clopidogrel administration to PCI in Figure 3 and the odds ratios of GUSTO bleeding rates for the entire studies vs. the median minutes from clopidogrel administration to PCI in Figure 4. I have also included in the figures the results for the PHOENIX subgroups by intended loading dose because the sites consistently administered the 300 mg loading dose earlier than the 600 mg as I showed in Figure 1Figure 2 above.



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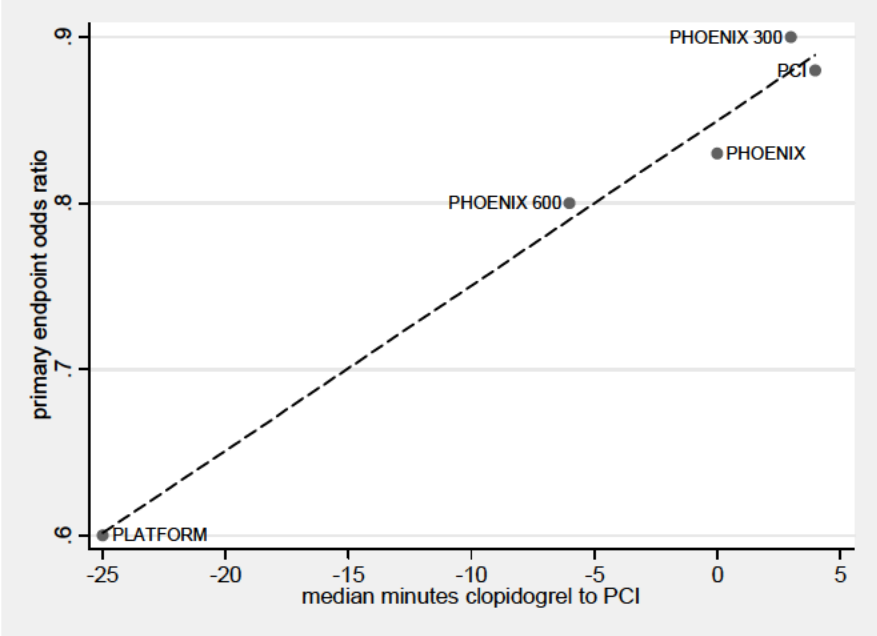
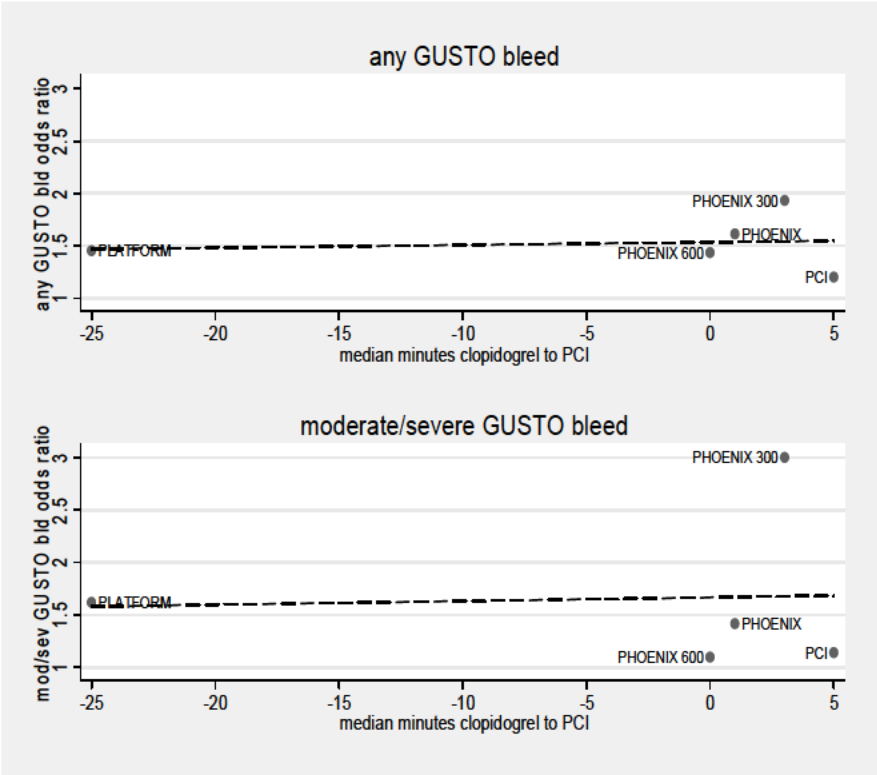
**Figure 3: Odds Ratios of the Primary Endpoints in the Stable Angina Groups of the CHAMPION Trials vs. Median Minutes from Clopidogrel Administration to PCI**




(PHOENIX 300 and 600 are the PHOENIX subgroups by intended loading dose)

**Figure 4: Odds Ratios of GUSTO Bleeding Rates in the CHAMPION Trials vs. Median Minutes from Clopidogrel Administration to PCI**



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*COMMENT: The greater the delay in administering clopidogrel the better cangrelor looked for efficacy. The relative risk of bleeding did not vary greatly by clopidogrel timing. While I did not include error bars or confidence limits in Figure 3, what is striking to me is the pattern of the point estimates. I also find it convincing that the pattern is real because PLATFORM showed more deaths and stent thromboses in the clopidogrel arm with the long delay in administration, the logistic regressions of the PHOENIX data suggest the same pattern, and there is biological plausibility based on the clopidogrel PK/PD data.*

*The various delays of clopidogrel administration likely explain the differing results from the three trials and all of the "superiority" of cangrelor: In PLATFORM, with clopidogrel delayed until after PCI, the clopidogrel regimen performed poorly as also evidenced by its greater death and stent thrombosis rates. In PCI, with the earliest but still not optimal timing for clopidogrel administration, there is no clear evidence for superiority of the cangrelor regimen. In PHOENIX, with intermediate timing, the results for the overall trial are also intermediate and segregate for the different timings in the two intended loading dose groups consistent with the cross-trial comparisons—timing of clopidogrel appears to be the more significant factor than the magnitude of the loading dose.*

*Note that the data do not suggest that administering clopidogrel five minutes before PCI is optimal. There is no suggestion that the diminishing relative efficacy with increasing time of clopidogrel administration before PCI is plateauing at the right of Figure 3. If we extrapolate the line the predicted time at which the odds ratio is 1.0 is about 15 minutes prior to PCI. The data are biologically plausible and consistent with clopidogrel PK and PD that, if the critical time for antiplatelet effect is the start of PCI when plaques and endothelium are eroded, more than five minutes is needed for optimal clopidogrel antiplatelet effect. While we do not know how the cangrelor regimen would compare to clopidogrel administered earlier than 5 or 15 minutes prior to PCI, our expectation based on these data is that the "superiority" of cangrelor would erode more and possibly clopidogrel would be superior to cangrelor. The European guidelines, based on similar analyses of non-randomized timings of clopidogrel in the clopidogrel trials, suggest that administering clopidogrel 6 to 24 hours prior to PCI is advantageous.*

*For prasugrel, the results of the ACCOAST trial suggest that loading prasugrel prior to angiography produced more bleeding but not greater efficacy than loading prasugrel after angiography at the time of PCI. (Montalescot, Bolognese et al. 2013) However, prasugrel is a faster, better platelet inhibitor than clopidogrel so I do not think that the ACCOAST results can be extrapolated to clopidogrel. Furthermore, prasugrel may offer the same advantage of cangrelor (delaying administration until after angiography) plus possibly a mortality benefit early in STEMI.*

*Finally, ticagrelor also may offer advantages over clopidogrel but we do not know whether use with cangrelor affects these advantage. Hence we don't know whether to use ticagrelor with cangrelor or instead of cangrelor.*



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## *Cangrelor in Added to Background Clopidogrel in the PCI Study*

PCI was the only one of the CHAMPION trials that allowed patients already taking a thienopyridine to be randomized. In PCI 34% of patients had taken a thienopyridine (clopidogrel in all but a handful) within the five days prior to randomization. I show the primary endpoint rates by arm and prior clopidogrel use in Table 19.

**Table 19: Primary Endpoint and Bleed Rates by Prior Clopidogrel Use in PCI**

| | primary endpoint | | GUSTO mod/sev | | any GUSTO bld | |
|---|---|---|---|---|---|---|
| | clopidogrel | cangrelor | clopidogrel | cangrelor | clopidogrel | cangrelor |
| no prior clopidogrel | 6.6% | 7.3% | 0.9% | 1.2% | 17.0% | 21.3% |
| prior clopidogrel | 6.8% | 6.5% | 1.3% | 1.0% | 18.3% | 18.4% |

The point estimate for the primary endpoint rate in the cangrelor arm in patients without prior clopidogrel use is slightly higher than those for the other subgroups. However, the interaction between treatment and prior clopidogrel use is not statistically significant. The bleeding rates were also higher in the cangrelor arm in patients without prior clopidogrel use. The interaction between bleeding and cangrelor use is nominally statistically significant as shown in the logistic regression in Table 20.

**Table 20: Logistic Regression of Any GUSTO Bleed in the PCI Study**

```
Logistic regression                               Number of obs   =       8880
                                                  LR chi2(6)      =      43.85
                                                  Prob > chi2     =     0.0000
Log likelihood = -4279.4506                       Pseudo R2       =     0.0051

------------------------------------------------------------------------------
any GUSTO bld| Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
   cangrelor |   1.325022   .0886596     4.21   0.000     1.162164      1.5107
prior clop.  |   1.094032   .0905058     1.09   0.277     .9302779    1.286611
             |
 interaction |   .7651691   .0883201    -2.32   0.020     .6102488     .959418
             |
         age |   .9997847   .0024814    -0.09   0.931      .994933     1.00466
      weight |    .999617   .0015198    -0.25   0.801     .9966428      1.0026
        male |   .7421594   .0462227    -4.79   0.000     .6568758    .8385157
       _cons |   .2646358   .0605331    -5.81   0.000     .1690222    .4143367
------------------------------------------------------------------------------
```

*COMMENT: I do not have a clinical explanation for cangrelor use in patients on clopidogrel leading to both greater efficacy and lower bleeding than cangrelor use in patients not on clopidogrel but nearly identical to clopidogrel use in patients on clopidogrel. There is no strong evidence for an interaction between prior clopidogrel use and cangrelor effect but neither do the data rule one out.*



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## Benefit-Risk of Cangrelor

My interpretation of the CHAMPION trials is that they demonstrated that a cangrelor regimen including a clopidogrel 600 mg loading dose is slightly more efficacious than a bad clopidogrel regimen with delayed clopidogrel loading. The major limitation of any perceived greater efficacy is that clopidogrel was loaded badly ranging from questionably (after angiography) in PCI to horribly (after PCI) in PLATFORM. The CHAMPION trials provide evidence that earlier administration of clopidogrel is better by both the cross-trial comparisons and by logistic regressions of the PHOENIX data. If clopidogrel had been administered consistently earlier in the CHAMPION trials it is possible that clopidogrel would be shown superior to cangrelor.

There are several other limitations of the cangrelor "superior" efficacy:

- The cangrelor regimen was only statistically significantly superior for the sponsor's primary endpoint including predominantly "chemical" MIs. The fact that the primary endpoint rates in PHOENIX in the stable angina arm were about 6% at 48 hours illustrates that the PHOENIX endpoint was not a typical MACE endpoint. For benefit-risk evaluations I favor using the site-reported endpoints which reflect events rather than troponin increases. There is no cangrelor superiority for site-reported events.

- We can't even be confident that the "superiority" is related to cangrelor: The only successful trial was PHOENIX, in which both 300 mg and 600 mg loading doses were used in the clopidogrel arm while only 600 mg was used in the cangrelor arm. In PCI and PLATFORM 600 mg was used in both arms and the cangrelor regimen was not superior to the clopidogrel alone regimen. PHOENIX provides some evidence that the 600 mg loading dose was more effective than the 300 mg loading dose for the sponsor's primary endpoint in the clopidogrel arm. However, it also provides some evidence that the cangrelor regimen with 600 mg loading was superior to the delayed 600 mg loading alone. We don't know whether clopidogrel 600 mg is the optimal loading dose for cangrelor—but the more important question is whether prasugrel or ticagrelor should be used with cangrelor rather than clopidogrel.

- The "superiority" is only statistically significant in the stable angina subgroup. While there are no statistically significant interactions between index event type and treatment in PHOENIX, the point estimate for the odds ratio for the primary endpoint is neutral at 48 hours and unfavorable for cangrelor at 30 days—with mortality unfavorable at 30 days. The PCI and PLATFORM results also suggest that the cangrelor benefit is predominantly for stable angina. Yet stable angina is the condition for which cangrelor offers minimal advantages if any: We can easily load stable angina patients with clopidogrel 24 hours before PCI (as the ESC guidelines recommend) and we can delay CABG for days if the anatomy elucidated at angiography is unsuitable for PCI.



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- Both prasugrel and ticagrelor are superior to clopidogrel for efficacy. We don't know how a cangrelor regimen compares to a prasugrel or ticagrelor regimen. We don't know whether there is any advantage to using cangrelor at all.

There does not appear to be any real superiority for efficacy of the cangrelor regimen over a clopidogrel regimen with clopidogrel administered sufficiently prior to PCI. Furthermore, even the alleged efficacy "superiority" shown in PHOENIX is further limited by the facts that the superiority is predominantly based on "chemical" MIs and not events, is marginal in the UA/NSTEMI subgroup and nonexistent in the STEMI subgroup, and is completely uncertain compared to ticagrelor and prasugrel. For the STEMI subgroup in PHOENIX the 30 day data even provide some evidence of concerning inferiority, i.e., more deaths. The UA/NSTEMI and STEMI subgroups, and not the stable angina subgroup, are the ones for which a rapid onset and offset of platelet inhibition would be clinically useful.

Against this lack of substantial evidence of superiority or even noninferiority regarding efficacy there is consistent evidence that the cangrelor regimen caused more bleeding in all three CHAMPION trials. I will not review all of the bleeding data here but suggest reading the safety section of the primary clinical review. Figure 4 above shows that the odds ratios for GUSTO bleeding, both any and severe, were typically about 1.5 for the CHAMPION trials. Moderate or severe bleeding was uncommon so that the absolute difference in moderate or severe bleeds within 48 hours in PHOENIX was about 0.2%, rising to 0.4% if one considers any transfusion to convey an increased thrombotic risk. Relative bleeding risk did not increase with earlier administration of clopidogrel, so the net clinical "benefit" of the cangrelor regimen compared to an appropriately timed clopidogrel only regimen is a net clinical detriment of an increased net event rate of about 0.2% to 0.4%.

Our laws do not require a new drug to be superior to older drugs in order to be approved. Our laws require substantial evidence of safety and effectiveness. One could argue that the CHAMPION trials provide such evidence despite the lack of clear superiority. I would argue that, for irreversible outcomes such as mortality and MIs, we should not approve a drug if we do not have substantial evidence that such outcomes are not adversely affected. For STEMI patients with cangrelor we lack such substantial evidence and one could argue that the evidence for noninferiority is not substantial for the UA/NSTEMI patients either.

Finally, there is another reason for denying approval of cangrelor: the ethicalness of the cangrelor trials. I discuss that reason in detail in a parallel review. (Marciniak 2014)



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THOMAS A MARCINIAK
01/13/2014

# 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: January 10, 2014

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

NDA: 204-958
Drug: cangrelor

Indication: For the reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with coronary artery disease undergoing percutaneous coronary intervention (PCI)

Subject: Ethicalness of the cangrelor development program

## Summary and Recommendation

Cangrelor is an intravenously (IV) administered $P2Y_{12}$ platelet inhibitor studied in three large clinical outcomes trial in patients undergoing percutaneous coronary intervention (PCI). The ethicalness of all three trials is questionable because all three protocols specified delaying the use of clopidogrel to varying degrees. One of the two earlier trials, PLATFORM, delayed clopidogrel use until after the PCI; PLATFORM showed dramatically higher rates of stent thrombosis and of death in the clopidogrel arm. The last trial, PHOENIX, was unethical because it delayed use of clopidogrel until after coronary angiography or later and because it prohibited routine use of prasugrel, ticagrelor, and glycoprotein IIb/IIIa inhibitors (GPIs). The PHOENIX informed consent documents (ICDs) failed to inform patients regarding the advantages of earlier use of clopidogrel and the use of prasugrel, ticagrelor, and GPIs. The patients in PHOENIX were not informed about "appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject" as required by 21 CFR §50.25.

21 CFR §314.125 states that "(b) FDA may refuse to approve an application for any of the following reasons" including:

> "(16) Any clinical investigation involving human subjects described in the application, subject to the institutional review board regulations in part 58 of this chapter or informed consent regulations in part 50 of this chapter, was not conducted in compliance with those regulations such that the rights or safety of human subjects were not adequately protected."



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Hence we have the authority to refuse approval of this NDA based on ethical grounds alone. However, while such a nonapproval addresses well the ethical issues, it possibly creates a different problem: If PHOENIX did show that cangrelor is a fast-acting and reversible platelet inhibitor with acceptable benefit-risk, then cangrelor would prove a useful addition to the available treatments for managing patients undergoing PCI in the US. We do want to make effective treatments available as rapidly as possible.

Besides the ethical issues the delayed use of clopidogrel has a second implication: Because clopidogrel was used badly in all of the CHAMPION trials, they can not demonstrate that a cangrelor regimen[1] is superior to—or even noninferior to—clopidogrel used appropriately. There are other defects in the trials and problems with the results that I detail in a parallel review on the benefit-risk of cangrelor. (Marciniak 2014) Because the downsides of being inferior are not mere inconvenience but irreversible harm and death, the sponsor needs to document prior to approval the benefit-risk of a cangrelor regimen compared to the approved regimens with superiority claims over clopidogrel.
I recommend not approving cangrelor until another trial succeeds in correcting the flaws that I have documented in this review and in my parallel review on the benefit-risk of cangrelor.

## Background

Cangrelor is a new platelet inhibitor studied for use with PCI for the treatment of stable angina or acute coronary syndromes (ACS, or myocardial infarction (MI) and unstable angina (UA)). Cangrelor is a platelet $P2Y_{12}$ receptor inhibitor like clopidogrel, the first approved $P2Y_{12}$ inhibitor. Cangrelor, unlike orally-administered clopidogrel, is administered intravenously and is a reversible rather than an irreversible inhibitor. Cangrelor has a quick onset and offset and short half-life compared to clopidogrel and other approved $P2Y_{12}$ inhibitors, potentially making it very useful in situations in which these qualities are desirable, such as recent onset ACS.

The PHOENIX trial was a randomized, double-blind, active-controlled trial comparing a bolus and infusion of cangrelor to a loading dose of 300 or 600 mg of clopidogrel. (Bhatt, Stone et al. 2013) The trial was conducted from September 30, 2010, to October 3, 2012, in 11,145 patients who were undergoing either urgent or elective PCI, i.e., in both stable angina and ACS patients, and who did not receive pretreatment with platelet inhibitors (except aspirin). The trial was an international trial conducted in the US, Europe (including Austria, Germany, and the Czech Republic), Brazil, New Zealand, and Thailand. The primary endpoint was the composite of death, MI, ischemia-driven revascularization, or stent thrombosis at 48 hours. The rate of this endpoint was significantly lower in the cangrelor arm than in the clopidogrel arm (4.7% vs. 5.9%; odds ratio, 0.78; 95% confidence interval 0.66 to 0.93; P = 0.005).

[1] In this review for brevity I refer to the "cangrelor" regimen or arm and the "clopidogrel" regimen or arm. The more complete references are the "cangrelor infusion followed by clopidogrel" regimen or arm and the "clopidogrel alone" regimen or arm.



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More details on the trial can be found in the NEJM publication (Bhatt, Stone et al. 2013). NEJM also posted additional trial documentation including the protocol), the financial disclosures (not discussed here), and supplementary material including lists of investigators and sites. The investigators also published a rationale for the design. (Leonardi, Mahaffey et al. 2012)

I assert that the protocol has three serious flaws: (1) Administration of clopidogrel was delayed until after angiography or after PCI. (2) The use of prasugrel and ticagrelor, other approved $P2Y_{12}$ inhibitors with superior efficacy to clopidogrel, was not allowed. (3) The use of GPIs, another class of platelet inhibitors having approved IV formulations, was prohibited except as bailout therapy. These three flaws should have been addressed differently in the protocol and in the ICDs. The editorial accompanying the PHOENIX NEJM publication mentions the first two flaws. (Lange and Hillis 2013). Furthermore, if all three of these approved alternative or supplemental therapies were not discussed in the informed consent document (ICD), then the trial was unethical. Because these flaws are the primary focuses of this review, I discuss them in detail below.

PHOENIX was not the first clinical outcomes trial of cangrelor. Two similar trials preceded it: CHAMPION PCI and CHAMPION PLATFORM. (Bhatt, Lincoff et al. 2009; Harrington, Stone et al. 2009) Both were conducted in patients undergoing PCI, both used clopidogrel with a 600 mg loading dose, and both had a primary endpoint of death, MI, or ischemia-driven revascularization at 48 hours. The major difference was that in CHAMPION PCI clopidogrel was given prior to the PCI (but after angiography except early use was allowed in STEMI) while in PLATFORM clopidogrel administration was delayed until after the PCI. CHAMPION PCI included ST segment elevation MI (STEMI) patients while PLATFORM excluded them; both included 5-15% stable angina. At second planned interim analyses (at 70% enrollment) the sponsor terminated both trials early allegedly because the estimated conditional power to demonstrate superiority was low, i.e., for futility. I summarize relevant published results in Table 1.

**Table 1: Cangrelor CHAMPION Trials Results at 48 Hours**

| | | PCI | PLATFORM |
|---|---|---|---|
| N | | 8877 | 5301 |
| clopidogrel within 5 days | | 34% | 0% |
| study clopidogrel timing | | immediately prior to PCI | after PCI |
| primary endpoint | cangrelor | 7.5% | 7.0% |
| | clopidogrel | 7.1% | 8.0% |
| efficacy OR* | | 1.05 NS† | 0.87 NS† |
| deaths | cangrelor | 0.2% | 0.2% |
| | clopidogrel | 0.1% | 0.7% |
| death OR* | | 1.59 NS† | 0.33 (p=0.02) |
| stent thrombosis | cangrelor | 0.2% | 0.2% |
| | clopidogrel | 0.3% | 0.6% |
| stent thrombosis OR* | | 0.63 NS† | 0.31 (p=0.02) |
| bleeding ORs* | | 1.2-1.4 | 1.3-1.6 |



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* OR = odds ratio cangrelor:clopidogrel; †NS = not significant

For all three CV endpoints the rate that is substantially higher than those in the other three arms is the one in the clopidogrel arm of PLATFORM. In that latter arm clopidogrel use was delayed. For the PCI trial in which clopidogrel was given earlier—although still not optimally—the point estimates for the primary endpoint and death actually favor clopidogrel. For cangrelor the claim is that "When a bolus of cangrelor is administered, the antiplatelet effect is immediate." (Bhatt, Stone et al. 2013) For clopidogrel the label states that "Dose-dependent inhibition of platelet aggregation can be seen 2 hours after single oral doses of Plavix." (sanofi-aventis and Bristol-Meyers-Squib 2010) Hence we would expect that the differing effects in CHAMPION PCI compared to PLATFORM are related to the delayed use of clopidogrel in PLATFORM. The CHAMPION trials confirmed that delaying clopidogrel use is bad. These results should have been presented explicitly to the sites and their IRBs.

Because clopidogrel use was delayed longer in PLATFORM than it was in PHOENIX, we should also question whether PLATFORM was unethical. Furthermore, its termination would appear to be justified on the basis of safety—deaths and stent thromboses with delayed clopidogrel use—rather than futility. I discuss more details regarding the conduct of PLATFORM below after presenting the evidence regarding the timing of clopidogrel.

## Timing of Clopidogrel

I have presented above the evidence from the CHAMPION trials that delaying clopidogrel use is bad. Just as the comparison of the CHAMPION trials is not a randomized comparison, the overall evidence regarding the effects of different timings of clopidogrel administration has the same limitation: Despite the fact that clopidogrel was approved initially in 1997, there has never been an adequately powered clinical outcomes trial addressing timing of clopidogrel administration. Hence we depend upon the interpretation of small trials and non-randomized data, e.g., comparing CHAMPION PCI to PLATFORM or comparing outcomes of subgroups of patients with different, non-randomized clopidogrel timings in clinical trials designed for other purposes. The necessity of interpreting non-randomized data has led to differences between the US and Europe in the interpretation of the importance of clopidogrel timing, as I present next.

### *European Guidelines for Revascularization and MI*

The Europeans appear to consider valid the non-randomized timing comparisons in the clopidogrel trials, such as CREDO, that suggest that earlier use of clopidogrel is better. (Steinhubl, Berger et al. 2006) The 2007 European Society of Cardiology (ESC) guidelines for non-STEMI (NSTEMI) ACS discuss delaying clopidogrel and recommend against it:

> "Pre-treatment of unselected patients with clopidogrel before angiography results in better outcome of PCI. The approach of postponing clopidogrel administration until coronary anatomy is known in patients submitted to very early invasive angiography is not based on evidence. The potential advantage of this approach is to avoid



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> increased bleeding risk in patients requiring immediate surgery. However, this situation is rare, and frequently surgery can be deferred for a few days. Therefore, postponing clopidogrel to after angiography cannot be recommended, because the highest rates of events are observed in the early phase of NSTE-ACS." (Bassand, Hamm et al. 2007)

The ESC/European Association for Cardio-Thoracic Surgery (EACTS) 2010 Guidelines on myocardial revascularization (the European guidelines in effect during the PHOENIX trial) had the following recommendation regarding timing of clopidogrel:

> "Since the vast majority of PCI procedures eventually conclude with stent implantation, every patient scheduled for PCI should be considered for pre-treatment with clopidogrel, regardless of whether stent implantation is intended or not. To ensure full antiplatelet activity, clopidogrel should be initiated at least 6 h prior to the procedure with a loading dose of 300 mg, ideally administered the day before a planned PCI." (Wijns, Kolh et al. 2010)

The 2008 and 2012 ESC guidelines for STEMI recommend immediate treatment with clopidogrel:

> "Based on these data, clopidogrel should be given as soon as possible to all patients with STEMI undergoing PCI." (Van de Werf, Bax et al. 2008; Steg, James et al. 2012)

The 2011 ESC guidelines for NSTEMI ACS recommend immediate treatment with a $P2Y_{12}$ inhibitor:

> "A $P2Y_{12}$ inhibitor should be added to aspirin as soon as possible and maintained over 12 months, unless there are contraindications such as excessive risk of bleeding.
>
> "Ticagrelor (180-mg loading dose, 90 mg twice daily) is recommended for all patients at moderate-to-high risk of ischaemic events (e.g. elevated troponins), regardless of initial treatment strategy and including those pre-treated with clopidogrel (which should be discontinued when ticagrelor is commenced).
>
> "Prasugrel (60-mg loading dose, 10-mg daily dose) is recommended for $P2Y_{12}$-inhibitor-naïve patients (especially diabetics) in whom coronary anatomy is known and who are proceeding to PCI unless there is a high risk of life-threatening bleeding or other contraindications.
>
> "Clopidogrel (300-mg loading dose, 75-mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel." (Hamm, Bassand et al. 2011)

Note that the 2011 ESC guidelines recommend ticagrelor or prasugrel first rather than clopidogrel.



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The PHOENIX investigators should have been familiar with these ESC guidelines. In fact, some of the PHOENIX investigators chaired some of the ESC guideline committees and others co-authored the guidelines. In a non-exhaustive search I identified the following PHOENIX investigators who participated in the ESC guidelines:

- Christian Hamm (Germany, a member of the PHOENIX Executive Committee) was the co-chair for the 2007 ESC ASC guidelines and the chairperson for the 2011 ESC ACS guidelines.

- Magnus Ohman (US, a Duke member of the Data and Safety Monitoring Committee) and Freek Verheugt (the Netherlands, a member of the Data and Safety Monitoring Committee) were co-authors or document reviewers of both the 2007 and 2011 ESC ACS guidelines.

- Kurt Huber (Austria National Coordinator) and Petr Widimsky (Czech Republic National Coordinator) were co-authors of the 2011 ESC ACS and the 2010 ESC revascularization guidelines. Kurt Huber was a document reviewer and Petr Widimsky was a member of the Executive Committee for the 2007 ESC ACS guideline.

- Frans Van de Werf (Belgium, a member of the Data and Safety Monitoring Committee) was the chairperson for the 2008 ESC STEMI guideline. Kurt Huber, Frank Verheugt, and Gabriel Steg (France, a PHOENIX Executive Committee member) were co-authors and Petr Widimsky was a member of the committee.

- Kenneth Mahaffey (US, a Duke member of the PHOENIX Executive Committee) was a co-author of the 2012 ESC STEMI guideline as were Kurt Huber, Gabriel Steg, and Petr Widimsky.

Note that some of the investigators who are co-authors of ESC guidelines are from countries, e.g., the US, Austria, Germany, and the Czech Republic, in which PHOENIX was conducted.

While local standards of practice could differ, in Europe all of the published guidelines from 2007 to the present recommend against delaying clopidogrel administration. Regardless, many of the investigators, including US ones, appear to have endorsed the concept that delaying clopidogrel use is bad. The investigators should have explicitly described in the ICD the negative impact of delaying clopidogrel. They should have informed the sponsor that all IRBs should be explicitly informed regarding this issue.

## *US Guidelines for PCI and MI*

Several US medical professional organizations have issued guidelines for PCI and MI in two different series: (1) The American College of Chest Physicians (ACCP) has issued a series of anti-thrombotic guidelines, two of which in 2008 addressed antithrombotic therapy for non-ST-segment elevation ACS and for STEMI. (2) The American College of Cardiology (ACC) and the American Heart Association (AHA) have issued joint



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guidelines on many cardiology topics, including PCI and MI. The Society for Cardiovascular Angiography and Interventions also participated in the ACC/AHA PCI guidelines. I reference these joint guidelines as the "ACC" guidelines.

The 2008 ACCP ACS guideline recommended "upstream", i.e., early, clopidogrel administration:

> "For NSTE ACS patients who are at at least moderate risk for an ischemic event and who will undergo an early invasive management strategy, we recommend "upstream" treatment either with clopidogrel (300 mg po bolus, followed by 75 mg/d) or a small-molecule IV glycoprotein (GP) IIb/IIIa inhibitor (eptifibatide or tirofiban) [Grade 1A]. For NSTE ACS patients who are at least moderate risk for an ischemic event and for whom an early conservative or a delayed invasive strategy of management is to be used, we recommend "upstream" treatment with clopidogrel (300 mg oral bolus, followed by 75 mg/d) [Grade 1A]. For NSTE ACS patients who undergo PCI, we recommend treatment with both clopidogrel and an IV GP IIb/IIIa inhibitor (Grade 1A). We recommend a loading dose of 600 mg of clopidogrel given at least 2 h prior to planned PCI followed by 75 mg/d (Grade 1B)." (Harrington, Becker et al. 2008)

The 2008 ACCP STEMI guideline recommended immediate clopidogrel for STEMI patients:

> "However, given the very small chance that a patient would require emergent coronary artery bypass surgery coupled with the apparent benefit of clopidogrel administered 2 to 8 days prior to (nonprimary) PCI in patients with recent STE MI, clopidogrel could be administered immediately after the diagnosis of STE MI has been made and need not await visualization of the coronary anatomy in a patient about to undergo primary PCI." (Goodman, Menon et al. 2008)

Robert Harrington, the Duke co-Principal Investigator for PHOENIX, was the first author of the ACCP UA/NSTEMI guideline and the anchor author of the STEMI guideline. Gabriel Steg, a member of the PHOENIX Executive Committee, was a co-author of both and Magnus Ohman, a Duke member of the Data and Safety Monitoring Committee, was a co-author of the ACCP STEMI guideline. I could not find any updates to these guidelines.

The ACC guidelines have evolved from a position recommending early clopidogrel use in the guidelines prior to 2007 (similar to the ESC recommendations) to one recommending either early use or "when PCI is performed", with some ambiguity regarding the necessity of early use or what "when PCI is performed" means. The 2005 ACC PCI guidelines had the following recommendation:

> "A loading dose of clopidogrel should be administered before PCI is performed. (Level of Evidence: A) An oral loading dose of 300 mg, administered at least 6 hours before the procedure, has the best established evidence of efficacy. (Level of Evidence: B)" (Smith, Feldman et al. 2006)



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The 2007 ACC UA/NSTEMI guidelines were similar:

> "For UA/NSTEMI patients in whom an initial invasive strategy is selected, antiplatelet therapy in addition to aspirin should be initiated before diagnostic angiography (upstream) with either clopidogrel (loading dose followed by daily maintenance dose) or an intravenous GP IIb/IIIa inhibitor. (Level of Evidence: A)" (Anderson, Adams et al. 2007)

The 2007 ACC PCI update changed the PCI recommendation to the following:

> "A loading dose of clopidogrel, generally 600mg, should be administered before or when PCI is performed. (Level of Evidence: C) Inpatients undergoing PCI within 12 to 24 hours of receiving fibrinolytic therapy, a clopidogrel oral loading dose of 300 mg may be considered. (Level of Evidence: C)" (King, Smith et al. 2008)

However, the discussion of timing of clopidogrel in this guideline does not appear to justify this vague recommendation:

> "There is agreement that the loading dose should be administered before PCI. What is unclear is the precise time when the loading dose must be given to achieve a desirable therapeutic effect. Evidence from the CREDO (Clopidogrel for the Reduction of Events During Observation) trial suggests that with a 300-mg dose, 6 hours is the minimum time. With the 600-mg dose, 2 hours may be sufficient, although maximal platelet inhibition may not be achieved until 3 to 4 hours."

The 2011 ACC UA/NSTEMI update changed its recommendation to the following:

> "Patients with definite UA/NSTEMI at medium or high risk and in whom an initial invasive strategy is selected should receive dual-antiplatelet therapy on presentation. (Level of Evidence: A) ASA should be initiated on presentation. (Level of Evidence: A) The choice of a second antiplatelet therapy to be added to ASA on presentation includes 1 of the following:
>
> "Before PCI:
> - Clopidogrel (Level of Evidence: B); or
> - An IV GP IIb/IIIa inhibitor. (Level of Evidence: A) IV eptifibatide or tirofiban are the preferred GP IIb/IIIa inhibitors.
>
> "At the time of PCI:
> - Clopidogrel if not started before PCI (Level of Evidence: A); or
> - Prasugrel (Level of Evidence: B); or
> - An IV GP IIb/IIIa inhibitor. (Level of Evidence: A)" (Wright, Anderson et al. 2011)



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In general STEMI is viewed as a condition in which rapid action is indicated, i.e., primary PCI as rapidly as possible is indicated because "time is myocardium." The 2009 ACC update for STEMI, however, has the following complicated recommendations:

> "A loading dose of thienopyridine is recommended for STEMI patients for whom PCI is planned. Regimens should be 1 of the following:
> a. At least 300 to 600 mg of clopidogrel should be given as early as possible before or at the time of primary or nonprimary PCI. (Level of Evidence: C)
> b. Prasugrel 60 mg should be given as soon as possible for primary PCI. (Level of Evidence: B)
> c. For STEMI patients undergoing nonprimary PCI, the following regimens are recommended:
>
> (i) If the patient has received fibrinolytic therapy and has been given clopidogrel, clopidogrel should be continued as the thienopyridine of choice (Level of Evidence: C);
> (ii) If the patient has received fibrinolytic therapy without a thienopyridine, a loading dose of 300 to 600 mg of clopidogrel should be given as the thienopyridine of choice (Level of Evidence: C);
> (iii) If the patient did not receive fibrinolytic therapy, either a loading dose of 300 to 600 mg of clopidogrel should be given or, once the coronary anatomy is known and PCI is planned, a loading dose of 60 mg of prasugrel should be given promptly and no later than 1 hour after the PCI. (Level of Evidence: B)" (Kushner, Hand et al. 2009)

The PHOENIX investigators were typically not co-authors of the ACC guidelines. However, other physicians from their institutions were. For example, Duke physicians co-authored the 2007 and 2011 UA/NSTEMI updates as well as the 2009 STEMI/PCI update.

These guidelines suggest that early clopidogrel use is better. The ACCP guidelines are consistent with the ESC guidelines in stating that clopidogrel use should not be delayed while the later ACC guidelines are somewhat ambiguous regarding this issue. However, even if one believes that there is equipoise between early vs. delayed clopidogrel use in general, the results of CHAMPION PCI and PLATFORM tip the balance towards early clopidogrel use being preferable in cangrelor trials.

## *Other Investigator or Site Publications*

In addition to guidelines some investigators published articles expressing their opinions about clopidogrel timing (or prasugrel use). Publications by investigators are not the only relevant publications. Publications by other staff at the sites should reveal the local practices at the sites. I found the following examples of such investigator or site publications:

- Robert Harrington, the Duke PHOENIX co-Principal Investigator, co-authored a review of new antiplatelet agents published in 2009. (Sellers, Tricoci et al. 2009) He wrote that "The benefits of clopidogrel for patients with acute coronary



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syndromes and patients undergoing percutaneous coronary intervention (PCI) have been established by large, well done randomized clinical trials" but "The need for liver metabolism to convert clopidogrel from the prodrug to the active form delays the onset of the antiplatelet effect, which may not be optimal for the treatment of acute coronary thrombosis or in the setting of coronary intervention." This publication suggests that delaying clopidogrel is bad.

- Depak Bhatt, the other PHOENIX co-Principal Investigator who is affiliated with the VA Boston Healthcare System (one of the PHOENIX sites), co-authored a review "Antiplatelet Agents in Acute Coronary Syndromes" published in March 2010. (Sakhuja, Yeh et al. 2010) He wrote that "While clopidogrel pretreatment 2-24 hours before PCI has been shown to be beneficial, practitioners are often hesitant to initiate clopidogrel in NSTE-ACS before defining the anatomy given concerns over coronary artery bypass grafting (CABG)-related bleeding if patients require surgical revascularization" and "Earlier initiation of clopidogrel must be reconciled with delays in surgical revascularization. It is contraindicated (class III) to use clopidogrel around the time of CABG. Preliminary data suggest that a 600-mg load at the time of angiography may be sufficient, which may alter initiation of clopidogrel in NSTE-ACS." This review implies that, in 2010, the standard of practice was clopidogrel pretreatment 2-24 hours before PCI.

- Depak Bhatt also authored a perspective on "Prasugrel in Clinical Practice" published in NEJM on September 3, 2009. (Bhatt 2009) He wrote that "Prasugrel represents an advance in antiplatelet therapy for acute coronary syndromes. TRITON–TIMI 38 supports its use in patients with such syndromes when there is a very high probability of PCI, such as in myocardial infarction with ST-segment elevation or after coronary angiography in patients with non–ST-segment elevation myocardial infarction." (After angiography in NSTEMI patients was the way TRITON was conducted because prasugrel, like cangrelor, has a more rapid onset than clopidogrel.[2]) This publication supports allowing prasugrel use in PHOENIX.

- Eric Topol, a cardiologist and Senior Consultant, Scripps Clinic, Division of Cardiovascular Diseases (the Scripps Green Hospital was a PHOENIX site), co-authored a meta-analysis of three trials of clopidogrel pretreatment published in 2008. He wrote that "We have previously shown that pretreatment with clopidogrel before PCI significantly reduces cardiovascular death and ischemic complications after PCI" and concluded that "Clopidogrel pretreatment before PCI is beneficial and safe regardless of whether a GPI is used at the time of PCI." This publication strongly supports early use of clopidogrel.

- John Kim and other Duke staff performed an observational study regarding clopidogrel use and bypass surgery published in 2008. (Kim, Newby et al. 2008) They concluded "Clopidogrel administration ≤5 days before CABG was not

[2] The prasugrel TRITON trial is another trial whose ethicalness is questionable because of forced delayed use of clopidogrel.



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significantly associated with reoperation for bleeding or a bleeding composite and only weakly with red cell transfusion after surgery. The impact of withholding clopidogrel acutely in those for whom clopidogrel has proven benefits and the impact of delaying CABG to prevent bleeding among patients treated with clopidogrel should be viewed in the context of other stronger determinants of bleeding." This publication supports early clopidogrel use.

- John Alexander of Duke authored a review of antiplatelet therapy published in 2009. (Alexander 2009) He quoted the guidelines that "For patients in whom an early invasive strategy is planned, therapy with either clopidogrel or a glycoprotein IIb/IIIa inhibitor should be started upstream (before diagnostic angiography) in addition to aspirin (class I, level A)." He described "In my practice, if a patient is high risk and has a low likelihood of early CABG, I use both clopidogrel and a glycoprotein IIb/IIIa inhibitor upstream (prior to going to the catheterization laboratory)." This publication supports early clopidogrel use and use of GPIs.

- Petr Widimsky, the Czech national coordinator, published a study alleging to show that pretreatment with clopidogrel was not beneficial in patients with stable angina undergoing PCI. (Widimsky, Motovska et al. 2008) However, the study was powered (80%) to detect a decrease in absolute incidence of the primary endpoint (death/MI/stroke/re-intervention within 7 days) from 3% to 0.5%, an 83% relative decrease. The observed decrease was 20%, from 1% to 0.8%, so the study was grossly underpowered. The efficacy endpoints numerically but not statistically significantly favored pretreatment but bleeding was higher with pretreatment. The authors state that "Our results cannot be extrapolated to patients with acute coronary syndromes, in whom the benefit from early clopidogrel therapy is unequivocal." While their results in stable angina are arguable, these Czech investigators believed that early clopidogrel was beneficial in ACS.

The publications by the PHOENIX investigators and by site staff support the early use of clopidogrel.

## Ethicalness of CHAMPION PLATFORM

PLATFORM enrolled patients from October 2006 to May 2009. At its start both the European and US guidelines recommended early use of clopidogrel (see the above discussion of the guidelines) so it is questionable why PLATFORM was allowed to proceed delaying clopidogrel use until after the PCI.

On July 6, 2005, the FDA and the sponsor discussed plans for the two CHAMPION trials at the end-of-phase-2 meeting chaired by Dr. Robert Temple. For the proposed placebo-controlled trial (PLATFORM) the sponsor estimated that about 10% of the patients would present with NSTEMI or ACS—STEMI patients were to be excluded. The planned protocol discouraged the use of GPIs, which the FDA advised against. The minutes state that "Once the procedure is stopped patients will all get clopidogrel" but



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there is no reported discussion of delaying clopidogrel use in the FDA minutes. The sponsor's minutes state that "The protocol defined use of a clopidogrel loading dose following the procedure was discussed. It was noted that this means the patients will be on different therapies only during the short time of the PCI (1-2 hours)." There is no mention in either version of the minutes that the guidelines recommended administering clopidogrel prior to the start of the procedure.

The CHAMPION Executive Committee (EC) and the DSMB did discuss concerns about the delayed use of clopidogrel. The EC meeting minutes from March 13, 2006, stated the following:

> "Site Selection – EC advised careful scrutiny of potential sites to ensure:
> - Plavix admin post procedure is true 'standard of practice'; **Action**: provide market data/ local guidelines/ site statistics where feasible. [bolding in original]
> - Sites are motivated to enroll correct patients
> - Number of developing countries – limit? Increase number of NA sites."

The DSMB discussed the issue of delaying clopidogrel use at its open meeting on March 24, 2007. The minutes state the following:

> "It was pointed out that it is the DSMB role to ensure safety of patient. In a country where clopidogrel use pre-procedure is pretty standard there is a concern over the ethics of excluding clopidogrel pre-procedure in the U.S. Dr. Bhatt acknowledged that criticism will be there. There is no FDA indication that clopidogrel is required pre-procedurally. It is not evidence-based medicine, therefore it is not considered unethical. Clopidogrel will be given in PLATFORM two hours after start of cangrelor."

Despite this directive the discussion apparently continued:

> "The issue of not allowing pre-procedural clopidogrel continued to arise. It was recommended that TMC survey their PLATFORM sites and determine what is SOC. TMC responded by saying that they had done this during the site selection process. Sites couldn't participate if they couldn't treat patients per protocol. Each site IRB reviewed and approved the protocol."

The sponsor implemented the protocol unchanged with the delayed clopidogrel use. The sponsor amended the protocols on May 8, 2007, to restrict enrollment to patients with ACS and to exclude patients with upstream GPI use. The amended protocols also discouraged concomitant use of GPIs, from "These agents should be administered per the site standard of care" to "The use of these agents should be considered carefully based on the anti-platelet effect already provided by the study drug, i.e. clopidogrel 600 mg or cangrelor." The estimated enrollment in PLATFORM was increased from 4400 to 6400. The reported justification was to increase the estimated event rate to be consistent with



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the expected event rate. At this time enrollment in PCI was about 39% and in PLATFORM about 20% of the original estimated enrollment.

The sponsor discussed with the FDA at a meeting on December 7, 2007, a proposal for an adaptive sequential test to occur at the second planned interim analysis. The meeting minutes state that "The statistical design and calculation of sample size for both of these studies assumed that at least 60% of the patients enrolled in these studies will be a higher risk ACS patients, such as Troponin + patients" while, as noted above, at the EOP2 meeting the estimate for NSTEMI/ACS patients in PLATFORM was 10%. The sponsor presented a complex approach for assessing futility for the 70% enrollment interim analyses based on conditional probabilities; the FDA statisticians agreed that the approach preserved alpha. The meeting minutes also state that clopidogrel in PLATFORM was to be delayed until after the PCI but do not report any discussion of this topic. The focus of the discussion was upon the interim analyses.

*COMMENT: The meeting minutes summarized above document that some FDA staff were aware of and did not object to the delayed clopidogrel use in PLATFORM (and PCI). This lack of objection seems inappropriate. For the original discussion at the EOP2 meeting the sponsor presented PLATFORM as primarily enrolling non-ACS patients, i.e., ones for whom delayed use of clopidogrel might be acceptable. The FDA staff reviewing the one amendment appear to have missed the implications of restricting enrollment to ACS patients in that amendment.*

Besides the guidelines and publications authored by the CHAMPION investigators a CHAMPION newsletter documents that the investigators and sites knew the problems of delaying clopidogrel. The September 2008 CHAMPION CANGRELOR Newsletter had a "Q&A" article featuring a cangrelor investigator. The response for question 1, "Other than we are conducting a research protocol, what is the rationale for not loading subjects with clopidogrel?", was "Delayed and variable onset of oral PLAVIX – In some situations it isn't possible to adequately load a patient – minimum of 2 hour delay after 600mg and 15 to 24 hours after 300mg". (See Attachment 1).

*COMMENT: If one can't load patients in less than 2 hours, why did CHAMPION allow loading at best 30 minutes before PCI and at worst after PCI? The wording of the response for question 1 also implies a mistaken belief that, because they "are conducting a research protocol", inappropriate care is ethical.*

There is an additional ethical issue with PLATFORM: Its NEJM publication states that "After a second interim analysis, trial enrollment was terminated because the review committee decided that the trial was unlikely to show the superiority of cangrelor." However, the results in Table 1 suggest that PLATFORM should have been terminated for safety in the clopidogrel arm rather than or in addition to futility as the NEJM article reported. Hence I examined the DSMB minutes to determine whether the DSMB had noted any problems during the trial.



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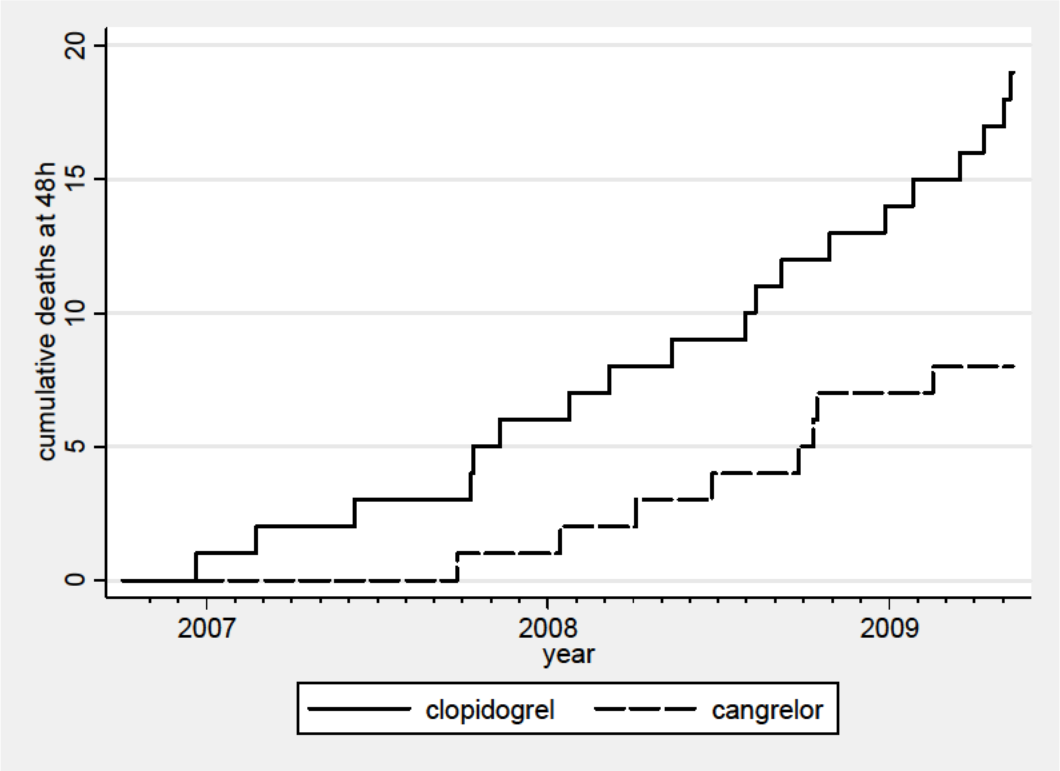
The DSMB, at its November 8, 2008, meeting for reviewing the PLATFORM results at 50% enrollment, noted a mortality signal: "The all-cause mortality rates are significantly higher in the placebo arm ($p \approx 0.04$ according to Dr. Hasselblad, using Fishers mid-p formula). . . The significant mortality difference noted at 48 hours was also seen at 30 days, though not statistically significant ($p \approx 0.06$)." However, the DSMB also noted then that "The overall trend in the composite endpoint was still present at 30 days, with the cangrelor arm having a higher event rate than the placebo arm." The DSMB made the following recommendation to the sponsor:

> "The DSMB did note a potential safety signal with respect to mortality differences between the treatments. In order to properly protect the patients enrolling in the PLATFORM study, the DSMB has asked to reconvene after enrollment of 70% of patients to determine if the mortality differences persist."

The DSMB did not meet again. I analyzed the 48-hour mortality results in PLATFORM by enrollment date to determine whether the mortality trend changed such that the DSMB shouldn't have met. I show the results of that analysis in Figure 1.

**Figure 1: Cumulative Deaths at 48 Hours by Enrollment Date in PLATFORM**




From the date of the last DSMB meeting (November 8, 2008) to the date of 70% enrollment (February 19, 2009) the mortality safety signal in PLATFORM strengthened. The DSMB should have reviewed the mortality findings at the time.



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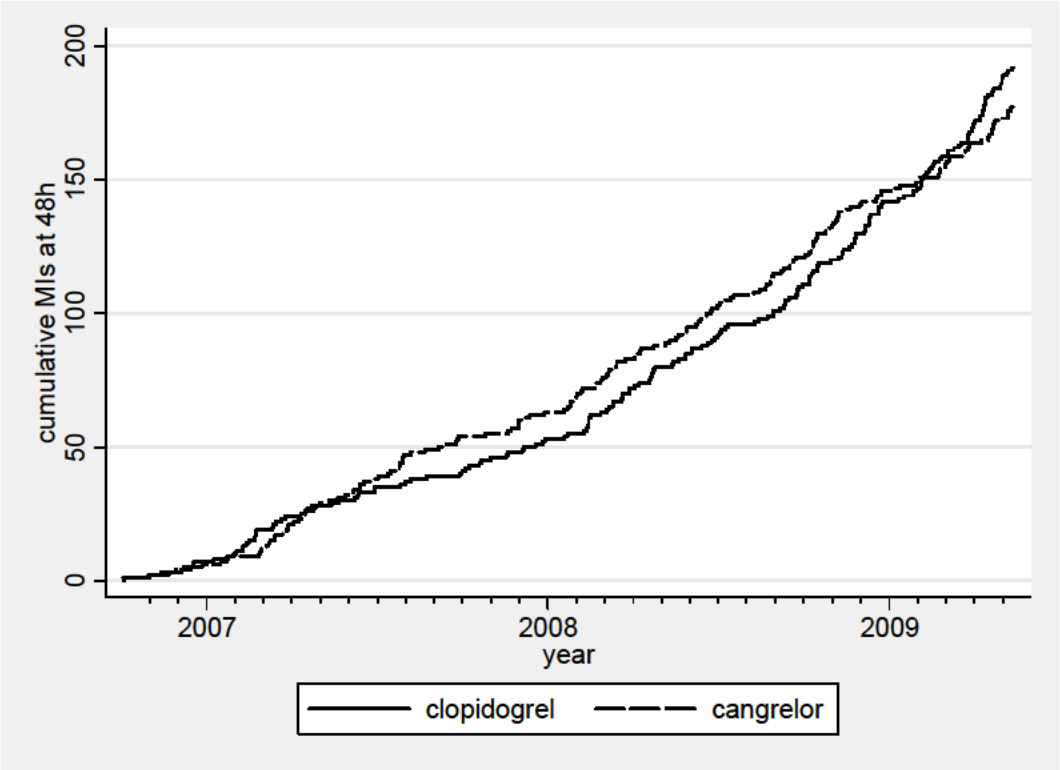
One reason why the DSMB may not have recommended terminating the trial early was that reported myocardial infarction (MI) results numerically favored clopidogrel despite mortality and ischemia-driven revascularization favoring cangrelor. I show the cumulative adjudicated MIs at 48h by enrollment date in Figure 2.

**Figure 2: Cumulative Adjudicated MIs at 48 Hours by Enrollment Date in PLATFORM**




The relatively neutral adjudicated MI results do appear inconsistent with the dramatic difference in deaths. Because Figure 2 portrays adjudication MIs and because I have observed inconsistencies between adjudicated and site-reported MIs, I also analyzed site-reported MIs. The CRFs included a "MI Header" CRF with a single question "Did patient experience an MI?" with the directions for the 48 hours follow-up of "Select YES or NO to indicate if this patient experienced a myocardial infarction since randomization and prior to the 48-hour follow up." I show the cumulative site-reported MIs at 48h (from the MI Header CRF) by enrollment date in Figure 3.



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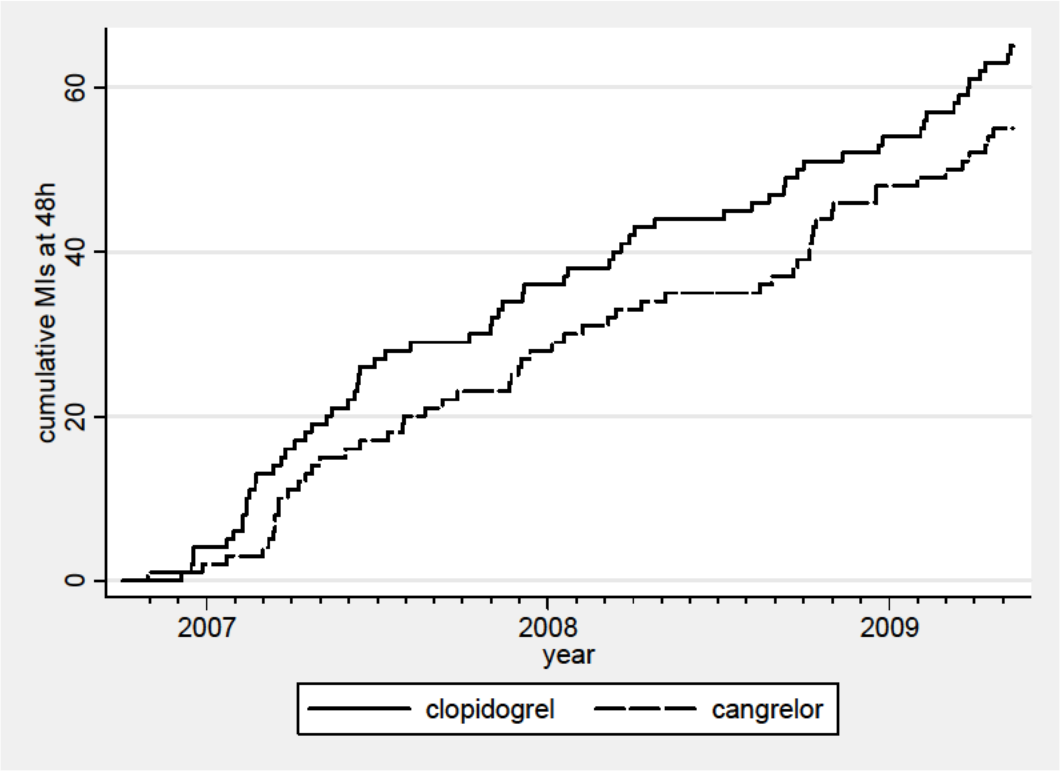
**Figure 3: Cumulative Site-Reported MIs at 48 Hours by Enrollment Date in PLATFORM**




The sites reported fewer MIs than were adjudicated, but the site-reported MI results favor cangrelor and hence are consistent with the mortality results. The sponsor and the investigators have claimed that there were problems with the MI definition used for adjudication. The inconsistency of the adjudicated MIs and the consistency of the site-reported MIs with other endpoints would appear to confirm a problem with the adjudicated MIs. Regardless, the DSMB should have been greatly concerned about the mortality results because of another potentially explanatory event: stent thrombosis. I show the cumulative stent thromboses at 48h by enrollment date in Figure 4.



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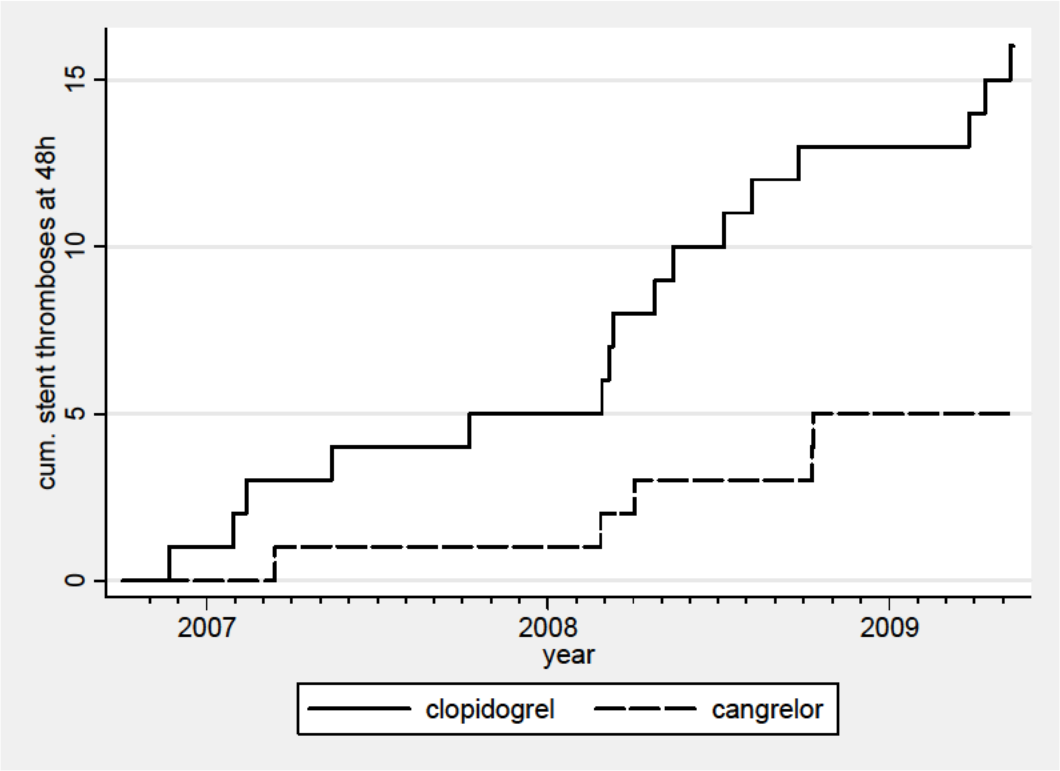
**Figure 4: Cumulative Stent Thromboses at 48 Hours by Enrollment Date in PLATFORM**




*COMMENT: PLATFORM demonstrates the dangers of delaying clopidogrel use.* (b) (4) [redacted].

[redacted] (b) (4). Instead, the CHAMPION Interim Analysis Review Committee (IARC), chaired by Dr. Califf from Duke, met on May 1, 2009, to review the 70% enrollment results for it. (See Attachment 2 for the minutes.) The unusual charge given to the committee by the sponsor was stated as follows:

> "Dr. Meanwell [TMC] had written to Dr. Califf encouraging the IARC to play an expanded role in the PLATFORM trial, allowing them more flexibility to review any information they considered of interest, above and beyond the guidelines written in the IARC Charter."

Per the minutes an IARC statistician member initially noted that mortality results in both PLATFORM (6:14) and PCI (1:3) favored cangrelor but later a DCRI statistician "reported that the current PCI trial mortality favored the clopidogrel arm (8 cangrelor and 5 clopidogrel)." The IARC member reviewed the interim futility analyses and the minutes record that "Based on this analysis, the recommendation prescribed by the protocol is to terminate the trial for futility."



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(b) (4)

The IARC appears to have ignored the possibility that the data supported an adverse effect of delayed clopidogrel or that patients were being denied a better treatment, i.e., clopidogrel administered earlier.

The minutes record further that "Under the expanded IARC role, the IARC wanted to look at the bleeding data as presented to the DSMB. The DSMB had determined that they did not have any safety concerns after reviewing this information." The minutes do not relate that the DSMB had safety concerns regarding the mortality data.

The IARC provisionally recommended that the study be terminated due to futility, (b) (4) The sponsor terminated both trials allegedly for futility.

*COMMENT:* (b) (4) *the sponsor and the CHAMPION principal investigators should have presented explicitly the results regarding mortality and regarding stent thromboses to the IRBs for PHOENIX. The sponsor and principal investigators should have discussed the likelihood that these negative results reflected delayed use of clopidogrel and raised the question of what is the optimal timing for clopidogrel use, i.e., is just prior to PCI adequate?*

## Availability and Benefit-Risk of Prasugrel

PHOENIX specified clopidogrel as the only comparator and excluded patients administered any $P2Y_{12}$ antagonist within 7 days prior to randomization. However, prasugrel, like clopidogrel, is an approved thienopyridine antagonist of the platelet $P2Y_{12}$ receptor. Prasugrel, like clopidogrel, is administered as a prodrug that requires metabolic activation to an active metabolite. The advantage of prasugrel is that its metabolic activation is less susceptible to metabolic inhibition and pharmacogenomic variation than clopidogrel's activation. Prasugrel is supposed to produce faster, more consistent platelet inhibition than clopidogrel and pharmacodynamic studies and the TRITON outcomes trial support this premise. However, in the marketed dosages prasugrel also leads to more bleeding than clopidogrel so the efficacy benefits of prasugrel must be weighed against the bleeding risks. I present below the different interpretations of the benefit-risk of prasugrel in the US and European labels.

### *European Approval and Labeling*

The European Medicines Agency (EMA) approved prasugrel (Efient—European spelling) on February 25, 2009, for marketing in the European Union. The EMA public assessment report is available at

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000984/WC500021971.pdf

(EMA 2009) The approved indication is the following:



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> "Efient, co-administered with acetylsalicylic acid (ASA), is indicated for the prevention of atherothrombotic events in patients with acute coronary syndrome (i.e. unstable angina, non-ST segment elevation myocardial infarction [UA/NSTEMI] or ST segment elevation myocardial infarction [STEMI]) undergoing primary or delayed percutaneous coronary intervention (PCI)."

While the indication statement does not mention superiority to clopidogrel, the description of the TRITON study does:

> "Efient showed superior efficacy compared to clopidogrel in reducing the primary composite outcome events as well as the pre-specified secondary outcome events, including stent thrombosis (see Table 3). The benefit of prasugrel was apparent within the first 3 days and it persisted to the end of study. The superior efficacy was accompanied by an increase in major bleeding."

Efient has a warning regarding bleeding risk. The EMA recommendation is that "the use of Efient in patients at increased risk of bleeding should only be considered when the benefits in terms of prevention of ischaemic events are deemed to outweigh the risk of serious bleedings." The label states that this concern applies especially to the elderly (age ≥75); those with a propensity to bleed from recent trauma, surgery, or gastrointestinal bleeding, or active peptic ulcer disease; body weight < 60 kg; or with concomitant administration of drugs that increase bleeding risk. Use in the elderly is not generally recommended but may be undertaken with a careful individual benefit-risk evaluation.

## *US Approval and Labeling*

We approved prasugrel (Effient—US spelling) on July 1, 2009. The approved labeling effective at the start of PHOENIX is available at

http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022307s001lbl.pdf.

(Lilly 2010) The approved indication is the following:

> "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 (1.1)."

The indication does not include a stated superiority claim over clopidogrel, although the Indications and Usage section continues "Effient has been shown to reduce the rate of a combined endpoint of cardiovascular death, nonfatal myocardial infarction (MI), or



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nonfatal stroke compared to clopidogrel." The rationale for not stating a superiority claim follows:

> "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."

Effient has a boxed warning regarding bleeding risk. As the label states, "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." For TIMI Major or Minor bleeding the rates were 4.5% for prasugrel vs. 3.4% for clopidogrel, about 24% higher. In the elderly (age ≥75) rates of fatal and intracranial bleeding were increased such that prasugrel is not recommended for the elderly except in high-risk patients (diabetes or prior MI.)

*COMMENT: Prasugrel demonstrated superior efficacy to clopidogrel but also increased risk of bleeding. Hence prasugrel represents a contemporaneously available alternative treatment that should have provided superior benefit-risk for many patients who had higher cardiac event risks but low or average bleeding risks. Prasugrel should have been allowed as a comparator or, as a minimum, discussed in the protocol, investigator's brochure, and ICDs.*

## Availability and Benefit-Risk of Ticagrelor

Ticagrelor is another approved oral $P2Y_{12}$ antagonist. However, ticagrelor was approved in Europe on December 3, 2010, and in the US on July 20, 2011—both approvals are during the conduct of PHOENIX. Ticagrelor is unlike clopidogrel in that ticagrelor is not a thienopyridine and does not require activation. It, like prasugrel, provides faster, more consistent platelet inhibition than clopidogrel. Furthermore, it is a reversible inhibitor, while clopidogrel and prasugrel are irreversible inhibitors. Reversibility should provide some advantages when the inhibitor needs to be discontinued for active bleeding. Finally, in its pivotal PLATO trial in ACS it allegedly showed a long term mortality benefit, something that both clopidogrel and prasugrel have not shown. Also noteworthy regarding PLATO is that it allowed prior thienopyridine use and specified study drug use immediately after randomization without requiring a delay for angiography. I summarize below the relevant parts of the European and US labels.



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## *European Approval and Labeling*

The EMA approved ticagrelor (Brilique) on December 3, 2010, for marketing in the European Union. The EMA product information report is available at

> http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001241/WC500100494.pdf

(EMA 2010) The approved indication is the following:

> "Brilique, co-administered with acetylsalicylic acid (ASA), is indicated for the prevention of atherothrombotic events in adult patients with Acute Coronary Syndromes (unstable angina, non ST elevation Myocardial Infarction [NSTEMI] or ST elevation Myocardial Infarction [STEMI]); including patients managed medically, and those who are managed with percutaneous coronary intervention (PCI) or coronary artery by-pass grafting (CABG)."

The Clinical efficacy and safety section of the label has this statement regarding superiority to clopidogrel:

> "On a background of daily ASA, ticagrelor 90 mg twice daily showed superiority to 75 mg daily clopidogrel in preventing the composite endpoint of cardiovascular [CV] death, myocardial infarction [MI], or stroke, with the difference driven by CV death and MI."

The label text does not discuss the lower all-cause mortality with ticagrelor. Table 3, Outcome Events in PLATO, has a row for all-cause mortality listing 4.3% of patients dying with ticagrelor vs. 5.4%with clopidogrel, p = 0.0003, with the footnote "nominal significance value; all others are formally statistically significant by pre-defined hierarchical testing".

## *US Approval and Labeling*

We approved ticagrelor (Brilinta) on July 20, 2011. The initial approved labeling is available at

> http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022433s000lbl.pdf .

(AstraZeneca 2011) The approved indication is the following:

> "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."



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The Clinical Studies section of the label has the following description of the PLATO results:

> "The difference between treatments on the composite resulted from effects on CV death and MI; each was statistically significant when considered as a secondary endpoint and there was no beneficial effect on strokes. For all-cause mortality the benefit was also statistically significant (p = 0.0003) with a hazard ratio of 0.78."

*COMMENT: Both the European and US labels describe the superiority of ticagrelor to clopidogrel for the primary endpoint. Both note that CV death and MI contributed to the superiority with no beneficial effects upon stroke. The US label mentions the mortality benefit in text while the European label includes it in a table. Note that, as documented above, the European (ESC) 2011 guidelines recommend ticagrelor or prasugrel over clopidogrel, relegating clopidogrel use "for patients who cannot receive ticagrelor or prasugrel". Ticagrelor upon approval should have been allowed as an option in PHOENIX.*

## Gycoprotein IIb/IIIa Inhibitors (GPIs)

Three GPIs are approved in the US and Europe: abciximab (ReoPro), eptifibatide (Integrilin), and tirofiban (Aggrastat). All three are administered IV; oral agents have been tested but abandoned because of safety problems or lack of efficacy. Many of the studies supporting GPI use were conducted prior to the widespread use of clopidogrel for PCI. GPIs have been studied in trials with clopidogrel as well as the newer $P2Y_{12}$ inhibitors but the optimal use of GPIs and $P2Y_{12}$ inhibitors is not well defined. In particular the GPI labels do not address well how GPIs and $P2Y_{12}$ inhibitors should be used. Because of the limitations of the labels and the fact that there are six of them (between the US and Europe), I have not included excerpts of the labels in this review. I summarize the guideline recommendations regarding GPIs below.

### *European Guidelines for Revascularization and MI*

The 2007 ESC guidelines for NSTEMI ACS recommended the following:

> "They may be used as first-line treatment in addition to other antithrombotic agents, before invasive evaluation of the patient is undertaken. This so-called 'upstream' use of GP IIb/IIIa inhibitors prior to revascularization has been shown in meta-analyses to further reduce the risk of death and MI at 30 days, if GP IIb/IIIa inhibitors are prescribed upstream of and maintained during the PCI procedure." (Bassand, Hamm et al. 2007)

The recommended use was in addition to oral antiplatelet agents.

The 2011 ESC guidelines for NSTEMI ACS recommend the following:

> "The choice of combination of oral antiplatelet agents, a GP IIb/IIIa receptor inhibitor, and anticoagulants should be made in relation to the risk of ischaemic and bleeding events."



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> "Among patients who are already treated with DAPT [dual antiplatelet therapy, i.e., aspirin plus a $P2Y_{12}$ inhibitor$P2Y_{12}$ inhibitor], the addition of a GP IIb/IIIa receptor inhibitor for high-risk PCI (elevated troponin, visible thrombus) is recommended if the risk of bleeding is low."
>
> "In high-risk patients eptifibatide or tirofiban may be considered prior to early angiography in addition to DAPT, if there is ongoing ischaemia and the risk of bleeding is low." (Hamm, Bassand et al. 2011)

These 2011 guidelines do not recommend routine use before angiography.

The ESC/ EACTS 2010 Guidelines on myocardial revascularization recommended GPI use, along with unfractionated heparin, in NSTEMI ACS with very high-risk of ischemia and in both NSTEMI ACS and STEMI in patients with evidence of high intracoronary thrombus burden. (Wijns, Kolh et al. 2010) For elective PCI it recommended GPI use for bailout only.

The 2008 ESC guideline for STEMI listed all three GPIs as "Anti-platelet cotherapy" for "Primary PCI" in a table of "Reperfusion therapy".(Van de Werf, Bax et al. 2008) It discussed that abciximab was the GPI most studied, that upstream use did not appear to be beneficial, and that "it remains to be elucidated whether abciximab provides an additional benefit to STEMI patients who receive an optimal clopidogrel treatment prior to PCI."

The 2012 ESC guideline for STEMI state similarly that "there is no definitive answer regarding the current role of routine use of GP IIb/IIIa inhibitors in primary PCI in the era of potent DAPT, particularly when prasugrel or ticagrelor is used, and the value of starting upstream of the catheterization laboratory is, at best, uncertain." (Steg, James et al. 2012) It does recommend, however, that "routine use of a GP IIb/IIIa inhibitor as an adjunct to primary PCI performed with unfractionated heparin may be considered in patients without contraindications."

## *US Guidelines for PCI and MI*

The 2008 ACCP ACS guideline recommended upstream treatment with a GPI and, for patients undergoing PCI, both clopidogrel and a GPI. (Harrington, Becker et al. 2008) See the quote under Timing of Clopidogrel above. The 2008 ACCP STEMI guideline recommended abciximab and a GPI prior to coronary angiography. (Goodman, Menon et al. 2008)

The 2007 ACC UA/NSTEMI guideline stated that "An intravenous platelet GP IIb/IIIa inhibitor is generally recommended in UA/NSTEMI patients undergoing PCI. (Level of Evidence: A)" (Anderson, Adams et al. 2007) The 2007 ACC PCI update was similar and stated that "an intravenous platelet GP IIb/IIIa inhibitor is useful in UA/NSTEMI patients undergoing PCI. (Level of Evidence: A)" and "it is reasonable to give . . . GP IIb/IIIa antagonists, administered at the time of PCI. (Level of Evidence: C)" The 2011



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ACC UA/NSTEMI update modified these recommendations to designate eptifibatide or tierofiban as the preferred GPIs before PCI as quoted under Timing of Clopidogrel above.

The 2009 ACC update for STEMI stated the following:

> "It is reasonable to start treatment with glycoprotein IIb/IIIa receptor antagonists (abciximab [Level of Evidence: A], tirofiban [Level of Evidence: B] or eptifibatide [Level of Evidence: B] at the time of primary PCI (with or without stenting) in selected patients with STEMI."
>
> "Early GP IIb/IIIa therapy in patient groups continues to appear reasonable if they are judged clinically to be at high risk of thrombotic events relative to bleeding risk." (Kushner, Hand et al. 2009)

*COMMENT: There is more uncertainty regarding the optimal use of GPIs than there is regarding timing of clopidogrel or the use of prasugrel and ticagrelor. However, I do not see a justification for excluding their use during the trial in patients for whom GPI use is standard of care. The ethical alternative would have been to exclude such patients.*

# PHOENIX Ethicalness and PHOENIX Documentation

## *Ethical Options for PHOENIX*

Considering the PCI and PLATFORM results, the guidelines (European and US), the investigator and site publications, and the availability and risk/benefit of prasugrel, I believe that there were only the following options for conducting PHOENIX ethically:

- For patients in the cangrelor arm prasugrel or ticagrelor (after approval) should have been allowed after the cangrelor infusion. Because of their rapid onset the transition from cangrelor to prasugrel or ticagrelor should be advantageous compared to the transition to clopidogrel. However, ideally the pharmacodynamics of the transition should be studied and understood. Because the latter is valuable for the post-approval use of cangrelor—we should presume it will be used with prasugrel and ticagrelor as well clopidogrel—I do not see this requirement as disadvantageous or unduly burdensome.

- STEMI patients randomized to the control arm should have been given early (on presentation) clopidogrel or prasugrel or ticagrelor (after approval).

- UA/NSTEMI should have been handled in one of the following ways:

    - Control patients should have been additionally randomized to early (on presentation) clopidogrel or ticagrelor (after approval) vs. delayed prasugrel. If one judges that there is equipoise between early vs. delayed clopidogrel for UA/NSTEMI patients, then an alternative would be randomization to early vs. delayed clopidogrel or prasugrel or ticagrelor. (Allowing delayed ticagrelor can be debated because PLATO did not



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specify delaying for angiography.) However, the PLATFORM results argue against allowing any delayed use of clopidogrel. PLATFORM established that delaying clopidogrel until after the PCI is bad but it and CHAMPION PCI are not informative regarding the optimal timing of clopidogrel use. The preponderance of evidence still suggests that clopidogrel should be administered six or more hours prior to PCI.

  - Control patients should have been given early clopidogrel (or ticagrelor when approved) or prasugrel after angiography.

  - The ICD should have described the potential benefits of early clopidogrel and prasugrel (and ticagrelor when approved) and advised patients that these latter alternatives are not available to trial participants. While full disclosure in the ICD of potentially beneficial but unavailable options seems consistent with the US regulations, I believe that the ethics of this option are still questionable and it would be impractical because of subject recruitment problems.

- Stable angina patients should have been given early clopidogrel. One could argue for randomizing these patients or allowing standard of care. Prasugrel and ticagrelor have not been studied and are not approved for stable angina patients so their specification for stable angina patients is not justified.

- GPIs should have been allowed per standard of care. Alternatively, the protocol should have stated that patients in whom a GPI would ordinarily be used per standard of care should be excluded. GPIs have been used in patients concurrently receiving clopidogrel, prasugrel, and ticagrelor. If the sponsor believes that it is not safe to use cangrelor and a GPI simultaneously, then the alternative of excluding patients in whom a GPI would ordinarily be used per standard of care should have been implemented.

There are trial conduct complications introduced by the necessity of allowing prasugrel and ticagrelor in addition to clopidogrel. The study drug stocking is more complex because prasugrel and its dummy and ticagrelor and its dummy must be stocked in addition to clopidogrel and its dummy. Note that PHOENIX had an additional problem (not discussed in this review) because the clopidogrel study drug was simply overencapsulated clopidogrel tablets, making it trivial to break the blind by opening the capsule.

I summarize the PHOENIX documentation relevant to the above options next.

## *Cangrelor Investigator's Brochure (IB)*

I have included the Cangrelor IB dated May 4, 2010, as Attachment 3. The one problem I identified in the IB is that the descriptions of the CHAMPION studies are misleading. The IB includes the following descriptions of them:



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- "The PCI study (TMC-CAN-05-02) planned enrollment of 9,000 patients within the following categories: SA, UA, NSTEMI, or STEMI. Patients received a dose of clopidogrel at the start of the PCI procedure and the study was designed to demonstrate superiority to a 600 mg loading dose of clopidogrel.

- "The Platform study (TMC-CAN-05-03) planned enrollment of 6,400 patients within the following categories: SA, UA, or NSTEMI. In contrast to PCI, STEMI patients were not enrolled in the Platform study. The other key difference was that patients did not receive a dose of clopidogrel at the start of the PCI procedure; instead, clopidogrel was given at the end of the PCI procedure. Therefore, the study was designed to demonstrate superiority to usual care. Exclusion criteria required patients to be clopidogrel-naïve, eg, no clopidogrel within 7days prior to randomization."

Because clopidogrel should be given at presentation, the PCI study could not demonstrate superiority to clopidogrel used appropriately. Because in PLATFORM clopidogrel was given at the end of PCI, PLATFORM did not compare to usual care.

## *PHOENIX Protocol*

The protocol version in effect for the entire trial included one amendment and was dated September 28, 2010. An FDA protocol advice letter dated September 9, 2010, motivated the amendment. Among other suggestions that letter recommended the following:

> "The protocol stipulates a loading dose of clopidogrel (300 to 600 mg) will be administered to subjects randomized to clopidogrel "at the time of PCI". The onset of action of clopidogrel is not rapid; therefore delaying administration of clopidogrel may result in inadequate platelet inhibition at the time of PCI. Please revise your protocol to allow the investigator to determine the timing of clopidogrel administration."

The intent was to allow clopidogrel administration on presentation, rather than waiting for angiography. I present below how the sponsor implemented that recommendation.

The protocol synopsis has what appears to be an appropriate (except for lack of prasugrel) description of the reference treatment:

> **"Reference Therapy, Dose and Mode of Administration:** Clopidogrel standard of care: Clopidogrel loading dose administered in patients undergoing PCI as soon as possible following randomization as directed by the investigator. Placebo IV bolus and infusion with dosing to match active treatment."

"Clopidogrel standard of care" sounds appropriate but the specifications are immediately hedged by "as directed by the investigator". Is it "clopidogrel standard of care" or "directed by the investigator"? The full protocol confirms that it is the latter with additional inappropriate wordings.

The "Duration of Treatment" section in the synopsis confirms one problem:



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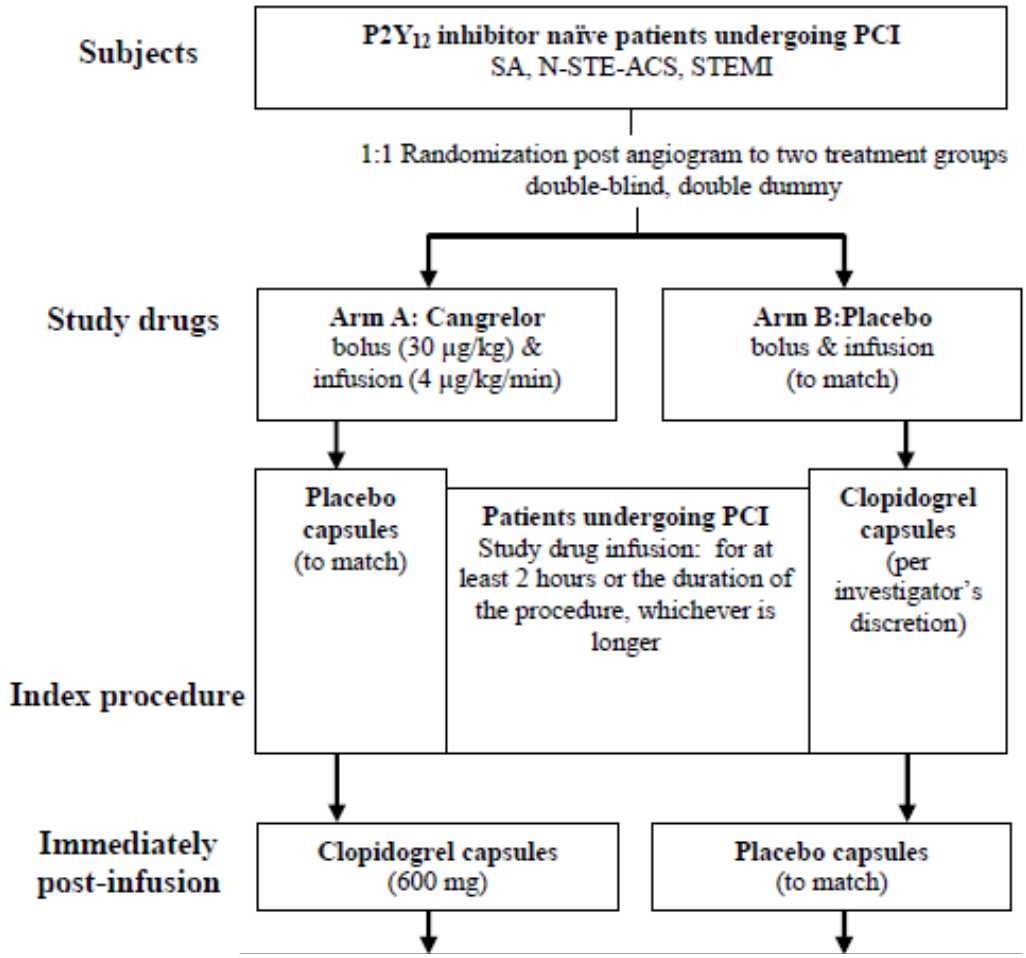
**"Duration of Treatment**: Initiated immediately prior to the index procedure . . ."

What the synopsis failed to state explicitly is that the protocol specified randomization to be done after angiography. The following excerpt from Figure 2, the Trial Design, shows this specification:

**Figure 2: Trial Design**




This Trial Design figure, however, has two flaws:

1. The intent of the FDA advice letter—and standard of care—was to allow clopidogrel use at any time after presentation, not only after angiography as the figure portrays.

2. The protocol did not require STEMI patients to undergo angiography prior to randomization as the figure implies. The protocol mentions the lack of this requirement under Inclusion Criterion 2 "Patients undergoing PCI", "c. STEMI patients (diagnostic angiography not required)." The protocol does elaborate as follows:



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> "Importantly, the treating physician must have knowledge of the coronary anatomy and suitability for PCI prior to randomization, except for patients diagnosed with STEMI. Due to the compelling nature of STEMI and the high likelihood of a percutaneous intervention, these subjects may be randomized on diagnosis, allowable in the emergency department, provided there is no impediment to primary PCI."

*COMMENT: Regarding the delay in randomization and clopidogrel loading for most patients until after angiography my FDA colleagues appear to have missed that the protocol changes were not responsive to the advice letter. Given that the synopsis starts out by declaring "Clopidogrel standard of care" it should not be surprising that IRBs also missed the inappropriate treatment in the control arm.*

*Regarding STEMI patients not requiring angiography, the investigators appear to have followed the figure rather than the text recommendation. I document in a parallel review on the benefit-risk of cangrelor that the majority of STEMI patients were randomized after angiography. (Marciniak 2014)*

The protocol appears to have been both misleading and ambivalent regarding the timing of clopidogrel. In the Study Rationale section it begins the discussion of the comparator with the following statements:

> "The comparator is clopidogrel standard of care. In line with guidelines and common practice, it is expected that the majority of patients will receive 600 mg loading dose given as soon as possible after randomization per investigator's discretion."

However, randomization was after angiography (except perhaps in STEMI patients) and the ESC guidelines recommend giving clopidogrel earlier. The discussion of the comparator continues as follows:

> "It is recognized that there are clinical settings in which the administration of a 600 mg loading dose pre-PCI is not feasible or desirable. Such clinical settings could include patients who are sedated, those with nausea or vomiting, patients who are intubated, patients in whom gastrointestinal absorption may be questionable; patients in whom the anatomy is unknown and are likely to require surgery, patients at high risk of bleeding or any other circumstance deemed appropriate by the treating physician. In these clinical settings, the administration of 600 mg clopidogrel following PCI is allowed per investigator's discretion."

*COMMENT: The protocol provides a wide range of excuses for delaying clopidogrel including "patients in whom the anatomy is unknown and are likely to require surgery". This latter argument justifies delaying clopidogrel until after angiography, not following PCI. Regardless, the expectation that "the majority of patients will receive 600 mg loading dose given as soon as possible after randomization" was not achieved: Only about 39% of patients in the clopidogrel arm received a 600 mg loading dose pre-PCI. About 30% of patients in the clopidogrel arm received the loading dose after completion*



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*of PCI. The control arm did not represent clopidogrel standard of care even by the protocol expectations, much less by the guidelines.*

There are other problems with the protocol besides the delay in clopidogrel use:

- Exclusion of prasugrel. An exclusion criteria excluded "1. Receipt of any $P2Y_{12}$ inhibitor at any time in the 7 days preceding randomization." The section on Required Medication During Follow-up Period states that "All patients should receive standard of care antiplatelet therapy per ACC/AHA/ESC guidelines. 75 mg of clopidogrel will be used for $P2Y_{12}$ inhibition during the first 48 hours post PCI." However, the ACC/AHA guidelines allow the use of prasugrel, including during the first 48 hours and the later ESC guidelines even specify prasugrel (and ticagrelor) as preferable to clopidogrel.

- Exclusion of routine GPIs. The exclusion criteria excluded "2. Eptifibatide and tirofiban usage within 12 hours preceding randomization (most recent dose must have been administered ≥12 hours prior to randomization)" and "3. Abciximab usage within 7 days preceding randomization". Excluding patients with prior use of GPIs is acceptable. However, the section on Permitted Concomitant Medications states that "Physicians may administer a GP IIb/IIIa inhibitor during the index PCI as bailout therapy only when new or persistent thrombus formation during PCI, slow or no reflow, side branch compromise, dissection or distal embolization is observed." Excluding concurrent use of GPIs is acceptable only if the exclusion criteria clearly stated that patients for whom GPIs are considered standard of care were to be excluded.

- Incomplete description of the CHAMPION trials. The protocol describes CHAMPION PCI and CHAMPION PLATFORM briefly as follows:

  > "Two Phase III multinational, randomized, double-blind, double dummy, active controlled, parallel group studies (CHAMPION PCI and CHAMPION PLATFORM) were designed to enroll approximately 15,400 patients with coronary atherosclerosis who require PCI. The primary objective for both studies was to demonstrate the superior efficacy of cangrelor versus placebo as measured by a composite of all cause mortality, MI, and IDR at 48 hours post randomization."

  Note that this brief description does not mention the difference in timing of clopidogrel between the two studies.

- Incomplete quotes from the guidelines. The protocol quotes the ACC 2009 update on STEMI and PCI, the ESC 2007 NSTEMI guidelines, and the ESC 2008 STEMI guidelines. While the quote from the ACC 2009 STEMI update includes that clopidogrel "should be given as early as possible before or at the time of non-primary PCI", the quote from the ASC 2008 guideline does not include that "clopidogrel should be given as soon as possible to all patients with STEMI undergoing PCI." The quote from the 2007 ESC guideline for NSTEMI does



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include that "an immediate 300 mg loading dose of clopidogrel is recommended" but does not include the more specific advice that "Pre-treatment of unselected patients with clopidogrel before angiography results in better outcome of PCI."

- No amendments to allow ticagrelor use after the US and European approvals.

The protocol concludes its section on Study Rationale, immediately following its discussion of guidelines, with "This study is designed to demonstrate that in patients requiring PCI, cangrelor provides superior efficacy to clopidogrel standard of care." The protocol does not appear to support clopidogrel standard of care nor the contemporaneous standard of care including prasugrel, ticagrelor, and GPI use.

## *PHOENIX Informed Consent Document (ICD)*

One could argue that, if the ICD fully informed patient regarding the possible advantages of early clopidogrel and of prasugrel and GPIs and ticagrelor (when approved), then the trial as conducted was ethical. Hence analyzing the ICD is appropriate.

For a multicenter international trial such as PHOENIX there is not one ICD. The ICDs ultimately used vary by the languages and local practices within the countries in which the sites are located. The institutional review boards (IRBs) or independent ethics committees involved may also edit the ICDs. What the trial sponsor typically provides to the FDA is a model ICD or ICD template. The PHOENIX sponsor provided an ICD template for the US that I have included as Attachment 4.

Note the following about the PHOENIX ICD template:

- The ICD does not mention prasugrel, e.g., from the introductory Background and purpose: "The initial dose of Plavix that you will receive when you have a PCI can be up to two times the approved dose depending on your institution's standard of care. The purpose of this study is to compare the safety and effectiveness of cangrelor combined with Plavix to the safety and effectiveness of Plavix alone."

- The ICD specifies giving clopidogrel in the placebo arm at the time of PCI: "Per your institutions' standard of care, you will receive 2 - 4 150 mg capsules of Plavix at the time of the PCI." There is no mention that delaying clopidogrel might be bad.

- The ICD does not mention the possible benefits of and exclusion of GPIs.

- The ICD was not updated for ticagrelor after the US approval.

Because the IRBs involved could have modified the template, I requested copies of the actual ICDs used from several sites. I picked two US sites (the VA Boston and Scripps Institute) for which physicians at the sites had published articles describing clopidogrel use and two European countries (Austria and Germany) from which PHOENIX investigators had co-authored the European guidelines. I obtained a copy from Scripps,



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which I have included as Attachment 5. I did not obtain a copy from the VA Boston. I did obtain copies of the versions (in the original German) used in Austria and Germany and translated them. I have included parallel versions of the original German and translated English for the ICD from Austria as Attachment 6 and from Germany as Attachment 7.

The Scripps ICD also does not mention prasugrel. It does differ slightly from the sponsor's US ICD template regarding clopidogrel use:

> "Prior to the start of the infusion, you will also be required to take 2 to 4 capsules of either Plavix or placebo. The number of pills you receive will depend on your doctor's decision what is best for your procedure." "These drugs [cangrelor, Plavix] will be given during the procedure."

The Scripps ICD also does not discuss that delaying clopidogrel might be bad. It includes a California Experimental Subject's Bill of Rights that states one right as the following:

> "Learn about the risks and benefits of any other available procedures, drugs or devices that might be helpful to me."

I also queried Scripps regarding what documentation the sponsor had provided to them for IRB use. I've included their response as Attachment 8. The sponsor provided to Scripps the IB (dated May 4, 2010), the protocol, an ICD, a CKMB manual, and a pharmacy manual.

The Austrian and German ICDs had limitations similar to those of the US ICD template and the Scripps ICD. They do not mention prasugrel, that delaying clopidogrel may be bad, and the possible benefits of and exclusion of GPIs. Given that the copies provided are the final versions, the ICDs were not updated for ticagrelor after the EMA approval.

## FDA Interactions

The primary clinical review dated July 29, 2010, of the PHOENIX protocol included as its first comment the following:

> "We believe that delayed administration of clopidogrel may not be optimal medical care. The onset of action of clopidogrel is known to be delayed; therefore delaying administration of clopidogrel may not result in adequate platelet inhibition at the time of PCI. Please revise your protocol to leave the timing of a thienopyridine to the investigator's discretion."

It also commented:

> "In addition, compared to clopidogrel, prasugrel has faster onset of action and does not interact with CYP2C19 inhibitors. Therefore, please revise your protocol to leave the choice of a thienopyridine to the investigator's discretion."



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It did not comment on the exclusion of GPIs.

I could not find a letter in DARRTS communicating the comments to the sponsor. However, there is an email from the sponsor dated August 12, 2010, referencing an August 10, 2012, tcon with the following comment:

- We agree that the administration of clopidogrel should be both as early as possible after definitive diagnosis as directed by the investigator, and will amend the protocol in Section 5.1.2 to state the following:

*Clopidogrel: to be administered as soon as possible following randomization as directed by the investigator*

The protocol was amended with the latter statement. However, because randomization was not done until after angiography, clopidogrel use was delayed in the trial. In fact, the addition of "as directed by the investigator" appears to have increased the delay of clopidogrel use for many patients. As I summarize below, clopidogrel administration was delayed until after the completion of PCI in a substantial fraction of patients rather than after angiography but before the start of PCI.

The email did not address prasugrel use. It also did not address GPI use.

The only other communication in DARRTS regarding these issues is an FDA letter dated September 9, 2010, to the sponsor. I quoted the paragraph in that letter regarding the timing of the loading dose under PHOENIX Protocol above. The letter also included the following regarding prasugrel:

> "Please revise your protocol to prohibit concomitant use of clopidogrel with moderate or strong CYP2C19 inhibitors. Alternatively, you could revise the protocol to leave the choice of a platelet $P2Y_{12}$ inhibitor to investigator discretion. Compared to clopidogrel, prasugrel has faster onset of action and does not interact with CYP2C19 inhibitors."

The protocol prohibited "CP2C19 inhibitors (eg. omeprazole)" for the first 48 hours post-randomization.[3]

None of the FDA documents or sponsor communications discusses informed consent. I did not find further follow-up on these issues beyond the September 9, 2010, letter.

## Actual Timings of Clopidogrel Loading

I have documented above that the protocol-specified timings of clopidogrel administration in all three studies were not consistent with the contemporaneous practice guidelines. A good question is how closely did sites adhere to the protocol-specified

[3] I disagree that prohibiting CYP2C19 inhibitors was adequate. Prasugrel is a more effective platelet inhibitor that demonstrated superior results to clopidogrel particularly in patients with STEMI. Furthermore, in August 2010 we added a boxed warning to the clopidogrel label regarding diminished effectiveness in poor metabolizers and advising prescribers to consider alternative treatments, e.g., prasugrel. Prohibiting CYP2C19 inhibitors accomplishes nothing regarding pharmacogenomics.



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timings. In particular, while the protocols specified that oral study drug be administered after angiography for stable angina and UA/NSTEMI patients, the protocols for the two trials that enrolled STEMI patients (PCI and PHOENIX) allowed earlier administration of oral study drug for the STEMI patients.

I document the actual timing results in a parallel review on the benefit-risk of cangrelor. (Marciniak 2014) I summarize selected timing results below:

- About 78% of STEMI patients in PCI and 71% in PHOENIX received clopidogrel after angiography.
- About 17% of STEMI patients in PCI and 9% in PHOENIX received clopidogrel after the completion of PCI.
- About 22% of the UA/NSTEMI patients and 39% of the stable angina patients in PHOENIX received clopidogrel after the completion of PCI.
- The median times from clopidogrel administration to PCI were 0 minutes in the stable angina subgroup, 2 minutes in the UA/NSTEMI subgroup, and 4 minutes in the STEMI subgroup of PHOENIX.

*COMMENT: The sites appeared not to have endorsed the concept that "time is myocardium" in STEMI and frequently delayed clopidogrel loading. They delayed loading until after PCI in substantial fractions of the UA/NSTEMI and stable angina patients despite the frightening PLATFORM results. I doubt that the sponsor adequately presented the PLATFORM results to the sites and their IRBs.*

## Discussion

While I argue that PHOENIX was unethical and I present below the reasons why I believe so, the counterarguments are that, other than the cangrelor infusion, PHOENIX used "standard of care" and that the control arm received an "established effective intervention" (the latter the terminology of the CIOMIS International Ethical Guidelines for Biomedical Research).
(Council_for_International_Organizations_of_Medical_Sciences 2002) I address these counterarguments below and discuss the reasons why I believe PHOENIX was unethical.

- Regarding timing of clopidogrel, the US guidelines appear to allow delayed use while the European guidelines do not. The investigators' publications and participations in guideline writing indicate that the principal investigators believed that delaying clopidogrel use increases cardiac events. It seems inappropriate to me that they would support studies forcing delayed use. One could argue that PHOENIX was ethical if the standard of care at all participating sites was delayed clopidogrel use. However, I argue that that would only be acceptable if the following conditions were also satisfied:
    - The IRBs were fully informed about the data supporting early use of clopidogrel.



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- The IRBs were fully informed about the evidence from the cangrelor CHAMPION trials that delaying clopidogrel was disadvantageous.
- The IRBs confirmed that delaying clopidogrel was the standard of care at the sites for which they were responsible and that they had considered the evidence from the CHAMPION trials that delaying clopidogrel was bad.
- The patients were fully informed in the ICDs that delaying clopidogrel might be harmful and that other treatments were available, i.e. prasugrel, GPIs, and later ticagrelor, that might be beneficial to them but that were not allowed in the trial.

Because these conditions were not met in PHOENIX, I believe that PHOENIX was unethical.

- The disadvantage of delayed clopidogrel use is not just a matter of inconvenience or a transient adverse effect. The evidence strongly suggests that delaying clopidogrel leads to adverse effects with irreversible consequences, i.e., MI and death. The prohibitions of prasugrel, ticagrelor, and GPIs have the same dire implications. When interventions involve irreversible consequences the ethical standard should not be any "established effective intervention" but the "best current interventions." If there is uncertainty about the "best current intervention" then it should be the discretion of the IRB—not the sponsor—to confirm the "best current interventions" based on complete information. The latter was not done for PHOENIX.

- While the US ethical conduct regulations do not state explicitly the "best current intervention" requirement, they do require at 21 CFR §50.2 that the subjects receive information about "appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject." The PHOENIX ICDs did not inform patients about the appropriate alternative procedures that the protocol excluded.

- Cangrelor is allegedly a faster onset $P2Y_{12}$ inhibitor than clopidogrel and its pharmacodynamic data support this assertion of the sponsor. As such, delaying clopidogrel gave cangrelor an artificial advantage over clopidogrel. As such, prohibiting prasugrel, ticagrelor, and GPIs—all of which are faster onset platelet inhibitors than clopidogrel—maintained the artificial advantage of cangrelor over the inappropriately restricted control. However, an artificial advantage means that PHOENIX patients suffered, and the PHOENIX patients' sufferings included irreversible harm such as MIs and death.



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# Q&A with Dr. Steven Steinhubl

1. **Other than the fact that we are conducting a research protocol, what is the rationale for not loading subjects with PLAVIX?**
   - Delayed and variable onset of oral PLAVIX – In some situations it isn't possible to adequately load a patient – minimum of 2 hour delay after 600mg and 15 to 24 hours after 300mg
   - Unpredictable effect – while the clinical implications of variability in response to clopidogrel are not clearly understood a number of small studies suggest that lower levels of inhibition are associated with an increased incidence of thrombotic events. Cangrelor provides immediate and dependable high levels of platelet inhibition.
   - Prolonged effect – the major limitation to using an irreversible platelet inhibitor in the treatment of an ACS patient is that a significant minority of ACS patients will require surgical revascularization.
   - Activation inhibition only (Both Plavix and cangrelor inhibit activation only.)

2. **What are the potential advantages of cangrelor?**
   - Fast onset to peak: <5 minutes (vs. clopidogrel 2+ hours)
   - Fast reversal: <60 minutes (vs. clopidogrel 5 days)
   - Optimal inhibition: >95% suppression (vs. clopidogrel ~40-60%)
   - Direct effect (vs. clopidogrel indirect effect)
   - Mechanism of action: suppresses platelet activation (vs. GPIIb/IIIa inhibitors—suppress platelet aggregation
   - No dose adjustment for renal/hepatic dysfunction
   - Linear, weight-based IV dosing; therefore a consistent, predictable high level of inhibition.


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CHAMPION PLATFORM

# Interim Analysis Review Committee (IARC) Meeting for the CHAMPION Program: PLATFORM Trial

## May 1, 2009
## Washington, D.C

Attendees:

| IARC Members | Duke Clinical Research Institute |
|---|---|
| Robert Califf, M.D. (Chairman) | Steven McNulty, M.S. |
| Christian Hamm, M.D. (via conference call) | |
| Cyrus Mehta, Ph.D. | |
| Carl Pepine, M.D. | |
| James Ware, Ph.D. | |

The Closed Session commenced at 11:45 a.m. There was no Open Session.

Dr. Califf opened the meeting by stating that he has had several conversations with Dr. Clive Meanwell of The Medicines Company (TMC) concerning the PCI trial. Dr. Califf reiterated that the IARC had followed all of the prescribed processes when reviewing the PCI trial, determining that the futility criteria had been met. No safety issues had been reported by the Data and Safety Monitoring Board (DSMB) concerning the PCI study at that time. TMC decided to continue to enroll in the PCI trial despite the IARC recommendations since no safety issues had been noted. Enrollment in the PCI trial is expected to finish in June 2009.

Dr. Meanwell had written to Dr. Califf encouraging the IARC to play an expanded role in the PLATFORM trial, allowing them more flexibility to review any information they considered of interest, above and beyond the guidelines written in the IARC Charter. Per Dr. Califf, Dr. Meanwell's letter had been sent to all of the IARC members.

Dr. Mehta reported that he had looked at the trend in mortality for both trials and that the combined results favored the cangrelor arm. He noted that PCI had 4 deaths (1 cangrelor and 3 clopidogrel) and PLATFORM 20 (6 cangrelor



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and 14 placebo). Based on these data, the p-value when combining the samples together without adjustment is 0.04, favoring cangrelor. When stratifying by study, since they do differ in study drug application, the p value is 0.06.

Before the data were reviewed, Dr. Califf explained the potential clinical importance of cangrelor in real-world care. $P_2Y_{12}$ inhibition (clopidogrel, prasugrel) has proven to be quite successful, even though it was not clear it would be when the drugs first became available. All oral inhibitors are long-acting but must be discontinued for at least 5-7 days prior to interventions or surgeries. The discontinuation itself and the 5-7 days without effective $P_2Y_{12}$ inhibition expose patients to increased risk for atherothrombotic adverse events. In the setting of PCI, cangrelor was thought to be an important addition to cover the period from when $P_2Y_{12}$ drugs were terminated until the start of PCI ("bridging"). Cangrelor is rapid acting and can be loaded quickly via IV to cover the period before the oral drugs can be restarted. Clinicians would welcome this option since it is believed that the patients are at increased risk for adverse events in that interval. It would be much more challenging to prove that cangrelor is superior to the other oral drugs so they could be replaced altogether. The IV nature of cangrelor would be a problem and new trials would need to be developed to explicitly test that hypothesis.

There is the possibility that TMC may be willing to test for non-inferiority versus the current superiority noted in the protocol. In the clinical world, non-inferiority would be demonstrated by showing that the cangrelor effects fall within a narrow confidence interval around the effect of the current treatment. The FDA requires that same criterion but also adds the need for a putative placebo comparison. With the change in FDA leadership, the non-inferiority rules could be more stringent or less so. TMC is not looking for a blockbuster drug. Instead they would like a product that could be used in a specialty market, such as the PCI setting. TMC can either do another trial to satisfy the



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putative placebo requirement, needing a lot of sites and patients, or they could argue with the FDA that an adequate placebo controlled trial doesn't exist in the setting of PCI. Clopidogrel made it to the market for another indication, bypassing that requirement. If TMC can declare that cangrelor is not worse than standard of care, it implies that it can be used when other oral treatments are not possible.

There was a concern that the IARC is being asked to make a business decision. Based on the results provided by Dr. Mehta, it was felt that there is an ethical obligation to recommend futility and stop the trial. If any other recommendation is made, there would be a perception that there is something positive in the results that really is not there.

A question was raised about whether TMC would actually stop the trial since they chose to ignore the IARC recommendation concerning the PCI study. The early preference of the IARC members would be to recommend futility but provide secondary recommendations, if any, after that.

Another question was raised concerning the mortality signal mentioned by Dr. Mehta earlier in the meeting. If the mortality signal across both trials persisted if they both completed enrollment, that could be lost if we stopped PLATFORM at this time. This would deny TMC some benefit to their drug. Mr. McNulty reported that the current PCI trial mortality favored the clopidogrel arm (8 cangrelor and 5 clopidogrel) so the issue may be moot.

Dr. Mehta proceeded to review the steps leading to his recommended conclusions. He started by discussing what is called the $G_0$ population, which consists of the mITT patients. He pointed out that the Z statistic did not cross the efficacy boundary. Using a sample size of 6400 maximum, he had computed the conditional power and announced that it was 0.6% if the true effect size equals the observed effect size based on accumulating data. Even if



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the sample size was increased to 15,000, the conditional power would only rise to 2.1%. Since the design specification calls for increasing the sample size only if such an increase could raise the conditional power to 80%, the sample size of the $G_0$ population should not be increased.

For completeness, Dr. Mehta also presented conditional power results under the assumption that the effect size is 0.73, as specified in the original study design. If the true effect size is that assumed in the original study design, the conditional power is 11.5%. To attain 80% power under this assumption, a sample size of 13,900 would be required. The 95% confidence interval on the odds ratio estimate (0.945) for the observed data is 0.75 to 1.18. Thus, the effect size hypothesized in the protocol, 0.73, is not consistent with the data accumulated thus far. Therefore, even by this criterion, the sample size of the $G_0$ population should not be increased. The next step is to proceed in analyzing the $G_1$ population, which is a subset of $G_0$ containing only diabetic or baseline cardiac marker positive patients.

If the assumption is made that future enrollment will be restricted to the $G_1$ population, the results are similar to that seen with $G_0$. The conditional power is 0.5% under the assumption that the event rates estimated in the $G_1$ population continue to hold for the duration of the study. If the sample size is increased to 15,000, the conditional power only increases to 1.6%. The method of computing conditional power using event rates specified at the design stage is not applicable here since the case for population enrichment can only be based on the observed data at the interim analysis.

Based on this analysis, the recommendation prescribed by the protocol is to terminate the trial for futility. The next step is to determine, under the broader role of the IARC, if any other recommendation can be made.



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Several positions were presented for discussion. The IARC members thoroughly reviewed the two trial schema to determine the differences in study treatment between the trials. It is expected that enrollment in PCI will finish in June and PLATFORM will finish in July or August.

One suggestion would be to terminate both projects, cutting TMC losses, and designing a bridging trial using the currently enrolling sites to provide patients.

Another suggestion was to provide the recommendation of futility, allowing TMC to continue enrollment as they saw fit. The integrity of the trial will be preserved since the IARC did their job. TMC has little incentive to stop enrollment at this time since it is only a few months from completion anyway. The only reason TMC may wish to stop the trial was if there were data supporting an adverse effect of cangrelor or if patients were being denied a better treatment.

The case was made that the IARC has an ethical obligation to recommend termination of the PLATFORM trial. Another aspect to consider is that cangrelor is a newer compound, without long term safety information. Continuing to treat patients with no possibility of benefit puts patients at risk if there are long-term safety issues with cangrelor. Declaring that it is unethical to continue would shift the burden of proof back to the IARC, since TMC will want to see the data supporting that recommendation. Hard data demonstrating a negative effect against cangrelor has not yet been noted during this data review.

A question was raised about potential FDA changes in requirements for non-inferiority trials. If the FDA rules that the putative placebo trial requirement is no longer needed, what effect on the two trials would there be? PLATFORM can't claim non-inferiority since there is a key period of placebo control. If you



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are equivalent to no treatment, your active treatment is not needed at all. PCI involves a comparison to clopidogrel, so could meet a less restrictive definition. The results are currently trending in favor of clopidogrel for the 48 hour primary endpoint.

It was noted that if the trial is stopped early, there would be a negative perception of the drug and TMC would not be able to control the message that is publically presented. The IARC decided that the image control issues were not their concern.

Under the expanded IARC role, the IARC wanted to look at the bleeding data as presented to the DSMB. The DSMB had determined that they did not have any safety concerns after reviewing this information. The DSMB role is purely for safety review and they can only stop the trial with an overwhelming negative safety signal.

In PLATFORM, cangrelor had an overall higher bleed rate than placebo (16% vs 12%). The ACUITY clinically significant category had almost double the bleed rate in cangrelor versus placebo (5% vs 3%). There were slightly more patients with GUSTO Moderate and Severe/Life threatening bleeds in the cangrelor arm. On the other hand, there were slightly more TIMI major bleeds in the placebo arm.

In PCI, the various bleed rates were nearly equivalent for each of the more severe bleed categories reviewed. Overall, the cangrelor arm had more minor bleeding than clopidogrel but the differences were not as pronounced as in PLATFORM.

There was a concern about using safety information as part of the recommendation since that review is completed by the DSMB. Dr. Califf said



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that he would talk to the DSMB Chair, Dr. Frans Van de Werf, about the bleeding issues already noted so that his opinion can be taken into account.

Another question was raised about how TMC could stop the trial, assuming they choose to do so. Would they stop it all at once or incrementally shut it down? Since enrollment is close to being complete, anything other than an abrupt stop would still allow continued enrollment towards the 6400 goal. Enrollment already stands at over 5200 as of April 30. Dr. Califf felt that even an "abrupt" trial termination would still take at least a week. If an incremental approach is taken, it was suggested to concentrate the site closings in the few countries that are contributing the most patients (Bulgaria, Czech Republic and the United States). There was also discussion that an abrupt closure is usually only reserved for severe safety problems, such as seen during Flolan where excess mortality was noted.

Regardless of whether TMC chooses to stop PLATFORM, even if the bleed information is taken into account, the IARC cannot force them to do so. TMC has the right to take the recommendation under advisement but does not have an obligation to follow it. The IARC will have fulfilled its role if they provide the recommendation to stop the trial for futility whatever decision TMC, in conjunction with the Principal Investigators, makes.

Dr. Califf stated that he would talk to Dr. Van de Werf over the weekend following the IARC meeting and prepare the correspondence for TMC. In an effort to provide a complete recommendation, he did ask that Cytel prepare the efficacy results for the following subgroups: age > 65 vs ≤ 65, male versus female, GP IIb/IIIa use versus not, Base anticoagulant type, patient categorization, geographic region (North America versus all others), and CK-MB assay type. The assay type is a site level variable but it is recognized that the sensitivity for detecting elevated CK-MB does differ between the methods.



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CHAMPION PLATFORM

**CONCLUSIONS AND RECOMMENDATIONS**

After reviewing all of the available data for PLATFORM, the IARC provisionally recommended that the study be terminated due to futility. Once the results of the remaining analyses are available, the conclusion will be finalized.

When the final data were received from Cytel, Dr. Califf planned to have a discussion with the DSMB Chair, Dr. Frans Van de Werf, concerning the recommendations and the potential excess clinically significant ACUITY bleeding. Depending on the outcome of the discussion with the DSMB Chair concerning the bleeding issue, there may be added emphasis placed on the excess cangrelor bleeding risk with respect to the futility recommendation.

Dr. Califf also indicated he would contact Dr. Clive Meanwell at TMC since the final recommendation was going to involve some modification to the trial, most likely through termination of enrollment.

The meeting adjourned at 1:45 p.m.



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## Interim Analysis Review Committee Meeting for the CHAMPION Program: PLATFORM Trial Addendum

Dr. Mehta emailed a summary document containing the results of the analyses performed after the conclusion of the IARC meeting. Per the request of Dr. Califf, the PLATFORM and PCI studies had the same subgroups analyzed to determine if cangrelor had any benefit in a specific population. As previously mentioned, the subgroups selected included: age > 65 vs ≤ 65, male versus female, GP IIb/IIIa use versus not, Base anticoagulant type, patient categorization, geographic region (North America versus all others), and CK-MB assay type. The tabled results provided by Dr. Mehta showed that no subgroups in either of the trials showed any indication of a cangrelor benefit.

Dr. Califf sent a brief response concerning his discussion with Dr. Van de Werf. Dr. Van de Werf felt that the IARC was being overly concerned about the ACUITY bleed criteria when there was not a similar signal in the other bleeding scales. Dr. Califf also asked Mr. McNulty if there was any additional mortality data to report that could influence the final decision. Mr. McNulty stated that the numbers reported to the IARC, and documented above, are accurate to the best of his knowledge.

**REVISED CONCLUSIONS AND RECOMMENDATIONS**

After reviewing all of the available data for PLATFORM, the IARC recommends termination of the study due to futility.



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**Interim Analysis Review Committee Meeting for the CHAMPION Program: PLATFORM Trial**

**May 1, 2009**

**Approval of Closed Session IARC Minutes Signature Page**

I have read and approve the attached Closed Session minutes.

_____

Robert Califf, M.D. (Chairperson) Date



Reference ID: 3434365

Dear Drs. Harrington, Bhatt and Meanwell,

The IARC met on May 1st, 2009 and considered up to date data on the PLATFORM Trial as well as reviewing limited updated information about the PCI Trial. We considered all alternatives allowed by the initial charge and incorporated in your recent letter to us.

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We have come to the conclusion that enrollment into PLATFORM should be discontinued in an orderly process as soon as it is feasible to do so. PCI is almost complete, and therefore could be discontinued simultaneously.

The following considerations drove us to this conclusion:

1. Futility was clearly met in both trials for efficacy. We believe that you should take satisfaction that you have adequately addressed the question of whether IV P2Y12 inhibition with cangrelor at the time of PCI adds to conventional standard of care either in patients pre-treated with clopidogrel or treated with clopidogrel at the end of the procedure. Your results will permit future trials to approach this question from an enlightened point of view.
2. The enriched samples did not change this assessment, nor did any relevant subgroups including: age, sex, clinical presentation (UAP, NSTEMI, STEMI), type of CK-MB assay, region of enrollment, type of anticoagulant and use of GPI.
3. The PLATFORM Trial has a period of placebo control and indeed there is a signal for an increase in "ACUITY defined" bleeding with cangrelor compared with placebo. No significant difference is observed with other bleeding scales. This excess of bleeding with no benefit leads us to the recommendation that there is no potential benefit and some risk to new participants in the trial.
4. In the preliminary data no such signal is present in the PCI trial with its active control. However, there is also no signal of benefit and many events have accrued at this point, making continuation of no value to sites or participants.
5. We recognize the importance of availability of an IV form of P2Y12 inhibition in those who cannot take the oral medication or in those who need "bridging" for short term therapy. In constructing an argument for non-inferiority compared with oral clopidogrel, the PLATFORM data are not relevant, while the PCI trial provides ample evidence that the 2 regimens yield similar results by conventional criteria. The absence of a "classical" putative placebo argument due to the lack of adequate data comparing clopidogrel with placebo in this setting will make this an uphill climb, although it may not be impossible.
6. We recommend that you discontinue enrollment, clean up the data and consider focusing on short term use when oral drugs cannot be used or when a short half-life is highly desirable.

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We have discussed this recommendation with Prof. Van de Werf and he is in agreement.

Robert M Califf for the IARC

THE MEDICINES COMPANY®

# CANGRELOR FOR INJECTION
# INVESTIGATOR'S BROCHURE

| | |
|---|---|
| Edition No. 5 | Replaces Edition No. 4 |
| Release Date: 4 May 2010 | Dated: 19 August 2008 |
| Data Cutoff Date:3 September 2009 | Data Cutoff Date: 23 May 2008 |

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The Medicines Company
8 Sylvan Way
Parsippany, New Jersey 07054
USA
973-656-1616

# SUMMARY OF CHANGES

The following changes have been made to this edition of the Investigator's Brochure since the previous edition (Edition 4) dated 19 August 2008.

| Section | Revision Description | Reason for Change |
|---|---|---|
| 1. Summary | Updated with Phase III information | New data available |
| 2. Introduction | Updated with Phase III information | New data available |
| 3. Physical, Chemical, and Pharmaceutical Properties | Reorganized/reformatted | More effective presentation of available data |
| 4.2 Nonclinical Pharmacokinetics and Metabolism | Reorganized | Data presented in ICH –preferred order (Distribution, Metabolism, Excretion) |
| 4.3.2 Repeated-Dose Toxicity Studies | Previous content reformatted into a table | More effective presentation of available data |
| 4.3.3. Reproductive Toxicity Studies | Previous content reformatted into a table | More effective presentation of available data |
| 5 Effects in Humans | Entire section reorganized. Some sections of legacy data rewritten or summarized (detailed below) | More effective presentation of legacy and new data. |
| 5 Overview of Completed Clinical Studies With Cangrelor | Updated with Phase III information. Previous "Overview of Clinical Safety and Efficacy" incorporated into this section | New data available; more effective presentation of available data |
| 5.2.4 Elimination | Summary shortened | More effective presentation of available data |
| 5.2.5 Interaction Study | Summary shortened | More effective presentation of available data |
| 5.2.6.4 Platelet Function During Infusion in PCI Patients | Updated information from Phase III PK substudy | New data available |
| 5.3.1 Efficacy Results in Phase II Clinical Studies | Information moved to this section from "Outcomes After Infusion: section in Edition 4 | More effective presentation of available data |
| 5.3.2 Efficacy Results in Phase III Clinical Studies | Updated with Phase III information | New data available |

| Section | Revision Description | Reason for Change |
|---|---|---|
| 5.3.3 Safety | Updated with Phase III information. Legacy information reorganized/rewritten. Some data moved to Appendix | New data available; more effective presentation of available data |
| 5.6 Conclusion | Updated with Phase III information | New data available |
| 6 Possible Risks and Adverse Events Associated With Use of Cangrelor | Rewritten | More effective presentation of available data, newly available data added. |
| Overall | Formatting/Editing | The entire document has been reformatted to conform with new corporate templates and edited for consistency. |

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# LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| Abbreviation | Definition |
|---|---|
| ACS | Acute coronary syndromes |
| ADP | Adenosine diphosphate |
| AE | Adverse event |
| ALT | Alanine aminotransferase (also known as serum glutamyl pyruvate transferase, SGPT) |
| AR-C69712XX | Major circulating metabolite (nucleoside) of the parent compound |
| AR-C69931MX | Tetrasodium salt of the parent compound |
| AR-C69931XX | Free acid of the parent compound |
| AST | Aspartate aminotransferase (also known as serum glutamyl oxalate transferase, SGOT) |
| ATP | Adenosine triphosphate |
| AUC | Area under the plasma concentration time curve |
| $AUC_{0-\infty}$ | Area under the plasma concentration time curve to infinity |
| BP | Blood pressure |
| BT | Bleeding time |
| CABG | Coronary artery bypass graft (surgery) |
| CFR | Cyclic flow reduction |
| CI | Confidence interval |
| $CL_p$ | Total plasma clearance |
| $C_{max}$ | Maximum concentration |
| CNS | Central nervous system |
| $C_{ss}$ | Concentration at steady state |
| CYP | Cytochrome P450 |
| ECG | Electrocardiogram |
| f | Molar fraction |
| GI | Gastrointestinal |
| GLP | Good Laboratory Practice |
| GP | Glycoprotein |
| GTN | Nitroglycerin |

| Abbreviation | Definition |
|---|---|
| HR | Heart rate |
| $IC_{50}$ | Concentration required to give 50% inhibition of metabolite formation |
| $ID_{50}$ | Dose required to give 50% inhibition of platelets |
| IDR | Ischemia-driven revascularization |
| IV | Intravenous |
| MI | Myocardial infarction |
| NADPH | Nicotinamide adenine dinucleotide phosphate |
| NF | National Formulary |
| non-Q-MI | Non-Q-wave myocardial infarction |
| NSTEMI | Non-ST-segment elevation myocardial infarction |
| OR | Odds ratio |
| PCI | Percutaneous coronary intervention |
| PD | Pharmacodynamics |
| PhEur | European Pharmacopeia |
| PK | Pharmacokinetics |
| PRU | $P2Y_{12}$ reaction units |
| PTCA | Percutaneous transluminal coronary angioplasty |
| PVC | Premature ventricular contractions |
| RBC | Red blood cell |
| SA | Stable angina |
| SAE | Serious adverse event |
| SC | Subcutaneous |
| SDS-PAGE | Sodium dodecylsulphate polyacrylamide gel electrophoresis |
| SOC | System organ class |
| STEMI | ST-segment elevation myocardial infarction |
| $t_{1/2}$ | Half-life |
| TIMI | Thrombolysis in Myocardial Infarction |
| t-PA | Tissue plasminogen activator |
| UA | Unstable angina |
| UK | United Kingdom |
| USP | United States Pharmacopeia |

| Abbreviation | Definition |
|---|---|
| VASP PRI | Vasodilator-stimulated phosphoprotein phosphorylation index |
| $V_{ss}$ | Volume of distribution at steady-state |
| w/v | Weight to volume |

# 1. SUMMARY

Cangrelor is an antiplatelet agent being developed for intravenous (IV) use during coronary procedures (eg, percutaneous coronary intervention [PCI]) as well as the management of patients experiencing acute coronary syndromes (ACS). Cangrelor, also denoted as AR-C69931MX, is a substituted nucleotide that is rapidly inactivated by dephosphorylation to the nucleoside. It is a novel $P2Y_{12}$ receptor antagonist that effectively blocks adenosine diphosphate (ADP)-induced platelet aggregation as demonstrated in several in vitro and ex vivo studies.

The metabolite array in man is qualitatively similar to that in the rat and dog. In man, the major route of elimination is urinary. There are no interactions between cangrelor and standard aspirin, heparin, and nitroglycerin (GTN) treatments.

The drug is non-genotoxic in a standard battery of tests. The main target organ for toxicity in rats and dogs is the kidney. Renal and upper urinary tract toxicity was seen after continuous IV infusion for up to 1 month. In the rat, the toxicity seen after 1 month of dosing was shown to be reversible.

Cangrelor was not teratogenic in rat and rabbit embryo-fetal development studies. In female rats, fertility was unaffected by cangrelor. Some effects were seen on male rat fertility including changes in sperm morphology and motility after 8 weeks of treatment at the highest dose. Sperm abnormalities were reversible in the majority of rats tested following cessation of dosing and no sperm abnormalities were seen in a 4 week rat study.

Cangrelor is ultra-short acting, effectively inhibiting platelet activation and aggregation during thrombosis in damaged arteries with less associated bleeding time (BT) prolongation than the glycoprotein (GP) IIb/IIIa receptor antagonists. In the dog coronary artery, cangrelor, when administered with tissue plasminogen activator (t-PA), resulted in abolition of post-thrombolytic re-occlusion without accelerating the time to reflow. This resulted in reducing the cardiac infarct size by half.

In total, cangrelor has been studied in over 14,800 patients in seven Phase I studies, five Phase II studies and two Phase III studies, to date. In clinical pharmacology studies, the drug produced dose-related inhibition of ex vivo ADP-induced platelet aggregation. It has a rapid onset and offset of action and to exhibits dose linearity. The drug was clinically safe and well tolerated at all infusion rates.

In an open-label dose-escalation study in unstable angina (UA)/non-Q-wave myocardial infarction (MI) (SC-931-5058, 39 subjects treated), administration of cangrelor caused >95% ex vivo inhibition of ADP-induced platelet aggregation at doses of 2 and 4 µg/kg/min. Cangrelor was well tolerated at doses up to 4 µg/kg/min infused for up to 72 hours, when given in addition to aspirin and unfractionated (IV) or low molecular weight (subcutaneous [SC]) heparin, plus other standard medication.

The safety of prolonged cangrelor infusions of up to 72 hours was assessed in two trials that in together enrolled 130 patients with ACS (Study SC-931-5058 and SC-931-5060). These studies demonstrated that cangrelor does not effect cardiac repolarization, and was well tolerated and safe, even at a supratherapeutic dose.

Two multi-national, randomized, double-blind, double dummy, active-controlled or placebo-controlled studies assessed the safety and efficacy of cangrelor (TMC-CAN-05-02 and TMC-CAN-05-03). The primary objectives of this program were to demonstrate that the efficacy of cangrelor is superior to placebo and superior to a 600 mg loading dose of clopidogrel. While both of these studies were terminated early due to the low likelihood of achieving the primary endpoint in both studies, cangrelor demonstrated greater efficacy in the clinically meaningful endpoints of death, Q-wave-MI, and ischemia-driven revascularization (IDR). In addition, it was shown to have a safety profile similar to the active comparator in both studies. Cangrelor was studied in 7036 patients in the Phase III studies, and clopidogrel/placebo was studied in 7015 patients. The incidence of adverse events (AEs) in the pooled datasets was 24.4% and 25.7%, for cangrelor and clopidogrel, respectively. The incidence of serious adverse events (SAEs) was 2.9% in both cangrelor and clopidogrel arms of study TMC-CAN-05-02 (CHAMPION PCI), and 1.8% and 2.1% of cangrelor– and placebo-treated patients, respectively, in study TMC-CAN-05-03 (CHAMPION Platform). There was a slight increase in minor bleeding events in cangrelor-treated patients in the Phase III studies, but this can be expected given cangrelor's potent platelet inhibition.

# 2. INTRODUCTION

Acute coronary syndromes (UA/stable angina [SA]/ non-ST-segment elevation MI [NSTEMI]/ ST-segment elevation MI [STEMI]) are associated with a high incidence of death and ischemic complications despite many recent improvements in the management of these conditions. Recent evolution in treatment strategies supports early cardiac intervention in combination with the use of anti-thrombotic therapies to lower the rate of procedural complications in PCI patients [Anderson, 2007]. The initial evaluation of PCI patients consists of an assessment of the risk of cardiac ischemic events (death, MI, and IDR) as well as the risk of bleeding complications from intensive medical therapy or invasive cardiac procedures. With this information in hand, the optimal treatment strategy can be determined, thereby reducing the occurrences of ischemic events and death [Antman et al; Hills and Lange, 2009].

Considerable evidence now supports the conclusion that inhibition of the platelet $P2Y_{12}$ receptor in patients undergoing PCI reduces platelet activation and aggregation, thereby reducing the risk of morbidity events such as MI and acute stent thrombosis – and can reduce mortality. [Wiviott et al, 2007; Vlaar et al, 2008, Wallentin 2009]. .

Cangrelor is a potent, $P2Y_{12}$ receptor antagonist that has been shown to strongly inhibit ADP-induced platelet aggregation ex vivo. The ADP $P2Y_{12}$ receptors are expressed on the surface of platelets and cangrelor is specific for this receptor. Since ADP plays a prominent role in platelet aggregation and activation, which are, in turn, important in arterial thrombosis, cangrelor possesses significant potential to diminish ischemic events in patients experiencing ACS.

Note: Throughout this document, the doses of the pharmaceutically acceptable tetrasodium salt (AR-C69931MX) are expressed in terms of the free acid (AR-C69931XX). The prefixes ARL and FPL [as in ARL 69931MX] are AstraZeneca internal notations used in some older study reports that have been superseded by AR [as in AR-C69931MX].

# 3. PHYSICAL, CHEMICAL AND PHARMACEUTICAL PROPERTIES

## 3.1. Drug Substance

The drug substance cangrelor is chemically similar to adenosine triphosphate (ATP), and has the following characteristics.

Chemical Name: N6-[2-(methylthio)ethyl]-2-[(3,3,3-trifluoropropyl)thio] -5′-adenylic acid, monoanhydride with (dichloromethylene) diphosphonic acid.

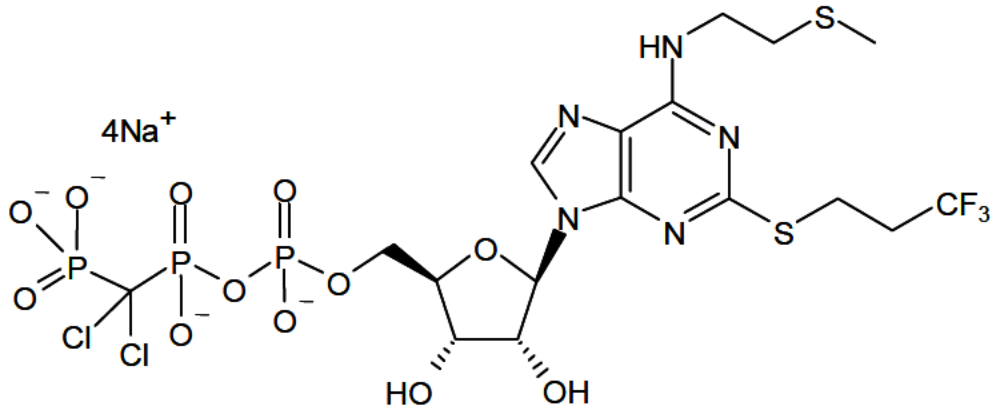
Alternative Names: AR-C69931XX = cangrelor free acid; AR-C69931MX = cangrelor tetrasodium salt.

Molecular Formula: $C_{17}H_{21}N_5Cl_2F_3Na_4O_{12}P_3S_2$

Molecular Weight: 864.3 g/mol

Chemical Structure: The chemical structure is shown in Figure 1.

**Figure 1 Chemical structure of cangrelor.**




Physicochemical characteristics: Cangrelor is a white to off-white hygroscopic solid.

Solubility: Cangrelor is freely soluble in water.

## 3.2. Drug Product

Formulation: Cangrelor is susceptible to hydrolytic degradation which led to its formulation as a lyophilized product (Cangrelor for Injection). The formulated product is supplied in 10 mL vials in order to deliver 50 mg and also contains the excipients Mannitol European Pharmacopeia/United States Pharmacopeia (PhEur/USP) and Sorbitol PhEur/USP-National Formulary (NF).

Storage: Vials of Cangrelor for Injection should be stored at controlled room temperature, 15°C to 30°C (59°F to 86°F).

Reconstitution: Cangrelor does not contain a preservative and should be not be reconstituted until immediately before infusion. Cangrelor drug substance requires reconstitution with 5.0 mL

of Sterile Water for Injection to give a solution of 10 mg/mL cangrelor. Cangrelor drug product has been formulated such that the labeled content (50 mg) may be withdrawn after reconstitution. Reconstituted vials of Cangrelor for Injection require further dilution with sodium chloride 0.9% weight per volume (w/v) infusion/injection before administration as below.

Preparation: Cangrelor infusion solutions are prepared by diluting the appropriate volume of reconstituted Cangrelor for Injection with sodium chloride 0.9% w/v infusion/injection. Instructions detailing the procedures for preparing and administering the infusion solutions are provided in individual protocols and/or pharmacy instructions. Infusion solutions are chemically stable for up to 30 hours (including administration time) at room temperature. They do not need to be protected from light after preparation or during administration.

# 4. NONCLINICAL STUDIES

## 4.1. Nonclinical Pharmacology

Cangrelor is an inhibitor of ADP-induced platelet aggregation. ADP secreted from platelet dense granules provides important autocrine and paracrine stimulation of platelet aggregation. This platelet aggregation induced by ADP is mediated, in part, by the $P2Y_{12}$ receptors, which are broadly expressed on the surface of platelets. ADP exerts its effects by coupling with inhibitory G-protein to inhibit adenylate cyclase, reducing the production and subsequent concentration of cyclic adenosine monophosphate. This results in platelet activation,amplification of platelet signaling effected by other agonists such as thrombin and sustaining stable platelet aggregation. Additionally, activation events result in the ability of platelets to interact with the leukocytes and the inflammatory process.

ATP is a competitive antagonist for the $P2Y_{12}$ receptor. Cangrelor is an ATP analogue and was therefore selected for clinical development. The results in this section summarize the nonclinical pharmacological basis for the development of cangrelor as an antiplatelet agent for use during PCI as well as in the management of ACS.

The studies described in this section demonstrate the potency, selectivity, and specificity of cangrelor as an inhibitor of ADP-induced platelet aggregation in vitro. In addition, the relationship between antiaggregatory, antithrombotic, and antihemostatic effects, as well as the effects when administered with thrombolytic drugs, were examined in vivo. Importantly, none of the metabolites of cangrelor contributes significantly to the pharmacological effects of administered drug.

Cangrelor is a potent, specific, and selective inhibitor of $P2Y_{12}$ receptor mediated aggregation of human washed platelets in vitro and produces dose-related, rapidly reversible inhibition of ex vivo ADP-induced platelet aggregation measured during IV infusion in the anesthetized and conscious dog.

In a model of dynamic arterial thrombosis in the anesthetized dog, cangrelor abolished thrombosis with only a modest effect on hemostasis (BT prolonged 1.6-fold). This effect was fully reversed within 10 minutes of cessation of infusion. Cangrelor infusion reduced re-occlusion and cyclical blood flow in the coronary artery of the dog following thrombolysis by t-PA and reduced the myocardial infarct size by about 50%. These findings are similar to those

made in the dog model with abciximab (Reopro®) when given after recombinant t-PA, where reduced re-occlusion was reported [Mickelson et al, 1990; Rote et al, 1994].

In the anesthetized dog, IV infusion of cangrelor had little or no effect on systemic hemodynamics, cardiac, respiratory, or autonomic function.

### 4.1.1. Actions Relevant to Proposed Therapeutic Use

#### 4.1.1.1. In Vitro Effects on Platelet Aggregation

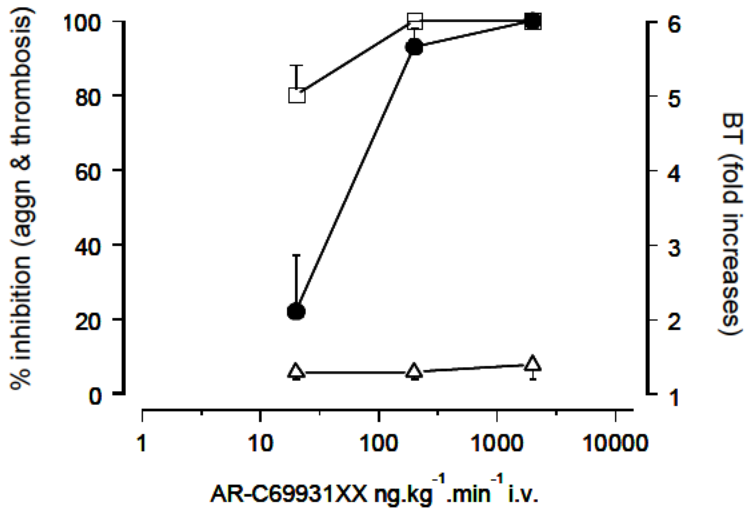
Cangrelor was shown to be a potent inhibitor of ADP-induced aggregation in human washed platelets (concentration required to give 50% inhibition of metabolite formation [$IC_{50}$] value 0.45 nM, n=9) [PR 30144] and in human ($IC_{50}$ value 0.71 nM, n=4) [PR 30145], dog ($IC_{50}$ value 0.72 nM, n=5) [PR 30146], and rat ($IC_{50}$ value 5.1 nM, n=4) [PR 30147] whole blood in vitro.

#### 4.1.1.2. Inhibition of Platelet Aggregation Measured Ex Vivo

***Anesthetized dog - coronary artery cyclic flow reduction***

In a model of dynamic arterial thrombosis in the left anterior descending coronary artery of the anesthetized dog [PR 40019], 30 minute stepped infusions of cangrelor (20, 200, 2000 ng/kg/min IV, n=6) produced dose-related inhibition of cyclic flow reduction (CFR), with little or no effect on BT (Figure 2). Measured ex vivo, full inhibition of ADP-induced platelet aggregation was necessary to achieve a full antithrombotic effect.

**Figure 2: Effect of intravenous infusion of cangrelor (20, 200, 2000 ng/kg/min) on coronary artery thrombosis, bleeding time, and ADP-induced platelet aggregation measured ex vivo in the pentobarbitone-anesthetized dog**




Legend:
● = coronary artery thrombosis, % inhibition compared with baseline, n=6
Δ = bleeding time (BT: fold increase compared with baseline), n=6
□ = ADP-induced platelet aggregation, % inhibition compared with baseline, n=5
ADP = Adenosine diphosphate; BT = bleeding time.
Note: Values are means ± standard error of the mean.

***Conscious dog***

Measured ex vivo in whole blood in the conscious male Beagle dog, infusion of cangrelor (7.7 to 230 ng/kg/min IV) produced dose-related inhibition of ADP-induced platelet aggregation (dose required to give 50% inhibition of platelets [$ID_{50}$] 15 ng/kg/min IV, n=2) [PR 30150]. Full recovery was seen within 30 minutes of stopping the infusion even at a dose 150-fold above the $ID_{50}$ (n=1).

***Cangrelor Additional Inhibitory Effect in Humans Receiving Clopidogrel***

Ex vivo studies showed that when added to blood from patients with ACS who were taking clopidogrel, cangrelor provided an additional inhibitory effect on platelet response to ADP as determined by whole blood impedance and light transmittance aggregometry [SC-931-9064; Storey et al. 2002].

#### 4.1.1.3. Pharmacodynamic Interaction With a Thrombolytic Drug

In a canine model of coronary arterial thrombosis, cangrelor, when administered with t-PA, improved coronary blood flow and reduced infarct size compared with saline control.

***Effects on t-PA-induced thrombolysis in dog coronary artery***

A fully occlusive thrombus was induced in anesthetized hound dogs by temporarily stenosing the circumflex artery and causing electrolytic damage [SC-102741]. At the start of the experimental procedure, each dog was treated with aspirin (325 mg orally) before anesthesia and by IV heparin (80 IU/kg + 17 IU/kg/hour for 2 hours). After 20 minutes of arrested blood flow (as measured by a periarterial Doppler probe), either saline (0.16 mL/min) or cangrelor (4 µg/kg/min) was infused IV for 2 hours. Approximately 10 minutes after starting the infusion, t-PA was administered (1 mg/kg IV over 20 minutes). Outcomes measured were: successful thrombolysis (≥30% baseline blood flow over the 2 hour observation period after t-PA infusion), partial thrombolysis (cyclic flow variation, ie, where there is an incidence of intermittent restoration of blood flow), total reflow duration (cumulative time when there is a measurable blood flow), time to re-occlusion, and the incidence of persistent occlusion (zero flow throughout the 2 hour period). Additional ex vivo measurements were made of infarct size (planimetry measurement of stained sections; triphenyltetrazolium chloride infused into the left anterior descending artery and Evans Blue into the left circumflex artery), blood pressure (BP), and electrocardiogram (ECG).

Animals in both treatment groups (saline or cangrelor, 10 per group), reperfused in response to t-PA with similar time to reflow. However, the saline group showed a high incidence of partial or full re-occlusion [SC-102741]. By contrast, there was virtually a full restoration of blood flow over the 2 hour observation period in the animals infused with cangrelor (4 µg/kg/min) (Table 1). The incidence of cyclic flow variation and re-occlusion was 0% in the cangrelor-treated animals and 50% and 60%, respectively, in the saline-infused dogs. As a consequence of the improved coronary blood flow restoration by adjunctive cangrelor, the resultant infarct size was halved (p=0.034) when expressed either in absolute terms or as a percent of the area at risk.

**Table 1: Effects of cangrelor on t-PA-induced thrombolysis in dog coronary artery**

| Parameter | Mean ± SD | |
|---|---|---|
| | Saline (n=10) | Cangrelor (n=10) |
| Baseline Blood Flow (mL/min) | 65.30 ± 7.47 | 62.33 ± 8.53 |
| Time to Arterial Occlusion (min) | 55.5 ± 14.03 | 62.33 ± 14.67 |
| Incidence of Reperfusion | 100% | 100% |
| Time to Arterial Reperfusion (min) | 21.50 ± 2.88 | 20.00 ± 6.09 |
| Total Reflow Time (min) | 75.00 ± 39.86 | 119.70 ± 0.67[a] |
| Cyclic Flow Variation Incidence | 50% | 0%[a] |
| Reocclusion Incidence | 60% | 0%[a] |
| Area at Risk ($cm^2$) | 48.70 ± 6.94 | 49.92 ± 8.41 |
| Infarct Size ($cm^2$) | 9.34 ± 4.37 | 4.70 ± 4.66[a] |

SD = standard deviation.
a. $p<0.05$ compared with saline control group

### 4.1.2. Other Actions Demonstrated or Sought (Secondary Pharmacology)

Cangrelor and its known and available metabolites have been studied in vitro and in vivo to confirm the selectivity for $P2Y_{12}$ receptors (compared with other P2- and P1-receptors) and specificity of action.

#### 4.1.2.1. Studies In Vitro

***Selectivity of action of cangrelor***

Cangrelor had no significant activity at other P2-receptor subtypes from a variety of species: $P2Y_1$; $P2Y_2$; $P2X_1$; $P2X_2$; $P2X_7$ at concentrations up to 100 µM (n=1 to 2) [PR 30136].

***Specificity of action of cangrelor***

Cangrelor (<100 µM, n=4) had no effect on aggregation of washed human platelets produced under ADP/$P2Y_{12}$ independent conditions by the thromboxane mimetic, U46619 [PR 30139], or on uptake of [$^3$H]adenosine by human erythrocytes [PR 30138].

***Studies with putative metabolites***

The putative monophosphate metabolite (AR-C88558KP), the base (AR-C71301XX), and S-oxidized base (AR-C90441XX) metabolites of cangrelor had no effect on ADP-independent platelet aggregation [PR 30139], no significant activity at $P2Y_1$-, $P2Y_2$-, $P2X_1$-, $P2X_2$-, or $P2X_7$-receptors (n=1 to 2) [PR 30136], and no effect on the uptake of radiolabeled adenosine by human erythrocytes (n=2 to 4) [PR 30138] at concentrations of 10 to 100 µM.

#### 4.1.2.2. Studies In Vivo

***Acute effects in the conscious mouse***

In conscious male CD-1 mice, a 10 minute infusion of cangrelor (58, 580 mg/kg IV) produced dose-related hypothermia, with maximal temperature reduction (3.6°C) within 30 minutes in the higher dose group (n=4) [PR 30143]. The maximal temperature reduction in an individual animal at the higher dose was 5.5°C. From 2 hours after infusion onwards, there was no significant difference in rectal temperature between the cangrelor-treated and saline-treated groups.

***Central nervous system effects in the conscious mouse***

Groups of 3 to 5 male CF1 mice were administered cangrelor (100, 200, 400 mg/kg IV), as a 10 minute infusion and examined for central nervous system (CNS) effects using a multi-parameter observational screen [PR 30154; Irwin, 1968]. Mainly transient stimulatory (increased motor activity) effects were observed at the lower doses and were judged to be relatively mild and free of concern. However, at the highest dose, severe symptoms of CNS depression were seen, including respiratory depression. These effects persisted at 1 hour after dosing with complete recovery at 24 hours.

***Cardiovascular and respiratory effects in the anesthetized rat***

In the anesthetized male rat, 30 minute stepped infusions of cangrelor (1, 10, 100, 200 µg/kg/min IV, n=3) had no obvious effect on phasic or mean BP, heart rate (HR), ECG (Lead II), respiratory flow, respiratory rate, or tidal volume [SE 9996].

***Cardiovascular and respiratory effects in the anesthetized dog***

When administered by stepped infusion in two pentobarbitone-anesthetized male dogs [PR 30098], cangrelor (up to 6 µg/kg/min IV) had no obvious effect on cardiovascular variables: BP, HR, cardiac output, total peripheral resistance, cardiac contractility, stroke volume, ECG, or respiratory (intratracheal pressure) variables. In a further group of three male dogs [SC-30174], infusion of cangrelor at 30 µg/kg/min IV for 6 hours also had no obvious effects on BP, HR, cardiac contractility, or ECG (12-lead).

## 4.2. Nonclinical Pharmacokinetics and Metabolism

Pharmacokinetics (PK) of the free acid of cangrelor (AR-C69931XX) and the nucleoside metabolite (AR-C69712XX) following IV infusion of cangrelor have been studied in male rats and dogs, and female rats, dogs, and rabbits. The metabolism and excretion of IV infusions of radiolabeled [$^3$H]cangrelor have been investigated in male and female rats and dogs. The protein binding and blood distribution of cangrelor and AR-C69712XX have also been investigated in relevant animal species and man. Tissue distribution of [$^3$H]cangrelor has been investigated by whole body autoradiography and quantitative tissue distribution, in pigmented and albino male rats and pregnant albino female rats.

The pharmacodynamic (PD) effect of inhibition of platelet aggregation is considered to be solely associated with the parent compound. Cangrelor is water soluble. The formulations administered to animals were prepared in sterile 0.9% (w/v) saline for injection.

Investigation of the PK and metabolism in rat, dog, and rabbit has demonstrated that cangrelor is rapidly eliminated to inactive metabolites, particularly in rat and dog. This is consistent with a

drug designed to have a short duration of action. A slower terminal elimination phase of cangrelor and the nucleoside (AR-C69712XX), characterized in the dog and rabbit, is apparent but contributes little to systemic exposure in the dog and is atypical in the rabbit. There is no evidence of retention of compound-related material from the administration of [$^3$H]cangrelor; radioactivity is mainly excreted in the first 24 hours after infusion. Importantly, there was no evidence of incorporation into endogenous macromolecules. The investigation of the metabolic route in the rat and dog reveals consistent findings indicative of the metabolic clearance of cangrelor to AR-C69712XX and sulphoxidation to AR-C90439XX. Approximately 60% of the dose is excreted in bile and, except for fecal exposures which are affected by microbial breakdown, further metabolism appears relatively insignificant.

Investigation of distribution in pregnant female rats indicates limited exposure to the fetus in utero.

### 4.2.1. Distribution

#### 4.2.1.1. Tissue Distribution

Tritiated [$^3$H]cangrelor was administered by IV infusion to male rats at 48 µg/kg/min for 30 minutes and animals were killed for autoradiography at the end of infusion, or at 10 minutes, 1, 6, and 24 hours later. A quantitative tissue distribution study was also conducted over a similar time course in male rats [SE10012]. In addition, distribution in pregnant female rats was investigated in a quantitative autoradiography study on Day 12 or Day 18 of gestation [SC-100295]. The infusion rate was the same as for the male rats, the duration was 20 minutes, and animals were examined at the end of infusion or 0.5, 6, or 24 hours later.

Autoradiographs of whole body sections of male rats, killed at the end of infusion with [$^3$H]cangrelor [SE 10012], indicated a widespread distribution of radioactivity, although none was evident in the CNS or testes. A quantitative tissue distribution study demonstrated highest concentrations of radioactivity in highly perfused tissues such as heart, spleen, lungs, and particularly in the excretory organs (liver and kidneys). Initially, high concentrations of radioactivity were observed in the liver, which declined by 1 hour after the end of infusion.

Autoradiography of the liver demonstrated a "speckled" distribution, consistent with concentration into the bile canaliculi. This, in conjunction with the high levels in the gastrointestinal tract, is consistent with the observed rapid biliary excretion. High concentrations of radioactivity were also observed throughout the kidney at the end of infusion, consistent with rapid urinary excretion. As concentrations of radioactivity declined, autoradiography revealed complex patterns of redistribution within the kidney with residual radioactivity highly localized to the inner cortex/outer medulla region 24 hours after the end of infusion. Although the regional distribution could not be quantified by autoradiography, in terms of the whole kidney, this residual radioactivity represented about 3% of the radioactivity originally present; for comparison the corresponding figure for liver at 24 hours was about 1%. Significant levels of radioactivity were observed in thyroid and bone marrow at the end of infusion. These decreased to low levels by 1 hour after the end of infusion. Low levels of radioactivity were also observed in the epiphysial plates of the femur up to 24 hours after the end of infusion.

Autoradiographs from pregnant female rats [SC-100295] were consistent with rapid excretion of the radiolabel in bile, feces and urine. Radioactivity in the ovaries and placenta were at a similar level to that of the heart blood. Radioactive exposure of the fetus was considerably less than that of the maternal tissues. Radioactivity, at the limit of quantification, was only detected in some fetuses 0.5 hours after the end of infusion on Day 18 of gestation.

#### 4.2.1.2. Protein Binding and Blood Distribution

Cangrelor (20 to 400 ng/mL) was largely excluded from blood cells, and was highly (>92%) protein bound in rat, dog, and man [SE 10009]. Protein binding was less in dog plasma (about 93%) than in plasma from rat or human (97% to 98%). The nucleoside (AR-C69712XX) was less protein bound (88% to 89%) and distributed into blood cells (about 30%) in all three species.

### 4.2.2. Metabolism in the Dog and Rat

The metabolism of cangrelor has been investigated by analysis of samples from the excretion balance studies above. Samples from male and female rats [SC-100358; SC-100141] and dogs [SC-100357; SC-100142] were investigated for metabolite identification. Since most of the radioactivity was recovered in feces, suggesting a biliary route of elimination, an additional study was carried out on bile-duct cannulated dogs [SE 10011], together with a separate biliary excretion study in bile-duct cannulated rats [SC-100371]. The biliary excretion studies, due to their relatively short-term nature, permitted the recovery of only a proportion of the dose administered (59.3% in dog; 71.9% in rat). However, this was a sufficiently large proportion to be regarded as representative. On the basis of the assumption that the entire fecal radioactivity originated from material excreted in the bile, biliary excretion data were normalized to total fecal recovery to facilitate quantitative comparison.

Metabolism of cangrelor was qualitatively similar in both sexes of the two species. No cangrelor was detected unchanged in excreta. AR-C69931MX was completely metabolized to the nucleoside (AR-C69712XX) and oxidized products of the nucleoside and its purine base (AR-C71301XX).

Numerous other metabolites were observed in excreta. These were products of combinations of S-oxidation, purine base oxidation, deribosylation, and glucuronidation. Analysis of fecal samples indicated that the metabolites excreted in bile may have been further metabolized by the gut microflora. There was evidence that these may have mediated deribosylation, glucuronide hydrolysis, and further oxidation. The main metabolites identified in feces were the base (AR-C71301XX), the sulphoxide (AR-C90441XX) of the base, and further oxidation products of the base and its sulphoxide.

### 4.2.3. Excretion in the Dog and Rat

Following a 30 minute infusion of cangrelor to male [SE 10010] and female [SC-100090] rats and dogs [SE 10011; SC-100091] (12 and 3.75 µg/kg/min IV, respectively), more than 73% of the radioactivity was recovered in the excreta within 24 hours, with quantitative recovery in 7 days (Table 2). This rapid excretion is consistent with the rapid elimination of cangrelor and its major circulating metabolite from plasma. Elimination of radioactivity in both sexes of both species occurred predominantly in feces (>60%), with lesser amounts in urine (<31%), although a slightly higher proportion was found in rat urine, and rather more in males than in females.

**Table 2: Recovery of radioactivity following intravenous infusion of cangrelor in the dog and rat**

| Recovery of radioactivity to 7 days | Dog (% radioactive dose) Dose rate = 3.75 µg/kg/min | | | | Rat (% radioactive dose) Dose rate = 12 µg/kg/min | | | |
|---|---|---|---|---|---|---|---|---|
| | Male | | Female | | Male | | Female | |
| | 24 h | 7 days | 24 h | 7 days | 24 h | 7 days | 24 h | 7 days |
| Urine | 11.7 | 12.9 | 10.2 | 11.8 | 29.9 | 31.0 | 17.4 | 18.4 |
| Feces | 61.1 | 86.0 | 64.3 | 82.6 | 54.3 | 60.3 | 68.5 | 76.9 |
| Total[a] | 73.4 | 100.4 | 75.1 | 95.9 | 86.2 | 94.3 | 86.9 | 97.0 |

a. Totals may include small contributions from radioactivity found in cage wash and/or expired air.

Fecal excretion suggests biliary elimination to be quantitatively more important than the renal route. The rate of excretion of radioactivity was rapid, with most of the dose being eliminated within 24 hours in both male and female rats and dogs.

### 4.2.4. Pharmacokinetics

#### 4.2.4.1. Cangrelor

The PK of the free acid (AR-C69931XX) following IV infusion of cangrelor to male [SE 10076] and female [SC-100124] Beagle dogs, male [SE 10075] and female [SC-100123] Sprague-Dawley rats, and female Dutch rabbits [SC-100962; SC-101314] are summarized in Table 3.

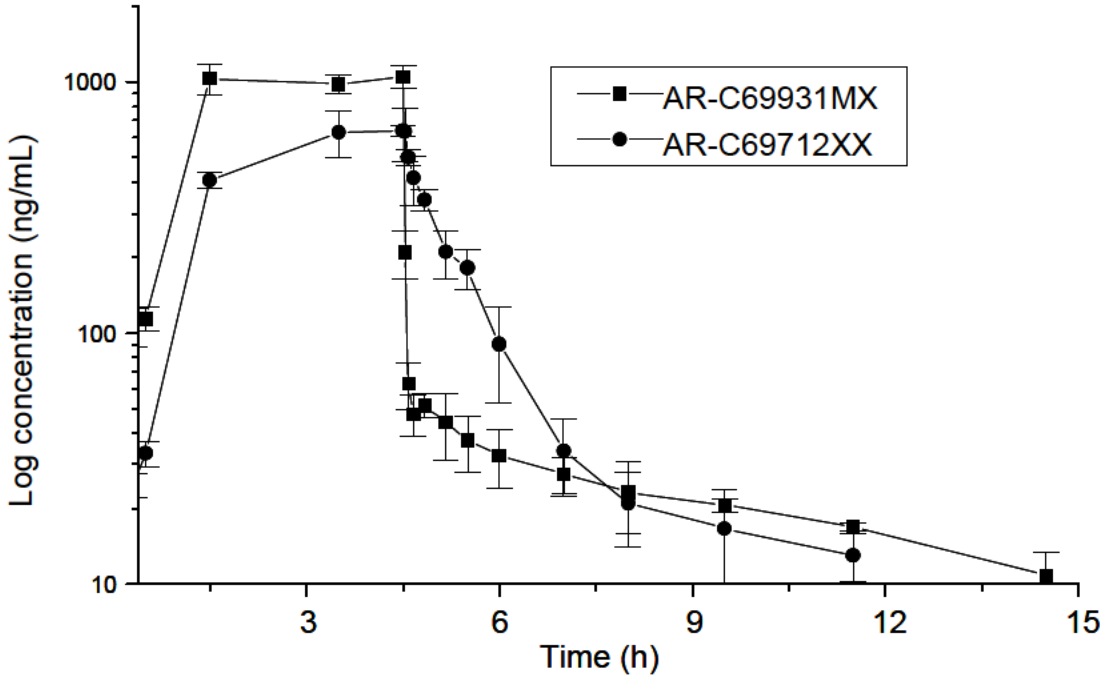
In dogs and rats, steady-state plasma concentrations ($C_{ss}$) were quickly attained and were stable throughout the infusion period. At the end of the infusion, plasma elimination resulted in concentrations declining by about 20-fold in 20 minutes; with an initial half-life ($t_{½}$) generally <1 minute. However, a more prolonged terminal elimination phase was apparent. This was best characterized in the male dog following a 4 hour infusion (Figure 3), where the terminal phase ($t_{½}$ = 5.9 hours) represented <10% of the total area under the curve ($AUC_{[0-\infty]}$). The PK appeared to be linear across the dose ranges (6 to 60 µg/kg/min and 4.8 to 48 µg/kg/min IV in dog and rat, respectively). Plasma clearance was high in the dog and moderate in the rat. The steady-state volume of distribution, which was best characterized in the male dog following a 4 hour infusion, was 2.8 L/kg (between 2.3 and 3.5 L/kg). This parameter was underestimated in the female dog and in male and female rats, when shorter infusion durations were investigated. The terminal phase contributed little to $AUC_{(0-\infty)}$ but, because the $t_{½}$ was at least 2 orders of magnitude greater than the initial elimination phase, it contributed significantly to the calculation of steady-state volume of distribution.

**Table 3: Pharmacokinetics of cangrelor in plasma after intravenous infusion to male and female dogs and rats and female rabbits**

| | Dog[a] | | | Rat[b] | | | Rabbit[c] | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Parameter | Male | Male | Female | Male | Male | Female | Female[d] | Female[d] | Female[d] | Female |
| Infusion rate (μg/kg/min) | 6 | 60 | 60 | 4.8 | 48 | 48 | 3 | 6 | 12 | 36 |
| Duration of Infusion (h) | 0.5 | 4.0 | 1.0 | 1.0 | 1.0 | 0.5 | 2.0 | 2.0 | 2.0 | 2.0 |
| $C_{ss}$ (ng/mL) | 110 | 1021 | 845 | [e] | [e] | [e] | 1300 | 2560 | 6240 | 1600 |
| Range | 99-127 | 947-1120 | 737-971 | 241-318 | 814-2810 | 1310-2270 | 1160-1420 | 2200-3030 | 4450-8230 | 12200-18900 |
| $CL_p$ (mL/min/kg) | NA | 59 | 74 | NA | 25 | 22 | NA | NA | NA | 2.07 |
| Range | NA | 53-62 | 64-83 | NA | NA | NA | NA | NA | NA | 1.85-2.28 |
| Initial $t_{½}$ (min) | NA | <1 | <1 | NA | <1 | <2 | NA | NA | NA | 22.7 |
| Range | NA | NA | NA | NA | NA | NA | NA | NA | NA | 17.9-26.5 |
| Terminal $t_{½}$ (h) | NA | 5.9 | ≈1 | NA | ≈3 | ≈0.8 | NA | NA | NA | 3.23 |
| Range | NA | 5.6-6.2 | NA | NA | NA | NA | NA | NA | NA | 2.13-5.3 |
| $V_{ss}$ (L/kg) | NA | 2.8 | 0.5 | NA | 0.7 | 0.3 | NA | NA | NA | 0.109 |
| Range | NA | 2.3-3.5 | 0.3-0.7 | NA | NA | NA | NA | NA | NA | 0.0767-0.139 |

$CL_p$ = total plasma clearance; $C_{ss}$ = steady-state plasma concentration; NA = Not applicable, not calculated; $t_{1/2}$ = half-life; $V_{ss}$ = volume of distribution at steady-state.
a. Includes studies SE 10076 and SC-100124
b. Includes studies SE 10075 and SC-100123
c. Includes study SC-101314
d. Stepped 2 hour infusion at each of 3 doses
e. Single samples from pairs of animals at each time point investigated, range of $C_{ss}$ reported

**Figure 3: Plasma concentrations of AR-C69931XX and AR-C69712XX in the male dog receiving cangrelor by intravenous infusion (60 µg/kg/min for 4 hours)**




The PK profile of cangrelor in the female rabbit was investigated to support the use of this species in reproductive toxicology studies. The findings from the PK pilot study and main study [SC-100962; SC-101314] indicated that the rabbit is atypical compared with the dog and rat. In the main study [SC-101314], the PK were investigated following a stepped, low-dose infusion at 3, 6, and 12 µg/kg/min and a high-dose infusion of 36 µg/kg/min. Although plasma concentrations were approaching steady state at the end of 2 hour infusion periods, and these were proportional to the infusion rates, the plasma exposure for a given dose was considerably higher in the rabbit than in the rat or dog. The elimination was biphasic in the rabbit, as was demonstrated in the male dog. However, the initial and terminal $t_{½}$ were 22.7 minutes and 3.23 hours, respectively, in the rabbit compared with <1 minute and 6 hours, respectively, in the dog. Plasma clearance was an order of magnitude lower in rabbit (2.07 mL/min/kg) than in the rat (22 to 25 mL/min/kg).

The mechanism of plasma clearance of cangrelor is dephosphorylation to the nucleoside (AR-C69712XX). The relative contribution of the liver, kidney, lung, and intestines to the plasma clearance of cangrelor was investigated in isolated perfused rat organs [SC-101599]. Determinations of efferent and afferent plasma concentrations of cangrelor [SC-101645] in the organs perfused at a target plasma concentration of 1500 ng/mL, indicated that the liver was the primary organ of elimination in the rat. An investigation of venous and arterial plasma concentrations of AR-C69931XX in infused anesthetized dog [SC-100188] indicated that up to 40% of circulating AR-C69931XX is eliminated in the pulmonary circulation. This pulmonary elimination may explain the higher plasma clearance of cangrelor in the dog, compared with the rat where there was little clearance in the isolated lung perfusions [SC-101599].

#### 4.2.4.2. AR-C69712XX

The main plasma metabolite is the nucleoside AR-C69712XX. The PK of AR-C69712XX following IV infusion of cangrelor to male [SE 10076] and female [SC-100124] Beagle dogs, male [SE 10075] and female [SC-100123] Sprague-Dawley rats, and female Dutch rabbits [SC-100962; SC-101314] are summarized in Table 4.

The PK of AR-C69712XX was estimated assuming complete conversion of cangrelor to the nucleoside. Under these conditions, plasma clearance of AR-C69712XX can be regarded as high in the rat and dog, and moderate in the female rabbit. Although the plasma clearance of AR-C69712XX was slightly lower in female rabbit than in the rat and dog, it did not reflect the significant differences observed in the PK of AR-C69931XX in that species. In the male dog and female rabbit, a terminal phase with a similar $t_{½}$ to that of cangrelor was apparent. This was regarded as evidence that the elimination of AR-C69712XX may be formation rate limited during the terminal phase.

**Table 4: Pharmacokinetics of AR-C69712XX, the nucleoside of cangrelor, in plasma after intravenous infusion of cangrelor to male and female dogs and rats and female rabbits**

| Species | Dog[a] | | | Rat[b] | | | Rabbit[c] | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Sex | Male | Male | Female | Male | Male | Female | Female[d] | Female[d] | Female[d] | Female |
| Infusion rate (µg/kg/min) | 6 | 60 | 60 | 4.8 | 48 | 48 | 3 | 6 | 12 | 36 |
| Duration of Infusion (h) | 0.5 | 4.0 | 1.0 | 0.1 | 1.0 | 0.5 | 2.0 | 2.0 | 2.0 | 2.0 |
| $C_{ss}$ (ng/mL) | NA | 635 | 270[b] | NA | [e] | [e] | 61.2[f] | 154[f] | 208[f] | 751[f] |
| Range | NA | 576-722 | 226-342 | NA | 290-509 | 281-307 | 46.3-88.3 | 73.9-294 | 151-266 | 685-817 |
| $CL_p$ (mL/min/kg)[g] | NA | 69 | 98 | NA | 85 | 72 | NA | NA | NA | 29.6 |
| Range | NA | 66-71 | 66-126 | NA | NA | NA | NA | NA | NA | 26.9-33.6 |
| Initial $t_{½}$ (min) | NA | 22 | 3.4 | NA | 4 | 5 | NA | NA | NA | NA |
| Range | NA | 17-28 | 2.6-3.9 | NA | NA | NA | NA | NA | NA | NA |
| Terminal $t_{½}$ (h) | NA | NA | 0.7 | NA | 0.7 | 0.4 | NA | NA | NA | 1.61 |
| Range | NA | 1.4-14.6 | 0.5-0.9 | NA | NA | NA | NA | NA | NA | 0.87-1.98 |

$CL_p$ = total plasma clearance; $C_{ss}$ = steady-state plasma concentration; NA = Not applicable, not calculated; $t_{1/2}$ = half-life.
a. Includes studies SE 10076 and SC-100124
b. Includes studies SE 10075 and SC-100123
c. Includes study SC-101314
d. Stepped 2 hour infusion at each of 3 doses
e. Single samples from pairs of animals at each time point investigated, range of $C_{ss}$ reported
f. Not at steady state observed maximum concentration reported
g. Calculation assumes equimolar dose of AR-C69712XX to cangrelor

### 4.2.5. Inhibition With Cytochrome P-450 Isozymes

As part of the program to evaluate clinically relevant drug interactions, the potential of cangrelor and the major metabolites, AR-C69712MX and AR-C90439XX, to inhibit individual cytochrome P450 (CYP) isozymes was determined in vitro [SC-102858-1].

Different concentrations of cangrelor, AR-C69712MX, and AR-C90439XX, and specific inhibitors (as control incubations) were incubated at 37°C with human liver microsomes, nicotinamide adenine dinucleotide phosphate [NADPH], and seven different substrates that act as markers for individual CYP isoform (1A2-phenacetin; 2A6-coumarin; 2C9-tolbutamide; 2C19-S-mephenytoin; 2D6-dextromethorphan; 2E1-chlorzoxazone and 3A4-testosterone). The formation of the respective marker metabolites was monitored to determine the degrees of inhibition of individual isozymes. The $IC_{50}$ determined for each individual CYP isoform is shown in Table 5.

**Table 5: Inhibition of cytochrome P450 enzymes, in vitro**

| CYP | $IC_{50}$ | | | |
|---|---|---|---|---|
| | Specific Inhibitor (controls) | Cangrelor | AR-C69712XX | AR-C90439XX |
| 1A2 | Furafylline (3.8 µM) | >100 µM | >100 µM | >100 µM |
| 2A6 | Pilocarpine (1.7 µM) | >100 µM | >100 µM | >100 µM |
| 2C9 | Sulfaphenazole (0.36 µM) | >100 µM | >100 µM | >100 µM |
| 2C19 | Omeprazole (4.1 µM) | >100 µM | 58 µM | 59 µM |
| 2D6 | Quinidine (0.097 µM) | >100 µM | >100 µM | >100 µM |
| 2E1 | Diethyldithioncarbamate (2.8 µM) | >100 µM | >100 µM | >100 µM |
| 3A4 | Ketoconazole (0.16 µM) | >100 µM | >100 µM | >100 µM |

$IC_{50}$ = concentration required to give 50% inhibition of metabolite formation; CYP = cytochrome P450.

The results showed that cangrelor did not inhibit any CYP studied ($IC_{50}$ >100 µM). AR-C69712XX and AR-C90439XX did not inhibit CP1A2, 2A6, 2C9, 2D6, 2E1, or 3A4, and inhibition of CYP 2C19 occurred only at high concentration ($IC_{50}$ >50 µM) and may be of no clinical relevance.

## 4.3. Toxicology

Nonclinical safety studies for cangrelor were conducted in rodents and dogs, with the dosing regimens studied ranging from single IV bolus dose up to 1 month continuous IV infusion. Studies on reproductive function include histopathology of the reproductive organs and semen

analysis (sperm count and motility) in a 1 month toxicity study, fertility and embryo-fetal development studies in rats and embryo-fetal development studies in rabbits. Genotoxicity was investigated in Ames tests (with an in vitro human lymphocyte assay), a mouse micronucleus test, and an in vitro mouse lymphoma assay.

All pivotal toxicity studies were performed in compliance with the principles of the Organization for Economic Cooperation and Development Good Laboratory Practice (GLP), the United Kingdom (UK) GLP regulations, and US Food and Drug Administration GLP regulations. Some early studies do not claim GLP compliance although they were conducted in a GLP compliant environment. Some of the toxicology reports do not contain the required quality assurance statements.

### 4.3.1. Single Dose Toxicity Studies

The toxicity of cangrelor was studied in mice [SE 9994/2; 96031; 97094-1] and rats [SE 9993; 96030; 97093-1] after a single IV bolus dose. Early studies used groups of 2 animals but this was later repeated with groups of 5. The minimal lethal dose of cangrelor was between 200 and 400 mg/kg in rats and mice. In the early studies, histopathological examination of major organs was conducted after a 14 day observation period. In mice [SE 9994/2; 96031] there were no histopathological findings related to treatment.

In male rats [SE 9993], histopathological changes were observed in the kidney of both animals that died after receiving 800 mg/kg. The change resembled a proliferation of endothelial cells in arcuate, interlobular, and hilar arteries and coagulative necrosis of the renal tubules in the immediate vicinity. These changes may have been postmortem artifact. Basophilic tubules were seen in the kidneys of some rats. In 1 of 2 females [96030] receiving 200 mg/kg this was of moderate severity and was associated with cortical tubular degeneration, interstitial mononuclear cell infiltration, and tubules distended with colloid.

### 4.3.2. Repeated-Dose Toxicity Studies

Results of the repeated-dose toxicity studies conducted with cangrelor are presented in Table 6. All of the following studies, except SC-30183 and SE9861 were conducted under GLP conditions.

**Table 6: Summary of repeated-dose toxicity studies**

| Study ID | Dose | Pertinent findings |
|---|---|---|
| **Three Day Toxicity Study in Male Rats** | | |
| SE 9299 | 25, 100, or 450 mg/kg/day IV | Minor signs of toxicity at 25 mg/kg/day. At 105 mg/kg/day, changes in plasma and urine chemistry indicated possible effects on kidney and liver. One rat dosed at 450 mg/kg/day died after 3 minutes. No histopathological evidence of a direct link between cangrelor and these events. |

| Study ID | Dose | Pertinent findings |
|---|---|---|
| **One Week Toxicity Study in Male Rats** | | |
| SE 9848 | 10, 25, 50, and 100 µg/kg/min IV | In the 25 µg/kg/min group, 1 rat showed slight inflammation of the hilar connective tissue and 1 showed moderately raised plasma urea, increased total urinary protein, and altered electrophoretic pattern of urinary proteins. |
| SR 97246/2 (interim kill at 1 week) | 25 or 75 µg/kg/min IV | Dose-related increases of plasma ALT, AST, ALP, albumin, and total protein. Low incidence of treatment-related histopathology changes in the renal pelvis and upper ureter. |
| **One Month Toxicity Study in Rats** | | |
| SE 9948 (male rats) | 3, 12, and 48 µg/kg/min IV | Dose-related increase in plasma AST, ALT, with reduced triglyceride and cholesterol. Dose-related decrease in liver weights, focal and widespread hepatic necrosis.<br>At 48 µg/kg/min, increased RBC and WBC count and severe pyelonephritis and ureteritis, congestion or distension and hemorrhage of the bladder.<br>At 3 and 48 µg/kg/min, increased intensity of albumin band and appearance of additional bands of proteins, potentially related to inflammation of urinary tract. |
| SE 10176 (female rats) | 3, 12, and 48 µg/kg/min IV | Dose-related increase in plasma AST, ALT, with reduced triglyceride and cholesterol. Dose-related decrease in liver weights.<br>At 48 µg/kg/min, increased RBC and WBC count, inflammation of the pelvis and hilum, sometimes accompanied by urothelial hyperplasia, pelvic necorsis, ureteritis, ureteral necrosis, or urothelial hyperplasia and urothelial erosion. Increased intensity of albumin band and appearance of additional bands of proteins, potentially related to inflammation of urinary tract. |
| SR 97246/2 | 25 or 75 µg/kg/min IV | Histopathological evidence of effect on kidney and upper urinary tract after 1 month shown to be reversible in the 1-month recovery group. Recovery group showed no inflammation in renal pelvis and ureter; 5 animals had residual renal changes.<br>Increased levels of plasma ALT, AST, albumin, and total protein shown to be reversible. Celluria and electrophoretic patterns of urinary protein completely reversed in all but 1 high-dose animal, which showed signs of recovery. |

| Study ID | Dose | Pertinent findings |
|---|---|---|
| **Thirteen Day Study in the Female Dutch Rabbit** | | |
| 96159-1 | 60 or 90 µg/kg/min IV | Conducted to support reproductive toxicity studies. Plasma concentrations of cangrelor ranged from 15900 to 55500 ng/mL at 60 µg/kg/min, and 13700 to 134000 ng/mL at 90 µg/kg/min. Results for AR-C69712XX ranged from 1830 to 3350 ng/mL at 60 µg/kg/min, and 6030 to 15100 ng/mL at 90 µg/kg/min. Dose-related toxicity demonstrated in 13% and 30% at 60 and 90 µg/kg/min, respectively. Renal dysfunction seen at both doses but most severe at 90 µg/kg/min. Cangrelor caused increased plasma ALT, AST, ALP, and GGT with most severe effects at 90 µg/kg/min. At this dose, 1 animal had marked periportal vacuolation. |
| **Preliminary Tolerability, and One Week Study in Male Dog** | | |
| SC-30183 | 18, 36, or 40 µg/kg/min IV | No signs of intolerance |
| SE 9861 | 40 or 60 µg/kg/min IV | Minor inflammatory changes occurred in the renal pelvis, ureter, and urinary bladder of 1 animal at 60 µg/kg/min IV. No other significant toxicology changes. |
| **One Month Study in Dogs** | | |
| SE 9862 (male dogs) | 0, 3.75, 15, and 60 µg/kg/min IV | Dose-related increase in mean plasma concentrations in both cangrelor and AR-C69712XX. Aminotransferases raised at 60 µg/kg/min IV.<br>Renal toxicity seen at 60 µg/kg/min IV (tubular necrosis and regeneration, pelvic and interstitial inflammation and urothelial necrosis proteinuria, raised plasma urea, raised plasma creatinine, glucosuria, and raised plasma creatinine).<br>Two dogs receiving 60 µg/kg/min IV showed increased severity and frequency of asynchronous PVCs.<br>Minor opthalmological changes in 3 dogs at 15 and 60 µg/kg/min IV, but no functional or behavorial perturbations. |
| SE 10177 (female dogs) | 0, 3.75, 15, and 60 µg/kg/min IV | Dose-related increase in mean plasma concentrations in both cangrelor and AR-C69712XX. Aminotransferases raised at 15 and 60 µg/kg/min IV.<br>Renal toxicity seen at 60 µg/kg/min IV (basophilic tubules and/or tubules distended with colloid, and inflammatory cell foci. Proteinuria, raised plasma urea, raised plasma creatinine, raised urinary ß-NAG). |

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; , ß-NAG = ß-N-acetylglucosaminidase; GGT = gamma-glutamyl transferase; IV = intravenous; PVC = Premature Ventricular Contraction; RBC = red blood cell; WBC = white blood cell.

### 4.3.3. Reproductive Toxicity Studies

A summary of the reproductive toxicity studies conducted with cangrelor is provided in Table 7. All of the following studies were conducted under GLP conditions.

**Table 7 Summary of reproductive toxicity studies**

| Study ID | Dose | Pertinent findings |
|---|---|---|
| **Dose-Finding Embryo-Fetal Development Study in the Rat (17 days)** | | |
| 96178 | 24, 48, or 96 µg/kg/min IV or vehicle control | Plasma chemistry and histopathology changes consistent with other rat studies.<br>Losses before and after implantation increased and fetal weight reduced at 96 µg/kg/min. Slight reduction in fetal weight at 24 and 48 µg/kg/min.<br>96 µg/kg/min selected as high dose in embryo-fetal development study (SR 98002) |
| **Embryo-Fetal Development Study in the Rat (17 days)** | | |
| SR98002 | 3, 12, or 48 µg/kg/min IV or vehicle control | Dose-related increase in plasma concentrations at Day 7 and 17 after coitum.<br>Slight reduction in fetal weights and increased incidence of unossified metatarsals at all dose levels of cangrelor<br>At 48 µg/kg/min, entire litter of 1 animal was dead at C-section. This animal had impacted large intestine at necropsy. Two animals at this dose had macroscopic necropsy findings that included pale kidney(s), pale liver, and/or renal dilation and experienced reduced body weight gain and food consumption from Day 18 after coitum. Also increased incidence of incomplete ossification of skull bones and sternebrae and a slight reduction in numbers of viable fetuses at this dose. |
| **Fertility and Early Embryo-Fetal Development Study in the Female Rat (14 days)** | | |
| SR98074-01 | 3, 12, or 48 µg/kg/min IV or vehicle control | No notable dose-related effects on food consumption or body weights. Clinical signs and macroscopic findings at necropsy consistent with previous studies. No effect on estrous cycles, mating performace, and losses before implantation. At 48 µg/kg/min IV, statistically significant increase in losses after implantation. |

| Study ID | Dose | Pertinent findings |
|---|---|---|
| **Fertility Study in the Male Rat (8 weeks)** | | |
| SR98073/1 | 3, 12, or 48 µg/kg/min IV or vehicle control | Dose-related incidence of blood in the urine, consistent with urinary tract toxicity seen in other rat studies.<br>No effect on body weight body weight or food consumption. Decrease in body temperature observed.<br>At 48 µg/kg/min, 4 of 18 males at high dose failed to produce pregnancy with partner. Five of the pregnancies at this dose experienced high loss. Abnormal sperm morphology and reduced sperm motility seen in all males at this dose, as well as reduced epididymal and vas deferens sperm counts, low epididymal weights, testicular tubular epithelial atrophy, tubular dilation. The latter were associated with epididymal oligospermia, spermatocele formation, and spermatocele degeneration.<br>In the recovery group, 3 of 8 males dosed at 48 µg/kg/min showed tubular epithelial atrophy with associated effects. In 1 of 9 control males and 1 of 9 males dosed at 12 µg/kg/min, tubular epithelial atrophy was seen alone. |
| **Dose-Finding Embryo-Fetal Development Study in the Rabbit (19 Days)** | | |
| 97241/1 | 24, 48, or 60 µg/kg/min IV or vehicle control | One animal (60 µg/kg/min) died. Maternal toxicity as indicated by reduced food and water consumption and consequent reduced fecal and urine production was seen at all doses. Dose-related body weight loss, tubular dilation, degeneration, and casts. Centrilobular necrosis seen at both 48 and 60 µg/kg/min. Diffuse vacuolation seen in the liver in all doses. Litter lost due to total or partial intrauterine death or abortion increased at 48 and 60 µg/kg/min. No effect seen on fetal weight. Both 48 and 60 µg/kg/min determined as too high for definitive embryo-fetal development study in Dutch rabbits. |
| **Embryo-Fetal Development Study in the Rabbit (19 Days)** | | |
| SR 97297 | 4, 12, and 36 µg/kg/min IV or vehicle control | Dose-related increase in plasma concentrations at Day 7 and 18 after coitum.<br>Increased incidence of total intrauterine death and abortion at 12 and 36 µg/kg/min. Maternal body weight, food and water consumption, and fecal production all reduced during the dosing period in all cangrelor-treated groups, which may have influenced small reduction in fetal weight and ossification at 36 µg/kg/min. Small increase in blood vessel and skeletal variants was also observed at the high dose. |

C-section = Ceasarean section; IV = intravenous.

### 4.3.4. Genotoxicity Studies

A comprehensive battery of genotoxicity studies has been completed, including bacterial and mammalian cell mutation assays and assays for cytogenetic damage using in vitro and whole animal systems. The in vitro tests were done both in the absence and presence of an exogenous metabolic activation system, derived from rat liver (S9 mix). These are described below.

In an Ames assay [SE 9940] using concentrations of up to 5000 µg/plate, the potential of cangrelor to induce point mutations was assessed using *Salmonella typhimurium* strains TA 1535, TA 1537, TA 98, TA 100, and TA 102. Prior to this study, during the early phase of development, limited Ames assays were conducted with cangrelor [SE 9389] and 2 of its metabolites, AR-C69712XX [SE 9563] and AR-C71301XX [SE 9564], using *Salmonella typhimurium* strains TA 1537, TA 98, TA 100, and TA 102. In addition, because 1 batch (4044G) contained an unknown impurity (N) not detected in previous batches, this was also tested in a limited Ames test [97036/1]. Cangrelor and its metabolic products were not mutagenic in any of the tests.

Cangrelor was not mutagenic when assayed for its ability to induce forward mutations in Mouse Lymphoma L5178Y cells at the thymidine kinase locus [96102]. Cangrelor was not clastogenic when tested for its ability to induce chromosomal aberrations in human peripheral blood lymphocytes in vitro [SE 9958]. There were no significant, reproducible increases in the frequency of structural chromosome aberrations or polyploidy that could be attributed to the test compound.

Two separate, completed, in vivo studies were designed to assess the potential of cangrelor to induce genetic damage when administered to male mice. A limited study [SE 9341] was completed during the early stages of development in which cangrelor was administered to groups of 7 male mice at 500 mg/kg as a slow IV bolus (5 minutes at 1 mL/kg/min). In the main study [96122], cangrelor was administered at 125, 250, and 500 mg/kg to groups of 9 male mice. Two animals receiving the highest dose of cangrelor died prior to the scheduled sampling times and the majority of animals exhibited adverse clinical signs. Animals were killed 24 or 48 hours later, the bone marrow extracted, and smear preparations made and stained. Polychromatic and normochromatic erythrocytes were scored for the presence of micronuclei. There was no evidence of an increase in the incidence of micronucleated polychromatic erythrocytes in either study and so it was concluded that cangrelor was nongenotoxic under the conditions of the tests.

### 4.3.5. Discussion

The results of animal toxicity studies predict that renal and urinary tract toxicity is the principal potential hazard associated with treatment with cangrelor. In the rat, the toxicity seen after 1 months dosing has been shown to be reversible. In respect to histopathology changes in rats, the no effect dose was 12 µg/kg/min for 1 month. In dogs, 1 week dosing at 40 µg/kg/min and 1 month dosing at 15 µg/kg/min produced no toxicologically significant changes in renal function or morphology. Female dogs were less affected, showing only minimal changes at 60 µg/kg/min after 1 month.

In Table 8, exposure to cangrelor in humans is compared with exposure in animals at a dose that was free from histopathology changes.

**Table 8: Human exposure to AR-C69931XX during continuous IV infusion compared with exposure in rats and dogs at the no-effect dose**

| Species | Sex | Fraction unbound in Plasma | Infusion Rate (µg/kg/min) [days] | $C_{SS}$ (ng/mL) | | $AUC_{0\text{-duration}}$ (µg/min/kg) Unbound |
|---|---|---|---|---|---|---|
| | | | | Total | Unbound | |
| Human | Male | 0.011 | 4 | 329 | 3.6 | 26.1 |
| | Female | 0.011 | 4 | 352 | 3.9 | 27.9 |
| Rat | Male | 0.013 | 12 [28] | 328 | 4.3 | 172 |
| | Female | 0.013 | 12 [28] | 300 | 3.9 | 157 |
| Dog | Male | 0.038 | 40 [7] | 551 | 20.9 | 211 |
| | Male | 0.038 | 15 [28] | 266 | 10.1 | 408 |
| | Female | 0.038 | 15 [28] | 219 | 8.3 | 336 |

AUC = Area under the concentration curve; AUC for human estimated for 0 to 5 days; $C_{ss}$ = Steady-state plasma concentration
Source: SE9948; SE10176; SE9861; SE9862; SE10177; SC-931-5014; SC-931-5036.

Because some of the comparisons presented above offer little or no margin when comparing the highest no-effect dose in animals with the dose used clinically, the clinical significance of these findings is questionable. Attempts to correlate plasma concentrations of cangrelor or the major plasma metabolite, AR-C69712XX, to renal toxicity have not shown a causal relationship. If the duration of dosing is considered, then a large margin of safety is evident, as shown by extrapolating AUCs at the no-effect doses after 4 weeks in animals to 5 days exposure in man.

It may be speculated that the renal effects seen in animals could be due to a metabolite present in the urine. Comparison of the metabolite profile in man and animals demonstrates that they are qualitatively similar. However, the predominant route of excretion is via the urine in man and via the bile in animals. The major urinary metabolite in man is AR-C90439XX, a sulphoxide of AR-C69712XX. Table 9 illustrates the estimated 24 hour urinary excretion of AR-C90439XX at the maximum expected therapeutic dose in man, and the no-effect dose in animal safety studies.

**Table 9: Estimated 24 hour urinary excretion data for AR-C90439XX following a 2 hour intravenous infusion of cangrelor**

| Species | Cangrelor (AR-C69931MX) (µg/kg/min) | AR-C90439XX excreted in urine in 24h (µg/kg) | References |
|---|---|---|---|
| Rat | 12 | 122 | Extrapolated from data in SE 10010 and SC-100358 |
| Dog | 15 | 26 | Extrapolated from data in SE 10011 and SC-100357 |

| Species | Cangrelor (AR-C69931MX) (µg/kg/min) | AR-C90439XX excreted in urine in 24h (µg/kg) | References |
|---|---|---|---|
| Dog | 40 | 69 | Extrapolated from data in SE 10011 and SC-100357 |
| Man | 4 | 123 | Extrapolated from data in SC-931-9017 |

Note: All data normalized to a 2 hour infusion period.

These data demonstrate that urinary excretion is comparable, and it can be assumed that this will be the case during continuous infusion. Importantly, studies in humans have included treatment for up to 72 hours at a dose of 4 µg/kg/min with no evidence of clinically significant adverse effects on the kidney or urinary tract [SC-931-9017].

Plasma enzyme (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) changes have been documented consistently in all animal species investigated. A rat study [SR 97246/2] has demonstrated that these changes are reversible following cessation of treatment. There has been no clear association with organ damage in rats and dogs, although liver changes noted in rabbits may be associated with the compound. Notably, the plasma concentration of cangrelor and AR-C69712XX observed in rabbits is considerably higher, dose-for-dose, than in rats and dogs.

Although whole body autoradiography showed some thyroid and bone marrow exposure during dosing [SE 10012], which declined rapidly thereafter, there was no evidence to indicate any adverse effects in these tissues.

Minor ECG changes observed during the 1 month toxicity study in two male dogs, consisting of an increased severity and frequency of asynchronous premature ventricular contractions (PVCs) at 60 µg/kg/min on 2 of 3 and 1 of 3 occasions during treatment, are considered to be of no toxicological importance because asynchronous PVCs are occasionally observed in controls. Asynchronous PVCs had been noted less frequently, prior to treatment in one of the affected dogs; there were no effects reported in female dogs.

Minor changes seen in the eyes of some male dogs are considered not to be of toxicological significance. The changes were seen in the tapetum, a structure present in dogs but not in man. Furthermore, there were no changes seen in female dogs dosed with cangrelor.

Effects on fertility, ability to produce a pregnancy with female partner(s), sperm morphology and sperm motility have been noted in the male fertility study [SR98073/1] at 48 µg/kg/min. These effects were not apparent at lower doses and were reversible following cessation of dosing. In this study, semen analysis was conducted after 8 weeks of continuous treatment. In a previous 1 month toxicity study [SE 9948], semen analysis conducted after 4 weeks treatment had shown no abnormalities. Together, these studies appear to indicate that the observed effects are produced only after continuous dosing for longer than 4 weeks and importantly, the effects are reversible. It is therefore considered that this finding has no toxicological significance in relation to the proposed clinical use of cangrelor. Female fertility (estrous cycles, mating performance, preimplantation losses) was unaffected by cangrelor.

There was no indication in rat and rabbit embryo-fetal development studies that cangrelor has the potential to cause malformations. These studies provide an extremely rigorous test of the compound's potential to affect in utero development. Exposure of the pregnant animals was maintained continuously, by IV infusion, from implantation of the blastocyst until the completion of major organogenesis. During this period the steady-state plasma concentration of AR-C69931XX, compared with likely human plasma concentration, was approximately 6 times higher in rats and 60 times higher in rabbits. Data from a tissue distribution study in pregnant rats [SC-100295] using radio labeled cangrelor show that exposure of the fetus was less than maternal tissue. This is consistent with the view that cangrelor does not readily cross membranes. Evidence of delayed fetal development was noted in both rats and rabbits. Although a direct effect of the compound on the fetus cannot be ruled out, it is likely that maternal stress due to the infusion procedure or the toxicity of the compound may have contributed to the observed effects.

Overall, the findings from the toxicology studies support the dose used in the Phase III clinical studies. Relative to cangrelor, there are no reasons to specifically exclude women of childbearing potential from clinical trials.

# 5. EFFECTS IN HUMANS

## 5.1. Overview of Completed Clinical Studies with Cangrelor

A total of 14 clinical studies with cangrelor have been completed to date, with 7,655 cangrelor-treated subjects.

Under the original sponsorship of AstraZeneca, five Phase I studies (SC-931-5014, SC-931-5036, SC-931-5109, SC-931-9017, and SC-931-5037) and four Phase II studies (SC-931-5058, SC-931-5060, SC-931-5129 Part 1, and SC-931-5129 Part 2) were completed. An additional Phase II study, SC-931-5135, was terminated prematurely due to reprioritization of drug development candidates by the former Sponsor (AstraZeneca).

Under the sponsorship of The Medicines Company, two additional healthy volunteer studies (TMC-CAN-04-02 and TMC-CAN-08-01) were completed, and two Phase III studies (TMC-CAN-05-02 and TMC-CAN-05-03) were initiated but terminated early. Details of all completed clinical studies are summarized in Table 10.

Healthy volunteer studies SC-931-5014 and SC-931-5036 examined the safety and tolerability of cangrelor at increasing infusion rates of up to 4 µg/kg/min in healthy male and female volunteers, respectively. Study SC-931-9017 assessed the distribution, metabolism, and excretion of a [$^3$H]cangrelor infusion (2 µg/kg/min). The possible interactions of aspirin, heparin, and GTN on the PK and PD of cangrelor were investigated in study SC-931-5037. Study SC-931-5109 compared the safety and tolerability of cangrelor in normal subjects to those with mild to severe renal impairment. Study TMC-CAN-04-02 was conducted to evaluate the PK and PD parameters of a bolus plus infusion dosing regimen of cangrelor in healthy volunteers. TMC-CAN-08-01 was designed to assess the safety of therapeutic and supratherapeutic doses of cangrelor on cardiac repolarization as measured by ECG.

The first study in patients with non-Q-wave myocardial infarction (non-Q-MI), SC-931-5058, determined the PK and PD of various infusion rates (up to 4 µg/kg/min) of cangrelor in patients

with UA/non-Q-MI. Study SC-931-5060 further assessed the safety, tolerability, and PK of 4 µg/kg/min cangrelor in UA/non-Q-MI patients when administered as a continuous infusion for 72 hours. The effects of cangrelor were studied in patients undergoing coronary revascularization in study SC-931-5129 Part 1 and SC-931-5129 Part 2. Study SC-931-5135 assessed the safety, tolerability, and the effect on coronary artery patency of cangrelor in patients with STEMI. The study was terminated due to changes in business priorities.

The cangrelor Phase III clinical development program (CHAMPION) was designed to demonstrate that cangrelor bolus and infusion followed by transition to oral therapy prevents platelet aggregation and is effective in preventing acute life-threatening events in patients undergoing PCI, while not increasing the risk of bleeding. This program was composed of two independent studies, CHAMPION PCI (TMC-CAN-05-02) and CHAMPION Platform (TMC-CAN-05-03).

The PCI study (TMC-CAN-05-02) planned enrollment of 9,000 patients within the following categories: SA, UA, NSTEMI, or STEMI. Patients received a dose of clopidogrel at the start of the PCI procedure and the study was designed to demonstrate superiority to a 600 mg loading dose of clopidogrel.

The Platform study (TMC-CAN-05-03) planned enrollment of 6,400 patients within the following categories: SA, UA, or NSTEMI. In contrast to PCI, STEMI patients were not enrolled in the Platform study. The other key difference was that patients did not receive a dose of clopidogrel at the start of the PCI procedure; instead, clopidogrel was given at the end of the PCI procedure. Therefore, the study was designed to demonstrate superiority to usual care. Exclusion criteria required patients to be clopidogrel-naïve, eg, no clopidogrel within 7days prior to randomization.

The primary efficacy endpoint in both studies was the 48-hour composite of all-cause mortality, MI, or IDR. Secondary efficacy endpoints included the composite of mortality or MI at 48 hours and 30 days; the composite of mortality, MI, or IDR at 30 days, the individual components of the composite endpoints at 48 hours and 30 days, the incidence of stroke at 48 hours, acute (24 hours) and subacute (48 hours) stent thrombosis, and the incidence of all-cause mortality at 6 months and 1 year.

The CHAMPION program was designed to enroll approximately 15,400 patients; however enrollment was terminated early following the Platform 70% interim analysis, with 98% (8882) patients enrolled in PCI and 84% (5364) patients enrolled in Platform, due to the low likelihood of achieving the primary endpoint in both studies.

**Table 10: Summary of completed clinical studies performed with cangrelor**

| Study Identifier (Phase) | Study Design | Region | Dose cangrelor | Study Treatments | Number of Subjects | Treatment Duration (h) | Status |
|---|---|---|---|---|---|---|---|
| SC-931-5014 (I) | Tolerability, safety, activity & pharmacokinetics in healthy male volunteers | UK | 0.25 ng/kg/min – 4 µg/kg/min | cangrelor<br>placebo | 28<br>12 | 23 | Completed 1996 |
| SC-931-5036 (I) | Tolerability, safety, activity & pharmacokinetics in healthy female volunteers | UK | 0.01 – 4 µg/kg/min | cangrelor<br>placebo | 15<br>8 | 23 | Completed 1996 |
| SC-931-9017 (I) | Metabolic profile, route of excretion in healthy male volunteers | UK | 2 µg/kg/min | cangrelor | 4 | 2 | Completed 1996 |
| SC-931-5037 (I) | Interactions with aspirin, heparin & GTN; 2-way crossover in healthy male volunteers | UK | 0.05 – 2 µg/kg/min | cangrelor | 12 | 3.75 | Completed 1996 |
| SC-931-5109 (I) | Safety, tolerability, pharmacokinetics & platelet aggregation in renally impaired patients | Germany | 0.05 – 4 µg/kg/min | cangrelor | 24 | 5 | Completed 1999 |
| TMC CAN 04-02 (I) | Randomized, open-label study of the effects of bolus plus infusion on healthy volunteers, administration with clopidogrel | US | 15 or 30µg/kg bolus + 2 or 4 µg/kg/min infusion | cangrelor +/- clopidogrel | 42 | 1 or 2 | Completed 2005 |
| TMC CAN 08-01 (I) | A double-blind, placebo-controlled, positive-controlled, randomized, crossover study to assess the effect of cangrelor at the therapeutic dose and a supratherapeutic dose level on the QT/QTc interval in healthy volunteers | US | 30 µg/kg IV bolus followed by 4 µg/kg/min or 60 µg/kg IV bolus followed by 8 µg/kg/min | cangrelor<br>placebo | 71 | 3 | Completed 2008 |
| SC-931-5058 (II) | Safety, tolerability, activity & pharmacokinetics in UA/non-Q-MI patients | UK, Netherlands | 0.05 – 2 µg/kg/min<br>0.2 – 4 µg/kg/min | cangrelor | 39 | 24/72 | Completed 1998 |

| Study Identifier (Phase) | Study Design | Region | Dose cangrelor | Study Treatments | Number of Subjects | Treatment Duration (h) | Status |
|---|---|---|---|---|---|---|---|
| SC-931-5060 (II) | Double-blind, placebo controlled safety, tolerability & pharmacokinetics in UA/non-Q-MI patients | Sweden | 4 µg/kg/min | cangrelor<br>placebo | 45<br>46 | 72 | Completed 1999 |
| SC-931-5129 Part 1 (II) | Double-blind, placebo controlled, safety, pharmacokinetics, platelet aggregometry & bleeding time in patients undergoing PTCA | US | 1, 2, 4 µg/kg/min | cangrelor<br>placebo | 149<br>51 | 18-24 | Completed 1999 |
| SC-931-5129 Part 2 (II) | Safety, platelet aggregometry & bleeding time in patients undergoing PTCA | US | 4 µg/kg/min | cangrelor<br>abciximab | 105<br>94 | 18-24<br>10-12 | Completed 1999 |
| SC-931-5135 (II) | Open-label, randomized paralled group safety, tolerability on coronary artery patency in ST-elevation MI patients | US, Canada | 35-280 µg/min | cangrelor & Activase<br>Activase only | 85<br>7 | 24-72 | Terminated Early 2001 |
| TMC-CAN-05-02 (PCI) (III) | Randomized, double-blind, double-dummy, active control, parallel grou comparing cangrelor to clopidogrel in subjects who require percutaneous coronary intervention | Multi-national | 30 µg/kg IV bolus + 4 µg/kg/min IV infusion | cangrelor<br>clopidogrel | 4374<br>4365 | 2-4 | Terminated May 2009 |
| TMC-CAN-05-03 (Platform) (III) | Randomized, double-blind, placebo-controlled, parallel group comparing treatment with cangrelor (in combination with usual care) to usual care, in subjects who require percutaneous coronary intervention | Multi-national | 30 µg/kg IV bolus + 4 µg/kg/min IV infusion | cangrelor<br>clopidogrel | 2662<br>2650 | 2-4 | Terminated May 2009 |

GTN = nitroglycerin; IV = intravenous; MI = myocardial infarction; non-Q-MI = non-Q-wave myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; QTc = QT interval corrected for heart rate; UA = unstable angina; UK = United Kingdom; US = United States.

## 5.2. Pharmacokinetics and Product Metabolism in Humans

### 5.2.1. Absorption

The absorption properties of cangrelor in humans were not evaluated due to its intended IV use.

### 5.2.2. Disposition

#### 5.2.2.1. Healthy Volunteer Studies

Plasma concentrations of the parent compound (AR-C69931XX) and the primary metabolite (AR-C69712XX) were determined in healthy volunteer studies [SC-931-5014; SC-931-5036]. Results from these ascending doses studies indicated that the plasma clearance of the compound was rapid in both male and female subjects, and that it has a short initial half-life (3.5 to 6.0 minutes). Steady-state plasma concentrations were rapidly achieved following IV administration, and plasma concentrations of both parent and metabolite were found to decline in a bi-exponential manner in both studies following termination of the infusion.

Plasma clearance (53 L/hour) of the parent compound did not change significantly over the administered dose range. Steady-state concentrations of cangrelor increased linearly with dose. There was no evidence of any clinically important sex-related differences in the PK of either cangrelor or the primary metabolite (
Table 11:). Assuming the molar fraction (f) of AR-C69931XX converted to AR-C69712XX was 1.0, the clearance of the primary metabolite was more rapid than that observed for the parent compound. Steady-state plasma concentrations of the primary metabolite were lower than those of the parent compound.

**Table 11:: Pharmacokinetic parameter estimates and steady-state plasma concentrations of cangrelor and the primary metabolite following administration to male and female volunteers**

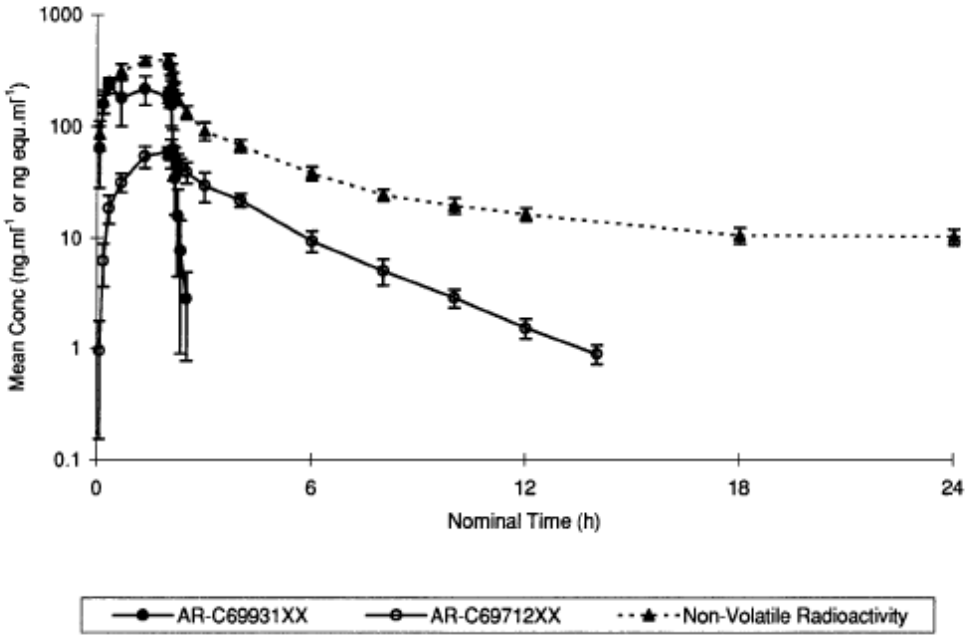
| Parameter | SC-931-5014 (male) (4 µg/kg/min) Mean (N = 6) | SC-931-5036 (female) (4 µg/kg/min) Mean (N = 3) |
|---|---|---|
| $C_{ss}$ parent | 329 ng/mL | 350 ng/mL |
| $C_{ss}$ metabolite | 204 ng/mL | 222 ng/mL |
| Clearance of parent | 13.2 mL/min/kg / 53 L/h | 12.7 mL/min/kg / 53 L/h |
| Clearance of metabolite[a]/f | 22.4 mL/min/kg / 92 L/h | 20.0 mL/min/kg / 108 L/h |
| Parent/metabolite ratio[b] | 0.92 | 1.04 |
| Half-life α phase of parent | 3.5 min | 6 min |
| Half-life β phase of metabolite | 2.7 h | 2.9 h |

$C_{ss}$ = plasma concentration at steady state; AR-C69931XX = parent compound; AR-C69712XX = metabolite; f = molar fraction.
a Estimates of metabolite clearance assume that f was approximately 1.0
b Derived from overall mean of late plateau measurements at and above rates of 100 µg/kg /min
Source: Studies SC-931-5014 and SC-931-5036.

***Radiolabelled Cangrelor Study***

Additional distribution and elimination information for cangrelor infusions was generated from study SC-931-9017 in which healthy male volunteers received [$^3$H]cangrelor IV infusions for 2 hours (2 µg/kg/min). During the infusion, the plasma concentration of radioactivity increased rapidly, reaching a plateau toward the end of the infusion period. In the first 10 hours after the end of infusion, total radioactivity declined in a bi-phasic manner, with the initial decline in total radioactivity attributable to the elimination of the cangrelor parent compound and distribution of the primary circulating metabolite (Figure 4).

**Figure 4: Mean (± SD) plasma concentrations for AR-C69931XX (ng·ml$^{-1}$), AR-C69712XX (ng·ml$^{-1}$) and non-volativle radioactivity (ng equ·ml-1) over the initial 24-hour period following an intravenous infusion of AR-C6991MX at a rate of 2 µg·kg$^{-1}$·min $^{-1}$ to healthy male volunteers (n=4) (Study SC-931-9017)**




Source: Study SC-931-9017, Figure 1.

Plasma analysis indicated that cangrelor rapidly reached steady-state. The half-life (5 minutes) was similar to that observed in volunteer studies [SC-931-5014; SC-931-5036], as was the estimated terminal half-life (2.1 hours). Mean clearance was approximately 10.3 mL/kg/min.

The primary metabolite (AR-C69712XX) reached a maximum concentration of 65 ng eq AR-C69931XX/mL (26% of AR-C69931XX $C_{max}$), and remained below the concentration achieved by the parent compound until after the end of infusion.

The profile of the remainder of plasma radioactivity not accounted for by the parent compound and primary metabolite appeared to rise and decay on a similar time course to the nucleoside metabolite. A maximum concentration of 402 ng eqAR-C69931XX/mL was reached very shortly after the end of infusion.

#### 5.2.2.2. Studies in Patients with Unstable Angina/Non Q-Wave Myocardial Infarction

The PK of cangrelor and the primary metabolite were estimated in patients with UA/non-Q-MI receiving a cangrelor infusion of up to 4 µg/kg/min in study SC-931-5058. Results indicated that the parent compound was cleared very rapidly from the plasma (44.3 L/hour), at a similar rate to that observed in healthy volunteers [SC-931-5014; SC-931-5036], and had a low initial volume of distribution (5.1 L). Estimates of the volume of distribution at steady state (13.4 L) suggested that the parent compound was not extensively distributed (Table 12). The population PK estimates for clearance were slightly less than the values calculated from healthy volunteer studies [SC-931-5014; SC-931-5036]. Mean population PK estimates suggested that the average half-life for cangrelor in this population was less than 5 minutes, and that the majority of patients (90%) had an estimated value of less than 9 minutes.

Inter-patient variability for clearance was low at 14.4% (Table 12).

**Table 12: Mean population pharmacokinetic parameters for cangrelor and the primary metabolite in patients with UA/non-Q-MI**

| Parameter | Mean ± SE | Inter-individual Variance (%) |
|---|---|---|
| **Parent** | | |
| Clearance (L/h) | 44.3 ± 2.16 | 14.4 |
| Initial volume of distribution (L) | 5.1 ± 0.53 | 3.46 |
| Tissue volume (L) | 8.3 ± 0.84 | NE |
| Volume at steady state (L) | 13.4 | |
| **Metabolite** | | |
| Clearance (L/h)/f | 74.3 ± 4.48 | 30.0 |
| Initial volume (L)/f | 24.1 ± 4.14 | NR |
| Volume of distribution at steady state (L)/f | 192 ± 9.23 | NE |

AR-C69931XX = parent compound; AR-C69712XX = metabolite; f = molar fraction (~ 1.0); NE = not estimated; NR = not reported; SE = standard error.
Source: Study SC-931-5058.

The PK profile of cangrelor was constant over the dosing interval; parameter estimates suggested that the mean $C_{ss}$ was 375 ng/mL for the 4 µg/kg/min dose, which is slightly higher than the value observed in healthy volunteers (Table 11

Table 11:). The PK profile in this group was unaffected by changes in either the infusion rate or the infusion duration (up to 72 hours). The plasma concentrations of the metabolite declined less rapidly than those for the parent compound after the end of the infusion, and had an estimated clearance/f higher than that for the parent compound (74.3 L/hour). Estimates of the metabolic half-life were larger than those for the parent compound (2 hours), mainly due to its larger volume of distribution at steady state (192 L), which suggested that the primary metabolite was extensively distributed (Table 12).

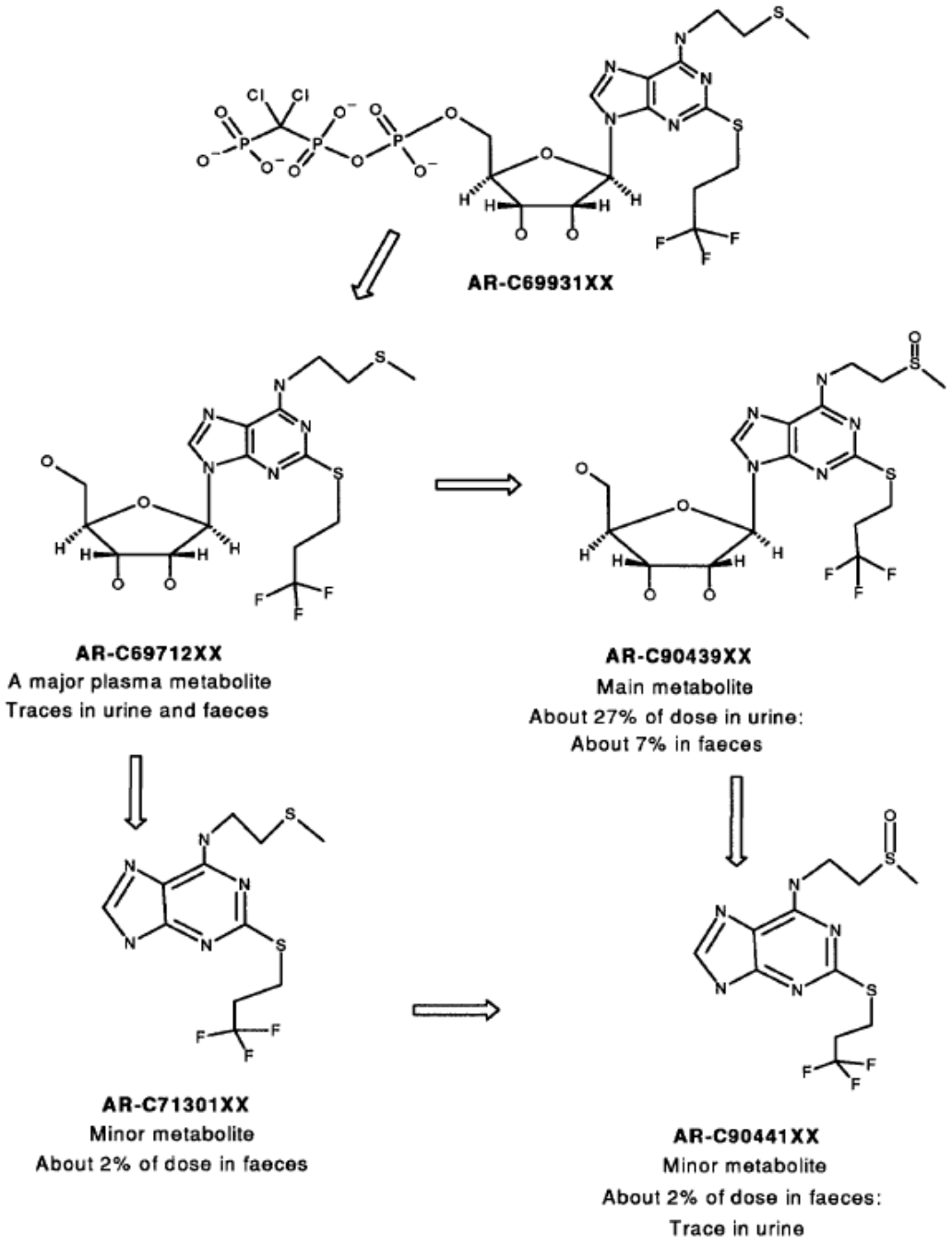
Steady-state plasma concentrations were analyzed from study SC-931-5060 in which patients with UA/non-Q-MI received cangrelor infusions of 4 µg/kg/min for up to 72 hours. Mean estimates of clearance (41.0 ± 1.58 L/hour) were similar to those from study SC-931-5058, with a low inter-individual variability (22.2%). Clearance estimates were not affected by the longer duration of infusion (72 hours).

### 5.2.3. Metabolism

The metabolic fate of the cangrelor parent compound was investigated in plasma and excreta samples from subjects following IV administration of [$^3$H]cangrelor in study SC-931-9017. This was qualitatively similar to that observed in animal studies (see Section 4.2.2). It appears that cangrelor is cleared rapidly by dephosphorylation to form the nucleoside (AR-C69712XX), as judged by the absence of significant quantities of the parent compound in excreta. AR-C69712XX was the major circulating metabolite. The major excreted metabolite cochromatographed with AR-C90439XX, a sulphoxide of the nucleoside. In contrast to findings in the rat and dog studies, this metabolite appeared mainly in urine, accounting for 27.3% of the dose, with only 6.6% of the dose in feces. The next most abundant metabolite was a corresponding sulphoxide of the base, AR-C90441XX, which accounted for <5% of the dose in both urine and feces. Only trace amounts of the nucleoside AR-C69712XX were found in either feces or urine, although this was initially the major metabolite circulating in plasma. The remainder of the dose consisted of the substituted purine base AR-C71301XX, and other products of S-oxidation, purine base oxidation, deribosylation, and glucuronidation. No products of oxidative de-amination at C6 of the purine ring of AR-C69712XX were detected in this study, which indicated that metabolism by endogenous purine nucleoside salvage pathways did not occur.

A scheme presenting the postulated routes of metabolism of cangrelor is given in Figure 5.

**Figure 5: Postulated major routes of metabolism of AR-C69931MX**




### 5.2.4. Elimination

Following IV administration of [$^3$H]cangrelor [SC-931-9017], 93% of total radioactivity was recovered but, contrary to findings in animal studies, 58% of this was in urine, and the remaining 35% was in feces, presumably following biliary excretion. Initial excretion was rapid, such that approximately 50% of the administered radioactivity was recovered in the first 24 hours, and

75% was recovered by 48 hours. The majority of the fecal load emerged more slowly and variably over the 72 hour period, and was attributed to delays caused by the frequency of bowel opening and latencies in gut transit time.

In study SC-931-5109, healthy volunteers and subjects with renal insufficiency were administered cangrelor infusions in ascending doses (50 to 4000 ng/kg/min) for 5 hours. The primary objective was to compare the plasma concentrations of the parent compound and the major circulating metabolite and to assess the safety and tolerability by monitoring appropriate clinical and laboratory parameters. The plasma concentration-time profiles for cangrelor and its primary metabolite were comparable to those observed previously in healthy volunteers. Importantly, the PK/PD relationship for the parent compound and the major circulating metabolites appeared to be unaffected by renal impairment. Table 13 shows a summary of the PK parameters.

**Table 13: Summary of main pharmacokinetic parameters (results expressed as arithmetic mean ± SD)**

| | | | Pharmacokinetic Parameter for | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | AR-C69931XX | | AR-C69712XX | | AR-C90439XX | |
| Group | Group Size | Maximum Infusion Rate (ng/kg/min) | $t_{½}$ (min) | CL (L/h) | $t_{½}$ (h) | CL/f (L/h) | $t_{½}$ (h) | CL/f (L/h) |
| Healthy Volunteers | 4 | 2000 | 3.7 ± 0.2 | 66.3 ±5.6 | 2.5 ± 0.3 | 112.7 ± 20.2 | 1.2 ± 0.1 | 231.3 ± 19.5 |
| Renally Impaired | 8 | 2000 | 3.9 ± 0.4 | 57.5 ± 8.2 | 2.5 ± 0.3 | 128.4 ± 52.9 | 1.3 ± 0.2 | 134.0 ± 52.2 |
| Healthy Volunteers | 4 | 4000 | 3.5 ± 0.1 | 72.9 ± 11.7[a] | 2.3 ± 0.1 | 142.8 ± 33.0 | 1.0 ± 0.1 | 287.3 ± 92.9 |
| Renally Impaired | 8 | 4000 | 3.8 ± 0.5[b] | 53.8 ± 17.4[b] | 2.6 ± 0.5 | 88.6 ± 30.6 | 1.7 ± 0.3 | 141.1 ± 37.0 |

CL = clearance; f = molar fraction; SD = standard deviation; $t_{1/2}$ = half-life.
a. n=3
b. n=7
Source: Study SC-931-5109, Table 14.2.1.4b, Table 14.2.1.5, and Table 14.2.1.6.

### 5.2.5. Interaction Study

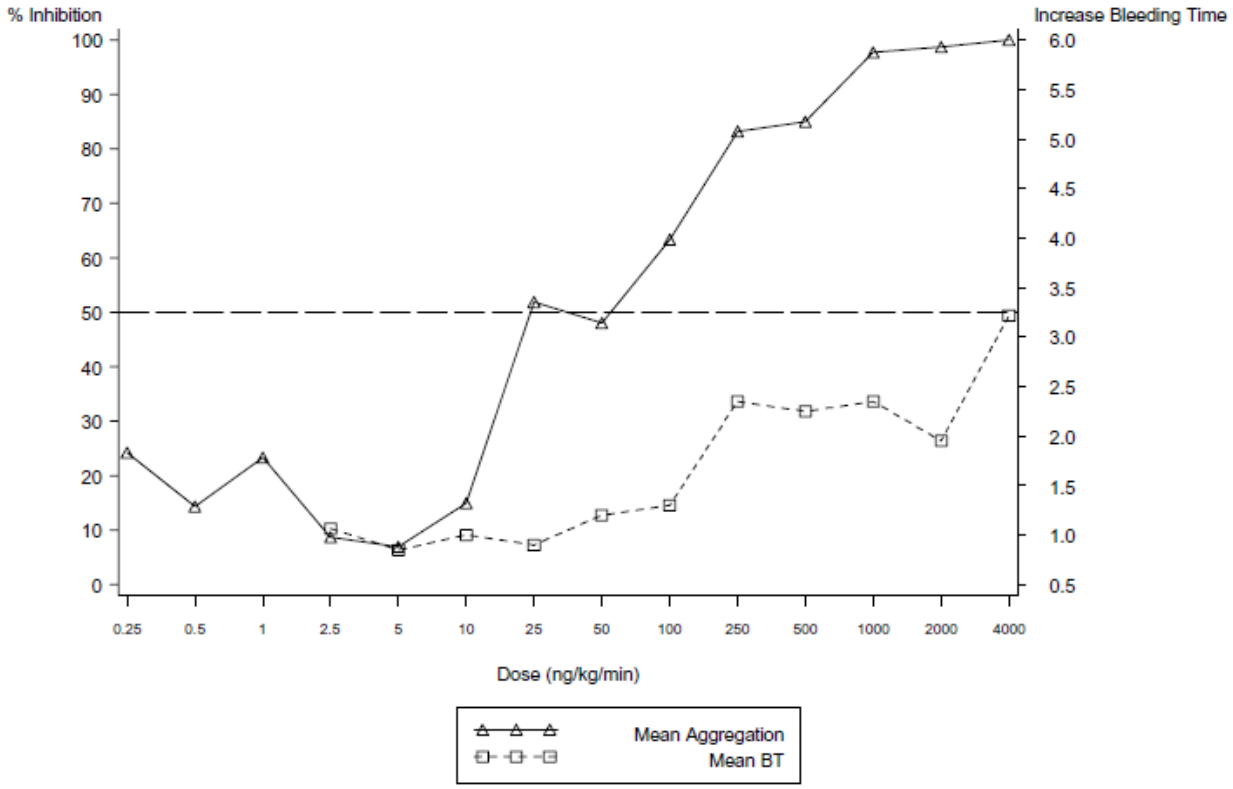
Cangrelor, administered with aspirin, heparin, and GTN, was examined in the healthy male volunteer study SC-931-5037. Results indicate that the PK of cangrelor were unaffected by therapeutically relevant doses of aspirin, heparin, and GTN, with the maximum plasma concentration ($C_{max}$), AUC, and total clearance similar between the two groups.

### 5.2.6. Pharmacodynamic Effects

#### 5.2.6.1. Dose Escalation Studies in Healthy Volunteers

In the double-blind, placebo-controlled, ascending-dose, step-plateau infusion study conducted in healthy male volunteers [SC-931-5014], cangrelor (0.25 to 4000 ng/kg/min) was administered as four 1 hour infusions, followed by a 19 hour plateau phase at the highest dose level. A dose-related inhibition of ADP-induced platelet aggregation ex vivo was observed, with over 80% inhibition achieved at doses of 250 ng/kg/min and above. Increases in bleeding time were also observed in this dose range. Adenosine diphosphate-induced aggregation and BT responses were stable during the plateau infusion, and were generally restored to control values when measured at 20 and 60 minutes after infusion, respectively, for all dose levels. Figure 6 illustrates the group mean responses at each infusion rate for the percentage inhibition of ADP-induced aggregation after 57 minutes, and the ratio of the BT after 19 hours of plateau infusion to the baseline BT. Due to the overlapping dose design, BT data means were derived from only two subjects at each intermediate level, whereas the top dose level mean was derived from six subjects.

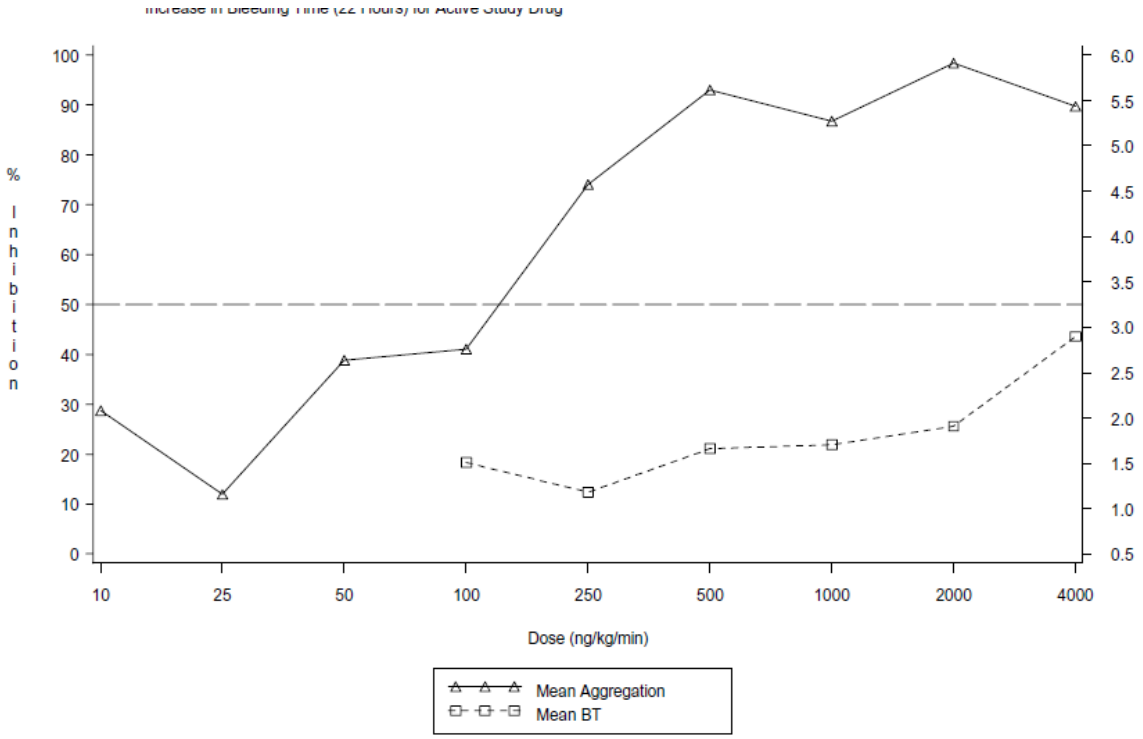
**Figure 6: Comparison of percent inhibition of ADP-induced platelet aggregation (after 57 mins) and increase in bleeding time (22 hours) in male subjects (Study SC-931-5014)**




Source: Study SC-931-5014, Figure F12.

In the corresponding ascending-dose, step-plateau, infusion study conducted in healthy female volunteers [SC-931-5036], (10 to 4000 ng/kg/min), cangrelor was administered as four 1 hour infusions, followed by a 19 hour plateau phase at the highest dose level. Bleeding time was increased by up to 2.9-fold at the highest dose. A dose-related inhibition of ADP-induced platelet aggregation ex vivo was observed, with over 80% inhibition achieved at doses of 500 ng/kg/min and above. Adenosine diphosphate-induced aggregation and BT responses were stable during the plateau infusion, and were generally restored to control values when measured at 20 and 60 minutes after infusion, respectively, for all dose levels. Figure 7 illustrates the group mean responses at each infusion rate for the percentage inhibition of ADP-induced aggregation after 57 minutes, and the ratio of the BT after 19 hours of plateau infusion to the baseline BT. Again, due to the overlapping dose design, BT data means are derived from only two subjects at each intermediate level, whereas the penultimate and top dose level means are derived from four and three subjects respectively. The dose-response curve for the percentage inhibition of ADP-induced platelet aggregation ex vivo in female subjects is similar to that for healthy males. There appears to be no evidence for any sex-related differences in the PD properties of cangrelor.

**Figure 7: Comparison of percent inhibition of ADP-induced platelet aggregation (after 57 minutes) and increase in bleeding time (22 hours) in female subjects (Study SC 931-5036)**

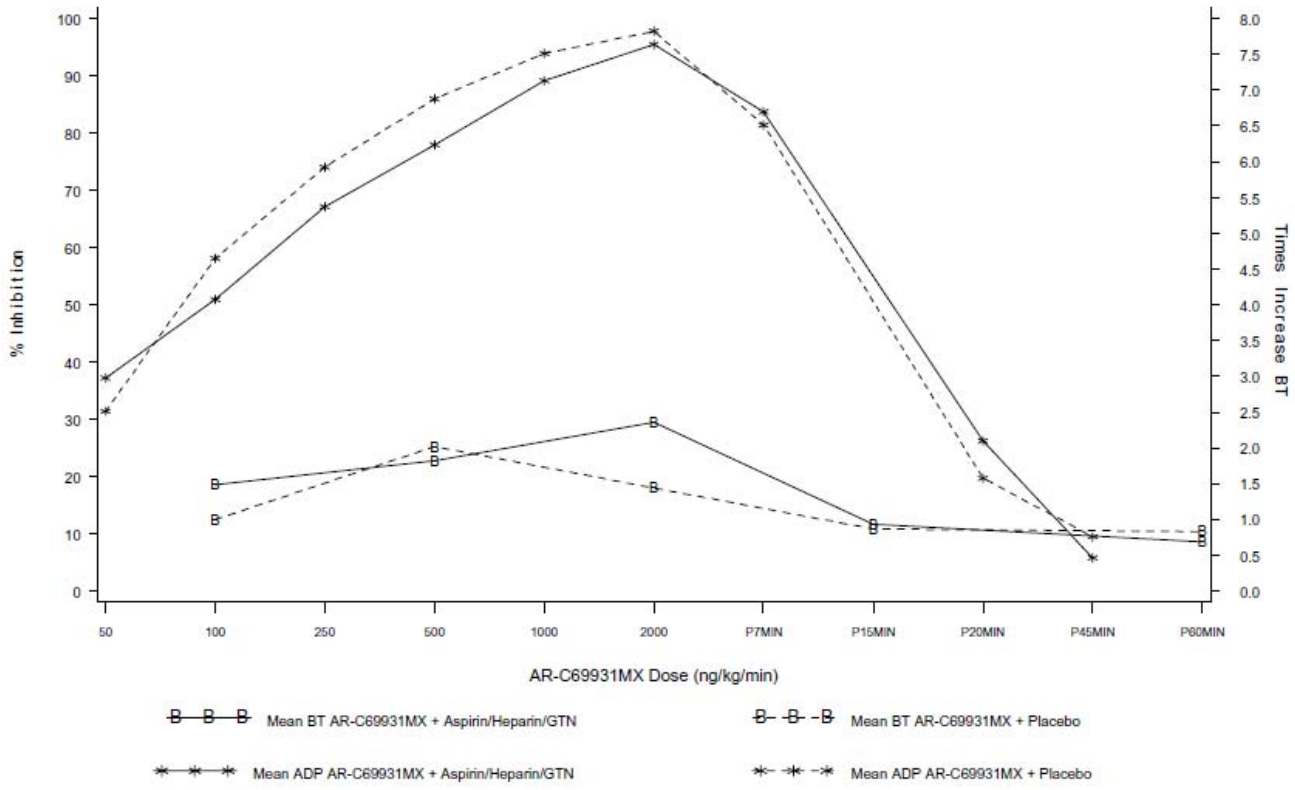



Source: Study SC-931-5036, Figure F9.

Similar assessments were made in the double-blind, placebo-controlled, two-way-crossover, incremental-dose, step-infusion interaction study conducted in healthy male volunteers receiving cangrelor alone (50, 100, 250, 500, 1000, and 2000 ng/kg/min) and in combination with aspirin, heparin, and GTN [SC-931-5037]. Figure 8 illustrates the group mean responses for the percentage inhibition of ADP-induced aggregation ex vivo measured after 15 minutes of infusion at each dose level, and at 7, 20, and 45 minutes after the end of infusion with the highest dose. Figure 7 also displays the increase in the ratio of BT following infusion with cangrelor compared with the baseline BT, and its restoration at 15 and 60 minutes after infusion. The linear portion of the infusion rate-inhibition response curve is similar to that observed for the male and female step-plateau studies (Figure 6 and Figure 7, respectively). Therefore, the percentage inhibition of ADP-induced aggregation does not appear to be influenced by the presence of aspirin, heparin, and GTN. The rapid restoration of normal platelet responsiveness was also unaffected by the presence of aspirin, heparin, and GTN, and was essentially complete 20 minutes after stopping infusion with the top dose of cangrelor. This further demonstrates that the mean ratio increase in BT was unaltered by aspirin, heparin, and GTN, and was no more than 2.4-fold at the highest

infusion rate; and that this had returned to normal values approximately 15 minutes after infusion. Therefore, aspirin, heparin, and GTN have no effect on the actions of cangrelor.

**Figure 8: Percent inhibition of ADP-induced platelet aggregation and effect on bleeding time (SC-931-5037)**




931= AR-C69931XX; A/H/N = aspirin/heparin/nitroglycerin.
Source: Study SC-931-5037, Figure F26.

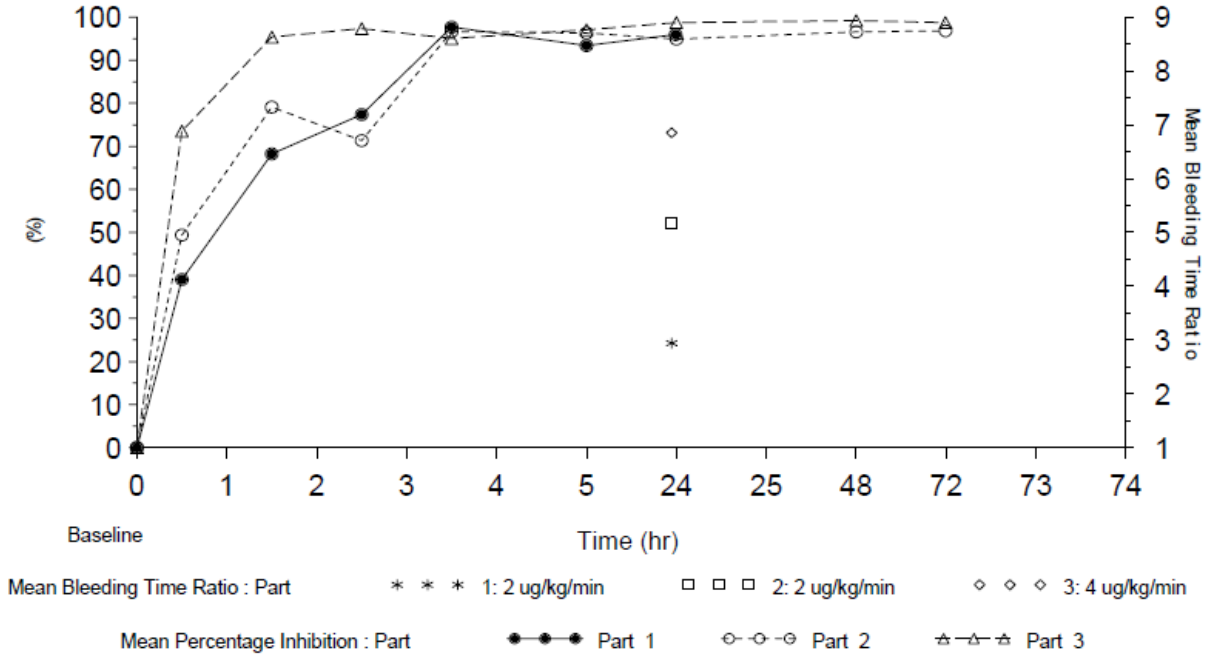
### 5.2.6.2. Dose Escalation Study in UA/Non-Q-MI Patients

In the dose-escalation study SC-931-5058, cangrelor was given as adjunctive therapy to aspirin, heparin, and GTN to subjects with UA/non-Q-MI. In this 3-part study, cangrelor was administered intravenously as a stepped dose titration followed by a plateau infusion phase at the top dose (Part 1, 0.05 to 2 µg/kg/min for 24 hours; Part 2, 0.05 to 2 µg/kg/min for 72 hours; and Part 3, 0.2 to 4 µg/kg/min for 72 hours). Cangrelor produced potent inhibition of ADP-induced platelet aggregation ex vivo ($IC_{50}$ 7.72 ± 1.95 ng/mL). Mean percentage inhibition exceeded 95% by 3.5 hours after the start of the infusion, and the inhibition remained above 90% for the duration of the infusion in all parts of the study (Figure 9).

Seven of the 11 (64%) subjects in Part 1, 10 of the 13 (77%) patients in Part 2, and 12 of the 14 (86%) patients in Part 3 attained 100% inhibition of platelet aggregation at some time during the study infusion. Patients in Parts 1, 2, and 3 attained a mean inhibition of platelet aggregation of

96.0%, 96.8%, and 99.2%, respectively, during plateau. For most patients, the inhibition was rapidly reversible and the platelet aggregation response was restored by 60% within 1 hour of stopping the infusion.

**Figure 9: Inhibition of ADP-induced platelet aggregation and mean bleeding time (SC-931-5058)**




Note: Only values for timepointes where patient was on study infusion will be calculated.
Source: Study SC-931-5058, Figure 14.2.

Descriptive statistics of mean BT for Parts 1, 2, and 3 are depicted in Table 14. There was considerable variability in the BT measurements, with a minimum of 0.0 seconds and a maximum of 1800.0 seconds. Aggregation inhibition data are presented in Table 15.

**Table 14: Summary of bleeding times (Study SC-931-5058)**

| Part | Dose (µg/kg/min) | Scheduled Timepoint (h:min) | Mean Bleeding Time (seconds) | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | N | Mean | SD | Median | Minimum | Maximum |
| 1 | Before Treatment | — | 12 | 185.4 | 86.30 | 150.0 | 85.0 | 370.0 |
| | 2 | 23:00 | 11 | 567.6 | 505.03 | 265.0 | 87.0 | 1414.0 |
| 2 | Before Treatment | — | 13 | 157.2 | 104.38 | 120.0 | 0.0 | 395.0 |
| | 2 | 23:00 | 13 | 841.2 | 581.77 | 600.0 | 238.0 | 1800.0 |
| 3 | Before Treatment | — | 14 | 185.8 | 116.38 | 166.5 | 30.0 | 440.0 |
| | 4 | 23:00 | 13 | 961.5 | 664.91 | 865.0 | 0.0 | 1800.0 |

SD = standard deviation.
Source: Table 14.12 in Clinical Study Report SC-931-5058.

**Table 15: Summary of mean platelet aggregation inhibition data (Study SC-931-5058)**

| Part | Mean % Inhibition of Aggregation at 24 Hours | % Subjects with 100% Inhibition of Aggregation during Infusion |
|---|---|---|
| 1 | 96.0 | 64 |
| 2 | 94.9 | 77 |
| 3 | 98.7 | 86 |

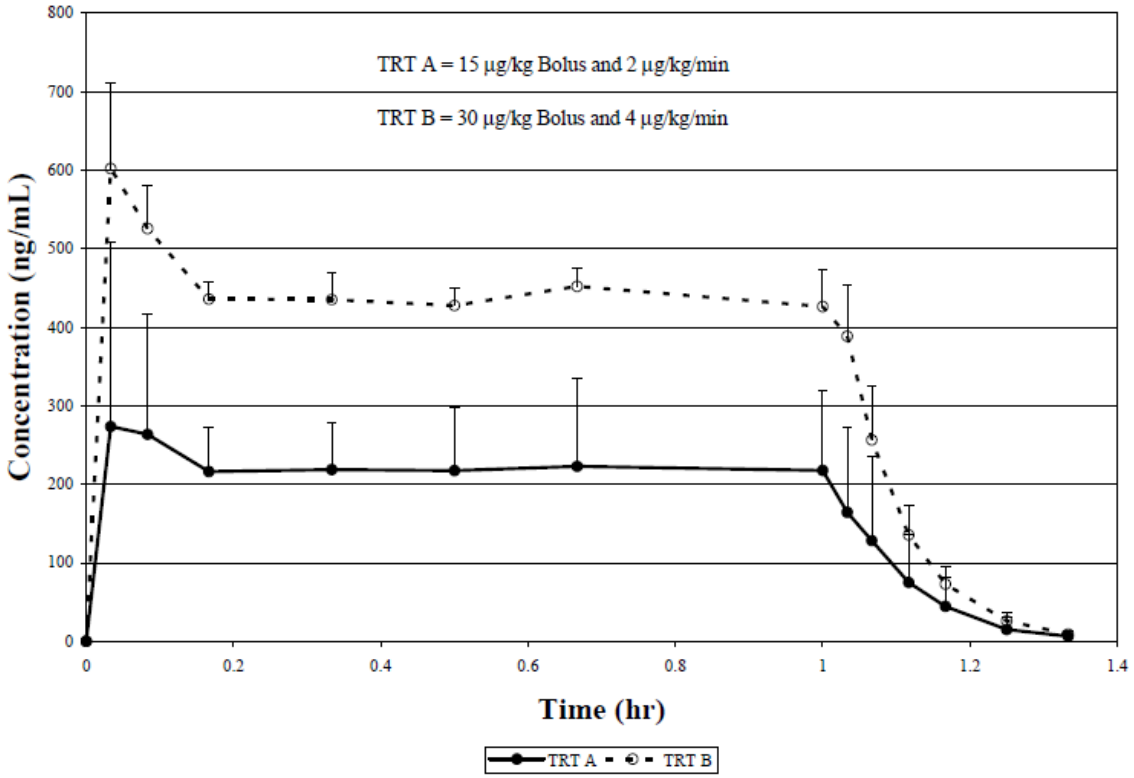
Souce: Table 14.16 and Table 14.17 in Clinical Study Report SC-931-5058.

#### 5.2.6.3. Bolus Plus Infusion Study in Healthy Volunteers

Study TMC-CAN-04-02 was conducted to evaluate the PK and PD parameters of a bolus plus infusion dosing regimen of cangrelor in healthy volunteers. Two cohorts of subjects also received clopidogrel to determine the effects of concomitant therapy. Forty-two subjects were treated (12 in Group A, 10 each in Groups B through D). Groups A and B received cangrelor only (Group A, 15 µg/kg bolus + 2 µg/kg/min infusion; Group B, 30 µg/kg bolus + 4 µg/kg/min infusion). Group C received a 30 µg/kg bolus + 4 µg/kg/min infusion of cangrelor immediately followed by clopidogrel 600 mg administered orally. Group D received a single dose of clopidogrel 600 mg administered orally. Following a 2 week washout, these subjects received a second 600 mg oral dose of clopidogrel followed by a 30 µg/kg bolus + 4 µg/kg/min infusion of cangrelor. On cessation of the infusion, the Group D subjects received clopidogrel 600 mg administered orally. Groups A, B, and C received 1 hour dosing with cangrelor; Group D was administered cangrelor infusion for 2 hours.

Cangrelor plasma concentration reached steady state at 10 minutes (see Figure 10). Steady state was maintained for the duration of the infusion and dropped off rapidly when the infusion was discontinued. The PK profile was found to be linear and dose proportional. The PK data from this study were consistent with data from prior studies.

**Figure 10: Plasma cangrelor concentration over time in Groups A and B (Study TMC-CAN-04-02)**

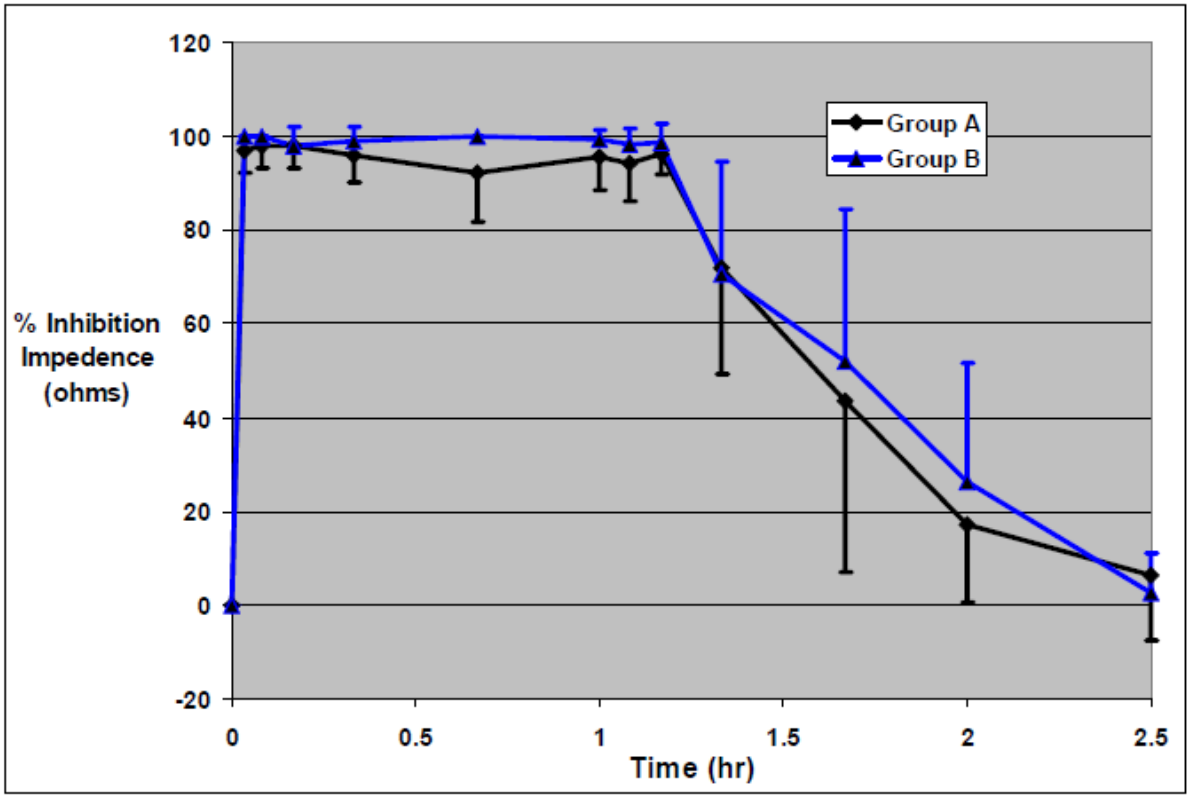



TRT = treatment group
Group A: Cangrelor 15 µg/kg IV bolus + 2 µg/kg/min x 1 hour
Group B: Cangrelor 30 µg/kg IV bolus + 4 µg/kg/min x 1 hour
Data presented are mean ± standard deviation plasma cangrelor concentration versus nominal time
SourceStudy TMC-CAN-04-02, Figure 3.

Consistent and complete ADP-induced inhibition of aggregation, as measured by whole blood impedance aggregometry, was achieved immediately after bolus administration (see Figure 11). The degree of inhibition was maintained throughout the infusion. Full recovery of platelet function was realized approximately 60 minutes after infusion cessation.

Furthermore, clopidogrel administration at the termination of the cangrelor infusion led to the expected degree of platelet inhibition for clopidogrel as measured by whole blood impedance aggregometry.

**Figure 11: Percent inhibition of platelet aggregation over time by WBIA (Groups A and B) (Study TMC-CAN-04-02)**




WBIA = whole blood electrical impedance aggregometry
Group A: Cangrelor 15 µg/kg IV bolus + 2 µg/kg/min x 1 hour
Group B: Cangrelor 30 µg/kg IV bolus + 4 µg/kg/min x 1 hour
Data presented are mean ± standard deviation.
Source: Study TMC-CAN-04-02, Figure 4.

### 5.2.6.4. Platelet Aggregometry and Bleeding Time

The correlation between platelet aggregometry and bleeding time was assessed in studies SC-931-5129 Part 1 and SC-931-5129 Part 2. In the cangrelor treatment groups in study SC-931-5129 Part 1, 52% of the patients achieved 100% platelet inhibition at some point during the study, which was significantly more than placebo. A correlation was not observed between platelet inhibition and change in bleeding time in this study. In study SC-931-5129 Part 2, the correlation was not applicable, as the entire cangrelor treatment group reached 100% platelet inhibition.

In study SC-931-5135, the mean platelet inhibition measurements were: 69.7%, 98.4%, 100%, and 100% for the 35 + Reduced, 140 + Reduced, 280 + Reduced, and 280 Alone groups, respectively, at 1 hour after the start of AR-C69931XX infusion. While all patients in the latter three treatment groups attained 100% platelet inhibition at some point during the study, only 43% of patients in the 35+ Reduced treatment group had 100% inhibition.

#### 5.2.6.5. Transition From Cangrelor to Clopidogrel

Study TMC-CAN-05-02 (CHAMPION PCI) was a Phase III study assessing cangrelor in patients with coronary atherosclerosis who required PCI. A substudy, TMC-CAN-05-02-S1 was conducted at 15 sites to confirm that a cangrelor infusion administered prior to 600 mg clopidogrel did not have an effect on clopidogrel's platelet inhibition. Patients in the substudy were required to be clopidogrel-naïve and could not have received GP IIb/IIIa inhibition during the procedure. Platelet function parameters were measured using the VerifyNow $P2Y_{12}$ Assay (Accumetrics, San Diego, CA), light transmission aggregometry and vasodilator-stimulated phosphoprotein phosphorylation index (VASP PRI) [Harrington et al. 2009].

The primary endpoint, which determined if cangrelor interfered with clopidgrol treatment, was the percentage of patients in each treatment group who achieved <20% change in $P2Y_{12}$ reaction units (PRU) from pre-clopidogrel levels approximately 10 hours after PCI ("non-responder"), as determined by the VerifyNow $P2Y_{12}$ assay. If 10 hour data were not available, data was collected the morning after PCI or at discharge (whichever was sooner). The original sample size was planned for 150 patients in each arm. This provided a power of 83% to exclude 15% or more absolute increase in the non-responder rate; however, only 167 patients of the 234 enrolled were evaluable. The number of patients with <20% change in PRU from baseline was 38.1% (32 of 84 patients) in the cangrelor arm and 25.3% (21 of 83 patients) in the clopidogrel arm, with an absolute increase of 12.79% (95% confidence interval -1.18, 26.77). This result indicates that prior administration of cangrelor had no interference with clopidogrel's effect and patients were adequately transitioned from IV to oral therapy.

#### 5.2.6.6. Platelet Function During Infusion

The platelet substudy TMC-CAN-05-02-S1 also evaluated platelet function during cangrelor infusion. The results regarding procedural platelet inhibition, which compared cangrelor's platelet inhibition during infusion versus the comparator arm are provided in Table 16. By all measures cangrelor demonstrated a high degree of platelet inhibition, which was significantly different from that comparator arm.

**Table 16: Comparison of platelet function tests for cangrelor and clopidogrel-treated patients within 2 hours of PCI (during cangrelor infusion in the cangrelor arm) in Study TMC-CAN-05-02-S1)**

| | Cangrelor median, (1Q.3Q ) | Clopidogrel median, (1Q.3Q ) | P-value |
|---|---|---|---|
| VerifyNow™ PRU, n=140 | 93.5 (37.0,175.0) | 277.0 (206.0,355.0) | <0.0001 |
| VerifyNow™ % inhibition , n=141 | 71.2 % (49.6,87.1) | 9.9 **%** (2.5,27.5) | <0.0001 |
| Aggregometry, n=30 (final response to 20 µM ADP) | 20.0 % (7.5,29.5) | 67.5 % (62.0,76.0) | <0.0001 |

| | Cangrelor median, (1Q.3Q ) | Clopidogrel median, (1Q.3Q ) | P-value |
|---|---|---|---|
| Aggregometry, n=30 (final response to 5 µM ADP) | 2.5% (0.0,10.5) | 49% (37.0,69.0) | <0.0001 |
| VASP-P PRI | 52.5% (32.7,61.1) | 84.2% (81.7,86.9) | <0.0001 |

ADP = adenosine diphosphate; PRI = platelet reactivity index; PRU = $P2Y_{12}$ reaction unit; VASP-P = vasodilator-sustained phosphoprotein phosphorylation.

## 5.3. Clinical Efficacy

### 5.3.1. Efficacy Results of Phase II Clinical Studies

Efficacy in Phase II clinical studies was assessed by determining patient outcomes.

In study SC-931-5060, efficacy outcomes measured were MI, percutaneous transluminal coronary angioplasty (PTCA), coronary artery bypass graft surgery (CABG) or re-admission to the hospital due to a further episode of UA or non-Q-wave MI at the 30-day follow-up. In the cangrelor treatment arm (45 patients) there was 1 death, 2 MI, 10 PTCA, 6 CABG, and 8 "other" events. In the placebo arm (46 patients), there were no deaths, 1 MI, 6 PTCA, 9 CABG, and 5 "other" events.

Studies SC-931-5129 Part 1 and SC-931-5129 Part 2 were safety studies of cangrelor in patients undergoing PTCA, and assessed efficacy as cardiac events, troponin levels, BT assessments and aggregometry assessments. Bleeding time and platelet aggregometry data from these studies are discussed in Section 5.2.6.4. The combined and individual outcomes of death (all cause mortality), MI/re-infarction and repeat coronary intervention (PTCA or CABG) were measured at Days 2 and 7, and at the 30-day post-infusion follow-up. The majority of combined cardiac events occurred within the first 2 days of treatment in both studies. In SC-931-5129 Part 1, which compared cangrelor at 1, 2 and 4 µg/kg/min (N = 149) with placebo (N = 51), 12% patients in the placebo group and 10%, 17% and 19% of patients in the 1, 2 and 4 µg/kg/min cangrelor treatment groups, respectively, experienced a combined cardiac event by 30 days post-infusion. However there were no statistically significant differences among the cangrelor groups compared to placebo at 2, 7 or 30 days post-infusion. In study SC-931-5129 Part 2, which compared cangrelor (N = 105) with abciximab (N = 94), 7.6% and 5.3% of patients in the cangrelor and abciximab arms, respectively, had experienced a combined cardiac event. There was 1 death in the cangrelor treatment group and no deaths in the abciximab treatment group at 30 days. MI occurred in four patients in the abciximab arm and six patients in the cangrelor arm, and two patients in the abciximab group and three patients in the cangrelor group required a repeat coronary intervention.

Study SC-931-5135 compared cangrelor alone or in combination with reduced-dose Activase (alteplase) with Activase alone, in patients with STEMI. The study was terminated early after 100 of the planned 180 patients had been randomized, and only 92 patients had been treated (85 in the cangrelor group and 7 in the Activase group). Measurements of ADP-induced platelet

aggregation were made for a subset of patients in this study and are discussed in Section 5.2.6.4. Efficacy was assessed by measurement of Thrombolysis in Myocardial Infarction (TIMI) grade flow, resolution of ST-segment elevation, and the combined endpoint of death, MI, and urgent coronary intervention. The proportion of patients who had TIMI Grade 3 flow following study drug infusion was 50% in the full dose Activase group, 53% to 59% in the cangrelor adjunctive therapy groups, and 18% in the cangrelor monotherapy group. By Day 30, three of the 92 patients had died, four had had another MI, 19 had undergone PTCA, CABG, and/or stent insertion, one had had a stroke, three had ECG changes, and three were rehospitalized. No conclusions regarding the efficacy of cangrelor given as an adjunct to reduced dose Activase or as monotheray can be made since the study was terminated prematurely.

### 5.3.2. Efficacy Results of Phase III Clinical Studies

The primary objective of the Phase III clinical studies in the CHAMPION program was to demonstrate that the efficacy of cangrelor is superior to that of clopidogrel in patients requiring PCI as measured by the composite of all-cause mortality, MI, and IDR assessed 48 hours after randomization. This primary objective was not met in either study in the CHAMPION program.

***PCI study (TMC-CAN-05-02)***

This was a randomized, double-blind, double-dummy, active-controlled, parallel group clinical trial in patients who required PCI, including patients with STEMI. Patients randomized to the cangrelor group received cangrelor (30 µg/kg bolus followed immediately by 4 µg/kg/min infusion) for at least 2 hours or for the duration of the PCI procedure, whichever was longer, followed by 600 mg clopidogrel after the end of the infusion. Patients randomized to the clopidogrel group received a 600 mg loading dose of clopidogrel before the start of the PCI procedure. The primary endpoint of all-cause mortality, MI and IDR in the population that included SA and UA patients, as well as patients with NSTEMI, was observed in 290/3889 (7.5%) patients in the cangrelor group and 276/3865 (7.1%) patients in the clopidogrel group (odds ratio [OR] 1.05, 95% confidence interval [CI] 0.88-1.24, p=0.5929).

***Platform study (TMC-CAN-05-03)***

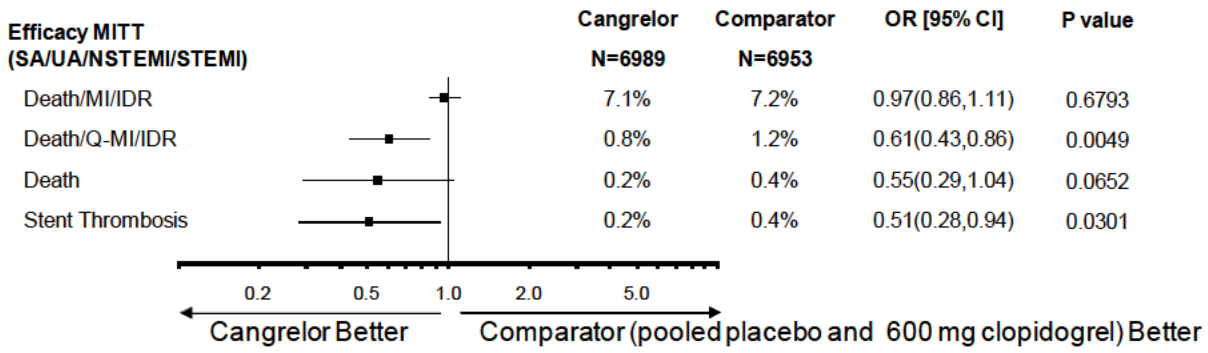
This was a randomized, double-blind, placebo-controlled, parallel group trial in patients with SA, UA, or NSTEMI who required PCI. In contrast to TMC-CAN-05-02, STEMI patients were not enrolled in the Platform study. Patients were randomized to receive either placebo or cangrelor (30 µg/kg bolus followed immediately by 4 µg/kg/min infusion) prior to the procedure. Unlike TMC-CAN-05-02, patients in the control group did not receive a dose of clopidogrel at the start of the PCI procedure; instead, clopidogrel was given at the end of the PCI procedure to both groups. Therefore, the study was designed to demonstrate superiority to usual care (hereafter, this group is referred to as the clopidogrel arm). The primary endpoint of all-cause mortality, MI and IDR was observed in 185/2654 (7.0%) patients randomized to cangrelor and 210/2641 (8.0%) patients randomized to clopidogrel (OR 0.87, 95% CI 0.71-1.07, p = 0.1746).

***CHAMPION Pooled Dataset (all patients including STEMI patients)***

When data from the two studies were pooled together, the primary endpoint for cangrelor treated patients was observed in 493/6989 (7.1%) and in 503/ 6953 (7.2%) of patients in the clopidogrel arm (OR 0.97, 95% CI 0.86 -1.11). Clinical components of the primary endpoint (death, Q-wave

MI, and IDR) were observed less frequently among patients given cangrelor (53/6989 [0.8%]) than patients in the clopidogrel arm (86/6953 [1.2%]) (OR 0.61, 95% CI 0.43-0.86). Mortality was 15/6989 (0.2%) for cangrelor and 27/6953 (0.4%) (OR 0.55, 95% CI 0.29-1.04) for placebo or clopidogrel. In addition, the incidence of stent thrombosis at 48 hours was lower in the cangrelor arm than in the clopidogrel arm (OR 0.51, 95% CI 0.28-0.94). Results are presented in Figure 12.

**Figure 12: Odds ratio plot of primary, secondary and additional endpoints in pooled dataset (all patients including STEMI patients; Studies TMC-CAN-05-02 and TMC-CAN-05-03)**




CI = confidence interval; IDR = ischemia-driven revascularization MI = myocardial infarction; OR = odds ration; Q-MI = q-wave myocardial infarction.

## 5.4. Safety

### 5.4.1. Serious Adverse Events/Serious Adverse Reactions

#### 5.4.1.1. Serious Adverse Events

Overall, cangrelor was well-tolerated in the clinical studies. The occurrence of SAEs in the cangrelor treatment groups was proportionately similar to that in the comparator groups in all phases of research.

No SAEs were reported in the healthy volunteer studies.

In the Phase II studies, a total of 84 of 621 patients experienced at least one SAE; 29 of 423 patients treated with cangrelor experienced SAEs which were considered possibly or probably related to cangrelor. The most common related SAEs were anemia, bleeding post vessel puncture, and gastrointestinal (GI) hemorrhage.

In the Phase III program there were no clinically relevant differences between the cangrelor and clopidogrel treatment groups with respect to the incidence of SAEs, as catergorised by sytem organ class (SOC).

In TMC-CAN-05-02 (CHAMPION PCI) the incidence of SAEs was 2.9% in both the cangrelor and clopidogrel groups. The most frequently reported SAEs in this study (>0.2% of patients in either treatment arm) were ventricular fibrillation (0.3% cangrelor versus 0.1% clopidogrel) and acute renal failure (0.3% versus 0.1%).

In TMC-CAN-05-03 (CHAMPION Platform) the incidence of SAEs was 1.8% in patients receiving cangrelor, and 2.1% in patients who received usual care prior to PCI. The most frequently reported SAE (>0.2% of patients in either treatment arm) was cardiogenic shock (0.2% cangrelor versus 0.4% clopidogrel). SAEs in the Cardiac disorders SOC were reported for 23 and 30 patients in the cangrelor and clopidgrel arms, respectively, and SAEs in the Respiratory, thoracic, and mediastinal SOC were reported for7 and 6 patients in the cangrelor and clopidogrel arms, respectively. Treatment-emergent SAEs that had occurred before the administration of clopidogrel were similar between the cangrelor and placebo groups in this study and are provided in Appendix 3 (Table A3-4).

#### 5.4.1.2. Serious Adverse Reactions

The most common serious adverse reactions reported for the Phase II and III clinical program were (Preferred Term, [Frequency]): Anaemia (19), Chest pain (4), Embolism (4), Gastrointestinal haemorrhage (3) and Hypotension (3).

A summary of all serious adverse reactions reported the Phase II and III program is provided in Appendix 1 (Table A1-1).

#### 5.4.1.3. Deaths

There were no deaths in the Phase I program, and six deaths in Phase II program (1%; N = 621). Of the six deaths, two were considered likely related to cangrelor [SC-931-5135, multi-organ failure; SC-931-5060, papillary muscle rupture].

In the Phase III study TMC-CAN-05-02 (CHAMPION PCI), nine patients (0.2%) in each treatment arm died within the first 48 hours after randomization. None of the AEs leading to death was reported for more than two patients in any treatment arm.

Forty patients (0.9%) of the cangrelor arm and 41 patients (0.9%) of the clopidogrel arm died within 30 days after randomization. Most commonly reported AEs leading to death (>2 patients in either treatment arm) were cardiogenic shock, death, cardiac arrest, and MI.

During the 1-year period of the study, registered until 30 day database lock on completion of the last included patient, 104 patients (2.4%) in the cangrelor arm and 119 patients (2.7%) in the clopidogrel arm had died. Most frequently associated AEs (>0.2% of patients in either treatment arm) were death, MI, and cardiac arrest. A complete listing of AEs in patients who died, by SOC, is provided in Appendix 3 (Table A3-1).

In the Phase III study TMC-CAN-05-03 (CHAMPION PLATFORM), 7 patients in the cangrelor treatment group died within the first 48 hours, compared with 18 patients in the clopiodgrel treatment group. The most common AE resulting in death was cardiogenic shock (3 patients [0.1%] in the cangrelor group and 10 deaths [0.4%] in the clopidgrel group).

Within the first 30 days, 35 (1.3%) and 40 (1.7%) patients died in the cangrelor and clopigrel groups, respectively. The most common AEs resulting in death in the cangrelor group were

cardiac failure (5 [0.2%]), cardiogenic shock (4 [0.2%]), and death (5 [0.2%]). In the clopidogrel treatment group, the most common AEs resulting in death were cardiogenic shock (12 [0.5%]), cardiac arrest (4 [0.2%]), and death (4 [0.2%]).

During the entire 1-year period of study, registered until 30 day database lock on completion of the last included patient, 70 (2.6%) and 79 (3.0%) patients died in the cangrelor and clopidogrel treatment arms, respectively. The only AEs resulting in death in >0.2% were cardiac failure death in the cangrelor treatment group, and cardiogenic shock and death in the clopidogrel treatment group. A complete listing of AEs in patients who died, by SOC, is provided in Appendix 3 ( Table A3-2).

#### 5.4.1.4. Withdrawals From Treatment Associated With Adverse Events

Four subjects were withdrawn from the Phase I studies due to AEs judged to be related to cangrelor. One subject was withdrawn after experiencing abnormal uterine cytology (SC-931-5037), one subject was withdrawn after losing consciousness and hyperventilating (SC-931-5109), and two subjects were withdrawn due to hypotension (TMC-CAN-04-02).

Overall, in the Phase II program, there were 44 withdrawals associated with adverse events. Twenty-one of these withdrawals were considered possibly or probably related to treatment with cangrelor. The most common treatment-associated withdrawals potentially related to cangrelor were: minor (nuisance) bleed, thrombosis coronary, and bleeding post-vessel puncture.

In the Phase III study TMC-CAN-05-02 (CHAMPION PCI), 23 patients (0.5%) in the cangrelor arm and 21 patients (0.5%) in the clopidogrel arm discontinued the study due to an AE. The only AE leading to discontinuation reported for >0.1% of patients in either treatment arm was coronary artery perforation.

In the Phase III study TMC-CAN-05-03 (CHAMPION Platform), 21 patients (0.8%) in the cangrelor arm discontinued the study due to an AE compared to 10 (0.4%) in the placebo arm.

### 5.4.2. Adverse Events/Adverse Reactions

#### 5.4.2.1. Adverse Events Reported in Phase I Studies

In general, cangrelor was considered safe and well tolerated in the Phase I studies. The most commonly reported AEs of clinical significance were petechiae and purpura. These were usually located at the ECG chest suction electrode positions, injection sites, under the blood pressure cuff, and access sites [SC-031-5014; SC-931-5036; SC-931-5037; TMC-CAN-04-02; TMC-CAN-08-02].

Nervous system AEs were also commonly reported, primarily headache and dizziness [SC-931-5037; SC-931-5109; TMC-CAN-08-01]; however, headache is a frequently-observed AE in studies of this type and, in study SC-931-5037, could be attributed to GTN infusion.

In study SC-931-9017, one subject experienced mild asymptomatic nonspecific T-wave changes on several ECGs that were considered not to be related to study medication. A resting ECG and exercise tolerance test were found to be normal for this subject.

One subject hyperventilated in study SC-931-5109, which was potentially clinically significant as another patient withdrew from this study due to hyperventilation and loss of consciousness.

#### 5.4.2.2. Adverse Events Reported in Phase II Studies

In the dose-escalation study in UA/non-Q-MI patients [SC-931-5058], the most frequently reported AEs during treatment were injection site reaction, increased ALT levels, and purpura, reported exclusively by patients in Parts 2 and 3 of the study. Injection site reaction (preferred term) was recorded as phlebitis/cellulitis at the cannula site (2 patients) or slight bleeding at an injection site (8 patients). Purpura (preferred term) was recorded as hematomas (3 patients) or small petechia (2 patients). Events of this type are expected because of the mode of action of cangrelor. Additional AEs were reported during the follow-up period (7 days after infusion). The most commonly reported were elevated AST and ALT, reported in 7/39 (18%) and 8/39 (21%) of patients, respectively.

In the placebo-controlled study conducted in UA/non-Q-MI patients [SC-931-5060], 80% of patients in both the cangrelor and placebo treatment arms experienced at least 1 AE.

In both study SC-931-5129 Part 1 and study SC-931-5129 Part 2, the most commonly reported AEs during infusion were purpura and bleeding post vessel puncture. The safety profile of cangrelor 4 µg/kg/min compared favorably with that of abciximab in patients undergoing PTCA.

In study SC-931-5135 in patients with STEMI, platelet, bleeding, and clotting disorders were the most common AEs reported during the infusion and follow-up periods in all treatment groups. The overall incidence of AEs throughout the study (during infusion and up through Day 7 or discharge, whichever came first) was comparable in the cangrelor groups and the control group.

Presented below (Table 17) is a summary of AEs reported in studies SC-931-5058, SC-931-5060, SC-931-5109, SC-931-5129 Part 1, SC-931-5129 Part 2, and SC-931-5135. The occurrence of AEs, by body system, is reported for patients receiving cangrelor, placebo, abciximab or Activase (alteplase). The data presented below were re-coded from the original AstraZeneca COSTART terminology to MedDRA Version 7.1 terminology.

**Table 17: Summary of most frequently reported (≥ 5%) adverse events by body system in early development studies**

| Adverse Event (AE) | Cangrelor N=448 n (%) | Placebo N=97 n (%) | Abciximab N=94 n (%) | Activase N=7 n (%) |
|---|---|---|---|---|
| **Patients with at Least 1 AE** | **413 (92.2)** | **90 (92.8)** | **87 (92.6)** | **7 (100.0)** |
| Vascular disorders | 276 (61.6) | 39 (40.2) | 59 (62.8) | 5 (71.4) |
| General disorders and administration site conditions | 183 (40.8) | 28 (28.9) | 30 (31.9) | 6 (85.7) |
| Cardiac disorders | 131 (29.2) | 36 (37.1) | 19 (20.2) | 5 (71.4) |
| Investigations | 130 (29.0) | 34 (35.1) | 25 (26.6) | 2 (28.6) |
| Musculoskeletal and connective tissue disorders | 120 (26.8) | 20 (20.6) | 29 (30.9) | 5 (71.4) |
| Surgical and medical procedures | 114 (25.4) | 16 (16.5) | 24 (25.5) | 0 (0.0) |
| Gastrointestinal disorders | 113 (23.2) | 9 (9.3) | 15 (16.0) | 2 (28.6) |

| Adverse Event (AE) | Cangrelor N=448 n (%) | Placebo N=97 n (%) | Abciximab N=94 n (%) | Activase N=7 n (%) |
|---|---|---|---|---|
| Nervous system disorders | 58 (12.9) | 11 (11.3) | 11 (11.7) | 1 (14.3) |
| Psychiatric disorders | 59 (13.2) | 7 (7.2) | 9 (9.6) | 3 (42.9) |
| Respiratory, thoracic, and mediastinal disorders | 60 (13.4) | 5 (5.2) | 5 (5.3) | 4 (57.1) |
| Renal and urinary disorders | 49 (10.9) | 5 (5.2) | 5 (5.3) | 3 (42.9) |
| Injury, poisoning, and procedural complications | 36 (8.0) | 5 (5.2) | 8 (8.5) | 1 (14.3) |
| Metabolism and nutrition disorders | 30 (6.7) | 4 (4.1) | 6 (6.4) | 3 (42.9) |
| Gastrointestinal signs and symptoms | 26 (5.8) | 3 (3.1) | 3 (3.2) | 0 (0.0) |

AE = adverse event.

#### 5.4.2.3. Adverse Events Reported in Phase III Studies

In the CHAMPION studies TMC-CAN-05-02 and TMC-CAN-05-03, the incidence of AEs was similar between patients in the cangrelor group and patients in the clopidogrel group. At lease one AE was reported for 1808/7036 (25.7 %) patients in the combined cangrelor arm and 1714/7015 (24.4%) patients in the clopidogrel/placebo arm.

The incidences for any type of AE in study TMC-CAN-05-02 (CHAMPION PCI) were similar between treatment arms, as shown in Appendix 3, Table A3-3. In the cangrelor arm, 1175 patients (26.9%) reported at least one AE compared to 1136 patients (26.0%) in the clopidogrel arm. The incidences for any type of AE in study TMC-CAN-05-03 (CHAMPION Platform) are shown in Appendix 3, Table A3-3. In the cangrelor arm, 633 patients (23.8%) reported at least one AE compared to 578 patients (21.8%) in the clopidogrel arm.

In TMC-CAN-05-03 (CHAMPION Platform), treatment-emergent AEs occurring before administration of clopidogrel were reported and were slightly less frequent in the cangrelor arm than in the placebo arm (2.9% vs 3.4%). A summary of AEs reported during this time period is provided in Appendix 3 (Table A3-5).

Table 18 summarizes the most common AEs in the pooled CHAMPION studies. The most frequently reported AEs were back pain, chest pain, nausea and headache, which were similar between both treatment groups. Dyspnea was reported for 1.1% of patients treated with cangrelor compared to 0.4% of patients in the clopidogrel group in study TMC-CAN-05-02 ($p \leq 0.0001$), and 0.6% of patients in the clopidogrel group in TMC-CAN-05-03. Dyspnea was reported as serious in one patient given cangrelor and one patient given comparator treatment. Other AEs occurred with similar frequency and severity among treatment groups. All other cases were mild or moderate and all were spontaneously reversible. Table A3-3 in Appendix 3 summarizes all AEs reported for more than 0.2% of patients in the pooled CHAMPION studies.

There were no clinically important differences in laboratory parameters between treatment groups.

**Table 18: Summary of most common (>0.9% in cangrelor arm) adverse events by Preferred Term in pooled Studies TMC-CAN-05-02 (CHAMPION PCI) and TMC-CAN-05-03 (CHAMPION Platform)**

| Preferred Term | Cangrelor N=7036 n/N (%) | Clopidogrel in PCI N=4365 n/N (%) | Clopidogrel in PF N=2650 n/N (%) |
|---|---|---|---|
| Back pain | 258 (3.7) | 164 (3.8) | 85 (3.2) |
| Chest pain | 251 (3.6) | 163 (3.7) | 69 (2.6) |
| Nausea | 183 (2.6) | 145 (3.3) | 66 (2.5) |
| Headache | 153 (2.2) | 97 (2.2) | 68 (2.6) |
| Hypotension | 140 (2.0) | 89 (2.0) | 38 (1.4) |
| Vomiting | 107 (1.5) | 78 (1.8) | 31 (1.2) |
| Puncture site pain | 88 (1.3) | 52 (1.2) | 29 (1.1) |
| Pyrexia | 81 (1.2) | 37 (0.8) | 20 (0.8) |
| Dyspnoea | 80 (1.1) | 16 (0.4) | 15 (0.6) |
| Hypertension | 60 (0.9) | 34 (0.8) | 22 (0.8) |

#### 5.4.2.4. Adverse Reactions Reported in Phase III Studies

There were 228 total non-serious adverse reactions reported in the Phase III studies (TMC-CAN-05-02 and TMC-CAN-05-03). The most common of these were (Preferred Term [Frequency]): nausea (24), vomiting (18), chest pain (14), hypotension (13), and dyspnoea (9). A summary of all non-serious adverse reactions reported in the Phase III studies is provided in Appendix 1 (Table A1-2).

### 5.4.3. Bleeding events

#### 5.4.3.1. Bleeding Events Reported in Phase II Studies

The majority of bleeding events reported in Phase II studies were minor bleeds associated with use of the study drug. In study SC-931-5058, 29 patients overall experienced a bleeding event, but the majority of these were injection site reactions. Red blood cells were found in the urine cytology of 11 patients; however, only 5 of these were recorded as AEs (haematuria). Fourteen patients were also positive for trace blood in urine.

In study SC-931-5060, there were no major bleeding events, but there were more episodes of bleeding in the cangrelor treatment arm than in the placebo arm (33 and 16 events, respectively). Bleeding events were reported for 17/45 (38%) of patients in the cangrelor arm and 12/46 (26%) patients in the placebo arm. The most frequently reported bleeding events (reported by >5% of patients in either treatment group) during treatment were anaemia, purpura, bleeding post-vessel puncture, epistaxis and haematuria.

Studies SC-931-5129 Part 1, SC-931-5129 Part 2 and SC-931-5135 analyzed bleeding events by TIMI criteria. Aggregately in these three studies, only 85 of 372 total events were categorized as

major bleeds; however, 78 of those events occurred in patients receiving cangrelor. Most of the major bleeds occurred in study SC-931-5135, in which major bleeds were reported in 18% of patients. Across these three studies, the majority of bleeding events were categorized as "other bleeding."

#### 5.4.3.2. Bleeding Events Reported in Phase III Studies

In the pooled CHAMPION studies, the overall incidence of bleeding events (non-CABG related) in the peri-procedural setting was similar between patients treated with cangrelor and patients treated with etiher placebo or clopidogrel.

These studies found that major bleeding defined by the TIMI scale at 48 hours post-randomization was not increased among patients treated with cangrelor (23/7036 [0.3%]) compared to 600 mg of clopidogrel (23/7015 [0.3%]) (Table A2-1) (OR 1.0, 95% CI 0.56-1.78). Severe bleeding defined by the GUSTO scale was also similar between groups.

Major bleeding defined by the ACUITY scale at 48 hours post-randomization was higher among cangrelor-treated patients (296/7036 [4.2%]) than among patients treated with comparators (211/7015 [3.0%]) (OR 1.42, 95% CI 1.18-1.70), and was primarily attributed to hematomas >5 cm. These data are presented in Appendix 2 (Tables A2-3 and A2-5). There was no difference in requirement for any blood transfusion. All reported bleeding events at 48 hours after randomization for both studies are summarized in Appendix 2 (Tables A2-2, A2-4, and A2-6).

In CHAMPION Platform (TMC-CAN-05-03), the time period post-administration of cangrelor and placebo, but before administration of clopidogrel, gives insight into the comparison of cangrelor versus placebo.. In the cangrelor group, the bleeding rate for ACUITY-definition was numerically higher, and was primarily driven by ACUITY-major bleeding. Alternately, following the GUSTO-definition it was driven by mild bleeding, and under TIMI-definition it was driven by minor bleeding. These results are provided in Appendix 2 (Table A2-7).

### 5.4.4. Clinically Significant Parameters in Clinical Studies

#### 5.4.4.1. Phase I and Phase II Clinical Studies

In the nonclinical studies with cangrelor, changes in hematology, clinical chemistry, urinalysis, and vital signs were observed. Because of these findings, these parameters were measured during the clinical trials.

Hematology: There were no clinically significant findings in either the Phase I or Phase II studies regarding hematology.

Clinical Chemistry: In two Phase II studies [SC-931-5058 and SC-931-5060], increases in AST and ALT were observed. In addition, in study SC-931-5058, 12 patients developed clinically-relevant abnormal clinical chemistry values, and 1 patient developed clinically relevant abnormal cardiac enzyme values.

Urinalysis: In the Phase I studies SC-931-5036 and SC-931-5037, positive results for urinalysis, urine cytology, sodium dodecylsulphate polyacrylamide gel electrophoresis (SDS-PAGE), and hematuria were observed. Thus urinary monitoring in the Phase I trials revealed natural

background variability in the quantity and type of cells excreted, and in SDS-PAGE, particularly in women. However no consistent or drug-related trends were observed.

A pilot study (SC-931-5092) was conducted in 25 subjects (age 44 to 80 years) with UA and/or non-Q-wave MI, to assess the incidence and range of coincidental fluctuations or abnormal findings in the array of tests to be used for monitoring the kidney and urinary tract in a subsequent study in this patient population (SC-931-5058). There was no study drug given in this pilot study. The study was intended to identify background variability in patients with UA and/or non-Q-wave MI. A high frequency of background abnormalities was observed in this population and all but one subject had at least one Class 1 abnormality in their urine cytology (epithelial cells, occasional polymorphs, and erythrocytes), two subjects had Class 2 abnormalities (inflammation/degeneration), and one subject had a Class 3 abnormality (atypia). In total, 10/25 subjects (40%) experienced a total of 17 bleeding events (bleeds as AEs, traces of blood in the dipstick urinalysis, and RBCs seen in urine cytology). Hence, renal/urinary tract safety monitoring in this patient population showed a higher frequency of abnormalities than that observed in the healthy volunteer studies. This would be anticipated for an older population with underlying medical conditions.

In study SC-931-5058 conducted in UA/non-Q-MI patients, six patients developed clinically relevant abnormal urine dipstick data. Eleven patients had urine cytology that was classed as normal throughout the study. However, 72 of all samples were classed as "no significant abnormality" (Class 1). No patients had Class 2 abnormalities and only one patient had a Class 3 abnormality. There were no significant renal changes. SDS-PAGE results showed additional protein bands for 10 patients (26%), of whom 5 patients had additional bands throughout the study, including before treatment.

Vital Signs: In the healthy volunteer studies, repeated measurements of BP, 12-lead ECG, and impedance cardiodynamic monitoring did not reveal any clinically-important dose-related or drug-related effects on the cardiovascular system. The most frequently encountered cardiac abnormalities were premature atrial beats in both active and placebo subjects, and transient T-wave changes in the ECG chest leads, predominantly in subjects receiving active medication. These subjects were otherwise asymptomatic, and the abnormalities were not recognized as ST-segment changes on Holter monitoring in the step-plateau studies [SC-931-5014; SC-931-5036; SC-931-5037]. There were no clinically-significant changes in BP or pulse rate in the dose-escalation study in UA/non-Q-MI patients [SC-931-5058], except for one episode of hypotension and one of bradycardia in the dose group receiving a stepped dose titration infusion of cangrelor up to 2 µg/kg/min over 72 hours. Both of these events were recorded as AEs. One patient in this dose group developed an ECG abnormality (biphasic anterior T waves).

#### 5.4.4.2. Phase III studies

For both Phase III studies, hematology and serum chemistry parameters were collected. Similar to the Phase I and II studies, there were no significant hematology findings in either study, and all parameters were similar between the cangrelor and comparator groups. Changes in the serum chemistry, specifically ALT and AST, which had been observed in the Phase II studies, were not observed in the Phase III CHAMPION program. Greater detail is provided in Table 19 through Table 22.

**Table 19: Incidence of potentially clinically significant tests in hematology parameters (Study TMC-CAN-05-02 [CHAMPION PCI])**

| | Cangrelor N=4310[a] n/N (%) | Clopidogrel N=4307[a] n/N (%) |
|---|---|---|
| Hematocrit[b] ≤0.8 x LLN (%) | 288 (6.7) | 279 (6.5) |
| Hemoglobin[b] ≤0.8 x LLN (g/dL) | 268 (6.2) | 253 (5.9) |
| Platelets ≥700 (k/µL) | 1 (0.0) | 3 (0.1) |
| Platelets ≤75 (k/µL) | 10 (0.2) | 11 (0.3) |
| WBC ≥16 (k/µL) | 101 (2.3) | 96 (2.2) |
| WBC ≤2.8 (k/µL) | 2 (0.0) | 4 (0.1) |

LLN = lower limit of normal; NSTEMI = non ST segment myocardial infarction; SA = stable angina; STEMI = ST segment myocardial infarction; UA = unstable angina; WBC = white blood cells.
a. Data from safety + SA/UA/NSTEMI/STEMI populations.
b. Adjusted for blood transfusion
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**Table 20: Incidence of potentially clinically significant tests in serum chemistry parameters (Study TMC-CAN-05-02 [CHAMPION PCI])**

| | Cangrelor N=4310[a] n/N (%) | Clopidogrel N=4307[a] n/N (%) |
|---|---|---|
| ALT/SGPT ≥3 x ULN | 46 (1.1) | 42 (1.0) |
| AST/SGOT ≥3 x ULN | 385 (8.9) | 377 (8.8) |
| Serum Creatinine ≥2 mg/dL | 89 (2.1) | 81 (1.9) |
| Total Bilirubin ≥1.5 x ULN | 141 (3.3) | 125 (2.9) |
| Alkaline Phosphatase ≥3 x ULN | 5 (0.1) | 1 (0.0) |

ALT/SGPT = alanine aminotransferase/serum glutamic pyruvic transaminase; AST/SGOT = aspartate aminotransferase/serum glutamic oxaloacetic transaminase; NSTEMI = non ST segment myocardial infarction; SA = stable angina; STEMI = ST segment myocardial infarction; UA = unstable angina; ULN = upper limit of normal.
a. Data from safety + SA/UA/NSTEMI/STEMI populations.
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**Table 21: Incidence of potentially clinically significant tests in hematology parameters (Study TMC-CAN-05-03 [CHAMPION Platform])**

| | Cangrelor N=2639[a] n/N (%) | Clopidogrel N=2616[a] n/N (%) |
|---|---|---|
| Hematocrit[b] ≤ 0.8 x LLN (%) | 167 (6.3) | 141 (5.4) |
| Hemoglobin[b] ≤ 0.8 x LLN (g/dL) | 156 (5.9) | 130 (5.0) |
| Platelets ≥ 700 (k/µL) | 12 (0.5) | 6 (0.2) |
| Platelets ≤ 75 (k/µL) | 3 (0.1) | 4 (0.2) |
| WBC ≥ 16 (k/µL) | 78 (3.0) | 70 (2.7) |
| WBC ≤ 2.8 (k/µL) | 2 (0.1) | 0 (0.0) |

LLN = lower limit of normal; NSTEMI = non ST segment myocardial infarction; SA = stable angina; STEMI = ST segment myocardial infarction; UA = unstable angina; WBC = white blood cells.
a. Data from safety + SA/UA/NSTEMI/STEMI populations.
b. Adjusted for blood transfusion
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**Table 22: Incidence of potentially clinically significant tests in serum chemistry parameters (Study TMC-CAN-05-03 [CHAMPION Platform])**

| | Cangrelor N=2639[a] n/N (%) | Clopidogrel N=2616[a] n/N (%) |
|---|---|---|
| ALT/SGPT ≥ 3 x ULN | 29 (1.1) | 28 (1.1) |
| AST/SGOT ≥ 3 x ULN | 187 (7.1) | 185 (7.1) |
| Serum Creatinine ≥ 2 mg/dL | 72 (2.7) | 66 (2.5) |
| Total Bilirubin ≥ 1.5 x ULN | 89 (3.4) | 108 (4.1) |
| Alkaline Phosphatase ≥ 3 x ULN | 1 (0.0) | 3 (0.1) |

ALT/SGPT = alanine aminotransferase/serum glutamic pyruvic transaminase; AST/SGOT = aspartate aminotransferase/serum glutamic oxaloacetic transaminase; NSTEMI = non ST segment myocardial infarction; SA = stable angina; STEMI = ST segment myocardial infarction; UA = unstable angina; ULN = upper limit of normal.
a. Data from safety + SA/UA/NSTEMIpopulations.
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## 5.5. Marketing Experience

Not applicable. Cangrelor has not been marketed in any country.

## 5.6. Conclusions

The results of the Phase I healthy volunteer studies (SC-931-5014, SC-931-5036) confirm that cangrelor is an ultra-short-acting antagonist of ex vivo ADP-induced platelet aggregation in male and female subjects. Dose-related activity was observed until complete inhibition of ex vivo ADP-induced platelet aggregation was achieved.

Cangrelor was well tolerated at all dose levels. No interaction was observed between cangrelor and concomitant aspirin, heparin, and GTN (SC-931-5037). The free acid of cangrelor (AR-C69931XX) has a short half-life (5 minutes) and a rapid clearance rate (10 mL/kg/min). The metabolic profile in man is qualitatively similar to that in the rat and dog, with the parent compound being rapidly cleared by dephosphorylation to form the nucleoside metabolite AR-C69712XX. The most abundantly excreted metabolite, the nucleoside sulphoxide AR-C90439XX, is predominantly eliminated in urine in humans, in contrast to animals where this metabolite is predominantly excreted in feces (SC-931-9017).

In the dose-escalation study SC-931-5058 in UA/non-Q-MI patients, cangrelor inhibited ex vivo ADP-induced platelet aggregation >95% at doses at or above 2 µg/kg/min, and showed a similar PK profile to that seen in healthy volunteers. Cangrelor infusions were well tolerated at doses up to 4 µg/kg/min. The most frequently reported AEs were injection site reactions and increased ALT. The elevations observed in AST and ALT were asymptomatic and did not result in discontinuation of drug in any patients. There were no major bleeding events reported.

In the placebo-controlled study SC-931-5060 in UA/non-Q-MI patients, cangrelor was well tolerated when administered as a continuous infusion for up to 72 hours (4 µg/kg/min). The AE profile was similar for the active and placebo groups. Progressive elevations in AST and ALT were observed, but there was no difference in frequency or degree of elevation between the cangrelor and placebo-treated patients.

From the results of the clinical studies described in this brochure, special hepatic, renal, or urinary monitoring will not be required in subsequent clinical trials.

While the two Phase III studies [TMC-CAN-05-02 and TMC-CAN-05-03] did not achieve their primary efficacy endpoints and were therefore terminated early, important safety and efficacy data were gained. When compared to clopidogrel, cangrelor was shown to have a similar safety profile in SAEs, AEs, and deaths. There was a small increase in minor bleeding events, but this can be expected given cangrelor's rapid and profound platelet inhibition. In addition, in meaningful clinical endpoints (death, Q-wave MI, and IDR), cangrelor was shown to have a better efficacy outcome than clopidogrel. Given these data and its unique PK profile, further efficacy research with cangrelor is warranted.

# 6. SUMMARY OF DATA AND GUIDANCE FOR THE INVESTIGATOR

## 6.1. Summary

Cangrelor is a potent, ultra-short acting and specific inhibitor of ADP-induced platelet aggregation mediated by its antagonism of the $P2Y_{12}$ receptor. It rapidly and reversibly inhibits

platelet activation and aggregations via the P2Y12 receptor in healthy volunteers and patients undergoing PCI.

Nonclinical safety evaluation studies have not revealed any mutagenic or clastogenic activities of parent drug, its nucleoside, or base metabolites, and there is no evidence from drug metabolism studies that any of these are substrates for adenosine deaminase. Toxicology studies indicate that renal and urinary tract toxicity is the principal potential hazard associated with treatment with cangrelor; however, careful monitoring in humans revealed no drug-related renal or urinary effects. Cangrelor was shown to be neither genotoxic or teratogenic.

Cangrelor has been evaluated in 14 clinical studies, including two Phase III studies. It has been dosed with an IV bolus of both 30 µg/kg and 60 µg/kg, and at infusions ranging from 0.01 µg/kg/min to 4 µg/kg/min. The pharmacology, safety, tolerability, and efficacy of cangrelor were studied in healthy subjects as well as patients with non-Q-MI, NSTEMI, and STEMI.

In the clinical pharmacology studies, the drug produced dose-related inhibition of ex vivo ADP-induced platelet aggregation. It was confirmed to have rapid onset and offset of action and to exhibit dose linearity.

The safety database consists of 7,655 cangrelor-treated subjects/patients. The safety profile of cangrelor was shown to be similar to the active comparator in all phases of clinical research; however, there was an increased frequency of minor bleeding events in the cangrelor groups. Bleeding events were carefully monitored and are presented in Section 5.4.3. More information on risks and AEs is available in Section 6.5.

The primary efficacy endpoint in the Phase III studies was to demonstrate that cangrelor is superior to clopidogrel in patients requiring PCI as measured by the composite of all-cause mortality, MI, and IDR. This endpoint was not met in either study in the CHAMPION program, which resulted in early termination of the two Phase III studies. However, in the clinically meaningful composit endpoint of death, Q-wave-MI, and IDR, cangrelor was shown to have greater efficacy than clopidogrel.

## 6.2. General Administration

Detailed instructions for preparing and administering cangrelor infusion solutions are provided in individual protocols and/or pharmacy instructions. Infusion solutions are prepared by diluting the appropriate volume of reconstituted Cangrelor for Injection with sodium chloride 0.9% w/v infusion/injection. Cangrelor infusions are compatible with a wide range of administration systems; however to achieve the required control of infusion rate, solutions must be administered by means of a motor-driven pump rather than a gravity-fed system. Infusion solutions are chemically stable for up to 30 hours (including administration time) at room temperature. They do not need to be protected from light after preparation or during administration.

### 6.2.1. Use in Women

Fertility and embryo-fetal development studies were performed in animals. These give no indication of the need to exclude women of childbearing potential from participating in studies with cangrelor.

### 6.2.2. Use in Patients With Hepatic and Renal Impairment

Animal toxicology studies revealed a low incidence of renal and upper urinary tract toxicity, and transient elevations in transaminase levels. Extensive safety monitoring in the human volunteer and patient studies has revealed no drug-related renal, urinary tract, or liver toxicities to date.

In man, the metabolite load of cangrelor is primarily excreted in urine. Clinical studies in subjects with compromised renal function, as determined by creatinine clearance, do not indicate a necessity for dose alterations or adjustments in this patient population.

### 6.2.3. Use in Elderly Patients

The oldest subject in the clinical pharmacology program was 66 years of age. Two 95-year-old patients received cangrelor; one in study TMC-CAN-05-02 (CHAMPION PCI) and one study TMC-CAN-05-03 (CHAMPION Platform). There is no evidence for any alteration in primary metabolic inactivation rate with age.

### 6.2.4. Use in Children

Not tested.

## 6.3. Drug Interactions

The potential interaction between cangrelor and standard therapy with aspirin, heparin, and GTN therapy in clinically effective doses was evaluated in study SC-931-5037. Standard triple therapy (aspirin, heparin, GTN) did not alter the dose-response for inhibition of ADP-induced platelet aggregation, extent of BT prolongation or the rapid metabolic clearance of cangrelor. There was also no evidence that the primary effects of any component of standard triple therapy were affected by cangrelor. Thus, the effects of cangrelor will remain rapidly reversible on slowing or stopping the infusion.

No interactions are expected with regularly used cardiovascular, antihypertensive, lipid lowering, antihyperglycemic, or antithrombotic drugs.

## 6.4. Contraindications and Precautions

### 6.4.1. Contraindications

Cangrelor is contraindicated in patients with:

- severe bleeding
- hypersensitivity to cangrelor or any of its excipients

### 6.4.2. Safety Implications of Metabolism and Excretion Data

Humans produce a metabolite array similar to rats and dogs, with the notable difference that in humans the S-oxide of the nucleoside appears predominantly in the urine. Thus, two-thirds of an administered dose of cangrelor is excreted in the urine.

## 6.5. Possible Risks and Adverse Events Associated With Use of Cangrelor

Cangrelor, an antiplatelet agent being developed for use during PCI and for the management of patients experiencing ACS, may be associated with increased risk of bleeding. Although bleeding with cangrelor may be expected to occur at the site of tissue damage or arterial puncture, bleeding may occur at any site and can result in death. This may be manifested as petechia, hematoma, decreases in hemoglobin or hematocrit, purpura, or ecchymosis as well as prolongation of bleeding time. Therefore, avoidance of tissue shear and trauma is necessary, and scrupulous attention should be given to vascular access and operative sites during and shortly after cangrelor infusions.

Subjects enrolled in cangrelor trials, due to their underlying cardiovascular disease, are at risk of death, myocardial infarction, recurrent myocardial infarction, stroke and other ischemic events that require revascularization. As a acompetitive $P2Y_{12}$ receptor antagonist that has been shown to inhibit ADP-induced platelet aggregation, cangrelor has significant potential to preclude thrombotic occlusion and therefore reduce the incidence of these ischemic events in patients experiencing ACS.

Adverse events from all completed Phase II and Phase III studies are summarized in Table 17 (Phase II) and Table 18 (Phase III). A list of expected serious adverse drug reactions is provided in Table A1-1 in Appendix 1. Non-serious adverse reactions from the Phase III studies are provided in Appendix 2 (Table A1-2).

## 6.6. Action to be Taken in the Event of an Overdose With Cangrelor

As cangrelor has a rapid onset and offset of action in humans, the simplest method of terminating its effects is to stop drug infusion. Patients and study subjects should be regarded as having impaired platelet function during and shortly after infusion, and platelet function should be checked if considered necessary.

There is no antidote to cangrelor. However, due to its very short half-life (5 minutes), the PD effects will rapidly diminish with full restoration of platelet function within 60 minutes of cessation of the infusion.

If no complication has ensued, the amount of overdose should be calculated and recorded. Correct the infusion rate to the protocol-specified rate and continue the infusion. If the overdose has caused any complication, stop the infusion and institute the therapeutically appropriate procedures per hospital protocol. Record the occurrence as an AE.

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SC-931-5129 Part 2. A multicentre pilot study to assess the safety and ex vivo platelet aggregation response of intravenous AR-C69931MX in patients undergoing percutaneous transluminal coronary angioplasty, with or without intracoronary stent placement. 16 February 2001.

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# APPENDIX 1: SERIOUS ADVERSE REACTIONS

**Table A1-1: Summary listing of serious adverse reactions considered probably or possibly related to cangrelor in cangrelor completed Phase II and Phase III studies**

| Preferred Term | Frequency (Total #) | Fatal | Life Threatening[a] |
|---|---|---|---|
| Acute pulmonary oedema | 2 | | 2 |
| Alanine aminotransferase increased | 1 | | |
| Angioneurotic oedema | 1 | | - |
| Asparate aminotransferase increased | 1 | | |
| Anaemia | 19 | | |
| Aneurysm | 1 | | |
| Angina pectoris | 2 | | |
| Angina unstable | 1 | | |
| Bradycardia | 2 | | |
| Cardiac arrest | 1 | | 1 |
| Cardiogenic shock | 1 | | 1 |
| Cellulitis | 1 | | |
| Cerebral haemorrhage | 1 | 1 | |
| Chest discomfort | 1 | | |
| Chest pain | 4 | | 1 |
| Collapse of lung | 1 | | |
| Coronary artery thrombosis | 2 | | |
| Embolism | 3 | | |
| Gastrointestinal haemorrhage | 3 | | |
| Haemorrhage intracranial | 1 | | |
| Haematoma infection | 1 | | |
| Hypertensive emergency | 1 | | |
| Hypotension | 3 | | |
| Laryngeal oedema | 1 | | |
| Liver function test abnormal | 1 | | |
| Melaena | 1 | | |
| Multi-organ failure | 1 | 1 | |
| Myocardial infarction | 2 | | |
| Overdose | 1 | | |

| Preferred Term | Frequency (Total #) | Fatal | Life Threatening[a] |
|---|---|---|---|
| Papillary muscle rupture | 1 | 1 | |
| Post procedural complication | 1 | | |
| Pulmonary embolism | 1 | | 1 |
| Pulmonary oedema | 1 | | |
| Purpura | 1 | | |
| Renal failure acute | 1 | | |
| Retroperitoneal haemorrhage | 2 | 1 | |
| Stridor | 1 | | |
| Thrombosis | 1 | | |
| Thrombocytopenia | 1 | | |
| Ventricular tachycardia | 1 | | |
| Vessel puncture site haematoma | 1 | | 1 |
| Vessel puncture site haemorrhage | 6 | | 0 |

Events that correlate with the mode of action for cangrelor are described in Section 6.5 and include modest prolongation of bleeding time, ecchymosis and petechia.
a. Life threatening data are only available for the Phase III studies.
Report generated by: SAE_A1_1.sas (Phase III data).

**Table A1-2 Summary listing of non-serious adverse drug reactions for studies TMC-CAN-02 (PCI) and TMC-CAN-03 (Platform)**

| Preferred Term | Frequency |
|---|---|
| Abdominal pain | 1 |
| Abdominal pain lower | 3 |
| Abdominal pain upper | 2 |
| Abdominal tenderness | 1 |
| Acute pulmonary oedema | 2 |
| Alanine aminotransferase increased | 1 |
| Anaemia | 4 |
| Angina pectoris | 1 |
| Angioneurotic oedema | 1 |
| Anxiety | 1 |
| Aspartate aminotransferase increased | 4 |
| Asthenia | 1 |
| Atrial fibrillation | 2 |

| Preferred Term | Frequency |
|---|---|
| Atrial tachycardia | 1 |
| Back pain | 7 |
| Blood bilirubin increased | 6 |
| Blood creatinine increased | 2 |
| Blood pressure increased | 1 |
| Bradycardia | 6 |
| Cardiac arrest | 1 |
| Cardiogenic shock | 1 |
| Catheter site haemorrhage | 1 |
| Catheter site pain | 1 |
| Cellulitis | 1 |
| Cerebral haemorrhage | 1 |
| Chest discomfort | 2 |
| Chest pain | 14 |
| Choking | 1 |
| Confusion postoperative | 1 |
| Constipation | 1 |
| Coronary artery occlusion | 1 |
| Diarrhoea | 3 |
| Dizziness | 1 |
| Dyspepsia | 3 |
| Dysphagia | 1 |
| Dyspnoea | 9 |
| Dysuria | 1 |
| Ecchymosis | 1 |
| Embolism | 1 |
| Flushing | 1 |
| Foreign body trauma | 1 |
| Haematoma infection | 1 |
| Haemoglobin decreased | 2 |
| Headache | 3 |
| Hepatic enzyme increased | 2 |
| Hot flush | 1 |

| Preferred Term | Frequency |
|---|---|
| Hypertension | 2 |
| Hypertensive crisis | 1 |
| Hypertensive emergency | 1 |
| Hypoaesthesia | 1 |
| Hypotension | 13 |
| Incorrect dose administered | 1 |
| Liver function test abnormal | 5 |
| Lymphadenopathy | 1 |
| Migraine | 1 |
| Musculoskeletal chest pain | 1 |
| Musculoskeletal pain | 1 |
| Nausea | 24 |
| Neck pain | 1 |
| Nodal arrhythmia | 1 |
| Oedema peripheral | 1 |
| Pain in extremity | 1 |
| Platelet count decreased | 3 |
| Pleural effusion | 1 |
| Post procedural discharge | 1 |
| Post procedural discomfort | 1 |
| Post procedural drainage | 1 |
| Procedural hypertension | 1 |
| Prothombin time prolonged | 1 |
| Pruritis | 2 |
| Pulmonary embolism | 1 |
| Puncture site pain | 4 |
| Purpura | 1 |
| Pyrexia | 1 |
| Rash | 6 |
| Rash erythematous | 1 |
| Rash pruritic | 1 |
| Reperfusion injury | 4 |
| Retroperitoneal haemorrage | 1 |

| Preferred Term | Frequency |
|---|---|
| Skin irritation | 1 |
| Syncope vasovagal | 4 |
| Tenderness | 1 |
| Thrombosis | 2 |
| Urticaria | 5 |
| Vascular procedural complication | 1 |
| Venipuncture site swelling | 2 |
| Vertigo | 1 |
| Vessel puncture site bruise | 1 |
| Vessel puncture site haematoma | 1 |
| Vomiting | 18 |

# APPENDIX 2 BLEEDING EVENTS IN PHASE III TRIALS

**Table A2-1: Summary of bleeding at 48 hour post-randomization in pooled Studies TMC-CAN-05-02 (CHAMPION PCI) and TMC-CAN-05-03 (CHAMPION Platform)**

| Category | Cangrelor n/N (%) | Clopidogrel n/N (%) |
|---|---|---|
| **Pooled Studies** | | |
| Any TIMI bleeding | 81 / 7036 (1.2) | 65 / 7015 (0.9) |
| Major | 23 / 7036 (0.3) | 23 / 7015 (0.3) |
| Minor | 58 / 7036 (0.8) | 42 / 7015 (0.6) |
| **PCI Study** | | |
| Any TIMI bleeding | 55 / 4374 (1.3) | 40 / 4365 (0.9) |
| Major | 19 / 4374 (0.4) | 14 / 4365 (0.3) |
| Minor | 36 / 4374 (0.8) | 26 / 4365 (0.6) |
| **Platform Study** | | |
| Any TIMI bleeding | 26 / 2662 (1.0) | 25 / 2650 (0.9) |
| Major | 4 / 2662 (0.2) | 9 / 2650 (0.3) |
| Minor | 22 / 2662 (0.8) | 16 / 2650 (0.6) |

TIMI = Thrombolysis In Myocardial Infarction.
Report generated by program (POOLED): T_BLD_CHG.SAS 23OCT09 13:20.

**Table A2-2: Summary of Non-CABG related bleeding by type at 48 hour post-randomization in Studies TMC-CAN-05-02 (CHAMPION PCI) and TMC-CAN-05-03 (CHAMPION Platform)**

| Category | PCI Study Cangrelor N=4374 n/N (%) | PCI Study Clopidogrel N=4365 n/N (%) | Platform Study Cangrelor N=2662 n/N (%) | Platform Study Clopidogrel N=2650 n/N (%) |
|---|---|---|---|---|
| Access site bleeding requiring radiologic or surgerical intervention | 6 (0.1) | 10 (0.2) | 8 (0.3) | 10 (0.4) |
| Hematoma ≥ 5 cm at puncture site | 84 (1.9) | 75 (1.7) | 115 (4.3) | 71 (2.7) |
| Intracranial hemorrhage | 1 (0.0) | 0 (0.0) | 2 (0.1) | 1 (0.0) |
| Intraocular | 2 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Reoperation for bleeding | 1 (0.0) | 1 (0.0) | 0 (0.0) | 1 (0.0) |

| Category | PCI Study Cangrelor N=4374 n/N (%) | PCI Study Clopidogrel N=4365 n/N (%) | Platform Study Cangrelor N=2662 n/N (%) | Platform Study Clopidogrel N=2650 n/N (%) |
|---|---|---|---|---|
| Retroperitoneal | 15 (0.3) | 10 (0.2) | 2 (0.1) | 1 (0.0) |
| Ecchymosis | 283 (6.5) | 233 (5.3) | 95 (3.6) | 57 (2.2) |
| Epistaxis | 9 (0.2) | 22 (0.5) | 6 (0.2) | 12 (0.5) |
| Hematoma < 5 cm at puncture site | 251 (5.7) | 222 (5.1) | 50 (5.6) | 119 (4.5) |
| Oozing at puncture site | 400 (9.1) | 316 (7.2) | 125 (4.7) | 91 (3.4) |
| Thrombocytopenia | 5 (0.1) | 7 (0.2) | 1 (0.0) | 3 (0.1) |
| Other | 112 (2.6) | 101 (2.3) | 50 (1.9) | 39 (1.5) |
| Clinically overt bleed (including bleeding seen on imagining) | 864 (19.8) | 747 (17.1) | 440 (16.5) | 319 (12.0) |
| Hemodynamic compromis | 9 (0.2) | 11 (0.3) | 7 (0.3) | 5 (0.2) |
| Transfusion | 41 (0.9) | 38 (0.9) | 24 (0.9) | 16 (0.6) |
| Drop in hemoglobin and/or hematocrit[a] | 84 (1.9) | 60 (1.4) | 32 (1.2) | 33 (1.2) |

PCI = percutaneous coronary intervention.
a. Drop ≥3g/dl for hemoglobin and/or drop ≥9% in hematocrit recorded in bleed case report form.
Report generated by programs (PF): T_BLD.SAS 24SEP09 15:54 and (PCI): T_BLD.SAS 24SEP09 15:55

**Table A2-3: Summary of bleeding at 48 hour post-randomization (Study TMC-CAN-05-02 [CHAMPION PCI])**

| Category | Cangrelor N=4374 n/N (%) | Clopidogrel N=4365 n/N (%) |
|---|---|---|
| **Non-CABG related bleeding** | | |
| Any ACUITY bleeding | 890 (20.3) | 769 (17.6) |
| Major | 151 (3.5) | 120 (2.7) |
| Minor | 765 (17.5) | 661 (15.1) |
| Any GUSTO bleeding | 890 (20.3) | 769 (17.6) |
| Severe/life threatening | 10 (0.2) | 11 (0.3) |
| Moderate | 36 (0.8) | 30 (0.7) |
| Mild | 853 (19.5) | 736 (16.9) |

| Category | Cangrelor N=4374 n/N (%) | Clopidogrel N=4365 n/N (%) |
|---|---|---|
| Any TIMI bleeding | 55 (1.3) | 40 (0.9) |
| Major | 19 (0.4) | 14 (0.3) |
| Minor | 36 (0.8) | 26 (0.6) |
| **CABG related bleeding** | | |
| Any ACUITY bleeding | 10 (0.2) | 8 (0.2) |
| Major | 7 (0.2) | 6 (0.1) |
| Minor | 3 (0.1) | 3 (0.1) |
| Any GUSTO bleeding | 10 (0.2) | 8 (0.2) |
| Severe/life threatening | 0 (0.0) | 0 (0.0) |
| Moderate | 5 (0.1) | 4 (0.1) |
| Mild | 5 (0.1) | 4 (0.1) |
| Any TIMI bleeding | 0 (0.0) | 0 (0.0) |
| Major | 0 (0.0) | 0 (0.0) |
| Minor | 0 (0.0) | 0 (0.0) |

ACUITY = Acute Catheterization and Urgent Intervention Triage strategY; CABG = coronary artery bypass graft (surgery); GUSTO = Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries; TIMI = Thrombolysis In Myocardial Infarction.
Report generated by program: T_BLD.SAS 24SEP09 15:54

**Table A2-4: Summary of non-CABG and CABG related bleeding by type at 48 hour post-randomization (Study TMC-CAN-05-02 [CHAMPION PCI])**

| Category | Cangrelor N=4374 n/N (%) | Clopidogrel N=4365 n/N (%) |
|---|---|---|
| **Non-CABG related bleeding** | | |
| Access site bleeding requiring radiologic or surgerical intervention | 6 (0.1) | 10 (0.2) |
| Hematoma ≥ 5 cm at puncture site | 84 (1.9) | 75 (1.7) |
| Intracranial hemorrhage | 1 (0.0) | 0 (0.0) |
| Intraocular | 2 (0.0) | 0 (0.0) |
| Reoperation for bleeding | 1 (0.0) | 1 (0.0) |
| Retroperitoneal | 15 (0.3) | 10 (0.2) |
| Ecchymosis | 283 (6.5) | 233 (5.3) |
| Epistaxis | 9 (0.2) | 22 (0.5) |

| Category | Cangrelor N=4374 n/N (%) | Clopidogrel N=4365 n/N (%) |
|---|---|---|
| Hematoma < 5 cm at puncture site | 251 (5.7) | 222 (5.1) |
| Oozing at puncture site | 400 (9.1) | 316 (7.2) |
| Thrombocytopenia | 5 (0.1) | 7 (0.2) |
| Other | 112 (2.6) | 101 (2.3) |
| Clinically overt bleed (including bleeding seen on imagining) | 864 (19.8) | 747 (17.1) |
| Hemodynamic compromis | 9 (0.2) | 11 (0.3) |
| Transfusion | 41 (0.9) | 38 (0.9) |
| Drop in hemoglobin and/or hematocrit[a] | 84 (1.9) | 60 (1.4) |
| **CABG related bleeding** | | |
| Access site bleeding requiring radiologic or surgerical intervention | 0 (0.0) | 0 (0.0) |
| Hematoma ≥ 5 cm at puncture site | 1 (0.0) | 1 (0.0) |
| Intracranial hemorrhage | 0 (0.0) | 0 (0.0) |
| Intraocular | 0 (0.0) | 0 (0.0) |
| Reoperation for bleeding | 0 (0.0) | 0 (0.0) |
| Retroperitoneal | 0 (0.0) | 0 (0.0) |
| Ecchymosis | 1 (0.0) | 1 (0.0) |
| Epistaxis | 0 (0.0) | 0 (0.0) |
| Hematoma < 5 cm at puncture site | 0 (0.0) | 0 (0.0) |
| Oozing at puncture site | 0 (0.0) | 3 (0.1) |
| Thrombocytopenia | 1 (0.0) | 0 (0.0) |
| Other | 0 (0.0) | 0 (0.0) |
| Clinically overt bleed (including bleeding seen on imagining) | 2 (0.0) | 3 (0.1) |
| Hemodynamic compromis | 0 (0.0) | 0 (0.0) |
| Transfusion | 5 (0.1) | 4 (0.1) |
| Drop in hemoglobin and/or hematocrit[a] | 7 (0.2) | 3 (0.1) |

CABG = coronary artery bypass graft (surgery).
a. Drop ≥3g/dl for hemoglobin and/or drop ≥9% in hematocrit recorded in Bleed case report form.
Report generated by program (PCI): T_BLD.SAS 24SEP09 15:55

**Table A2-5: Summary of bleeding at 48 hour post-randomization (Study TMC-CAN-05-03 [CHAMPION Platform])**

| Category | Cangrelor N=2662 n/N (%) | Clopidogrel N=2650 n/N (%) |
|---|---|---|
| **Non-CABG related bleeding** | | |
| Any ACUITY bleeding | 450 (16.9) | 326 (12.3) |
| Major | 145 (5.4) | 91 (3.4) |
| Minor | 320 (12.0) | 246 (9.3) |
| Any GUSTO bleeding | 450 (16.9) | 326 (12.3) |
| Severe/life threatening | 9 (0.3) | 6 (0.2) |
| Moderate | 18 (0.7) | 13 (0.5) |
| Mild | 427 (16.0) | 308 (11.6) |
| Any TIMI bleeding | 26 (1.0) | 24 (0.9) |
| Major | 4 (0.2) | 9 (0.3) |
| Minor | 22 (0.8) | 15 (0.6) |
| **CABG related bleeding** | | |
| Any ACUITY bleeding | 2 (0.1) | 2 (0.1) |
| Major | 2 (0.1) | 2 (0.1) |
| Minor | 0 (0.0) | 0 (0.0) |
| Any GUSTO bleeding | 2 (0.1) | 2 (0.1) |
| Severe/life threatening | 0 (0.0) | 0 (0.0) |
| Moderate | 2 (0.1) | 0 (0.0) |
| Mild | 0 (0.0) | 2 (0.1) |
| Any TIMI bleeding | 0 (0.0) | 1 (0.0) |
| Major | 0 (0.0) | 0 (0.0) |
| Minor | 0 (0.0) | 1 (0.0) |

ACUITY = Acute Catheterization and Urgent Intervention Triage strategY; CABG = coronary artery bypass graft (surgery); GUSTO = Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries; TIMI = Thrombolysis In Myocardial Infarction.
Report generated by program: T_BLD.SAS 24SEP09 15:54

**Table A2-6: Summary of non-CABG and CABG related bleeding by type at 48 hour post-randomization (Study TMC-CAN-05-03 [CHAMPION Platform])**

| Category | Cangrelor N=2662 n/N (%) | Clopidogrel N=2650 n/N (%) |
|---|---|---|
| **Non-CABG related bleeding** | | |
| Access site bleeding requiring radiologic or surgerical intervention | 8 (0.3) | 10 (0.4) |
| Hematoma ≥ 5 cm at puncture site | 115 (4.3) | 71 (2.7) |
| Intracranial hemorrhage | 2 (0.1) | 1 (0.0) |
| Intraocular | 0 (0.0) | 0 (0.0) |
| Reoperation for bleeding | 0 (0.0) | 1 (0.0) |
| Retroperitoneal | 2 (0.1) | 1 (0.0) |
| Ecchymosis | 95 (3.6) | 57 (2.2) |
| Epistaxis | 6 (0.2) | 12 (0.5) |
| Hematoma < 5 cm at puncture site | 150 (5.6) | 119 (4.5) |
| Oozing at puncture site | 125 (4.7) | 91 (3.4) |
| Thrombocytopenia | 1 (0.0) | 3 (0.1) |
| Other | 50 (1.9) | 39 (1.5) |
| Clinically overt bleed (including bleeding seen on imagining) | 440 (16.5) | 319 (12.0) |
| Hemodynamic compromise | 7 (0.3) | 5 (0.2) |
| Transfusion | 24 (0.9) | 16 (0.6) |
| Drop in hemoglobin and/or hematocrit* | 32 (1.2) | 33 (1.2) |
| **CABG related bleeding** | | |
| Access site bleeding requiring radiologic or surgerical intervention | 0 (0.0) | 0 (0.0) |
| Hematoma ≥ 5 cm at puncture site | 0 (0.0) | 0 (0.0) |
| Intracranial hemorrhage | 0 (0.0) | 0 (0.0) |
| Intraocular | 0 (0.0) | 0 (0.0) |
| Reoperation for bleeding | 1 (0.0) | 0 (0.0) |
| Retroperitoneal | 0 (0.0) | 0 (0.0) |
| Ecchymosis | 0 (0.0) | 0 (0.0) |
| Epistaxis | 0 (0.0) | 0 (0.0) |
| Hematoma < 5 cm at puncture site | 0 (0.0) | 0 (0.0) |

| Category | Cangrelor N=2662 n/N (%) | Clopidogrel N=2650 n/N (%) |
|---|---|---|
| Oozing at puncture site | 0 (0.0) | 0 (0.0) |
| Thrombocytopenia | 1 (0.0) | 0 (0.0) |
| Other | 0 (0.0) | 1 (0.0) |
| Clinically overt bleed (including bleeding seen on imagining) | 1 (0.0) | 1 (0.0) |
| Hemodynamic compromise | 0 (0.0) | 0 (0.0) |
| Transfusion | 2 (0.1) | 0 (0.0) |
| Drop in hemoglobin and/or hematocrit | 1 (0.0) | 2 (0.1) |

CABG = coronary artery bypass graft (surgery).
Report generated by program: T_BLD.SAS 24SEP09 15:54

**Table A2-7: Summary of bleeding events[a] that occurred post-randomization and before administration of clopidogrel in study TMC-CAN-05-03 (CHAMPION Platform)**

| Category | Cangrelor N=2662 n/N (%) | Placebo N=2650 n/N (%) |
|---|---|---|
| **Non-CABG related bleeding** | | |
| Any ACUITY bleeding | 15 (0.6) | 8 (0.3) |
| Major | 8 (0.3) | 0 (0.0) |
| Minor | 7 (0.3) | 8 (0.3) |
| Any GUSTO bleeding | 15 (0.6) | 8 (0.3) |
| Severe/life threatening | 0 (0.0) | 0 (0.0) |
| Moderate | 1 (0.0) | 0 (0.0) |
| Mild | 14 (0.5) | 8 (0.3) |
| Any TIMI bleeding | 2 (0.1) | 0 (0.0) |
| Major | 0 (0.0) | 0 (0.0) |
| Minor | 2 (0.1) | 0 (0.0) |
| **CABG related bleeding** | | |
| Any ACUITY bleeding | 0 (0.0) | 0 (0.0) |
| Major | 0 (0.0) | 0 (0.0) |
| Minor | 0 (0.0) | 0 (0.0) |
| Any GUSTO bleeding | 0 (0.0) | 0 (0.0) |

| Category | Cangrelor N=2662 n/N (%) | Placebo N=2650 n/N (%) |
|---|---|---|
| Severe/life threatening | 0 (0.0) | 0 (0.0) |
| Moderate | 0 (0.0) | 0 (0.0) |
| Mild | 0 (0.0) | 0 (0.0) |
| Any TIMI bleeding | 0 (0.0) | 0 (0.0) |
| Major | 0 (0.0) | 0 (0.0) |
| Minor | 0 (0.0) | 0 (0.0) |

ACUITY = Acute Catheterization and Urgent Intervention Triage strategY; CABG = coronary artery bypass graft (surgery); GUSTO = Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries; TIMI = Thrombolysis In Myocardial Infarction.

a. Data from safety + SA/UA/NSTEMI/STEMI populations.

Report generated by program: T_BLD_PLACEBO.SAS 15APR10 10:56

# APPENDIX 3 ADVERSE EVENTS IN PHASE III TRIALS

**Table A3-1: Summary of AEs with fatal outcome by system organ class, in patients in the cangrelor arm who had died at 1 year (safety population; Study TMC-CAN-05-02 [CHAMPION PCI])**

| System Organ Class | Number of Events |
|---|---|
| General disorders and administration site conditions | 26 |
| Cardiac disorders | 43 |
| Gastrointestinal disorders | 2 |
| Respiratory, thoracic and mediastinal disorders | 6 |
| Investigations | 1 |
| Nervous system disorders | 5 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 9 |
| Renal and urinary disorders | 3 |
| Injury, poisoning and procedural complications | 2 |
| Infections and infestations | 3 |
| Missing SOC term | 2 |

Report generated by program (PCI): T_AE_DEATH.SAS 24SEP09 16:15

**Table A3-2: Summary of AEs with fatal outcome by system organ class, in patients in the cangrelor arm who had died at 1 year (safety population; Study TMC-CAN-05-03 [CHAMPION Platform])**

| System Organ Class | Number of Events |
|---|---|
| Cardiac disorders | 30 |
| General disorders and administration site conditions | 15 |
| Nervous system disorders | 6 |
| Gastrointestinal disorders | 2 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 8 |
| Respiratory, thoracic and mediastinal disorders | 3 |
| Vascular disorders | 1 |
| Injury, poisoning and procedural complications | 1 |
| Infections and infestations | 2 |
| Missing SOC term | 2 |

Report generated by program: T_AE_DEATH.SAS 24SEP09 16:00

**Table A3-3: Summary of common (>0.2% on cangrelor arm) adverse events by Preferred Term in pooled Studies TMC-CAN-05-02 (CHAMPION PCI) and TMC-CAN-05-03 (CHAMPION Platform)**

| Preferred Term | Cangrelor N=7036 n/N (%) | Clopidogrel in PCI N=4365[a] n/N (%) | Clopidogrel in PF N=2650[b] n/N (%) |
|---|---|---|---|
| Back pain | 258 (3.7) | 164 (3.8) | 85 (3.2) |
| Chest pain | 251 (3.6) | 163 (3.7) | 69 (2.6) |
| Nausea | 183 (2.6) | 145 (3.3) | 66 (2.5) |
| Headache | 153 (2.2) | 97 (2.2) | 68 (2.6) |
| Hypotension | 140 (2.0) | 89 (2.0) | 38 (1.4) |
| Vomiting | 107 (1.5) | 78 (1.8) | 31 (1.2) |
| Puncture site pain | 88 (1.3) | 52 (1.2) | 29 (1.1) |
| Pyrexia | 81 (1.2) | 37 (0.8) | 20 (0.8) |
| Dyspnoea | 80 (1.1) | 16 (0.4) | 15 (0.6) |
| Hypertension | 60 (0.9) | 34 (0.8) | 22 (0.8) |
| Ventricular tachycardia | 48 (0.7) | 35 (0.8) | 11 (0.4) |
| Chest discomfort | 45 (0.6) | 24 (0.5) | 11 (0.4) |
| Bradycardia | 39 (0.6) | 35 (0.8) | 15 (0.6) |
| Atrial fibrillation | 34 (0.5) | 18 (0.4) | 9 (0.3) |
| Pain in extremity | 34 (0.5) | 24 (0.5) | 14 (0.5) |
| Angina pectoris | 31 (0.4) | 34 (0.8) | 17 (0.6) |
| Syncope vasovagal | 30 (0.4) | 26 (0.6) | 4 (0.2) |
| Anxiety | 29 (0.4) | 22 (0.5) | 3 (0.1) |
| Pain | 27 (0.4) | 13 (0.3) | 8 (0.3) |
| Dizziness | 26 (0.4) | 21 (0.5) | 9 (0.3) |
| Coronary artery dissection | 25 (0.4) | 15 (0.3) | 7 (0.3) |
| Dyspepsia | 24 (0.3) | 22 (0.5) | 8 (0.3) |
| Abdominal pain | 22 (0.3) | 10 (0.2) | 8 (0.3) |
| Ventricular fibrillation | 21 (0.3) | 6 (0.1) | 7 (0.3) |
| Diarrhoea | 20 (0.3) | 13 (0.3) | 3 (0.1) |
| Musculoskeletal pain | 20 (0.3) | 23 (0.5) | 13 (0.5) |
| Procedural pain | 20 (0.3) | 11 (0.3) | 0 (0.0) |
| Insomnia | 18 (0.3) | 6 (0.1) | 15 (0.6) |
| Blood creatinine increased | 17 (0.2) | 6 (0.1) | 3 (0.1) |

| Preferred Term | Cangrelor N=7036 n/N (%) | Clopidogrel in PCI N=4365[a] n/N (%) | Clopidogrel in PF N=2650[b] n/N (%) |
|---|---|---|---|
| Blood pressure increased | 17 (0.2) | 9 (0.2) | 2 (0.1) |
| Cardiac failure congestive | 16 (0.2) | 9 (0.2) | 4 (0.2) |
| Hypokalaemia | 16 (0.2) | 7 (0.2) | 2 (0.1) |
| Red blood cell sedimentation rate increased | 15 (0.2) | 16 (0.4) | 0 (0.0) |
| Renal failure acute | 15 (0.2) | 8 (0.2) | 1 (0.0) |

AE = adverse event; NSTEMI = non-ST segment myocardial infarction; PCI = percutaneous coronary intervention; PF = Platform; SA = stable angina; STEMI = ST segment myocardial infarction; UA = unstable angina.
a. Adverse event data from safety + SA/UA/NSTEMI/STEMI populations.
b. Adverse event data from safety + SA/UA/NSTEMI populations.

**Table A3-4 Summary of treatment-emergent serious adverse events that occurred post-randomization and before administration of clopidogrel in study TMC-CAN-05-03 (CHAMPION Platform)**

| System Organ Class/Preferred Term | Cangrelor (N=2662)[a] n (%) | Placebo (N=2650)[a] n (%) |
|---|---|---|
| **Patients with at least one SAE** | **8 (0.3)** | **11 (0.4)** |
| **Cardiac disorders** | **6 (0.2)** | **6 (0.2)** |
| Cardiac arrest | 1 (0.0) | 0 (0.0) |
| Cardiac failure congestive | 2 (0.1) | 1 (0.0) |
| Cardiogenic shock | 2 (0.1) | 1 (0.0) |
| Coronary artery occlusion | 0 (0.0) | 1 (0.0) |
| Coronary artery thrombosis | 0 (0.0) | 1 (0.0) |
| Left ventricular failure | 0 (0.0) | 1 (0.0) |
| Ventricular fibrillation | 1 (0.0) | 1 (0.0) |
| **Respiratory, thoracic and mediastinal disorders** | **1 (0.0)** | **3 (0.1)** |
| Pulmonary oedema | 1 (0.0) | 3 (0.1) |
| **Vascular disorders** | **1 (0.0)** | **2 (0.1)** |
| Hypertension | 0 (0.0) | 1 (0.0) |
| Hypotension | 1 (0.0) | 1 (0.0) |

SAE = serious adverse event; NSTEMI = non-ST segment myocardial infarction; SA = stable angina; STEMI = ST segment myocardial infarction; UA = unstable angina
Data from safety + SA/UA/NSTEMI populations.
Report generated by program: AE_YS.SAS 09APR10 16:23.

**Table A3-5 Summary of treatment-emergent adverse events that occurred post-randomization and before administration of clopidogrel in study TMC-CAN-05-03 (CHAMPION Platform)**

| System Organ Class/Preferred Term | Cangrelor (N = 2662)[a] n (%) | Placebo (N = 2650)[a] n (%) |
|---|---|---|
| **Patients with at least one AE** | **76 (2.9)** | **84 (3.4)** |
| **Cardiac disorders** | **25 (0.9)** | **35 (1.3)** |
| Angina pectoris | 3 (0.1) | 4 (0.2) |
| Angina unstable | 1 (0.0) | 0 (0.0) |
| Atrial fibrillation | 1 (0.0) | 0 (0.0) |
| Atrial flutter | 0 (0.0) | 1 (0.0) |
| Atrioventricular block | 1 (0.0) | 1 (0.0) |
| Antrioventricular block third degree | 1 (0.0) | 0 (0.0) |
| Bradycardia | 3 (0.1) | 8 (0.3) |
| Cardiac arrest | 1 (0.0) | 0 (0.0) |
| Cardiac failure congestive | 2 (0.1) | 1 (0.0) |
| Cardiogenic shock | 2 (0.1) | 1 (0.0) |
| Coronary artery dissection | 5(0.2) | 5 (0.2) |
| Coronary artery embolism | 0 (0.0) | 1 (0.0) |
| Coronary artery occlusion | 3 (0.1) | 5 (0.2) |
| Coronary artery thrombosis | 1 (0.0) | 1 (0.0) |
| Left ventricular failure | 0 (0.0) | 1 (0.0) |
| Nodal rhythm | 1 (0.0) | 0 (0.0) |
| Sinus bradycardia | 0 (0.0) | 1 (0.0) |
| Ventricular extrasystoles | 0 (0.0) | 1 (0.0) |
| Ventricular fibrillation | 2 (0.1) | 5 (0.2) |
| **Gastrointestinal disorders** | **10 (0.4)** | **7 (0.3)** |
| Abdominal pain | 1 (0.0) | 0 (0.0) |
| Nausea | 8 (0.3) | 5 (0.2) |
| Vomiting | 4 (0.2) | 3 (0.1) |
| **General disorders and administration site conditions** | **17 (0.6)** | **20 (0.8)** |
| Asthenia | 1 (0.0) | 0 (0.0) |

| System Organ Class/Preferred Term | Cangrelor (N = 2662)[a] n (%) | Placebo (N = 2650)[a] n (%) |
|---|---|---|
| Chest discomfort | 3 (0.1) | 5 (0.2) |
| Chest pain | 12 (0.5) | 11 (0.4) |
| Chills | 0 (0.0) | 1 (0.0) |
| Paradoxical drug reaction | 0 (0.0) | 1 (0.0) |
| Puncture site pain | 0 (0.0) | 2 (0.1) |
| Pyrexia | 1 (0.0) | 0 (0.0) |
| **Injury, poisoning and procedural complications** | **4 (0.2)** | **4 (0.2)** |
| Device breakage | 1 (0.0) | 0 (0.0) |
| Incorrect dose administered | 1 (0.0) | 0 (0.0) |
| Post procedural headache | 1 (0.0) | 0 (0.0) |
| Procedural hypertension | 0 (0.0) | 1 (0.0) |
| Procedural hypotension | 0 (0.0) | 1 (0.0) |
| Vascular procedure complication | 0 (0.0) | 2 (0.1) |
| **Investigations** | **1 (0.0)** | **0 (0.0)** |
| Blood pressure increased | 1 (0.0) | 0 (0.0) |
| **Metabolism and nurtirion disorders** | **0 (0.0)** | **1 (0.0)** |
| Hyopglycaemia | 0 (0.0) | 1 (0.0) |
| **Musculoskeletal and connective tissue disorders** | **3 (0.1)** | **5 (0.2)** |
| Back pain | 2 (0.1) | 2 (0.1) |
| Musculoskeletal pain | 1 (0.0) | 2 (0.1) |
| Pain in extremity | 0 (0.0) | 2 (0.1) |
| **Nervous system disorders** | **4 (0.2)** | **3 (0.1)** |
| Headache | 0 (0.0) | 1 (0.0) |
| Hypoasthesia | 1 (0.0) | 1 (0.0) |
| Lethargy | 0 (0.0) | 1 (0.0) |
| Paraesthesia | 1 (0.0) | 0 (0.0) |
| Syncope vasovagal | 2 (0.1) | 1 (0.0) |
| **Psychiatric disorders** | **4 (0.2)** | **1 (0.0)** |
| Anxiety | 3 (0.1) | 1 (0.0) |

| System Organ Class/Preferred Term | Cangrelor (N = 2662)[a] n (%) | Placebo (N = 2650)[a] n (%) |
|---|---|---|
| Panic attack | 1 (0.0) | 0 (0.0) |
| **Respiratory, thoracic and mediastinal disorders** | **6** (0.2) | **4** (0.2) |
| Dyspnoea | 3 (0.1) | 1 (0.0) |
| Pulmonary oedema | 3 (0.1) | 3 (0.1) |
| **Skin and subcutaneous tissue disorders** | **4 (0.2)** | **3 (0.1)** |
| Dermatitis allergic | 0 (0.0) | 1 (0.0) |
| Pruritis | 1 (0.0) | 1 (0.0) |
| Rash | 2 (0.1) | 1 (0.0) |
| Skin ulcer | 1 (0.0) | 0 (0.0) |
| **Vascular disorders** | **16 (0.6)** | **13 (0.5)** |
| Embolism | 1 (0.0) | 1 (0.0) |
| Hypertension | 4 (0.2) | 2 (0.1) |
| Hypotension | 8 (0.3) | 7 (0.3) |
| Reperfusion injury | 3 (0.1) | 2 (0.1) |
| Shock | 0 (0.0) | 1 (0.0) |
| Thrombosis | 1 (0.0) | 0 (0.0) |

AE = adverse event.
a. Data from safety + SA/UA/NSTEMI populations.
Report generated by program: AE_YS.SAS 09APR10 16:23.

THE MEDICINES COMPANY®

# CANGRELOR FOR INJECTION
# INVESTIGATOR'S BROCHURE

| | |
|---|---|
| Edition No. 6 | Replaces Edition No. 5 |
| Release Date: 20 June 2011 | Dated: 4 May 2010 |
| Data Cutoff Date: 30 April 2011 | Data Cutoff Date: 23 September 2009 |

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The Medicines Company
8 Sylvan Way
Parsippany, New Jersey 07054
USA
973-656-1616

# SAMPLE INFORMED CONSENT

STUDY NAME: **CHAMPION PHOENIX: A clinical trial comparing cangrelor to clopidogrel standard of care therapy in subjects who require percutaneous coronary intervention.**

**PROTOCOL NUMBER:** [TMC-CAN-10-01]
**INVESTIGATOR:** [Investigator to add]

## Introduction

You are being asked to take part in a research study. Taking part in this study is completely voluntary. This study will be run by Dr. [Investigator] at [Name of Hospital]. It is important that you read and understand this consent form. Please read it carefully. Take time to ask the research doctor or staff as many questions about this research study as you would like. If there are any words or information that you do not understand, the research doctor or staff will explain them to you. Reading this form and talking to the research doctor or staff should help you decide whether or not to take part in this research study. If you do decide to participate, you must sign and date this form before your participation in this research study begins. You will be consenting to participate in this study before your doctor will know if you are eligible. Your doctor will need to review pictures of your heart vessels. You are eligible for this study if your doctor determines that you need a procedure to open clogged vessels in your heart. Your doctor will let you know if you are eligible to participate.

## Background and Purpose

You are being asked to be a volunteer in this research study because you are having signs and symptoms of coronary heart disease. This may be a serious heart problem where the heart does not get enough oxygen. This condition may be caused by a partial blockage in one or more of the blood vessels in your heart.

This research study involves the use of an investigational drug called cangrelor, which is being tested for its ability to prevent blood clots in patients having a balloon procedure known as a percutaneous coronary intervention (PCI) to open blocked blood vessels in the heart. This study also uses the FDA-approved drug clopidogrel (Plavix®). Plavix is approved to treat heart attacks and strokes. The initial dose of Plavix that you will receive when you have a PCI can be up to two times the approved dose depending on your institution's standard of care. The purpose of this study is to compare the safety and effectiveness of cangrelor combined with Plavix to the safety and effectiveness of Plavix alone. Cangrelor has not been approved by the US Food and Drug Administration (FDA); therefore, the use of cangrelor is experimental in this study.

This research study will enroll approximately 10,900 people at approximately 200 sites globally.

**Description of the Study**

Your doctor will also perform a complete medical evaluation to find out if you can participate in this research study. It will include medical history, a physical exam, demographic questions, blood tests, a urine sample and an electrical tracing of the heartbeat (ECG). For the blood tests, about 4 teaspoons (approx 20 mLs or ¾ ounce) of blood will be drawn by a trained person through a single needle puncture of a vein. All of these evaluations are usually conducted as part of the standard patient care. Standard of care means that you would have these tests or procedures performed whether you are in the study or not. In addition to the normal blood tests that you will have as part of your standard of care, you will have 4ml (approximately 1 teaspoon) of blood drawn for the study which will be sent to a central lab. You should tell your doctor about your medical history, including all medicines that you are taking (even herbal treatments or over-the-counter products) and if you are taking part in any other studies. You should also tell your doctor if you are pregnant, or if you think that you may be pregnant. Females of childbearing age must receive a pregnancy test that is confirmed to be negative before participating in this study.

**Study Procedures**

If you qualify and wish to continue, you will be randomly assigned (by chance) to 1 of 2 study groups:

- **Cangrelor Group** - during the PCI procedure you will get cangrelor through an IV (intravenous) catheter (plastic tubing) inserted into your vein that will slowly inject the cangrelor into your body for at least 2 hours. However, your physician may choose to continue the infusion for up to a total of 4 hours if the duration of the PCI procedure is longer than 2 hours. Per your institutions' standard of care you will receive 2 - 4 placebo capsules (capsules containing no medication) at the time of the PCI procedure. Finally, you will receive four (4) 150 mg capsules of Plavix (600 mg total) immediately after the cangrelor drip is stopped.

- **Placebo Group** - during the PCI procedure you will get placebo (a medically inactive substance) through an IV catheter inserted into your vein that will slowly inject into your body for at least 2 hours. However, your physician may choose to continue the infusion for up to a total of 4 hours if the duration of the PCI procedure is longer than 2 hours. Per your institutions' standard of care, you will receive 2 - 4 150 mg capsules of Plavix at the time of the PCI. Finally, you will receive four (4) placebo capsules immediately after the placebo drip is stopped.

- You will have an equal chance of getting either of the intravenous study drugs (cangrelor or placebo). Neither you nor the research study doctor will know which study drug you are getting. However, in the event of a medical emergency, the research doctor will be able to find out which study drug you are taking.

During your hospitalization, you will need to have at least 2 more ECG's and 4 blood samples taken [about 5 teaspoons (approx 25 mLs or 1 ounce)]. Three of the blood samples (4 mls each) will be drawn and sent to the central lab for analysis. As a part of standard medical treatment you may also receive Aspirin and other medications to prevent complications related to your procedure based on your physician's judgment. The day after the procedure, medication to prevent blood clots from forming and Aspirin will be prescribed for you. These need to be taken for at least one month or more based up on your physician's judgment.

**Follow-Up**

You will get follow-up phone calls in about 2 days (if you are no longer in hospital) and 1 month after the PCI procedure to see how you are doing and if there are any changes in your medical history and condition since the previous contact. You will be asked to inform the research staff if there are any changes in your contact information during the follow-up period.

**Length of Participation**

Your participation in this research study will begin when you sign this consent form and continue for approximately 35 days after your procedure.

**Withdrawal from Study**

You can end your participation in this study at any time. Your doctor may also decide to end your participation in the study early, if:

- new information about the treatment suggests that it will not work
- new information about the treatment suggests that it will be unsafe for you
- you do not follow the study rules
- you have a new injury or illness

If you or your doctor decides to stop your participation in the study, you may be asked to have additional laboratory tests and examinations that your doctor thinks are necessary.

**Risks/Benefits**

Cangrelor: Cangrelor has been administered to approximately 7,600 people in other studies. The most common side effect seen with cangrelor is bleeding. As with any blood-thinning medication, bleeding can occur at or into any place in the body including at the site of needle sticks, in the digestive system, inside the belly, or into the urine. This may be manifested as but not limited to bruising, hematoma, decreases in hemoglobin or hematocrit (both signs of blood loss seen in laboratory examinations) , purpura (red or purple discoloration on the skin caused by bleeding underneaththe skin which can be small or large), as well as prolongation of bleeding time ; rarely (< 1/1000), bleeding can occur inside the eyes or the brain. Bleeding events may be severe and result in other complications, including death.

The other common side effects reported include: Back pain, chest pain, nausea (uneasiness of the stomach), headache, low blood pressure, vomiting, puncture site pain, fever, shortness of breath, and high blood pressure.

Serious side effects have been reported very rarely which included heart attacks , multiple organ failure, or that a clot can form inside the lung or coronary arteries.

**Clopidogrel Risks**
Clopidogrel (Plavix®) is an approved prescription medication used in the treatment of heart attacks and strokes. The initial dose you will receive in this trial is two times the approved dose; however, it is currently used in the treatment of subjects undergoing a PCI.

As a medication that affects the function of blood platelets, the most common side effects associated with clopidogrel are bleeding. Severe bleeding events that resulted in death have occurred in 0.2% of patients treated. In extremely rare cases (about 4 in a million), a serious bleeding problem called thrombotic thrombocytopenic purpura (TTP) can occurwhich is a rare disorder which affects the ability for your blood to clot.

The most common side effects of clopidogrel reported in clinical trials more than 54,000 patients at the approved doses were headache, dizziness, stomach pain, chest pain, a drop in your blood cells (which could lead to an increased risk of infection), diarrhea, indigestion, an increase in cholesterol levels, rash, nausea, or a drop in the number of platelets (small particles in the blood that help with blood clotting).

**Reproductive Risks**
The effects of cangrelor on the unborn child are unknown. There is no information on the long-term effects of cangrelor on either male or female fertility. Similarly, there are no adequate and well controlled studies of Clopidigrel on pregnant women. Do not participate in this study if you are pregnant or if you think you might be pregnant. Be sure to tell your doctor if you think you may be pregnant, or if you are unsure.

**Unknown Risks**
You might have side effects or discomforts that are not listed in this form. Some side effects may not be known yet. New ones could happen to you. Tell the research doctor or staff right away if you have any problems.

**Benefits associated with participation in this research study**
You may or may not receive personal benefits from taking part in the study; however, in the future, other people [with heart disease, undergoing heart procedures] may benefit from the information we learn from this study.

**Alternative Treatments**
You will receive the standard treatments for your condition if you decide not to take part in this study, depending on what your doctor feels best for you in this condition.

**Costs**
The regular cost of treatment for your condition and your procedure will be billed to you or your insurance carrier. You will receive the study drug and the medical testing needed for this research study for free.

**Compensation**
You will not be paid for your participation in this study.

**Research related injury**

If you have any adverse reaction (side effect) from the study or changes in your physical or mental condition during the course of your participation in this research study, you should immediately seek treatment and contact the research staff or study doctor at (phone #.....) as soon as you are able.

If you are injured as a result of participating in this study, The Medicines Company, the Sponsor of the study, will provide for medical treatment to the extent that the injuries resulted from: (a) cangrelor, the drug being studied in the trial, so long as it was administered according to the study protocol, or (b) procedures your doctor performed as part of the study, so long as they were performed according to the study protocol. The costs of treatment will be paid by the Sponsor to the extent they are not covered by your health insurance. No further compensation for research-related injury is available.

**Privacy and Confidentiality**

**Purpose for collecting Protected Health Information**

If you join in this study, you are giving permission for your health information to be collected. Record of your participation in this study will be kept confidential except as required by law, but strict confidentiality cannot be guaranteed. The study doctor, the sponsor, representatives of sponsor, the Food and Drug Administration (FDA), other governmental agencies in the US and other countries, and the IRB (institutional review board or group of people at your medical center who are responsible for reviewing research and protecting your rights.) will be able to inspect and have access to confidential data.

You will not be identified by name, street address, social security number, etc. in any information used outside of the medical center. If the study results are published, no information will be included that can identify you. The information that will be collected could be a part of your medical record filed at [Hospital Name]. You may ask for your medical records at any time. Your agreement to allow the research staff to use your information begins when you sign this document and does not have an expiration date. If you do not agree to allow the use and sharing of your health information, you cannot take part in this study.

The following health information will be collected from you for this study:

- [Your [initials, age, gender, race]
- The dates that you were admitted and discharged from the hospital, relating to this study.
- Any past illnesses or risk factors that may have helped lead to your diagnosis of [heart] disease
- Your medication, schedule for taking medication, and any changes
- Your present health and medical condition
- Information about your heart procedure(s)
- Any changes in your health and medical condition for a period of approximately [x] days after your heart procedure(s)

**Access to your Protected Health Information**

Your personal health information is protected by The Health Insurance Portability and Accountability Act of 1996 (HIPAA). The research staff at the medical center will use your Protected Health Information to treat you correctly, manage the medical center, and perform research. To make sure that your information is kept confidential, you will be assigned a code number. All information needed for the study will be recorded and tracked using that code.

You should know that by signing this form, you are giving permission for employees or other people connected with the groups listed below to see your medical records. This makes it possible for your safety to be assured, for the research procedures and result of the study to be verified as reliable, and for information to be sent to health care insurers. To the extent that the law allows, your original medical records or copies may be given to the following groups:

- The Medicines Company (the company that sponsors this study) or individuals associated with The Medicines Company
- Members, consultants and staff of the Institutional Review Board at your medical center
- Billing or quality assurance staff at your medical center
- The Joint Commission of Accreditation of Health Care Organizations
- The Food and Drug Administration or other authorities

Your Protected Health Information will be kept as confidential as possible, but the medical center cannot promise complete privacy. Laws stop the medical center from using your Protected Health Information in any way other than described in this form. Once your information leaves the medical center, we will not be able to control how it is used because laws no longer protect the information. If your research records are kept with your medical records, only the information that is needed for the research will be sent to the groups listed above. This information will show why you have been asked to participate in this research study.

The use and sharing of your health information from this study will continue for an indefinite time. However, you have the right to stop allowing the use or sharing of your health data. You can do this at any time by writing to the study doctor. If you do this, the collecting of any new health data from you will stop, except if needed to follow-up on a side effect you were having in the study. Any data that is collected before you wrote your letter may continue to be used.

## QUESTIONS ABOUT RESEARCH

If you have any questions about the research, you should contact **Dr. Name** at **phone #.** During non-business hours you should contact **Dr. Name** at **phone #.**

If you have questions about your rights as a participant in this research, you should contact **Name** at the **Organization/IRB at phone #.** You will receive a copy of this form.

**Statement of Consent:**
I understand that this study involves research. I have read this informed consent. My questions have been answered. I will be given a copy of this document. I know that taking part in this study is voluntary. I may refuse to be in the study without losing any benefits I would otherwise receive. The study and its risks and benefits, alternative treatments, procedures and purpose have been explained to me. By signing this form, I have not lost any legal rights. I allow access of my medical records to government agencies and The Medicines Company or their designees for this purpose. My identity will be kept confidential if the data collected from this study is used for publication or educational purposes.

I will be told about new findings the investigators learn during the study that may affect my willingness to stay in the study. If I want to have this information sent to my personal doctor, I should tell [Dr. investigator].

**Statement of Consent:**

By signing below, you (the participant) acknowledge that you have read, or have had read to you, this informed consent document, have talked with research personnel about this study, have been given the opportunity to ask questions and have them satisfactorily answered, and voluntarily consent to participate **in this study** as described in this form.

_____
Printed name of Patient

_____
Signature of Patient Date/Time

_____
Signature of Patients' Legally Authorized Representative (if applicable) Date/Time

I explained the study to the patient and witnessed their consent to the study:

_____
Investigator/Designee Name

_____
Investigator/Designee Signature Date/Time

# CONSENT TO PARTICIPATE IN RESEARCH

## A Clinical Trial Comparing Cangrelor Treatment Strategy to Clopidogrel Standard of Care Treatment Strategy In Subjects Who Require Percutaneous Coronary Intervention

## Champion PHOENIX

**Principal Investigator:** Matthew Price, MD

**Sub-Investigators:**
Paul Teirstein, MD
Curtiss Stinis, MD
Marvin Eng, MD
Paul Hudson, MD
John Ko, MD
Peter Mohr, MD
Louis Salvaggio, MD

**Study Coordinator:**
Eileen Anderson, RT(R), CCRC (858) 554-5046
Heather Catchpole, MS, CCRC (858) 554-5258
Chelsea Ehlert, CCRC (858) 554-5374
Sara Endemann, MS, CCRC (858) 554-5255
Ann nsen, MPH, CRC (858) 554-5091
Karen Parsons, MSc, RD (858) 554-9905
Erin Miller, MPH, CCRC (858)271-3536
Alissa Slankard, CCRC (858) 554-5338
Divina Valbuena, CCRC (858) 554-5214

**Research Site(s):** Division of Cardiovascular Diseases. Scripps Clinic/Scripps Green Hospital
10666 North Torrey Pines Road, La Jolla, CA 92037

**Sponsor:** The Medicines Comp ny

*Before you start reading about this research, please read e California Experimental Subjects' Bill of Rights, which is page 10 of this form.*

This is a clinical trial (a type of research study or medical experiment). Clinical trials include only patients who choose to take part. Please take your time to make your decision. Discuss it with your friends and family. Be sure to ask questions about anything you do not understand.

### Why is this research being done?

You have been asked to participate in a study because you have chest pain or other sy ptoms of heart disease. Your symptoms are caused by a blockage in the arteries supplying b od to p t of your heart muscle. To open this blockage, your doctors agree that you should undergo a angiog am and possible angioplasty in a procedure called cardiac catheterization. The doctor can lo k h blood vessels in your heart to see if they are blocked by using an x-ray machine and angioplasty uses small balloons and other devices to unblock the artery if necessary. During angioplasty, drugs are given to thin the blood and prevent clotting. Drugs can also be given before the procedure or immediately after the procedure to help thin the blood and prevent clotting.

This research study involves the use of an investigational drug called cangrelor, which is being tested for its ability to prevent blood clots in patients having a balloon procedure known as a percutaneous coronary intervention (PCI) to open blocked blood vessels in the heart. This study also uses the FDA-approved drug clopidogrel (Plavix®). Plavix is approved to treat heart attacks and strokes. The initial dose of Plavix that you will receive when you have a PCI can be up to two times the approved dose depending on your institution's standard of care. The purpose of this study is to compare the safety and effectiveness of cangrelor combined with Plavix to the safety and effectiveness of Plavix alone. Cangrelor has not been approved by the US Food and Drug Administration (FDA); therefore, the use of cangrelor is experimental in this study.

The sponsor, he co pany that pays Scripps and the study doctor to do the study, is The Medicines Company. Thi res arch study will enroll approximately 10,900 people at approximately 200 sites globally; appro mately 75 will be enrolled at Scripps. Approximately 7,600 have already received this drug in studi like this one.

**What makes this different from usual treatment?**
*Cangrelor is an ex*perimental drug that has not been approved by the US Food and Drug Administration (FDA) for general use.

Neither you nor your doctor will know wh ther you are being given cangrelor or Plavix. You will be given an intravenous infusion (I ) (a liquid drug solution dripped down a tube and into a thin needle in your vein) with cangrelor or pla bo durin your angioplasty or stent placement procedure. Placebo looks like the study drug but does ot con ain cangrelor or Plavix. The infusion will be given for at least 2 hours; however, your physician may choose to continue the infusion for up to a total of 4 hours if the duration of the PCI procedure is longer than 2 hours. Prior to the start of the infusion, you will also be required to take 2 to 4 capsules of either Plavix or placebo. The number of pills you receive will depend on your doctor's decision what is best for your procedure. When the infusion stops you will take another 4 capsules of either Plavix or placebo. One of these two sets of 4 capsules will have contained active Plavix so all subjects will have received Plavix b th pletion of study drug administration.

To make sure you cannot tell which drug you will receive, ou will have an equal chance (like flipping a coin) of being in one of two groups. **Group A:** You will re eive placebo (pills), Cangrelor (IV), Plavix (pills) **Group B:** You will receive Plavix (pills), placebo (I ) placebo (pills).

**How long will I be in the study?**
If the study suits you and you agree to join, you will be in it for approximately 35 days after your procedure.

**What will happen to me during the study?**
*Sign Consent:* After reading this form and having any questions answered th t you m ght have, you will sign this form if you are interested in joining this study.

*All these procedures are part of Standard of Care for your condition and would be done even if you did not join the study. They are:*

- **A pregnancy test is required for all women of childbearing age**

VOID

- **EKG: Self- stick pads will be placed on your chest and legs. Wires will be attached to the pads and to a machine that will record the electrical activity of your heart. An electrocardiogram (EKG) is a tracing of your heart's activity.**
- **Vital Signs: Your blood pressure, heart rate, temperature and weight (vital signs) will be measured**
- **Angiogram (procedure to look at the blood vessels in your heart)**
- **Blood tests (About 5 teaspoons of blood will be drawn from your vein to look at your heart, and body functions), every 6 hours until discharge**

*The following procedures will be performed if you join this study. They are:*

- **A separate IV will be started for the study drug.**
- **If an ECG was done more than 7 days before your procedure, another ECG will be done.**
- **If blood tests for cardiac enzymes (substance released from heart muscles that indicates heart attack) were drawn more than 72 hours before your procedure they will be drawn again.**
- **Another teaspoon of blood will be drawn from the access site during your procedure to look at your heart function.**

***During your angiogram***: Your doctor will put a plastic tube, called a sheath, in the blood vessel in your groin. Your groin is the area of your leg right below your hip bone. Once the sheath is in, your doctor will be able to put long narrow tubes, called catheters, through the sheath and into the blood vessel in your groin. The catheter is passed up the blood vessel into the heart's blood vessels. Your doctor will then inject dye through the catheter. The dye will allow your doctor to look at any blockages in your heart's blood vessels under the x-ray machine.

If there is a blockage in one of your heart's blood vessels, doctors can open up that blockage by putting a balloon or stent inside the blood vessel. The stent is made of stainless steel and looks like a chain linked fence. The stent is able to keep your blood vessel open and allow blood to flow through.

If you agree to participate and if your doctor performs angioplasty and/or stenting to open your blood vessel, you will be assigned by chance (like flipping a coin) to one of the following treatments:

- Cangrelor through an IV line plus 2-4* placebo capsules that look like Plavix
  OR
- Placebo (salt water) through an IV line to mimic cangrelor plus 2-4* capsules of Plavix

  **The number of capsules you will receive in either treatment group depend on your doctor's decision what is best for your procedure.*

These drugs will be given during the procedure. You will have an equal chance of getting either of the study drugs (cangrelor or placebo). Additionally, you will also receive 4 capsules of either placebo or Plavix after the procedure. You won't know which you get and neither will the study doctor or staff. However, in the event of a medical emergency, the research doctor will be able to find out which study drug you are taking.

VOID

***After the procedure and prior to discharge*** you will need to have at least 2 more ECG's and 4 blood samples taken, about 5 teaspoons. Three of the blood samples will be drawn and sent to the central lab for analysis. As a part of standard medical treatment you may also receive Aspirin and other medications to prevent complications related to your procedure based on your physician's judgment. The day after the procedure, medication to prevent blood clots from forming and Aspirin will be prescribed for you. These need to be taken for at least one month or more based up on your physician's judgment.

***Follow-Up:*** You will be contacted 2 days after your procedure on the telephone as well as 30 days after your procedure. During these contacts, you will be interviewed about your health and any changes in your medication since your last visit and/or contact. If you move or change your telephone number, please notify the study doctor/ or the study staff so he/she will be able to contact you at these times.

The study procedures are broken up into six parts: Before Angiogram, During Procedure, After Procedure/ Discharge, 2 Day follow-up and 30 Day follow-up. Please refer to the visit schedule below.

**Visit Schedule**

| Test | Before Procedure | During Procedure | After Procedure/Discharge | 2 Day Telephone Follow Up | 30 Day Telephone Follow Up |
|---|---|---|---|---|---|
| **Answer questions about your health.** | X | | | X | X |
| **Doctor Examines you** | X | | X | | |
| **Vital Signs** | X | | X | | |
| **ECG** | X | | X | | |
| **Blood Samples** | X | X | X | | |
| **Randomization of Study Drugs** | | X | | | |
| **Administration of Study Drugs** | | X | X | | |

**Could I experience any side effects or discomforts?**

***Risks associated with an angiogram, Standard of Care:***

All angiograms and stent procedures can cause reactions or side effects. If you have an angiogram you may get any of the following:

*Likely*

- chest pain or discomfort
- bruising
- pain at the access site, the site where the catheters were inserted in the body, usually the groin

These side effects are usually mild and go away either on their own or with medication.

*Less likely*

- renewed formation of a narrowing in the treated vessel
- coronary spasms

VOID

These side effects can be serious. If you get any of these, you may need treatment, which could include medication or another angiogram.

*Not very likely*

- Irregular heart beat
- Unnatural connection between vein and artery
- Injury or tearing of blood vessel possibly requiring surgical repair
- Part of the wall of the artery cracks during the procedure and may block part or all of the artery reducing blood flow to the heart which may lead to a heart attack
- Side effects due to contrast dye or heparin
- Air, tissue, or clots which can block the vessel
- Bleeding that could require a blood transfusion
- High or low blood pressure
- Infection
- Inadequate supply of blood to the heart
- Bruising which resides on a blood vessel
- Movement of the stent as it is sliding from the balloon into the blood vessel
- Plugging of the stent with blood clots
- Stroke or other neurological event
- Total blockage of the vessel
- Collection of blood or fluid in the lining of the heart
- Worsening of heart, lung and kidney function, which could lead to heart, lung failure, or kidney failure
- Fluid in the lung tissues
- Allergic reaction to the contrast dye (including kidney failure), to the stent materials, or to the drugs which prevent blood clots
- Low blood pressure resulting in inadequate blood flow to the body
- Increased risk of non-Q wave myocardial infarction called a heart attack, if multiple stents implanted
- Emergency surgery
- Death

***Risks with being in this research study:***

All drug treatments whether a part of this study or not, have the potential to cause side effects. All side effects should be reported to your study doctor or staff member at every visit or by phone between visits.

**Cangrelor Risks**

Cangrelor has been given to about 7,600 people in other studies. Below are the known side effects associated with the study medication, Cangrelor.

*Likely*

- Bleeding

*Less likely*

- Bruising

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- Oozing at puncture site
- Drop in red blood cell count, which can cause tiredness
- Back pain
- Chest pain
- Nausea
- Headache
- Low blood pressure
- Vomiting
- Pu t sit in
- Fever
- Shortn ss of breath

*Not very likely*

- High blood pressure
- Dangerous, rapid heart rate
- Chest discomfort
- Slow heartbeat less than 60
- Irregular heart beat
- Pain in arms or legs
- Fainting
- Anxiety
- Dizziness
- Tearing of coronary artery
- Upset stomach
- Abdominal pain
- Dangerous, rapid irregular heartbeat
- Diarrhea
- Pain in your muscles or bones
- Sleeplessness
- Failure of heart's pumping ability
- Low potassium in the blood
- Kidney failure
- Bleeding into digestive system, abdomen and urine
- Death due to serious bleeding

You will be carefully monitored before, during and after your procedure and any side effects you may experience will be treated.

**Medications**

There are possible risks from the medications Clopidogrel (Plavix ®) and asp rin, the DA approved medications used to prevent your blood from clotting. For example, there is a small risk of bleeding from an ulcer, if you have one. You could also bleed at the puncture site in your groin or arm.

· **Tell your study doctor about any unusual bleeding that you experience**
· **Tell your regular doctor or dentist that you are taking blood-thinning medication before any procedure**

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Blood thinning medications such as aspirin and clopidogrel can cause diarrhea, nausea, digestive problems, vomiting, lack of appetite, and skin rash. In rare cases, the number of white blood cells decreases. If the number decreases markedly, you could be less able to fight an infection. TTP (thrombotic thrombocytopenic purpura) is a rare but possible side effect of clopidogrel. TTP is a rare disease in which small blood clots form suddenly throughout the body.

**Reproductive Risks**
The effects of Cangrelor on the unborn child are unknown. There is no information on the long-term effects of Cangrelor on either male or female fertility. Similarly, there are no adequate and well controlled studies of Clopidogrel on pregnant women. Do not participate in this study if you are pregnant or if you think you might be pregnant. Be sure to tell your doctor if you think you may be pregnant, or if you are unsure.

If you are female you will have a pregnancy test. You can't be in the study if you are pregnant or plan to get pregnant. You can't be in the study if you are nursing a baby. The drugs used could hurt a baby.

**Unknown Risks**
You might have side effects or discomforts that are not listed in this form. Some side effects may not be known yet. New ones could happen to you. Tell the research doctor or staff right away if you have any problems.

**Is there anything else I should know?**

- You may not be enrolled in this study even if you sign this consent form.
- If you have been in another research study in the last month, you should tell the study doctor.
- You cannot give the drug to anyone else and you should keep it away from children.

**Blood Sampling:** It may hurt when the needle pokes your skin. You could be sore and bruised for a day or two. You could get an infection, but that's not likely. If you have ever felt dizzy or fainted while having blood drawn, you should tell the person drawing your blood. If you lie down, you might not get dizzy.

**Will I benefit from participating?**
You may or may not benefit from taking part in the study. However, in the future, other people [with heart disease, undergoing heart procedures] may benefit from the information we learn from this study.

**Will I be paid?**
No, you will not be paid to be in the study.

**Will it cost anything to be in the study?**
The regular cost of treatment for your condition and your procedure will be billed to you or your insurance carrier. You will receive the study drug and the medical testing needed for this research study for free.

**What if I end the study early?**
Being in this study is absolutely <u>voluntary.</u> If you do not want to be treated in this study or if you decide to stop the study before you complete your follow-up, your decision to do so will have no effect on your further treatment. Also, the study may be stopped for other reasons or your doctor may have you not be

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in the study, with or without your consent, for medical reasons. If you quit the study or are taken out early, you may be asked to do tests to be sure you are as healthy as you were when you started. You can quit the study whenever you want to.

You must write to the study doctors at the address below and tell them you no longer want to be part of the research:

Matthew Price, MD
Scripps Clinic, Department of Cardiovascular Diseases
10666 North Torrey Pines Road, Rm S-1056
La Jolla, CA 92037

The study doctors or the sponsor can take you out of the study:

- If you do not follow the study requirements
- If the study is cancelled by the sponsor or the FDA
- The study doctors thinks it is necessary for your health or safety

**What treatments could I take instead of joining this study?**
You will receive the standard treatments for your condition if you decide not to take part in this study, depending on what your doctor feels best for you in this condition.

**What are my rights?**

- You can call the staff to ask any questions about this study. The telephone number is listed at the top of this form.
- You can decide not to be in this study or you can quit after starting. Whatever you do, your medical care at Scripps will not be affected.
- If you have any questions about your rights, call the Scripps Office for the Protection of Research Subjects at (858) 652-5500. You should also read the *Experimental Subject's Bill of Rights,* which is toward the end of this form.
- You do not have to be in this study. You still have all your legal rights whether you join the study or not.
- You have the right to be told about any new information that might make you change your mind about staying in the study

**What are my responsibilities if I join?**
If you are in this study, you are expected to:

- Follow the instructions of the research staff
- Report any serious or unusual side effects to the study doctor
- Take study drugs as directed
- Keep your study appointments

**What about confidentiality?**
The study doctor and the sponsor will keep your personal information confidential whenever they can. We can't promise that no one will see it. Your identity as a participant in this study will remain strictly confidential. Authorized representatives of this institution, the FDA and the sponsor, The Medicine's Company can view your medical files to ensure that the information provided to them is correct. Information received and processed by The Medicines Company, or its representatives will not include your name or personal data. You will only be identified in the study under a study specific code. If the

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study results are published, no information will be included that can identify you. For more information, see the **Authorization to use your Private Health Information** at the end of this consent form.

**What if I get hurt while in the study?**
You can call Dr. Matthew Price at 858-554-9859 Monday through Friday, 8:00 a.m. to 5:00 p.m. if you get sick or injured while in this study. If you get sick or injured at night or on a weekend, call (858) 455-9100 ask for the doctor on call for the Division of Cardiology.

If you need medical or urgent care during the study, it will be provided. You or your medical insurance will be billed for any treatment given.

Scripps and the sponsor of the study do not plan to pay for anything else. You are not giving up any of your legal rights by being in this study

**Will Scripps, the study doctor or sponsor benefit from this study?**
Scripps and the study doctors are being paid by The Medicines Company to do this study. You have the right to ask and be told about any financial interests they might have in this study. The investigators have no financial conflict of interest to report.

**********

**I agree to participate.**
*I have read and understood the explanation of the study. The study has also been explained to me by Dr. Price or his designee. I have had a chance to ask questions and have them answered to my satisfaction. I agree to take part in this study. I have not been forced or made to feel obligated to take part.*

*I have read the attached* ***Experimental Subject's Bill of Rights*** and the ***Authorization to use my Private Health Information*** *that contains some important information about research studies. I must sign this consent form, the* ***Experimental Subject's Bill of Rights*** *and the* ***Authorization to use my Private Health Information****. I will be given a signed copy of each to keep.*

_____
Printed Name of Subject

_____ _____
*Signature of Subject* *Date*

_____ _____
*Signature of person conducting the informed consent discussion* Date

_____
Role of person named above in the research project

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**EXPERIMENTAL SUBJECT'S BILL OF RIGHTS***

*If I am asked to consent to be a subject in a research study involving a medical experiment, or if I am asked to consent for someone else, I have the right to:*

*Learn the nature and purpose of the experiment (also called "study" or "clinical trial").*

*Receive an explanation of the procedures to be followed in the study, and any drug or device to be used.*

*Receive a description of any discomforts and risks that I could experience from the study.*

*Receive an explanation of any benefits I might expect from the study.*

*Learn about the risks and benefits of any other available procedures, drugs or devices that might be helpful to me.*

*Learn what medical treatment will be made available to me if I should be injured because of the study.*

*Ask any questions about the study or the procedures involved.*

*Quit the study at any time, and my decision will not be used as an excuse to withhold necessary medical treatment.*

*Receive a copy of the signed and dated consent form.*

*Decide to consent or not to consent to a study without feeling forced or obligated.*

If I have questions about a research study, I can call the contact person listed on the consent form. If I have concerns about the research staff, or need more information about my rights as a subject, I can contact the Scripps Office for the Protection of Research Subjects, which protects volunteers in research studies. I may telephone the Office at **(858) 652-5500**, 8:00 a.m. to 4:00 p.m. weekdays, or I may write to the Scripps Office for the Protection of Research Subjects, 11025 North Torrey Pines Road, Suite 200, La Jolla, CA, 92037.

*By signing this document, I agree that I have read and received a copy of this Bill of Rights.*

_____ _____

Signature of Subject or Legal Representative Date

**California Health & Safety Code, Section 24172*

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Scripps

## Authorization to use your Private Health Information

**Name of Study:** **Champion PHOENIX**

**Principal Investigator: Matthew Price, MD** **IRB Study Number: 11-5664**

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### What is private health information?

Private health information is any information that can be traced back to you. We need your authorization (permission) to use your private health information in this research study. The private health information that we will use and share for this study includes:

- Your past and present health information, including progress notes and history and physical in your medical record
- Information that can be used to contact you, such as your home address, phone number(s), and/or emergency contacts if you can not be reached any other way
- Results of your medical tests including cardiac stenting procedures, treadmill exercise tests, EKG's, physical exams, and laboratory (blood and urine) tests
- Research records
- Records about phone calls made as part of this research
- Records about your study visits

### Who else will see my information?

In addition to the Principal Investigator, this information may be shared with:

- the sponsor of the research study, The Medicine Company and any groups or companies that work with the sponsor.
- government agencies, such as the US Food and Drug Administration and agencies like it in other countries, or agencies of the Department of Health and Human Services, and
- Scripps committees that review research to help protect people who join research studies.

Once we have shared your information we cannot be sure that it will stay private. If ***you*** share your information with people outside the research team, it will no longer be private. Your name will not be used in any report that is written.

### How long will Scripps use and share my information?

- Your information will be used and shared until the research is completed, which we think will be in 2021.

**What if I change my mind about sharing my research information?**
If you decide not to share your information anymore:

- The sponsor and the research team can continue to use any of the private information that they already have.
- You will no longer be a part of the research study.
- You will still get the same medical care that you've always had at Scripps.
- You must write to the investigator and tell him that you no longer want to share your information. Write to the investigator at:

**Matthew Price, MD**
**Scripps Clinic Torrey Pines**
**Division of Cardiovascular Diseases**
**10666 N. Torrey Pines Road**
**La Jolla, CA 92037**

**Do I have the right to see and copy my research information?**
You cannot see your research information while the study is going on, unless it is also being used for your health care. Once the study is over, you can ask to see any research information that is in your Medical Record that is kept at Scripps.

If you agree to share your information you should sign this form below. You will be given a copy of this form.

********** **********

***I agree to share my information as described in this form***

_____
Print your name

_____ _____
Sign your name Date

*If you have questions or concerns about your privacy and the use of your personal medical information, contact the investigator at the telephone number listed in the consent form.*

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Attachment 6: Austrian ICD

**PATIENTENINFORMATION UND EINWILLIGUNGSERKLÄRUNG**

**TITEL DER STUDIE:**
CHAMPION Phoenix: Eine klinische Studie zum Vergleich von Cangrelor mit Clopidogrel als Standardbehandlung bei Patienten, die eine perkutane Koronarintervention benötigen

**PRÜFPLANNUMMER:** TMC-CAN-10-01

**PRÜFARZT:** Prim. Prof. Dr. Kurt Huber

**Sehr geehrte Patientin, sehr geehrter Patient,**
Sie haben die Möglichkeit, an einer klinischen Studie teilzunehmen. Die Teilnahme an dieser Studie ist vollkommen freiwillig. Diese Studie wird von Prim. Prof. Dr. Kurt Huber im Krankenhaus Wilhelminenspital durchgeführt. Es ist wichtig, dass Sie diese Patienteninformation lesen und verstehen. Bitte lesen Sie sie aufmerksam durch. Nehmen Sie sich Zeit, um dem Prüfarzt oder dem Studienpersonal so viele Fragen über die klinische Studie zu stellen, wie Sie möchten. Bitte wenden Sie sich an den Prüfarzt oder das Studienpersonal, wenn Sie die Bedeutung bestimmter Begriffe nicht kennen oder Fragen zum Inhalt haben. Das Lesen dieser Patienteninformation und das Gespräch mit dem Prüfarzt oder dem Studienpersonal sollen Ihnen helfen zu entscheiden, ob Sie an der klinischen Studie teilnehmen möchten oder nicht. Wenn Sie sich für eine Teilnahme entscheiden, müssen Sie vor Ihrer Teilnahme an der klinischen Studie die Einwilligungserklärung unterzeichnen und datieren. Sie werden in die Teilnahme an der Studie einwilligen, bevor Ihr Prüfarzt weiß, ob Sie dafür geeignet sind. Ihr Prüfarzt muss Bilder Ihrer Blutgefäße im Herzen überprüfen. Sie sind für die Studie geeignet, wenn Ihr Prüfarzt feststellt, dass die blockierten Gefäße in Ihrem Herzen operativ geöffnet werden müssen. Ihr Prüfarzt wird Ihnen mitteilen, ob Sie für eine Studienteilnahme geeignet sind.

**Hintergrund und Ziel der Studie**
Sie werden gebeten, freiwillig an dieser klinischen Studie teilzunehmen, weil Sie Anzeichen und Symptome einer koronaren Herzkrankheit aufweisen. Dabei kann es sich um ein schwerwiegendes Herzproblem handeln, bei dem das Herz nicht ausreichend mit Sauerstoff versorgt wird. Diese Erkrankung kann durch eine teilweise Blockierung eines oder mehrerer

**PATIENT INFORMATION AND CONSENT**

**STUDY TITLE:**
CHAMPION Phoenix: A clinical trial comparing cangrelor with clopidogrel as a standard treatment in patients requiring percutaneous coronary intervention

**PROTOCOL NUMBER**: TMC-CAN-10-01

**INVESTIGATOR:** Principal Prof. Kurt Huber

**Dear patient, dear patient,**
You have the opportunity to participate in a clinical trial. Participation in this study is completely voluntary. This study will be performed by Principal Professor Kurt Huber at Hospital Wilhelminenspital. It is important that you read and understand this patient information. Please read them carefully. Take time to ask the investigator or the study staff as many questions about the clinical trial as you like. Please contact the investigator or the study staff, if you do not know the meaning of certain terms or have questions about the content. Reading this patient information and conversing with the investigator or the study staff will help you to decide if you wish to participate in the clinical trial or not. If you decide to participate, you must sign and date the informed consent form prior to participation in the clinical trial. You will agree to participate in the study before your investigator knows if you are suitable. Your investigator must review the images of the blood vessels in the heart. You are eligible for the study if your investigator finds that the blocked vessels in your heart must be opened surgically. Your investigator will tell you whether you qualify for participation in the study.

**Background and purpose of the study**
You are being asked to participate voluntarily in this clinical trial because you have signs and symptoms of coronary heart disease. It may be a serious heart problem in which the heart does not receive enough oxygen. This condition may be caused by partial blockage of one or more blood vessels in your heart.



Reference ID: 3434365

Blutgefäße in Ihrem Herzen verursacht werden.

In dieser klinischen Studie wird ein in der Erprobung befindliches Medikament namens Cangrelor angewendet. Es soll untersucht werden, ob Congrelor in der Lage ist, die Bildung von Blutgerinnseln bei Patienten zu verhindern, bei denen eine Ballondilatation (eine sogenannte perkutane Koronarintervention oder PKI) durchgeführt wurde, um blockierte Blutgefäße im Herzen wieder durchgängig zu machen. Im Rahmen dieser Studie wird auch das von der US-amerikanischen „Food and Drug Administration“ (FDA) zugelassene Arzneimittel Clopidogrel (Plavix®) angewendet. Plavix ist für die Behandlung von Herzinfarkten und Schlaganfällen zugelassen Die Anfangsdosis Plavix, die Sie erhalten, wenn bei Ihnen eine PKI durchgeführt wird, kann bis zum Zweifachen der zugelassenen Dosis betragen, abhängig von der in Ihrer Einrichtung angewendeten Standardbehandlung.

In this clinical study an investigational drug called cangrelor is used. It will be investigated whether cangrelor is able to prevent blood clots in patients in whom a balloon dilation (a so-called percutaneous coronary intervention or PKI) was performed to make blocked blood vessels in the heart consistent again. This study will also use the U.S. 'Food and Drug Administration "(FDA) approved drug clopidogrel (Plavix®). Plavix is used for the treatment of heart attacks and strokes. The initial dose of Plavix, which you get when you get a PKI, can be up to twice the approved dose dependent upon the standard treatment applied in your facility

In dieser Studie soll die Sicherheit und Wirksamkeit einer Kombinationstherapie von Cangrelor und Plavix mit der Sicherheit und Wirksamkeit einer Behandlung mit Plavix alleine verglichen werden. Cangrelor wurde bisher nicht von der US-amerikanischen „Food and Drug Administration“ (FDA) zugelassen; daher ist die Anwendung von Cangrelor in dieser Studie experimentell.

This study will evaluate the safety and efficacy of combination therapy with cangrelor and Plavix compared to the safety and efficacy of treatment with Plavix alone. Cangrelor has not yet been licensed by the U.S. “Food and Drug Administration” (FDA), so the use of cangrelor in this study is experimental.

In diese klinische Studie werden etwa 10.900 Patienten an etwa 200 Prüfzentren weltweit aufgenommen.

In this clinical study about 10,900 patients at 200 clinical sites will be enrolled worldwide.

**Beschreibung der Studie**

Ihr Prüfarzt wird auch eine vollständige medizinische Untersuchung durchführen, um festzustellen, ob Sie an der klinischen Studie teilnehmen können. Dies umfasst Ihre Krankengeschichte, eine körperliche Untersuchung, Fragen zu Ihrer ethnischen Zugehörigkeit, Ihrem Alter und Geschlecht, Blutuntersuchungen, eine Urinprobe und eine elektrische Aufzeichnung Ihres Herzschlags (EKG). Für die Blutuntersuchungen werden Ihnen von einer Fachkraft etwa 4 Teelöffel (ca. 20 ml) Blut durch einen Einstich in eine Vene entnommen. Die Blutproben werden verwendet um die Hämatologie sowie die Biomarker für die myokardiale Infarktbildung (Troponin I und T) zu analysieren. Alle diese Beurteilungen werden im Labor des Krankenhauses durchgeführt. Alle diese Untersuchungen werden für gewöhnlich im Rahmen

**Description of the study**

Your investigator will perform a complete medical examination to determine if you can participate in the clinical trial. This includes your medical history, physical examination, questions about your ethnicity, age and gender, blood tests, a urine sample and an electric recording of your heart (ECG). For the blood tests about 4 teaspoons (20 ml) of blood will be removed from you through a puncture into a vein by a specialist. The blood samples will be analyzed for hematology and biomarkers of myocardial infarction (troponin I and T). All of these tests will be performed in the hospital laboratory. All of these investigations are usually performed in the context of standard of care. Standard of care means that these studies and measures would be carried out in any case regardless of whether you are participating in the study or not. In addition to the regular blood tests



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der Standardversorgung durchgeführt. Standardversorgung bedeutet, dass diese Untersuchungen und Maßnahmen auf jeden Fall durchgeführt würden, unabhängig davon, ob Sie an der Studie teilnehmen oder nicht. Zusätzlich zu den normalen Blutuntersuchungen, die im Rahmen Ihrer Standardversorgung durchgeführt werden, werden für die Studie 4 ml (etwa 1 Teelöffel) Blut entnommen, die an ein amerikanisches Zentrallabor geschickt werden. Bei dieser Probe wird eine weitere Analyse vorgenommen, und zwar die CK-MB Bestimmung, die bei der Diagnose des Herzinfarktes hilft. Der Zugang zu den Proben ist nur berechtigtem Laborpersonal gestattet. Die Proben werden xxxxx Tage nach der Analyse zerstört. Sie sollten Ihren Prüfarzt über Ihre Krankengeschichte – einschließlich aller Medikamente, die Sie derzeit einnehmen (auch pflanzliche Heilmittel oder frei verkäufliche Produkte) – sowie über Ihre Teilnahme an anderen Studien informieren.

as part of your standard care, 4 ml (about 1 teaspoon) of blood are taken for the study which are sent to a central American lab. On this sample a further analysis is carried out, namely a CK-MB determination that helps in the diagnosis of myocardial infarction. Access to the sample is only by qualified laboratory personnel. The samples are destroyed xxxxx days after the analysis. You should inform your investigator about your medical history - including any medications you are currently taking (including herbal remedies or OTC products) - as well as your participation in other studies.

**Studienablauf**

Wenn Sie für die Studienteilnahme geeignet sind und weiterhin teilnehmen möchten, werden Sie nach dem Zufallsprinzip einer von zwei Studiengruppen zugeteilt, entweder der Cangrelor und Plavix- oder der Placebo und Plavix-Gruppe. Der Grund für die Verabreichung von Placebo ist, die Behandlung zu verblinden, damit weder Sie noch Ihr Prüfarzt wissen, ob Sie das Studienmedikament Cangrelor erhalten haben, bevor Sie die Plavix Standardbehandlung verabreicht bekommen. Dies ist wichtig, damit Ihre Erwartungen nicht das Ergebnis beeinflussen:

**Study procedure**

If you are eligible for study participation and wish to participate, you will be randomly assigned to one of two study groups, either the cangrelor and Plavix or placebo and Plavix groups. The reason for the administration of placebo is blinding of the treatment, so neither you nor your investigator know whether you have received the study drug cangrelor before the standard treatment Plavix gets administered. This is important so that your expectations do not influence the result:

• **Cangrelor-Gruppe** – während der PKI wird Ihnen Cangrelor langsam über mindestens 2 Stunden durch einen intravenösen (IV-) Katheter (Plastikröhrchen) in eine Vene verabreicht. Ihr Prüfarzt kann die Infusion jedoch auf bis zu insgesamt 4 Stunden verlängern, wenn die PKI länger als 2 Stunden dauert. Gemäß der Standardversorgung in Ihrer Einrichtung erhalten Sie zum Zeitpunkt der PKI 2 bis 4 Placebo-Kapseln (Kapseln, die keinen Wirkstoff enthalten). Abschließend erhalten Sie unmittelbar nach Ende der Cangrelor-Infusion vier (4) Kapseln Plavix zu je 150 mg (insgesamt 600 mg).

• **Cangrelor group** – During the PKI you will be administered cangrelor slowly into a vein over at least 2 hours through an intravenous (IV) catheter (plastic tube). However, your investigator can extend the infusion up to 4 hours in total when the PKI takes longer than 2 hours. According to the standard of care in your facility, you will receive at the time of PKI 2-4 placebo capsules (capsules containing no active ingredient). Finally, you will receive immediately after the end of the cangrelor infusion four (4) capsules, containing 150 mg of Plavix (total 600 mg).

• **Placebo-Gruppe** – während der PKI wird Ihnen ein Placebo (eine wirkstofffreie Substanz) langsam über mindestens 2 Stunden durch einen IV-Katheter in eine Vene

• **Placebo group** - During the PKI you will be administered a placebo (a drug-free substance) slowly into a vein over at least 2 hours through an IV catheter. However, your investigator



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verabreicht. Ihr Prüfarzt kann die Infusion jedoch auf bis zu insgesamt 4 Stunden verlängern, wenn die PKI länger als 2 Stunden dauert. Gemäß der Standardversorgung in Ihrer Einrichtung erhalten Sie zum Zeitpunkt der PKI 2 bis 4 Kapseln Plavix zu je 150 mg. Abschließend erhalten Sie unmittelbar nach Ende der Placebo-Infusion vier (4) Placebo-Kapseln.

can extend the infusion up to 4 hours in total when the PKI takes longer than 2 hours. According to the standard of care in your facility, you will receive at the time of PKI 2-4 capsules each with Plavix 150 mg. Finally, you will receive immediately after the end of the placebo infusion, four (4) placebo capsules.

Die Wahrscheinlichkeit der Zuteilung ist für beide intravenös verabreichten Studienmedikamente (Cangrelor oder Placebo) gleich hoch. Weder Sie noch der Prüfarzt werden wissen, welchem Studienmedikament Sie zugeteilt wurden. In einem Notfall kann der Prüfarzt jedoch in Erfahrung bringen, welches Studienmedikament Sie erhalten.

The probability of allocation is equal for both intravenous study medications (cangrelor or placebo). Neither you nor the investigator will know which study drug you have been allocated. In an emergency, however, the investigator can find out which study drug you received.

Während Ihres Krankenhausaufenthalts müssen mindestens 2 weitere EKGs aufgezeichnet und 4 Blutproben [etwa 5 Teelöffel (ca. 25 ml)] entnommen werden. Drei der Blutproben (jeweils 4 ml) werden entnommen und zur Analyse an ein Zentrallabor geschickt. Im Rahmen der medizinischen Standardbehandlung können Sie auch Aspirin oder andere Medikamente erhalten, um Komplikationen in Zusammenhang mit dem Eingriff vorzubeugen. Dies liegt im Ermessen Ihres Prüfarztes. Am Tag nach dem Eingriff werden Ihnen Medikamente zur Vorbeugung von Blutgerinnseln sowie Aspirin verordnet. Diese Medikamente müssen nach Ermessen Ihres Prüfarztes mindestens einen Monat oder länger eingenommen werden.

During your hospital stay at least 2 more ECGs must be recorded and 4 blood samples [about 5 teaspoons (25 ml)] are removed. Three blood samples (4 ml each) will be removed and sent for analysis to a central laboratory. Under standard medical treatment, you can also obtain aspirin or other medicines in order to prevent complications related to the procedure. This is at your investigator's discretion. The day after surgery you will be prescribed drugs to prevent blood clots and aspirin. These drugs need to taken at your investigator's discretion at least a month or more.

**Nachbeobachtung**

Sie werden etwa 2 Tage (sofern Sie nicht länger im Krankenhaus sind) und 1 Monat nach der PKI telefonisch kontaktiert, damit festgestellt werden kann, wie es Ihnen geht und ob es seit dem letzten Kontakt Veränderungen in Ihrer Krankengeschichte und Ihrer Erkrankung gab. Sie werden gebeten, das Studienpersonal zu informieren, wenn sich Ihre Kontaktinformationen während der Nachbeobachtungsphase ändern.

**Follow-up**

You will be contacted by phone about 2 days (if you are no longer in the hospital) and 1 month after the PKI so that it can be determined how you are and whether there were changes in your medical history and your condition since the last contact. You are asked to contact the study staff if your contact information changes during the follow-up period.

**Dauer der Studienteilnahme**

Ihre Teilnahme an dieser klinischen Studie beginnt, wenn Sie diese Einwilligungserklärung unterzeichnen, und dauert bis etwa 35 Tage nach Ihrem Eingriff.

**Duration of study participation**

Your participation in this clinical trial starts when you sign this consent sign and lasts until about 35 days after your procedure.

**Abbruch der Studienteilnahme**

Sie können Ihre Teilnahme an dieser Studie jederzeit beenden. Ihr Prüfarzt kann ebenfalls

**Discontinuation of study participation**

You can always cancel your participation in this study. Your investigator may also decide to



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beschließen, Ihre Studienteilnahme vorzeitig zu beenden, wenn:
• neue Erkenntnisse über die Behandlung darauf hindeuten, dass diese nicht wirkt
• neue Erkenntnisse über die Behandlung darauf hindeuten, dass diese für Sie nicht sicher ist
• Sie sich nicht an die Studienvorschriften halten
• bei Ihnen neue Gesundheitsschäden oder Erkrankungen auftreten

terminate your participation in the study early if:
• new findings suggest that the treatment does not work
• new findings suggest that the treatment is not for safe for you
• you do not adhere to the study requirements
• new health problems or illnesses occur for you

Wenn Sie oder Ihr Prüfarzt beschließen, Ihre Studienteilnahme zu beenden, können Sie gebeten werden, zusätzliche Laboruntersuchungen und andere Untersuchungen zu absolvieren, die Ihr Prüfarzt für notwendig erachtet.

If you or your investigator decides to terminate your participation in the study, you may be asked to complete additional laboratory tests and other examinations that your investigator considers necessary.

**Risiken und Nutzen**
Cangrelor: Cangrelor wurde im Rahmen anderer Studien etwa 7600 Personen verabreicht. Die am häufigsten in Zusammenhang mit Cangrelor beobachtete Nebenwirkung sind Blutungen. Wie bei allen blutverdünnenden Medikamenten kann es zu Blutungen am oder im Körper kommen, z. B. an Einstichstellen, im Verdauungssystem, im Bauch oder es kann Blut im Urin
auftreten. Anzeichen dafür sind insbesondere blaue Flecken, Blutergüsse (Hämatome), Absinken des Hämoglobins oder des Hämatokrits (beides Anzeichen für Blutverlust, erkennbar in den Laborbefunden), punktförmige oder flächige rote oder violette Verfärbungen der Haut, die durch Blutungen unter der Haut entstehen (Purpura), sowie Verlängerung der Gerinnungszeit; in seltenen Fällen (< 1/1000) kann es zu Blutungen in den Augen oder im Gehirn kommen. Blutungsereignisse können schwerwiegend sein und zu weiteren Komplikationen bzw. sogar zum Tod führen.

**Risks and benefits**
Cangrelor: Cangrelor was administered to approximately 7600 persons in other studies. The most frequently observed side effect with cangrelor is bleeding. As with all blood-thinning medicines it can cause bleeding on or in the body, for example, at injection sites, in the digestive system, in the stomach, or in the urine. Signs are particularly bruises, bruising (hematoma), decrease in hemoglobin or hematocrit (both signs of blood loss, recognizable in the laboratory findings), point or area red or purple discoloration of the skin caused by bleeding under the skin (purpura), and extension of the clotting time and, only in rare cases (<1/1000), it can cause bleeding in the eyes or in the brain. Bleeding events may be severe and can lead to complications or even death.

Weitere häufig berichtete Nebenwirkungen sind: Rückenschmerzen, Brustschmerzen, Übelkeit, Kopfschmerzen, niedriger Blutdruck, Erbrechen, Schmerzen an der Einstichstelle, Fieber, Kurzatmigkeit und hoher Blutdruck.

Other commonly reported side effects are back pain, chest pain, nausea, headache, low blood pressure, vomiting, pain at the injection site, fever, shortness of breath and high blood pressure.

Zu den schwerwiegenden, aber sehr selten auftretenden Nebenwirkungen gehören Herzinfarkt, das Versagen mehrerer Körperorgane (multiples Organversagen) sowie Gerinnselbildung in der Lunge oder den Koronararterien
.

The serious, but very infrequent, side effects include heart attack, the failure of multiple body organs (multiple organ failure), and clot formation in the lung or the coronary arteries.

**Risiken in Zusammenhang mit Clopidogrel**
Clopidogrel (Plavix®) ist ein zugelassenes verschreibungspflichtiges Medikament zur

**Risks associated with clopidogrel**
Clopidogrel (Plavix®) is a prescription medication approved for the treatment of heart attacks and



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Behandlung von Herzinfarkten und Schlaganfällen. Die Anfangsdosis, die Sie in der Studie erhalten werden, entspricht dem Zweifachen der zugelassenen Dosis. Diese Dosis wird jedoch derzeit zur Behandlung von Patienten angewendet, die sich einer PKI unterziehen.

strokes. The initial dose that you will be given in the study corresponds to twice the approved dose. This dose, however, is currently used to treat patients who undergo a PKI

Da es sich bei Clopidogrel um ein Medikament handelt, das sich auf die Funktion der Blutplättchen auswirkt, sind die häufigsten Nebenwirkungen Blutungen. Bei 0,2% der Patienten traten schwerwiegende Blutungsereignisse auf, die zum Tod führten. In extrem seltenen Fällen (bei etwa 4 von einer Million Patienten) kann ein schwerwiegendes Blutungsereignis – eine sogenannte thrombotische thrombozytopenische Purpura (TTP) – auftreten. Dabei handelt es sich um eine seltene Erkrankung, die die Gerinnungsfähigkeit des Blutes beeinträchtigt.

Since clopidogrel is a drug that affects the function of platelets, the most common side effects are bleeding. In 0.2% of patients serious bleeding events occurred that led to death. In extremely rare cases (about 4 in a million patients), a serious bleeding event – so called thrombotic thrombocytopenic purpura (TTP) - occurred. This is a rare disease that affects the clotting ability of the blood.

Die Nebenwirkungen, die in klinischen Studien mit 54.000 Patienten am häufigsten in Zusammenhang mit Clopidogrel in zugelassenen Dosierungen berichtet wurden, sind Kopfschmerzen, Schwindel, Magenschmerzen, Brustschmerzen, verminderte Anzahl der Blutzellen (was zu einem erhöhten Infektionsrisiko führen könnte), Durchfall, Verdauungsstörungen, erhöhter Cholesterinspiegel, Hautausschlag, Übelkeit oder verminderte Anzahl der Blutplättchen (kleine Blutbestandteile, die die Blutgerinnung unterstützen).

The side effects in the clinical trials with 54,000 patients most associated with clopidogrel at approved doses are headache, dizziness, stomach pain, chest pain, decreased number of blood cells (which could lead to an increased risk of infection), diarrhea, indigestion, high cholesterol, rash, nausea, or decreased number of platelets (small blood components that help blood clotting).

**Informationen für gebärfähige Frauen – Schwangerschaftstest**

Sie müssen Ihren Prüfarzt auch informieren, wenn Sie schwanger sind oder stillen oder wenn Sie den Verdacht haben, schwanger zu sein. Gebärfähige Frauen (Frauen, die schwanger werden können) müssen einen Blut- oder Urin-Schwangerschaftstest durchführen lassen, der negativ ausfallen muss, bevor sie an dieser Studie teilnehmen können. Schwangere und stillende Frauen dürfen NICHT an dieser klinischen Studie teilnehmen.

**Information for women of childbearing age - pregnancy test**

You must also tell your investigator if you are pregnant or nursing or if you suspect you may be pregnant. Women of childbearing potential (women who can become pregnant) have to perform a blood or urine pregnancy test, which must be negative, before they can participate in this study. Pregnant and lactating women may NOT participate in this clinical trial.

**Risiken für die Fortpflanzung**

Es ist nicht bekannt, welche Auswirkungen Cangrelor auf ein ungeborenes Kind haben kann. Es gibt keine Informationen zu den Langzeitauswirkungen von Cangrelor auf die Fruchtbarkeit von Männern und Frauen. Ebenso gibt es keine ausreichenden und gut kontrollierten Studien zur Anwendung von Clopidogrel bei schwangeren Frauen. Nehmen Sie nicht an der Studie teil,

**Reproductive risks**

It is not known whether cangrelor can have an impact on an unborn child. There is no information on the long-term effects of cangrelor on fertility of men and women. Similarly, there are no adequate and well-controlled studies of the use of clopidogrel in pregnant women. Do not take part in the study if you are pregnant or suspect you may be pregnant. Be sure to inform your investigator if you suspect you may be pregnant or if you are uncertain in this



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wenn Sie schwanger sind oder den Verdacht haben, schwanger zu sein. Informieren Sie unbedingt Ihren Prüfarzt, wenn Sie vermuten, schwanger zu sein oder wenn Sie diesbezüglich unsicher sind.

respect.

**Unbekannte Risiken**
Es könnten auch Nebenwirkungen oder Beschwerden bei Ihnen auftreten, die nicht in dieser Einverständniserklärung aufgeführt sind. Möglicherweise sind einige Nebenwirkungen zum jetzigen Zeitpunkt noch nicht bekannt. Bei Ihnen könnten auch neue Nebenwirkungen auftreten. Bitte informieren Sie umgehend den Prüfarzt oder das Studienpersonal, wenn bei Ihnen Probleme auftreten.

**Unknown risks**
You could also experience side effects or symptoms not listed in this consent. Some side effects may not yet be known at this time. You could experience new side effects. Please immediately inform the investigator or study staff if you have problems.

**Nutzen im Zusammenhang mit der Teilnahme an dieser klinischen Studie**
Die Teilnahme an dieser Studie bringt Ihnen nicht unbedingt einen persönlichen Nutzen; andere Patienten [mit einer Herzerkrankung, die sich einem Eingriff am Herzen unterziehen] können jedoch möglicherweise in Zukunft von den Informationen aus der Studie profitieren.

**Benefits associated with participation in this clinical study**
Participation in this study will not necessarily bring a personal benefit; other patients [with heart disease, who undergo heart interventions], however, may be able to benefit in the future from the information from the study.

**Andere Behandlungsmöglichkeiten**
Wenn Sie sich gegen eine Studienteilnahme entscheiden, erhalten Sie die Standardbehandlung für Ihre Erkrankung, je nachdem, welche Behandlung Ihr Arzt für Ihren Zustand als am besten erachtet. Die Standardbehandlung für Ihre Erkrankung ist Plavix, die identisch mit der Placebo-Gruppe in dieser Studie ist.

**Other treatment options**
If you choose not to participate in the study, you will receive the standard treatment for your condition, depending on which treatment your doctor deems best for your condition. The standard treatment for your condition is Plavix, identical with the placebo group in this study.

**Kosten**
Die normalen Behandlungskosten für Ihre Erkrankung und den Eingriff werden Ihnen oder Ihrer Krankenversicherung in Rechnung gestellt. Das Studienmedikament und die für die klinische Studie erforderlichen medizinischen Untersuchungen sind für Sie kostenfrei.

**Costs**
The normal cost of treatment for your condition and the procedure will be billed to your health insurance penalty. The study drug and the medical examinations required for this clinical study are free of charge

**Vergütung**
Sie werden für Ihre Teilnahme an dieser Studie nicht bezahlt.

**Payment**
You will not be paid for your participation in this study.

**Studienbedingte Gesundheitsschäden**
Wenn bei Ihnen infolge der Studienteilnahme Nebenwirkungen auftreten oder sich Ihr körperlicher oder geistiger Gesundheitszustand während Ihrer Teilnahme an der klinischen Studie verändert, müssen Sie sich umgehend in

**Study-related health injury**
If as a result of study participation side effects occur or your physical or mental health changes during your participation in the clinical study, you have to go immediately and seek treatment and as soon as possible contact the study staff or the investigator



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ärztliche Behandlung begeben und so bald wie möglich das Studienpersonal oder den Prüfarzt unter der Telefonnummer 01/ 491 50-2344 kontaktieren.

by phone 01/491 50-2344.

**Versicherung**

Als Teilnehmer dieser klinischen Studie besteht für Sie der gesetzlich vorgeschriebene Versicherungsschutz (Personenschadenversicherung nach § 32 des Österreichischen Arzneimittelgesetzes [AMG]), der alle Schäden abdeckt, die an Ihrem Leben und Ihrer Gesundheit durch die an Ihnen durchgeführten Maßnahmen der Studie verursacht werden können. Diese Versicherung deckt keine Schäden, die aufgrund von Veränderungen im Erbgut Ihrer Fortpflanzungszellen entstanden sind. Die Versicherung wurde bei Lloyd`s, Kantgasse 3 in Wien
1010, Telefonnummer 01/ 71 30 713 unter der Versicherungsnummer 10ME222515KA103 abgeschlossen. Sie erhalten auf Anfrage Einsicht in die Versicherungsunterlagen. Im Schadensfall können Sie sich direkt an den Versicherer wenden, um den Schaden zu melden. Für
den Versicherungsvertrag ist österreichisches Recht anwendbar, die Versicherungsansprüche sind in Österreich einklagbar. Wenn Sie Hilfe benötigen, können Sie sich auch an die Patientenanwaltschaft oder die Patientenvertretung wenden. Um Ihren Versicherungsschutz nicht zu gefährden, sollten Sie die folgenden Verpflichtungen einhalten.

• Sie dürfen sich während Ihrer Teilnahme an der klinischen Studie ohne vorherige Zustimmung Ihres behandelnden Prüfarztes keiner anderen medizinischen Behandlung unterziehen. Davon ausgenommen sind Notfälle. Dies gilt auch für die Einnahme zusätzlicher Medikamente.
• Sie müssen den behandelnden Prüfarzt – oder das oben genannte Versicherungsunternehmen – umgehend über jegliche Gesundheitsschäden informieren, die infolge Ihrer Teilnahme an der klinischen Studie auftreten.
• Sie müssen sich bei der Einnahme des Studienmedikaments an die Anweisungen des Prüfarztes halten.
• Ihr Gesundheitsschaden darf nicht vorsätzlich verursacht sein.
• Sie müssen den medizinischen Rat des Prüfarztes befolgen.

**Insurance**

As a participant in this clinical trial there exists for you the statutory insurance coverage (personal injury insurance according to § 32 of the Austrian Medicines Law [AMG]), which covers all damage to your life and your health that may be caused by the actions you performed in the study. This insurance does not cover damage caused by alterations in the genetic material of your reproductive cells The insurance was completed at Lloyd's, Kantgasse 3 in Vienna 1010, telephone 01/71 30 713 under the insurance policy number 10ME222515KA103. You can get on request information on the insurance documents. In event of injury you can contact directly the insurance company to report the injury. The insurance contract is subject to Austrian law applicable to insurance claims enforceable in Austria. If you need help, you can also contact the contact patient advocate or the patient representative. In order no to compromise your insurance coverage you should comply with the following obligations.

• You may not undergo any other medical treatment during your participation in the clinical trial without permission from your treating investigator. The exceptions are emergencies. This also applies to taking additional medication.
• You must inform the treating investigator - or the above insurance companies - promptly of any adverse health effects that occur as a result of your participation in the clinical trial.
• You must take the study drug according to the instructions of the investigator.
• You should not cause harm to your health intentionally.
• You must follow the medical advice of the investigator.

**Datenschutz und Vertraulichkeit**

**Privacy and confidentiality**



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**Ziel der Erhebung geschützter Gesundheitsinformationen**

Wenn Sie an der Studie teilnehmen, erteilen Sie Ihre Genehmigung zur Erhebung Ihrer indirekt personenbezogenen Daten. Die Unterlagen zu Ihrer Studienteilnahme werden vertraulich behandelt, sofern nicht gesetzlich anderweitig vorgeschrieben; strikte Vertraulichkeit kann jedoch nicht garantiert werden. Der Prüfarzt, der Studienauftraggeber, Vertreter des Studienauftraggebers, die US-amerikanische „Food and Drug Administration" (FDA), die Europäische Arzneimittelagentur (EMA), andere Regierungsbehörden in den USA und in anderen Ländern sowie die Ethikkommission (eine Gruppe von Personen an Ihrem Prüfzentrum, die für die Überwachung der klinischen Studie und für den Schutz Ihrer Rechte verantwortlich ist) können vertrauliche Daten prüfen und darauf zugreifen.

Ihr Name, Ihre Adresse, Ihre Sozialversicherungsnummer und ähnliche Angaben werden in keiner Information erscheinen, die außerhalb des Prüfzentrums verwendet wird. Wenn die Studienergebnisse veröffentlicht werden, werden diese keine Informationen enthalten, anhand derer Sie identifiziert werden können. Die erhobenen Informationen könnten in Ihre Krankenakte im Krankenhaus aufgenommen werden. Sie können jederzeit in Ihre Krankenakte Einsicht nehmen. Ihre Genehmigung zur Verwendung Ihrer Informationen durch das Studienpersonal tritt in Kraft, sobald Sie dieses Dokument unterzeichnen. Wenn Sie mit der Verwendung und Weitergabe Ihrer Gesundheitsinformationen nicht einverstanden sind, können Sie nicht an dieser Studie teilnehmen.

Folgende Gesundheitsinformationen werden im Rahmen dieser Studie über Sie erhoben:

• Initialen, Alter, Geschlecht, ethnische Abstammung
• Die Daten Ihrer Aufnahme und Entlassung aus dem Krankenhaus in Zusammenhang mit dieser Studie
• Frühere Erkrankungen oder Risikofaktoren, die bei Ihnen möglicherweise zur Diagnose einer [Herz-] Erkrankung beigetragen haben
• Ihre Medikamente, deren Einnahmeplan sowie etwaige Änderungen
• Informationen zu Ihrem derzeitigen Gesundheitszustand und Ihrer Erkrankung
• Informationen zum Eingriff (bzw. den Eingriffen)

**The aim of the survey of protected health information**

If you participate in the study, you give your permission to collect your indirect personal data. The documents relating to your participation in the study will be confidentially treated, unless otherwise required by law; strict confidentiality, however, can not be guaranteed. The investigator, the study sponsor, representatives of the study sponsor, the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), other government agencies in the U.S. and in other countries, as well as the ethics committee (a group of people at your test center responsible for monitoring the clinical trial and the protection of your rights) may examine confidential data and access it.

Your name, your address, your social security number and similar information are information not to be used outside of the test center. If the study results are published, this information will not included, based on which you can be identified. The information collected could be recorded in your medical record in hospital. You can at any time inspect your medical record. Your permission to use the information by the study personnel will enter into force as soon as you sign this document. If you do not agree with the use and disclosure of your health information not agree, you can not participate in this study.

The following health information about you is collected during this study:

• initials, age, gender, ethnicity
• the data about your admission and discharge from the hospital in connection with this study
• previous disease or risk factors that have contributed to a diagnosis of a [heart] disease
• your medications, their dosing schedule and any changes
• information about your current health and your condition
• information about the intervention (or interventions) on your heart
• changes in your health and your condition within a period of about 30 days (+ 5 days) after the



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an Ihrem Herzen
• Veränderungen Ihres Gesundheitszustands und Ihrer Erkrankung innerhalb eines Zeitraums von etwa 30 Tagen (+ 5 Tage) nach dem Eingriff (bzw., den Eingriffen) an Ihrem Herzen

intervention (or interventions) on your heart

**Zugriff auf Ihre geschützten Gesundheitsinformationen**
Um sicherzustellen, dass Ihre Informationen vertraulich bleiben, wird Ihnen eine Codenummer zugeteilt. Dieser Code wird verwendet, um alle im Rahmen der Studie erforderlichen Informationen zu kennzeichnen und zurückzuverfolgen. Ihre medizinischen Informationen werden vom Prüfarzt und vom Studienpersonal vertraulich behandelt und nur dann weitergeleitet, wenn es das Gesetz verlangt, z. B. zur Benachrichtigung der Behörden im Falle schwerwiegender Nebenwirkungen.

**Access to your protected health information**
To ensure that your information remains confidential, you will be assigned a code number. This code is used by all required as part of the study to identify and trace information. Your medical information will be handled by the investigator and study staff confidentially and only forwarded if required by law, such as to inform authorities in the event serious side effects.

Die im Rahmen dieser Studie erhobenen Daten (die keine Informationen enthalten werden, anhand derer Sie identifiziert werden können) werden an den Studienauftraggeber und/oder seine Vertreter weitergeleitet und können veröffentlicht und/oder an die Zulassungsbehörden in Österreich oder in anderen Ländern, in denen ein Antrag auf Zulassung von Cangrelor gestellt wurde, sowie an die zuständige Ethikkommission weitergeleitet werden.

The data collected in this study (which will not contain information by which you can be identified) will be forwarded to the study sponsor and/or its agents and may be published and/or to the regulatory authorities in Austria or other countries in which an application for approval of cangrelor will be submitted, and will be forwarded to the relevant ethics committee.

Ihre Originalkrankenakte kann, soweit es das Gesetz erlaubt, überprüft werden von
o The Medicines Company (dem Unternehmen, das die Studie in Auftrag gegeben hat) und/oder seinen Vertretern
o den Zulassungsbehörden zum Zwecke der Bewertung von Verfahren und/oder von Daten der klinischen Studie.
o der Ethikkommission, die diese Studie überwacht.

Your original medical record may, where permitted by law, be checked by
o The Medicines Company (the company that commissioned the study) and/or its representatives
o the regulatory authorities for the purpose of evaluation of methods and/or the data of the clinical trial
o the Ethics Committee, which oversees the study.

Diese Personen sind zur Verschwiegenheit verpflichtet.

These individuals are bound to secrecy.

Wenn Sie diese Einwilligungserklärung unterzeichnen, erteilen Sie Ihre Genehmigung zur Verwendung der im Lauf der Studie erhobenen indirekt personenbezogenen Daten (anhand derer Sie nicht durch rechtliche zulässige Verfahren identifiziert werden können) durch den Studienauftraggeber, Unternehmen, die mit dem Studienauftraggeber zusammenarbeiten, Vertragspartner des Sponsors und vom Studienauftraggeber beauftragte Dienstleister sowie das Versicherungsunternehmen, bei dem die Personenschadenversicherung gemäß Art. 32

When you sign this consent form, you give your permission for the evidence to be collected in the course of the study indirect personal data (based on which you can not be identified by legal methods allowed) by the study contracting companies that cooperate with the study sponsor, contractors appointed by the sponsor and study customer service, and the insurance company, in which the personal injury insurance in accordance with Article 32 Paragraph 1 item. 11 AMG has been completed. When you sign the consent form, you also expressly consent to disclosure of such indirect personal



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Abs. 1 Ziff. 11 AMG abgeschlossen wurde. Wenn Sie die Einwilligungserklärung unterzeichnen, stimmen Sie außerdem ausdrücklich der Weitergabe derartiger indirekt personenbezogener Informationen an die oben genannten Stellen zu, einschließlich der Weitergabe von Daten in Länder außerhalb des EWR.

information to the above offices, including transfer of data to countries outside the EWR.

Die Verwendung und Weitergabe Ihrer Gesundheitsinformationen aus dieser Studie kann über einen unbestimmten Zeitraum erfolgen. Sie haben jedoch das Recht, die Einwilligung zur Verwendung oder Weitergabe Ihrer Gesundheitsinformationen zu widerrufen, indem Sie sich schriftlich an den Prüfarzt wenden. In diesem Fall werden keine neuen Gesundheitsinformationen mehr erhoben, es sei denn, dies ist im Rahmen der Nachbeobachtung einer Nebenwirkung erforderlich, die während der Studie bei Ihnen aufgetreten ist. Alle Daten, die vor Ihrem schriftlichen Widerruf erhoben wurden, können weiterhin verwendet werden.

The use and disclosure of your health information from this study can occur for an indefinite period. However, you have the right to revoke consent for use or disclosure of your health information by yourself writing to the investigator. In this case, no more new health information will be collected, unless it is required in the context of following a side effect that occurred to you during the study. All data collected prior to your written revocation may still be used.

**FRAGEN ZUR STUDIE**

Wenn Sie Fragen zur Studie haben, wenden Sie sich bitte an Herrn Prim. Prof. Dr. Kurt Huber unter 01/ 491 50-2309. Außerhalb der Sprechzeiten rufen Sie bitte die 24-Stunden Notfallnummer 01/ 491 50 - 2344 an.

Wenn Sie Fragen zu Ihren Rechten als Teilnehmer an dieser Studie haben, wenden Sie sich bitte an den Wiener Pflege-, Patientinnen- und Patientenanwalt, Schönbrunner Straße 108 in Wien 1050 unter der Telefonnummer 01/ 587 12 04. Sie erhalten ein Exemplar dieser Patienteninformation und Einwilligungserklärung.

**QUESTIONS ABOUT THE STUDY**

If you have questions about the study, please contact Principal Professor Kurt Huber at 01/491 50-2309. Outside of office hours please call the 24-hour emergency number 01/491 50-2344.

If you have questions about your rights as a participant in this study, please contact the Vienna Nursing and Patient Advocate, Schönbrunnerstraße 108 Vienna 1050 by phone 01/587 12 04. You will receive a copy of this patient information and consent form.

**Einwilligungserklärung:**

• Mir ist bekannt, dass diese Studie der Forschung dient.
• Ich habe diese Patienteninformation und Einwilligungserklärung gelesen und hatte Zeit, darüber nachzudenken.
• Alle Fragen wurden zu meiner Zufriedenheit beantwortet. Ich erhalte ein Exemplar dieses Dokuments für meine Unterlagen.
• Mir ist bekannt, dass eine Teilnahme an dieser Studie freiwillig ist.
• Ich erkläre mich damit einverstanden, den Studienablauf einzuhalten und dem Prüfarzt, den Pflegekräften und dem Studienpersonal auf Verlangen die erforderlichen Informationen zur Verfügung zu stellen.
• Ich kann meine Einwilligung zur Teilnahme an der

**Informed Consent:**

• I am aware that this study serves research.
• I have read this patient information and consent and have had time to think about it.
• All questions have been answered to my satisfaction. I have received a copy of this document for my records.
• I understand that participation in this study is voluntary.
• I hereby agree to comply with the study process and to provide the required information at the request of the investigator, caregivers and the study staff.
• I can revoke my consent to participate in the study at any time without giving reasons, without losing entitled benefits.
• I was informed about the study and its objectives,



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Studie jederzeit ohne Angabe von Gründen widerrufen, ohne mir zustehende Leistungen zu verlieren.
• Ich wurde über die Studie und ihre Ziele, den Studienablauf, die Risiken und den möglichen Nutzen, sowie über andere Behandlungsmöglichkeiten informiert.
• Ich gestatte die in diesem Dokument beschriebene Verwendung und Offenlegung meiner personenbezogenen Gesundheitsinformationen. Meine Identität wird vertraulich behandelt, wenn die im Rahmen dieser Studie erhobenen Daten veröffentlicht oder für Lehrzwecke verwendet werden. Bei der Verwendung der Daten werden die Regelungen des Datenschutzgesetzes eingehalten.

the study procedure, the risks and potential benefits, as well as information about other treatment options.
• I authorize the use and disclosure described in this document of my personal health information. My identity will be treated confidentially if the data collected in this study are published or used for teaching purposes. When using the data, the regulations of the Data Protection Act will be observed.

Der Prüfarzt wird mich über neue Erkenntnisse informieren, die sich im Verlauf der Studie ergeben und Einfluss auf meine Bereitschaft zur Fortsetzung der Studienteilnahme haben können. Wenn ich möchte, dass diese Informationen an meinen Hausarzt weitergeleitet werden, muss ich meinen behandelnden Prüfarzt in dieser Studie informieren.

The investigator will notify me of new information, which in the course of the study arises and can affect my willingness to continue participation in the study. If I want this information to be passed on to my family doctor, I must inform my treating investigator in this study.

**Einwilligungserklärung:**
Wenn Sie dieses Dokument unterzeichnen, bestätigen Sie (der Studienteilnehmer), dass Sie diese Patienteninformation und Einwilligungserklärung gelesen haben bzw. sie Ihnen vorgelesen wurde, dass Sie mit dem Studienpersonal über die Studie gesprochen haben, dass Sie Gelegenheit hatten, Fragen zu stellen und alle Fragen zufriedenstellend beantwortet wurden und dass Sie freiwillig in die Teilnahme an dieser Studie, wie in diesem Dokument beschrieben, einwilligen.

**Informed Consent:**
When you sign this document, you acknowledge (the study participant) that you have read this patient information and consent form or you will have read them, that you have spoken with the study staff about the study, that you have the opportunity to ask questions and all questions were answered satisfactorily, and that you voluntarily participate in this study, as in this document described.



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Attachment 7: German ICD

The Medicines Company TMC-CAN-10-01
Information Leaflet and lnformed Consent Form for the Participation in a Clinical Study, V1.0GER2.1 Germany, Final Version 2.1, 04 July 2011

Prof. Dr. med. Peter Radke
Universitaetsklinikum Schleswig-Holstein
Medizinische Klinik 2
Ratzeburger Allee 160, 23538 Luebeck Germany

**PATIENTENINFORMATION UND EINWILLIGUNGSERKLÄRUNG**

**TITEL DER STUDIE:**
CHAMPION Phoenix: Eine klinische Studie zum Vergleich von Cangrelor mit Clopidogrel als Standardbehandlung bei Patienten, die eine perkutane Koronarintervention benötigen

**PRÜFPLANNUMMER:** TMC-CAN-10-01

**PRÜFARZT:** Prof. Dr. Med. Peter Radke
(address & phone number)

**Einleitung**

**Sehr geehrte Patientin, sehr geehrter Patient,**
Sie wurden gefragt, ob Sie daran interessiert sind, an einer klinischen Studie teilzunehmen, die im Folgenden beshrieben wird. Die Teilnahme an dieser Studie ist vollkommen freiwillig. Sie konnen die Teilnahme auch ablehnen, ohne dass Ihnen hierdurch Nachteile bei Ihrer medizinischen Betreuung entstehen. Diese Studie wird von Ihrem Prufarzt durchgeführt. Es ist wichtig, dass Sie diese Patienteninformation lesen und die darin enthaltenen Informationen auch verstehen. Bitte lesen Sie das Dokument daher aufmerksam durch. Nehmen Sie sich Zeit, um dem Prüfarzt oder dem Studienpersonal so viele Fragen über die klinische Studie zu stellen, wie Sie möchten. Bitte wenden Sie sich an den Prüfarzt, wenn Sie die Bedeutung bestimmter Begriffe nicht kennen oder inhaltliche Fragen haben. Das Lesen dieser Patienteninformation und das Gespräch mit dem Prüfarzt oder dem Studienpersonal sollen Ihnen helfen zu entscheiden, ob Sie an der klinischen Studie teilnehmen möchten oder nicht. Wenn Sie sich für eine Teilnahme entscheiden, müssen Sie vor Ihrer Teilnahme an der klinischen Studie die Einwilligungserklärung unterzeichnen und datieren. Die Einwilligung in die Studientteilnahme findet statt, bevor der Prufarzt Ihre Eignung fur die

The Medicines Company TMC-CAN-10-01
Information Leaflet and lnformed Consent Form for the Participation in a Clinical Study, V1.0GER2.1 Germany, Final Version 2.1, 04 July 2011

Prof. Dr. med. Peter Radke
Universitaetsklinikum Schleswig-Holstein
Medizinische Klinik 2
Ratzeburger Allee 160, 23538 Luebeck Germany

**PATIENT INFORMATION AND CONSENT**

**STUDY TITLE:**
CHAMPION Phoenix: A clinical trial comparing cangrelor with clopidogrel as a standard treatment in patients requiring percutaneous coronary intervention

**PROTOCOL NUMBER**: TMC-CAN-10-01

**INVESTIGATOR:** Prof. Dr. Med. Peter Radke
(address & phone number)

**Introduction**

**Dear patient, dear patient,**
You were asked if you are interested in participating in a clinical trial that is described below. Participation in this study is completely voluntary. You can also refuse to participate, without thereby suffering disadvantages in your medical care. This study will be carried out by your investigator. It is important that you read this patient information and understand the information contained therein. Please read the document carefully. Take time to ask the investigator or the study staff as many questions about the clinical trial as you like. Please contact the investigator or the study staff, if you do not know the meaning of certain terms or have substantive questions. Reading this patient information and conversing with the investigator or the study staff will help you to decide if you wish to participate in the clinical trial or not. If you decide to participate, you must sign and date the informed consent form prior to participation in the clinical trial. Consent for study participation takes place before the investigator has checked your eligibility for the study. Your investigator must check the image recordings of your coronary arteries. You are eligible for the study if your investigator finds that certain closed coronary arteries must be opened surgically. Your investigator will tell you whether



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Studie uberpruft hat. Ihr Prufarzt muss hierfur Bildaufnahmen Ihrer Herzkranzgefasse uberprufen. Sie sind für die Studie geeignet, wenn Ihr Prüfarzt feststellt, dass bestimmte verschlossene Herzkranzgefasse operativ geöffnet werden müssen. Ihr Prüfarzt wird Ihnen mitteilen, ob Sie für eine Studienteilnahme geeignet sind.

you qualify for participation in the study.

**Hintergrund und Ziel der Studie**

Sie werden gebeten, auf freiwilliger Basis an dieser klinischen Studie teilzunehmen, weil bei Ihnen Anzeichen und Symptome einer koronaren Herzkrankheit vorliegen. Diese konnen auf ein schwerwiegendes Herzproblem hinweisen, bei dem das Herz nicht ausreichend mit Sauerstoff versorgt wird. Diese Storung kann durch eine teilweisen Verschluss eines oder mehrerer Herzkranzgefasse verursacht werden.

**Background and purpose of the study**

You are being asked on a voluntary basis to participate in this clinical trial because you have signs and symptoms of coronary heart disease. These may indicate a serious heart problem in which the heart does not receive enough oxygen. This condition may be caused by partial blockage of one or more coronary arteries.

In dieser klinischen Studie wird ein in der Phase der Arzneimittelprufung befindliches Medikament namens Cangrelor angewendet. Es soll untersucht werden, ob Congrelor die Blutgerinnselbildung bei Patienten zu verhindern kann, bei denen eine Ballondilatation (eine sogenannte perkutane Koronarintervention oder PKI) durchgeführt wurde, um verschlossene Herzkranzgefasse zu offnen. Im Rahmen dieser Studie wird auch das von der Europaischen Union zugelassene Arzneimittel Clopidogrel (Plavix®) angewendet. Plavix ist für die Behandlung von Herzinfarkten und Schlaganfällen zugelassen. Wenn bei Ihnen eine PKI durchgeführt wird, kann die Anfangsdosis Plavix bis zum Zweifachen der zugelassenen Dosis betragen. Die Dosis hangt davon ab, welches der ubliche Standard an Ihrer Einrichtung ist. In dieser Studie soll die Sicherheit und Wirksamkeit einer Kombinationstherapie von Cangrelor und Plavix mit der Sicherheit und Wirksamkeit einer Behandlung mit Plavix alleine verglichen werden. Cangrelor ist bisher nicht von der Europaischen Arzneimittelagentur (EMA) zugelassen; daher ist die Anwendung von Cangrelor in dieser Studie experimentell.

In this clinical study an investigational drug called cangrelor is used. It will be investigated whether cangrelor can prevent the formation of blood clots in patients in whom a balloon dilation (a so-called percutaneous coronary intervention or PKI) was performed to open blocked coronary arteries. This study will also use the European Union approved drug clopidogrel (Plavix®). Plavix is used for the treatment of heart attacks and strokes. When you get a PKI, the starting dose of Plavix can be up to twice the approved dose. The dose depends upon the usual standard in your facility. This study will evaluate the safety and efficacy of combination therapy with cangrelor and Plavix compared to the safety and efficacy of treatment with Plavix alone. Cangrelor is not yet licensed by the European Medicines Agency (EMA); hence the use of cangrelor in this study is experimental.

In diese klinische Studie werden etwa 10.900 Patienten an etwa 200 Prüfzentren weltweit aufgenommen.

In this clinical study about 10,900 patients at 200 clinical sites will be enrolled worldwide.

**Beschreibung der Studie**

Ihr Prüfarzt wird auch eine vollständige medizinische Untersuchung durchführen, um festzustellen, ob Sie an der klinischen Studie teilnehmen können. Dies umfasst Ihre Krankengeschichte, eine körperliche Untersuchung, demographische, Blutuntersuchungen, Abgabe einer

**Description of the study**

Your investigator will perform a complete medical examination to determine if you can participate in the clinical trial. This includes your medical history, physical examination, demographics, blood tests, provision of a urine sample and an electric recording of your heart (ECG). For the blood tests



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Urinprobe und eine elektrische Aufzeichnung Ihres Herzschlags (EKG). Für die Blutuntersuchungen werden Ihnen von einer Fachkraft etwa 20 ml Blut durch einen Einstich in eine Vene entnommen. Alle diese Untersuchungen werden für gewöhnlich im Rahmen der Standardversorgung durchgeführt. Standardversorgung bedeutet, dass diese Untersuchungen und Maßnahmen auf jeden Fall durchgeführt würden, unabhängig davon, ob Sie an der Studie teilnehmen oder nicht. Zusätzlich zu den normalen Blutuntersuchungen, die im Rahmen Ihrer Standardversorgung durchgeführt werden, werden für die Studie 4 ml Blut entnommen, die an ein Zentrallabor geschickt werden. Sie sollten Ihren Prüfarzt über Ihre Krankengeschichte – einschließlich aller Medikamente, die Sie derzeit einnehmen (auch pflanzliche Heilmittel oder frei verkäufliche Produkte) – sowie über Ihre Teilnahme an anderen Studien informieren. Sie mussen Ihren Prufarzt auch dann informieren, wenn Sie schwanger sind oder den Verdacht haben, schwanger zu sein. Gebarfahige Frauen mussen einen Schwangerschaftstest durchfuhren, der negative ausfallen muss, bevor sie an diser Studie teilnehmen konnen.

about 20 ml of blood will be removed from you through a puncture into a vein by a specialist. All of these investigations are usually performed in the context of standard of care. Standard of care means that these studies and measures would be carried out in any case regardless of whether you participate in the study or not. In addition to the regular blood tests as part of your standard care, 4 ml of blood are taken for the study which are sent to a central lab. You should inform your investigator about your medical history - including any medications you are currently taking (including herbal remedies or OTC products) - as well as your participation in other studies. You must inform your investigator if you are pregnant or suspect you may be pregnant. Women of child-bearing potential must undergo a pregnancy test, which must turn out negative, before they participate in this study.

**Studienablauf**

Wenn Sie für die Studienteilnahme geeignet sind und weiterhin teilnehmen möchten, werden Sie nach dem Zufallsprinzip (wie beim Werfen einer Munze) einer von zwei Studiengruppen zugeteilt:

• **Cangrelor-Gruppe** – während der PKI wird Ihnen Cangrelor langsam über mindestens 2 Stunden durch einen intravenösen (IV-) Katheter (Plastikröhrchen) in eine Vene verabreicht. Ihr Prüfarzt kann die Infusion jedoch auf bis zu insgesamt 4 Stunden verlängern, wenn die PKI länger als 2 Stunden dauert. In Abhangigkeit von der Standardversorgung in Ihrer Einrichtung erhalten Sie zum Zeitpunkt der PKI 2 bis 4 Placebo-Kapseln (Kapseln, die keinen Wirkstoff enthalten). Abschließend erhalten Sie unmittelbar nach Ende der Cangrelor-Infusion vier (4) Kapseln Clopidogrel zu je 150 mg (insgesamt 600 mg).

• **Placebo-Gruppe** – Gemäß der Standardversorgung in Ihrer Einrichtung erhalten Sie zum Zeitpunkt der PKI 2 bis 4 Kapseln Clopidogrel. Während der PKI wird Ihnen eine Placebo-Infusion (eine Infusion, die keinen Wirkstoff enthalt) langsam über mindestens 2 Stunden durch einen IV-Katheter in eine Vene

**Study procedure**

If you are eligible for study participation and wish to participate, you will be randomly assigned (like tossing a coin) to one of two study groups,

• **Cangrelor group** – During the PKI you will be administered cangrelor slowly into a vein over at least 2 hours through an intravenous (IV) catheter (plastic tube). However, your investigator can extend the infusion up to 4 hours in total when the PKI takes longer than 2 hours. As a function of the standard of care in your facility, you will receive at the time of PKI 2-4 placebo capsules (capsules containing no active ingredient). Finally, you will receive immediately after the end of the cangrelor infusion four (4) capsules, containing 150 mg of clopidogrel (total 600 mg).

• **Placebo group** - According to the standard of care at your facility, you will receive at the time of PKI 2-4 capsules clopidogrel. During the PKI you will be administered a placebo (an infusion, which contains no active ingredient) slowly into a vein over at least 2 hours through an IV catheter. However, your investigator can extend the infusion



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verabreicht. Ihr Prüfarzt kann die Infusion jedoch auf bis zu insgesamt 4 Stunden verlängern, wenn die PKI länger als 2 Stunden dauert. Abschließend erhalten Sie unmittelbar nach Ende der Placebo-Infusion vier (4) Placebo-Kapseln (Kapseln, die keinen Wirkstoff enthalten).

up to 4 hours in total when the PKI takes longer than 2 hours. According to the standard of care in your facility, you will receive at the time of PKI 2-4 capsules each with Plavix 150 mg. Finally, you will receive immediately after the end of the placebo infusion, four (4) placebo capsules (capsules, which contain no active ingredient).

In dieser Studie wird das Studienmedikament Cangrelor mit dem bereits zugelassenen Medikament Clopidogrel verglichen. Um sicherzustellen, dass jede beobachtete Besserung in Ihrem Zustand tatsachlich das Ergebnis der moglicherweise hoheren Wirksamkeit des Studienmedikaments is und nicht durch andere Faktoren beeinflusst wurder, ist es notwendig, dass weder Sie noch der Prüfarzt werden wissen, welchem Studienmedikament Sie zugeteilt wurden. In einem Notfall kann der Prüfarzt jedoch in Erfahrung bringen, welches Studienmedikament Sie erhalten. Aufgrund der Tatsache, dass Cangrelor als Infusion in eine Vene verabreicht wird, wahrend Clopidogrel uber den Mund (oral) eingenommen wird, konnte leicht erkannt werden, welchem Studienmedikament Sie zugeteilt wurden. Um dies zu verhindern, erhalten Sie in jedem Fall eine Infusion sowie Kapseln zur oralen Einnahme. Nur eine Behandlung enthalt jedoch einen Wirkstoff (Cangrelor oder Clopidogrel). Die andere Behandlung ist ein Placebo (eine wirstofffreie Substanz, die in dieser Studie Angewendet wir, um die Verblindung der Studie aufrechtzuerhalten). Die Wahrscheinlichkeit der Zuteilung zu Cangrelor oder Clopidogrel ist gleich hoch.

In this study, the investigational drug cangrelor is compared with the already approved drug clopidogrel. To ensure that any observed improvement in your condition is actually the result of the possibly higher efficacy of the study drug and is not influenced by other factors, it is necessary that neither you nor the investigator will know which study drug you have been allocated. In an emergency, however, the investigator can find out which study drug you received. Due to the fact that cangrelor is administered as an infusion into a vein, while clopidogrel is taken by mouth (oral), it could be easily detected, which study drug you have been allocated. To prevent this, you will always receive an infusion and capsules for oral administration. However, only one treatment contains an active ingredient (cangrelor or clopidogrel). The other treatment is a placebo (an inactive substance, we used to maintain the blinding of the study). The probability of assignment to cangrelor or clopidogrel is the same.

Während Ihres Krankenhausaufenthalts müssen mindestens 2 weitere EKGs aufgezeichnet und 4 Blutproben (etwa 25 ml) abgenommen werden. Drei der Blutproben (jeweils 4 ml) werden nach der Entnahme zur Analyse an ein Zentrallabor geschickt. Im Rahmen der medizinischen Standardbehandlung können Sie auch Aspirin oder andere Medikamente erhalten, um Komplikationen in Zusammenhang mit dem Eingriff vorzubeugen. Dies liegt im Ermessen Ihres Prüfarztes. Am Tag nach dem Eingriff werden Ihnen Medikamente zur Vorbeugung von Blutgerinnseln sowie Aspirin verordnet. Diese Medikamente müssen nach Ermessen Ihres Prüfarztes mindestens einen Monat oder länger eingenommen werden.

During your hospital stay at least 2 more ECGs must be recorded and 4 blood samples [about (25 ml) removed. Three blood samples (4 ml each) will be removed and sent after removal for analysis to a central laboratory. Under standard medical treatment, you can also obtain aspirin or other medicines in order to prevent complications related to the procedure. This is at your investigator's discretion. The day after surgery you will be prescribed drugs to prevent blood clots and aspirin. These drugs need to taken at your investigator's discretion at least a month or more.

**Nachbeobachtung**

Sie werden etwa 2 Tage (sofern Sie nicht länger im Krankenhaus sind) und 1 Monat nach der PKI telefonisch kontaktiert, damit festgestellt

**Follow-up**

You will be contacted by phone about 2 days (provided you are no longer in the hospital) and 1 month after the PKI so that it can be determined



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werden kann, wie es Ihnen geht und ob es seit dem letzten Kontakt Anderungen bei Ihrer Krankengeschichte und Ihrer Erkrankung gab. Sie werden gebeten, das Studienpersonal zu informieren, wenn sich Ihre Kontaktinformationen während der Nachbeobachtungsphase ändern.

how you are and whether there were changes in your medical history and your condition since the last contact. You are asked to contact the study staff if your contact information changes during the follow-up period.

**Dauer der Studienteilnahme**
Ihre Teilnahme an dieser klinischen Studie beginnt, wenn Sie diese Einwilligungserklärung unterzeichnen, und dauert bis etwa 35 Tage nach Ihrem Eingriff.

**Duration of study participation**
Your participation in this clinical trial starts when you sign this consent sign and lasts until about 35 days after your procedure.

**Abbruch der Studienteilnahme**
Sie können Ihre Teilnahme an dieser Studie jederzeit beenden. Dies hat keinen Einfluss auf Ihre medizinische Versorgung. Ihr Prüfarzt kann ebenfalls beschließen, Ihre Studienteilnahme vorzeitig zu beenden, wenn:
• neue Erkenntnisse auf eine mangelnde Wirksamkeit der Behandlung hindeuten
• neue Erkenntnisse auf eine mangelnde Sicherheit der Behandlung hindeuten
• Sie sich nicht an die Studienvorschriften halten
• bei Ihnen neue Gesundheitsschadigung oder Erkrankungen auftritt

**Discontinuation of study participation**
You can always cancel your participation in this study. This does not affect your medical care. Your investigator may also decide to terminate your participation in the study early if:
• new findings suggest a lack of effectiveness of the treatment
• new findings suggest a lack of safety of the treatment
• you do not adhere to the study requirements
• new damage to health or illnesses occur for you

Wenn Sie oder Ihr Prüfarzt beschließen, Ihre Studienteilnahme zu beenden, können Sie gebeten werden, zusätzliche Laboruntersuchungen und andere Untersuchungen durchfuhren zu lassen, die Ihr Prüfarzt für notwendig erachtet.

If you or your investigator decides to terminate your participation in the study, you may be asked for additional laboratory tests and other examinations to be carried out that your investigator considers necessary.

**Risiken und Nutzen**
Cangrelor: Cangrelor wurde im Rahmen anderer Studien etwa 7600 Personen verabreicht. Die am häufigsten in Zusammenhang mit Cangrelor beobachtete Nebenwirkung sind Blutungen (betrifft mehr als 1 von 10 Patienten). Wie bei allen blutverdünnenden Medikamenten kann es zu Blutungen am oder im Körper kommen, z. B. an Einstichstellen, im Verdauungssystem, im Bauch oder es kann Blut im Urin auftreten. Anzeichen dafür sind insbesondere Blutergüsse (blaue Flecken ) und innere Einblutungen ins Gewebe(Hämatome), Absinken des roten Blutfarbsoffs (Hamoglobin) oder des Hämatokrits (beides Anzeichen für Blutverlust und aus den Laborbefunden ersichtlich), punktförmige oder flächige rote oder violette Verfärbungen der Haut, die durch Blutungen unter der Haut entstehen (Purpura), sowie Verlängerung der Gerinnungszeit; in seltenen Fällen (< 1/1000) kann es zu Blutungen in den Augen oder im Gehirn kommen. Blutungsereignisse können schwerwiegend sein und zu weiteren

**Risks and benefits**
Cangrelor: Cangrelor was administered to approximately 7600 persons in other studies. The most frequently observed side effect with cangrelor is bleeding (affects more than 1 in 10 patients). As with all blood-thinning medicines it can cause bleeding on or in the body, for example, at injection sites, in the digestive system, in the stomach, or in the urine. Signs are particularly bruises (bruising) and internal bleeding into the tissue (hematoma), decrease in red blood color (hemoglobin) or hematocrit (both signs of blood loss and recognizable in the laboratory findings), point or area red or purple discoloration of the skin caused by bleeding under the skin (purpura), and extension of the clotting time; only in rare cases (<1/1000), bleeding in the eyes or in the brain occurs. Bleeding events may be severe and can lead to complications or even death.



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Komplikationen bzw. sogar zum Tod führen.

Weitere häufig (<1/10) berichtete Nebenwirkungen sind: Rückenschmerzen, Shmerzen im Brustraum, Übelkeit, Kopfschmerzen, niedriger Blutdruck, Erbrechen, Schmerzen an der Einstichstelle, Fieber, Kurzatmigkeit und hoher Blutdruck.

Other commonly (<1/10) reported side effects are: back pain, chest pain, nausea, headaches, low blood pressure, vomiting, pain at the injection site, fever, shortness of breath and high blood pressure.

Zu den schwerwiegenden, aber sehr selten (<1/10.000) auftretenden Nebenwirkungen gehören Herzinfarkt, das Versagen mehrerer Körperorgane (multiples Organversagen) sowie Gerinnselbildung in der Lunge oder den Koronararterien
.

The serious, but very infrequent (<1/10,000), side effects include heart attack, the failure of multiple body organs (multiple organ failure) ,and clot formation in the lung or the coronary arteries.

**Risiken in Zusammenhang mit Clopidogrel**
Clopidogrel (Plavix®) ist ein zugelassenes verschreibungspflichtiges Medikament zur Behandlung von Herzinfarkten und Schlaganfällen. Die Anfangsdosis, die Sie in der Studie erhalten werden, entspricht dem Zweifachen der zugelassenen Dosis. Diese Dosis wird jedoch derzeit zur Behandlung von Patienten angewendet, die sich einer PKI unterziehen.

**Risks associated with clopidogrel**
Clopidogrel (Plavix®) is a prescription medication approved for the treatment of heart attacks and strokes. The initial dose that you will be given in the study corresponds to twice the approved dose. This dose, however, is currently used to treat patients who undergo a PKI

Da es sich bei Clopidogrel um ein Medikament handelt, das sich auf die Funktion der Blutplättchen auswirkt, sind die häufigsten Nebenwirkungen Blutungen. Bei 0,2% der Patienten traten schwerwiegende Blutungsereignisse auf, die zum Tod führten. In extrem seltenen Fällen (bei etwa 4 von einer Million Patienten) kann ein schwerwiegendes Blutungsereignis – eine sogenannte thrombotische thrombozytopenische Purpura (TTP) – auftreten. Dabei handelt es sich um eine seltene Erkrankung, die die Gerinnungsfähigkeit des Blutes beeinträchtigt.

Since clopidogrel is a drug that affects the function of platelets, the most common side effects are bleeding. In 0.2% of patients serious bleeding events occurred that led to death. In extremely rare cases (about 4 in a million patients), a serious bleeding event – so called thrombotic thrombocyto-penic purpura (TTP) - occurred. This is a rare disease that affects the clotting ability of the blood.

Die Nebenwirkungen, die in klinischen Studien mit 54.000 Patienten am häufigsten in Zusammenhang mit Clopidogrel in zugelassenen Dosierungen berichtet wurden, sind Kopfschmerzen, Schwindel, Magenschmerzen, Schmerzen im Brustraum, verminderte Anzahl der Blutzellen (was zu einem erhöhten Infektionsrisiko führen könnte), Durchfall, Verdauungsstörungen, erhöhter Cholesterinspiegel, Hautausschlag, Übelkeit oder verminderte Anzahl der Blutplättchen (kleine Blutbestandteile, die die Blutgerinnung unterstützen).

The side effects in the clinical trials with 54,000 patients most associated with clopidogrel at approved doses are headache, dizziness, stomach pain, chest pain, decreased number of blood cells (which could lead to an increased risk of infection), diarrhea, indigestion, high cholesterol, rash, nausea, or decreased number of platelets (small blood components that help blood clotting).

**Risiken für die Fortpflanzung**
Es ist nicht bekannt, welche Auswirkungen Cangrelor auf ein ungeborenes Kind haben kann. Es gibt keine Informationen zu den Langzeitauswirkungen von Cangrelor auf die Fruchtbarkeit von Männern und Frauen. Ebenso gibt

**Reproductive risks**
It is not known whether cangrelor can have an impact on an unborn child. There is no information on the long-term effects of cangrelor on fertility of men and women. Similarly, there are no adequate and well-controlled studies of the use of clopidogrel



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es keine ausreichenden und gut kontrollierten Studien zur Anwendung von Clopidogrel bei schwangeren Frauen. Nehmen Sie nicht an der Studie teil, wenn Sie schwanger sind oder den Verdacht haben, schwanger zu sein. Informieren Sie unbedingt Ihren Prüfarzt, wenn Sie vermuten, schwanger zu sein oder wenn Sie diesbezüglich unsicher sind.

in pregnant women. Do not take part in the study if you are pregnant or suspect you may be pregnant. Be sure to inform your investigator if you suspect you may be pregnant or if you are uncertain in this respect.

**Unbekannte Risiken**
Es könnten auch Nebenwirkungen oder Beschwerden bei Ihnen auftreten, die nicht in dieser Patienteninformation aufgeführt sind. Möglicherweise sind einige Nebenwirkungen zum jetzigen Zeitpunkt noch nicht bekannt. Bei Ihnen könnten auch neue Nebenwirkungen auftreten. Bitte informieren Sie umgehend den Prüfarzt oder das Studienpersonal, wenn bei Ihnen Probleme auftreten.

**Unknown risks**
You could also experience side effects or symptoms not listed in this patient information. Some side effects may not yet be known at this time. You could experience new side effects. Please immediately inform the investigator or study staff if you have problems.

**Nutzen im Zusammenhang mit der Teilnahme an dieser klinischen Studie**
Die Teilnahme an dieser Studie bringt Ihnen nicht unbedingt einen persönlichen Nutzen; andere Patienten [mit einer Herzerkrankung, die sich einem Eingriff am Herzen unterziehen] können jedoch möglicherweise in Zukunft von den Informationen aus der Studie profitieren.

**Benefits associated with participation in this clinical study**
Participation in this study will not necessarily bring a personal benefit; other patients [with heart disease, who undergo heart interventions], however, may be able to benefit in the future from the information from the study.

**Andere Behandlungsmöglichkeiten**
Wenn Sie sich gegen eine Studienteilnahme entscheiden, erhalten Sie die Standardbehandlung für Ihre Erkrankung, je nachdem, welche Behandlung Ihr Arzt für Ihren Zustand als am besten erachtet.

**Other treatment options**
If you choose not to participate in the study, you will receive the standard treatment for your condition, depending on which treatment your doctor deems best for your condition.

**Kosten**
Die normalen Behandlungskosten für Ihre Erkrankung und den Eingriff werden Ihnen oder Ihrer Krankenversicherung in Rechnung gestellt. Der Auftraggeber dieser Studie, The Medicines Company, tragt die Kosten fur das Studienmedikament und für die klinische Studie erforderlichen medizinischen Untersuchungen.

**Costs**
The normal cost of treatment for your condition and the procedure will be billed to your health insurance penalty. The sponsor of this study, The Medicines Company, bears the cost of he study drug and the medical examinations required for this clinical study.

**Vergütung**
Sie werden für Ihre Teilnahme an dieser Studie nicht bezahlt.

**Payment**
You will not be paid for your participation in this study.

**Studienbedingte Gesundheitsschäden**
In einer klinischen Arzneimittelstudie sind alle Teilnehmer gemass den Bestimmungen des deutschen Arzneimittelgesetzes versichert. Der Umfang des Versicherungsschutzes, der vom

**Study-related health injury**
n a clinical drug trial, all participants are insured pursuant to the provisions of the German Medicines Act. The scope of insurance coverage, to which the sponsor of the study, The Medicines Company,



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Auftraggeber der Studie, The Medicines Company, vereinbart wurde, ist aus den Versicherungsunterlagen ersichtlich, die Sie ausgehandigt bekommen.

agreed, is clear from the insurance documents, which you get.

Wenn Sie vermuten, dass durch die Teilnahme an der Studie Ihre Gesundheit geschadigt oder ein bestehendes Leiden verstarkt wurde, mussen Sie dies unverzuglich dem Versicherer

(Name und Adresse, Telefon, Fax, Versicherungsnummer)

direkt anzeigen (gegebenenfalls mit Unterstutzung durch Ihren Prufarzt), um Ihren Versicherungsschutz nicht zu gefarhrden. Falls Ihr Prufarzt Sie dabei unterstutzt, den Versicherer zu verstandigen, erhalten Sie eine Kopie der Meldung. Wenn Sie Ihre Anzeige direkt an den Versicherer richten, informieren Sie bitte Zusatzlich den Prufarzt.

If you suspect that by participating in the study your health was injured or an existing disease reinforced, you need to report this immediately to the insurer directly (possibly with the assistance of your investigator), so not to jeopardize your insurance coverage.

(Name, address, phone number, fax, insurance number)

If your investigator supported your communication to the insurer, you will receive a copy of the message. If you target your report directly to the insurer, please inform additionally the investigator.

Sie sind verpflichtet, samtliche geeigneten Schritte zu unternehmen, um die Ursachen und das Ausmass dieses Schadens zu ermitteln und die Folgen zu verhindern oder so gering wie moglich zu halten.

You are obliged to take all appropriate steps to determine the causes and extent of the damage and to prevent or keep the consequences as low as possible.

Wahrend der Dauer der klinischen Studie durfen Sie sich—ausser in Notfallen—nur nach vorheriger Rucksprache mit dem Prufarzt einer anderen medizinischen Behandlung unterziehen. Der Prufarzt is von einer Notfallbehandlung unverzuglich zu unterrichten.

During the duration of the clinical study—except in emergencies—you may undergo another medical treatment. only after prior consultation with the investigator. The investigator shall be notified immediately of any emergency treatment.

Sie erhalten ein Exemplar der Versicherungsbedingungen. Bitte beachten Sie insbesondere die Punkte 1.4 (ausschlusse), 3 (Versicherungsleistungen) und 4 (Pflichten des Versicherungsnehmers).

You will receive a copy of the insurance conditions. Please note in particular points 1.4 (exclusions), 3 (insurance) and 4 (obligations of the insured).

Bitte beachten Sie auch, dass Sie auf dem Weg vom und zum Prufzentrum nicht unfallversichert sind.

Please also note that you are not insured against accidents on the way to and from the test center.

**Datenschutz und Vertraulichkeit**

Informationen zum Datenschutz entnehmen Sie bitte dem separaten Dokument „Patienteninfomration und Einwilligungserklarung zum Datenschutz“.

**Privacy and confidentiality**

For privacy information, please refer to the separate document "Patient information and consent form for data protection."

**FRAGEN ZUR STUDIE**

Wenn Sie Fragen zur Studie haben, wenden Sie sich bitte an Ihren Prufarzt (siehe Seite 1).. Außerhalb

**QUESTIONS ABOUT THE STUDY**

If you have questions about the study, please contact your investigator (see page 1). Outside of



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der Sprechzeiten konnen Sie Herrn Prof. Dr. Med. Peter Radke unter 0451-5000-6000 erreichen.

Nach dem Deutschen Arzneimittelgesetz konnen Sie weitere Informationen uber die Durchfuhrung der klinischen Studie beim Bundesinstitut fur Arzneimittel und Medizinprodukte (BfArM) anfordern: Telefonnummer des BfArM: 0228/207-4318; Fax: 0228/207-4355; E-Mail: klinpruefung@bfarm.de
Sie erhalten ein Exemplar dieser Patienteninformation und Einwilligungserklarung.

Prof. Dr. med. Peter Radke
Universitaetsklinikum Schleswig-Holstein
Medizinische Klinik 2
Ratzeburger Allee 160, 23538 Luebeck Germany

Titel des Prufplans:
CHAMPION Phoenix: Eine klinische Studie zum Vergleich von Cangrelor mit Clopidogrel als Standardbehandlung bei Patienten, die eine perkutane Koronarintervention benötigen

Prufplannummer: TMC-CAN-10-01

In klinischen Studien werden personenbezogene Daten, insbesondere medizinische Befunde, erfasst, gespeichert und verarbeitet. Die Verwendung der Angaben uber Ihre Gesundheit erfolgt nach gesetzlichen Bestimmungen und setzt vor der Teilnahme an der klinischen Studie folgende freiwillig abgegebene Einwilligungserklarung voraus, d. h. ohne Unterzeichnung der folgenden Einwilligungserklarung konnen Sie nicht an der klinischen Studie teilnehmen.

PATIENTENINFORMATION UND EINWILLIGUNGSERKLARUNG ZUM DATENSCHUTZ

1) Mir ist bekannt, dass im Rahmen dieser klinischen Studie Informationen, insbesondere Angaben uber meine Gesundheit, erhoben und in Papierform und auf elektronischen Datentragern vom Prufarzt (Adresse siehe oben) aufgezeichnet werden. Soweit erforderlich, werden die erhobenen Informationen pseudonymisiert (d. h. verschlusselt mit einem Zahlencode) weitergegeben:

a) an The Medicines Company (den Studienauftraggeber) 8 Sylvan Way, Parsippany, NJ 07054, USA – in der Europaischen Union (EU) vertreten durch The Medicines Company UK Ltd., 11 Milton Park, Abingdon, Oxfordshire, OX 144RS,

office hours you cancan Professor Dr. Peter Radke reached 0451-5000-6000.

According to the German Drug Law you can request more information about the carrying out of the clinical trial at the Federal Institute for Drugs and Medical Devices (BfArM): Phone number of the BfArM: 0228/207-4318, Fax: 0228/207-4355; Email: klinpruefung @ BfArM.de
You will receive a copy of the patient information and consent form.

Prof. Dr. med. Peter Radke
Universitaetsklinikum Schleswig-Holstein
Medizinische Klinik 2
Ratzeburger Allee 160, 23538 Luebeck Germany

Study title:
CHAMPION Phoenix: A clinical trial comparing cangrelor with clopidogrel as a standard treatment in patients requiring percutaneous coronary intervention

Protocol number: TMC-CAN-10-01

In clinical studies, personal data, in particular medical findings, are collected, stored and processed. Use of the information about your health is in accordance with legal provisions and participating in the clinical study depends upon voluntarily giving consent in advance, i.e. without the signing of the consent form, you are not allowed to participate in the clinical trial.

PATIENT INFORMATION AND CONSENT TO PRIVACY

1) I am aware that in the context of this clinical trial information, in particular information about my health, can be collected and recorded on paper and on electronic media by the investigator (see address above). Where necessary, the information collected is anonymized (i.e., encrypted with a numerical code):

a) at The Medicines Company (the study principal) 8 Sylvan Way, Parsippany, NJ 07054, USA -. represented by The Medicines Company UK Ltd, in European Union (EU), 11 Milton Park, Abingdon, Oxfordshire, OX 144RS, UK - or a person



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UK – oder eine von diesem beauftragte Stelle zur wissenschaftlichen Auswertung.

appointed by this body for scientific evaluation.

b) im Falle eines Antrags auf Zulassung oder Erneuerung der Zulassung: an den Antragsteller und die fur die Zulassung zustãndige Behõrde (innerhalb und ausserhalb der EU)
c) im Falle unerwunschter Ereignisse: an den Studienauftraggeber, The Medicines Company, an die zustãndige Ethikkommission und die zustãndige Bundesoberbehõrde;
letztere kann die Daten ihrerseits an die Europãische Datenbank, auslãndische Behõrden (innerhalb und ausserhalb der EU) sowie an die beteiligten Prufãrzte weitergeben.

b) in the case of an application for approval or renewal of approval: the applicant and the authority competent for the appropriate authorization authority (within and outside the EU)
c) in the case of undesired events: to the study sponsor, The Medicines Company, to the appropriate Ethics Committee and the appropriate government authority; the latter can pass on the data to the European database, foreign authorities (within and outside the EU) and to the participating investigators.

Mir ist bekannt, dass meine Daten mittels einer Patientenidentifikationsnummer pseudonymisiert werden. Demographische Daten, darunter auch mein Alter und mein Geschlecht, werden ebenfalls erhoben. Die Daten werden ausschliesslich verwendet, um die Richtigkeit meiner medizinischen lnformationen zu bestãtigen und eine Verwechslung mit anderen Studienteilnehmern zu verhindern. Es kann nicht vollkommen ausgeschlossen werden, dass ich durch die Verwendung dieser zusãtzlichen lnformationen identifiziert werde.

I am aware that my data using a patient identification number are pseudonyms. Demographic data, including my age and my gender will also be collected. The data will be used exclusively to confirm the accuracy of my medical information and prevent confusion with other study participants. It can not be completely excluded that I will be identified through the use of this ancillary information.

2) Mir ist auch bekannt, dass autorisierte und zur Verschwiegenheit verpflichtete Beauftragte des Studienauftraggebers sowie Mitarbeiter nationaler Behõrden (der zustãndigen nationalen Oberwachungsbehõrden, d. h. Landes- oder Bezirksbehõrden) oder der Bundesbehõrden und/oder Vertreter vergleichbarer Behõrden in anderen Lãndern (innerhalb und ausserhalb der EU, z. B. die US-amerikanische Food and Drug Administration [FDA]) in meine beim Prufarzt vorhandenen personenbezogenen Daten, insbesondere meine Gesundheitsdaten, Einsicht nehmen kõnnen, soweit dies fur die Uberprufung der ordnungsgemässen Durchfuhrung der Studie notwendig ist. Fur diese Massnahme entbinde ich den Prufarzt hiermit von der ãrztlichen Schweigepflicht.

2) I am also aware that the authorized and committed to secrecy representative of the study sponsor and the staff of national authorities (the appropriate national oversight authorities, i.e. state or district authorities) or federal authorities and/or representatives of comparable authorities in other countries (within and outside the EU, such as the U.S. Food and Drug Administration [FDA]) can access my personal data, especially my health information, available from the investigator, as far as the review for the carrying out proper study is necessary. For this measure, I hereby absolve the investigator of the physician confidentiality.

3) Die Einwilligung zur Erhebung und Verarbeitung meiner personenbezogenen Daten, insbesondere der Angaben uber meine Gesundheit, ist unwiderruflich. Ich bin bereits daruber aufgeklärt worden, dass ich jederzeit die Teilnahme an dieser klinischen Studie beenden kann. Sollte ich meine Einwilligung in die Verarbeitung meiner Daten schriftlich widerrufen, werden fur die Zwecke der aben genannten

3) The consent to the collection and processing of my personal data, particularly the information about my health, is irrevocable. I'm already been informed that I can stop participating in this clinical trial anytime. Should I withdraw my consent to the processing of my personal data in writing, for the purposes of the clinical trial mentioned no further personal data will be collected and recorded. In the

klinischen Studie keine weiteren personen-bezogenen Daten erfasst und aufgezeichnet. lm Fall eines solchen Widerrufs meiner Einwilligung, an der klinischen Studie teilzunehmen, erklãre ich mich damit einverstanden,
dass die bis zu diesem Zeitpunkt gespeicherten Daten ohne Angabe meines Namens weiterhin verwendet werden durfen, soweit dies erforderlich ist, um
a) Wirkungen des zu prufenden Medikaments festzustellen,
b) sicherzustellen, dass meine schutzwurdigen Rechte nicht beeintrãchtigt werden,
c) der Pflicht zur Vorlage umfassender und vollstãndiger Zulassungsunterlagen zu genugen.

case of such a withdrawal of my consent to participate in the clinical trial, I declare my agreement that the stored data up to this point can still be used without giving my name, to the extent necessary to
a) determine the effects of the study drug,
b) ensure that my legitimate rights are not impaired,
c) satisfy the obligation to provide comprehensive and full registration documents.

4) Mir ist bekannt, dass meine Daten und der ldentifikationsschlussel, der erforderlich ist, um die Studiendaten mit mir in Verbindung zu bringen, bis zu 15 Jahre nach Beendigung oder Abbruch der klinischen Studie aufbewahrt werden, wie es die Vorschriften uber die klinische Prufung von Arzneimitteln bestimmen. Danach werden meine personenbezogenen lnformationen gelõscht, soweit nicht gesetzliche Aufbewahrungsfristen entgegenstehen. Ich weiss, dass nur der Prufarzt und seine Kollegen Zugriff auf den Schlussel haben, der benõtigt wird, um meine Studiendaten mit mir in Verbindung zu bringen.

4) I am aware that my data and identification key, required to associate the study data with me, are kept up to 15 years after completion or termination of the clinical trial as the requirements concerning the clinical trial of drugs specify. Then will my personal information be erased, unless there are statutory retention periods. I know that only the investigators and his colleagues have access to the key, needed to associate my study data with me.

5) Ich bin uber folgende gesetzliche Regelung informiert: Falls ich meine Einwilligung, an der Studie teilzunehmen, widerrufe, mussen alle Stellen, die meine personenbezogenen Daten, insbesondere Gesundheitsdaten, gespeichert haben, unverzuglich prufen, inwieweit die gespeicherten Daten fur die in Nr. 3 a) bis c) genannten Zwecke noch erforderlich sind. Nicht mehr benõtigte Daten sind unverzuglich zu lõschen.

5) I am informed about the following regulation: If I revoke my consent to participate in the study, all places that have my personal data, particularly health data, stored must, and without undue delay, be deleted immediately except the extent to which the stored data are still required for the purposes referred to in No. 3 a) to c).

6) Ich habe das Recht, alle uber mich erhobenen lnformationen sowie die Ergebnisse meiner Untersuchungen oder der Behandlung einzusehen, es sei denn, dies ist aus technischen Grunden nicht lãnger mõglich (d. h. wenn die Daten bereits pseudonymisiert wurden und eine Verbindung zwischen lhren lnformationen und lhrer Person nicht lãnger hergestellt werden kann). Sei fehlerhafter Erfassung personenbezogener Daten habe ich das Recht, eine Korrektur zu verlangen.

6) I have the right to view the information collected about me and the results of my investigations or treatment, unless this is no longer possible for technical reasons (i.e., if the data were already anonymized and a connection between your information and your person can no longer be produced. I have the right to require correction of faulty collection of personal data.

7) Informationen, die Ruckschlusse auf meine Person zulassen, werden spãtestens im Studienbericht pseudonymisiert (d. h., es kann keine

7) Information, that allows conclusions about my person, will be anonymized (i.e., no connection can be made to you) no later than in the study report.



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Verbindung mehr zu lhnen hergestellt werden). Der Abschlussbericht uber die Ergebnisse dieser klinischen Studie darf verõffentlicht, an die zustãndigen Gesundheitsbehõrden in verschiedenen Bundeslãndern weitergeleitet und einer oder mehreren Zulassungsbehõrderi vorgelegt werden.

The final published report about the results of this clinical study may be forwarded to the appropriate health authorities in different countries and submitted to one or more regulatory authorities.

8) Mir ist bekannt, dass der Prufarzt meinen Hausarzt uber meine Teilnahme an dieser klinischen Studie informieren und gegebenenfalls personenbezogene Gesundheitsdaten uber mich einholen wird.

8) I understand that the investigator will inform my personal physician about my participation in this clinical trial and possibly will seek personal health data on me.

Ja Nein

Yes No

(patient signature lines)

(patient signature lines)

Prof. Dr. med. Peter Radke
Universitaetsklinikum Schleswig-Holstein
Medizinische Klinik 2
Ratzeburger Allee 160, 23538 Luebeck Germany

Prof. Dr. med. Peter Radke
Universitaetsklinikum Schleswig-Holstein
Medizinische Klinik 2
Ratzeburger Allee 160, 23538 Luebeck Germany

EINWILLIGUNGSERKLÃRUNG FOR DIE TEILNAHME AN EINER KLINISCHEN STUDIE

CONSENT FORM FOR PARTICIPATION IN A CLINICAL STUDY

Titel des Prufplans: CHAMPION Phoenix: Eine klinische Studie zum Vergleich von Cangrelor mit Clopidogrel als Standardbehandlung bei Patienten, die eine perkutane Koronarintervention benõtigen

Study title:
CHAMPION Phoenix: A clinical trial comparing cangrelor with clopidogrel as a standard treatment in patients requiring percutaneous coronary intervention

Prufplannummer: TMC-CAN-1 0-01

Protocol number: TMC-CAN-10-01

• Ich habe diese Patienteninformation und Einwilligungserklãrung aufmerksam durchgelesen und alles verstanden.

• I have read this patient information and consent form carefully and understood everything.

• Ich wurde uber Wesen, Bedeutung, Risiken und Tragweite dieser klinischen Studie aufgeklãrt.

• I was enlightened about the nature, significance, implications, and risks of this clinical trial.

• Ich hatte Gelegenheit, Fragen zu stellen und alle meine Fragen wurden zu meiner Zufriedenheit beantwortet.

• I had the opportunity to ask questions and all my questions were answered to my satisfaction.

• Ich habe das Recht, die Teilnahme an der klinischen Studie jederzeit ohne Angabe von Grunden zu beenden. In diesem Fall habe ich keine Nachteile zu befurchten.

• I have the right to quit participation in the clinical trial at any time without giving reasons. In this case I have no disadvantages to fear.

• Ich werde die medizinischen Anweisungen fur die Durchfuhrung der klinischen Studie befolgen und meinem Prufarzt auf Anfrage sãmtliche Informationen mitteilen, die fur die klinische Studie erforderlich sind. Ich werde den

I will follow the medical instructions for carrying out the clinical trial and report to my investigator on request complete information that is required for the clinical study. I will inform my investigator immediately about every possible side effect. I am



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Prufarzt unverzuglich uber jede mõgliche Nebenwirkung informieren. Mir ist bewusst, dass ich meine Gesundheit gefãhrde, wenn ich unvollstãndige oder fehlerhafte Angaben mache.

aware that I endanger my health if I provide incomplete or erroneous information.

• Ich habe ein unterzeichnetes und datiertes Exemplar der Patienteninformation und Einwilligungserklãrung fur meine Unterlagen erhalten. Die Versicherungsbedingungen wurden mir ausgehändigt.

• I have received a signed and dated copy of the patient information and consent form for my records. The insurance conditions were delivered to me.

• Ich bestãtige hiermit, dass ich in keinem Abhängigkeitsverhältnis zum Prufarzt und/oder dem Auftraggeber der klinischen Studie stehe.

• I confirm herewith that I am in no dependent relationship with the investigator and/or the sponsor of the clinical trial.

• Ich nehme an dieser klinischen Studie aus freiem Willen teil. Ich kann die Teilnahme auch verweigern.

• I will participate in this clinical trial voluntarily. I can also refuse participation.

• Der Prufarzt wird mich uber neue Erkenntnisse informieren, die sich im Verlauf der Studie ergeben und die Einfluss auf meine Bereitschaft zur Fortsetzung meiner Studienteilnahme haben kõnnen.

• The investigator will inform me about new findings that in the course of the study arise and that can have an impact on my willingness to continue my study participation.

(patient signature lines)

(patient signature lines)

Ich bestãtige hiermit, dass ich dem oben genannten Patienten persõnlich den Zweck, die Dauer und die vorhersehbaren Risiken der klinischen Studie erlãutert und sämtliche Fragen vollstãndig beantwortet habe. Ich bestätige, dass kein Abhängigkeitsverhältnis zwischen dem oben genannten Patienten und mir und/oder dem Auftraggeber der klinischen Studie besteht. Weiterhin erkläre ich, dass ich die Datenschutzbestimmungen entsprechend § 7 (2) und (3) Nr. 15 der GCPVerordnung beachten und einhalten werde.

I confirm herewith that I personally explained to the patient mentioned above the purpose, duration and the foreseeable risks of the clinical trial and I have answered all questions completely. I confirm that no dependent relationship exists between the above referenced patient and myself and/or the sponsor of the clinical trial. Furthermore, I declare that I will observe and comply with the data protection regulations § 7 (2) and (3) No. 15 of GCP-regulation.

(investigator signature lines)

(investigator signature lines)



Reference ID: 3434365

Attachment 8

**From:** Bigby, Barbara [Bigby.Barbara@scrippshealth.org]
**Sent:** Thursday, April 04, 2013 3:48 PM
**To:** Marciniak, Thomas
**Cc:** Robert Bjork Jr MD ; Price, Matthew J. MD
**Subject:** RE: CHAMPION PHOENIX Study

1. CANGRELOR FOR INJECTION INVESTIGATOR'S BROCHURE

| | |
|---|---|
| Edition No. 5, | Replaces Edition No. 4 |
| Release Date: 4 May 2010 | Dated: 19 August 2008 |
| Data Cutoff Date:3 September 2009 | Data Cutoff Date: 23 May 2008 |

2. **Investigational New Drug**

**CANGRELOR**
**A clinical trial comparing cangrelor to clopidogrel standard of care therapy in subjects who require percutaneous coronary intervention:**
**CHAMPION PHOENIX**
**Cangrelor versus standard therapy to achieve optimal management of platelet inhibition**
**Protocol No. TMC-CAN-10-01**
**U.S. IND No. 56,812**
**PROTOCOL VERSION: Amendment 1**
**Amendment to Original Protocol Dated 15 June, 2010**

3. ICF dated 1-25-11, Quest Diagnostics CKMB Manual 08 Sept 2010, Pharmacy Manual 7-Sep-2010, 1572

4. No other information was provided.

5. The Scripps IRB was aware of the closing of the CHAMPION-PCI trial for lack of efficacy, not safety concerns, because Paul Teirstein, MD had participated in that trial at our site. There was a belief at the time that suboptimal study design might have been responsible for cangrelor's apparently poor performance. These discussions took place in 2009 and were not captured in the minutes for the PHOENIX study review.

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**From:** Marciniak, Thomas [mailto:Thomas.Marciniak@fda.hhs.gov]
**Sent:** Thursday, April 04, 2013 9:24 AM
**To:** Bigby, Barbara
**Cc:** Robert Bjork Jr MD ; Price, Matthew J. MD
**Subject:** RE: CHAMPION PHOENIX Study

Thanks. I would like to know the following:

1. The version of the Investigator's Brochure used for the initial IRB approval.
2. The version of the protocol used for the initial IRB approval.
3. What other materials The Medicines Company provided regarding cangrelor for IRB review.
4. Whether The Medicines Company communicated any aspects of the FDA review of the protocol.
5. Any discussion regarding study design or the CHAMPION PCI and PLATFORM results at the IRB meeting, e.g., IRB minutes.

Tom Marciniak

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**From:** Bigby, Barbara [mailto:Bigby.Barbara@scrippshealth.org]
**Sent:** Thursday, April 04, 2013 11:51 AM
**To:** Marciniak, Thomas
**Cc:** Robert Bjork Jr MD ; Price, Matthew J. MD
**Subject:** CHAMPION PHOENIX Study

Dear Mr. Marciniak,

I've attached the original, IRB-approved informed consent form for this study.
Please let us know if you need more information.

*Barbara G Bigby, ALM, CIP*
*Director, Regulatory Services*
*Scripps Clinical Research*
*11025 North Torrey Pines Road, Suite 200*
*La Jolla CA 92037*
*Tel: 858 652-5410; Fax: 858 652-5554*

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**From:** Marciniak, Thomas [Thomas.Marciniak@fda.hhs.gov]
**Sent:** Wednesday, April 03, 2013 12:55 PM
**To:** Bjork, Robert L. MD
**Subject:** IND 56,812 CHAMPION PHOENIX Protocol # TMC-CAN-10-01 informed consent document

I am doing some preliminary checking in preparation for a review of this study. It is possible to get a copy of the informed consent document used at Scripps for this study for comparison to what The Medicines Company has submitted?

Thomas A. Marciniak, M.D.
Medical Team Leader, Cardiovascular & Renal Products
Food and Drug Administration
10903 New Hampshire Avenue
Building 22, Room 4166
Silver Spring, MD 20903-0002
301-796-1118 (voice)
301-796-9841 (fax)

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

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/s/

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THOMAS A MARCINIAK
01/10/2014

# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

**NDA/BLA Number: 204958** **Applicant: The Medicines Company** **Stamp Date: 01 May 2013**

**Drug Name: Cangrelor** **NDA/BLA Type: 505(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. | | | | eCTD |
| 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? | x | | | |
| **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 | | | |
| 11. | Has the applicant submitted a benefit-risk analysis for the product? | x | | | 2.7.4 SCS, page 12 |
| 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)?<br>• Study Number: 1) TMC-CAN-0402; 2) TMC-CAN-08-02<br>• Study Title: 1) The PK and PD of Cangrelor Bolus Plus Infusion in Healthy Volunteers; 2) BRIDGE<br>• Sample Size: 1) n=40 (10/arm); 2) Stage 1: n=11 (5 cohort 1, 6 cohort 2). Stage 2: n=210 (106 Cangrelor arm, 104 Placebo arm)<br>• Arms: 1) 4; 2) Stage 1: 2 sequential cohorts of 5 possible; Stage 2: two parallel arms (Cangrelor, Placebo)<br>• Location in submission: 1) 2.7.2.2.3 linked to | x | | | TMC-CAN-0402 (basis of PCI proposed dose and derived from 2 legacy studies {SC-931-5058; SC-931-5060}) studied 4 arms:<br>1. 15upk bolus + 2upk/min 1 hour infusion<br>2. 30 upk bolus + 4upk/min 1 hour infusion<br>3. dose in 2) followed by PO |



Reference ID: 3332054

| | Content Parameter | Yes | No | NA | Comment |
|---|---|---|---|---|---|
| | 5.3.4.1; 2) 2.7.3 →5.3.4.1 | | | | clopidogrel 600mg<br>4. Clopidogrel 600 followed by dose in 2).<br>BRIDGE trial was a Phase 2 PD dose-finding and dose confirming trial for the bridging indication. |
| **EFFICACY** | | | | | |
| 14. | Do there appear to be the requisite number of adequate and well-controlled studies in the application?<br><br>Pivotal Study #1: CHAMPION PHOENIX (TMC-CAN-10-01)<br>Indication: Reduction of thrombotic events (including stent thrombosis) in patients with CAD undergoing PCI.<br><br>Pivotal Study #2: BRIDGE (Phase 2-TMC-CAN-08-02)<br>Indication: Maintain P2Y12 inhibition in ACS or stented patients who are at increased risk of thrombotic events (such as stent thrombosis) when P2Y12 therapy is interrupted due to surgery. | x | | | Caveat: the BRIDGE trial was under-powered for clinical events. |
| 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 | | • CHAMPION PHOENIX appears adequate and well-controlled.<br>• BRIDGE trial is under-powered for clinical events in support of the proposed "bridge-to-CABG" indication. |
| 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 | | The BRIDGE primary endpoint (i.e. PRU) remains questionable with respect to clinical correlates. |
| 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 | | | 2.7.4 SCS, page 22 |
| **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 arrhythmogenic potential of the product (*e.g.*, QT interval studies, if needed)? | x | | | TMC-CAN-08-01 Thorough QTc study |



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# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

| | Content Parameter | Yes | No | NA | Comment |
|---|---|---|---|---|---|
| 20. | Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product? | x | | | |
| 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 | | | IR sent to applicant with additional terms for AE dataset. |
| 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? | | x | | Following were not provided by Sponsor although requested by Division:<br>• Actual ST event rate from BRIDGE in those patients who discontinued clopidogrel (+/- stent data).<br>• Adjudication dataset to analyze for concordance (IR sent) |
| 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 | | | |
| **ABUSE LIABILITY** | | | | | |
| 29. | If relevant, has the applicant submitted information to assess the abuse liability of the product? | | | 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 |
|---|---|---|---|---|---|
| **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 | | |
| **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 previously by the Division? | x | | | |
| 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? ___yes_____**

If the Application is not fileable from the clinical 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.

Potential review issues are:

- CHAMPION PHOENIX: since the composite endpoint is driven by UDMI-type 4a (associated with PCI) and Stent Thrombosis (ST), the Sponsor should:
  - Provide data on UDMI-type 4b (associated with ST), if available, or explain why such data was not collected and/or provided.
  - Provide data on inter/intra variability of angiographically-driven ST as characterized by the ARC.
  - Provide data on Intra-Procedural Stent Thrombosis (IPST) which drives the ST component endpoint: who defined IPST, validation procedures, relation to ARC definitions pertaining to grades of IPST, confounding variables (i.e. type of stent deployed, length and diameter of stent, stent location, inter/intra variability of angiographically-determined IPST).
  - Provide meeting minutes of all groups (EC, CEC, SC, and DMC) and newsletters as requested by the Division.
- BRIDGE:
  - Bridge is underpowered for clinical events associated with ST and peri-CABG hemorrhage.



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- The Sponsor's explanation in response to the Division's concern about the Verify-Now PRU assay: although there is no correlation between specific biomarker values and clinical risk, thresholds has been identified in the setting where prognostic significance is still evolving (in CTD 2.7.3.1.3.6), may not be sufficient to justify approval for the bridging indication.
- The Division's concern about potential bias in the BRIDGE trial has not been addressed by the Sponsor:
  - There is greater baseline PRU >240 in the placebo group: 47.7% versus 37.6% in the Cangrelor group.
  - There is a significant difference in mean duration of study drug infusion: 75.6 hours in Cangrelor arm, 89.3 hours in placebo arm with corresponding difference in time from infusion start to procedure start in the two arms, thereby creating tendency to bias CV event and hemorrhagic rates in favor of Cangrelor.
- Actual ST event rate from BRIDGE in those patients who discontinued clopidogrel which includes, if possible, data on stent (DES or BMS as well as stent diameter and length), should have been submitted as requested by the Division.

| | |
|---|---|
| Fred Senatore and Nhi Beasley | 6/26/13 |
| Reviewing Medical Officer | Date |
| Tom Marciniak | 6/26/13 |
| Clinical Team Leader | Date |



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

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/s/

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BACH N BEASLEY
06/26/2013

FORTUNATO F SENATORE
06/26/2013

THOMAS A MARCINIAK
06/27/2013
While the PHOENIX study appears to be unethical because of inadequate informed consent, there is a statement of Good Clinical Practice (Item 39 in the checklist). Hence this will be a review issue rather than a refusal to file.