CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204958Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	19 June 2015
From	Stephen M Grant
Subject	Deputy Division Director Summary Review
NDA #	204958
Applicant Name	The Medicines Company
Date of Resubmission	23 December 2014
PDUFA Goal Date	23 June 2015
Proprietary Name / Established (USAN) Name	KENGREAL/ cangrelor
Dosage Forms / Strength	Single-use 10 ml vial containing 50 mg cangrelor as a lyophilized powder for reconstitution
Proposed Indication	Reduction of thrombotic cardiovascular events in patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI) (b) (4)
Recommended Action	Approval

Reviews I reference in this memo are as follows:

Discipline	Reviewers	Dates
Chemistry	Wilson-Lee, Eradiri, Shanks	15 June 2015
Clinical pharmacology	Sabarinath	15 March 2015
Clinical	Senatore, Beasley	19 March 2015, 17 June 2015
Statistics	Zhang	25 March 2015
Scientific Investigations	Gershon	03 March 2015

1. Introduction

Cangrelor is an intravenous platelet P2Y12 inhibitor with a rapid onset and offset of platelet inhibition developed to overcome two problems attendant to the use of oral platelet P2Y12 inhibitors for prevention of thrombotic complications of percutaneous coronary intervention (PCI):

1. Delayed anti-platelet activity: If not administered prior to initiation of PCI, the thienopyridines ticlopidine, clopidogrel and prasugrel will have little anti-platelet activity

while PCI is being performed and shortly thereafter (i.e., at the time when the risk of pathogenic thrombosis is highest) because they are prodrugs requiring metabolic activation to have their effects. The non-thienpyridine ticagrelor, the other commonly used oral platelet P2Y12 inhibitor, does not require metabolic activation and so the onset of its antiplatelet effect is more rapid occurring about an hour after administration.

2. Prolonged anti-platelet activity: The inability to reverse the anti-platelet effects of all currently available oral P2Y12 inhibitors when required, for example, in the event of significant bleeding or need for emergent or urgent coronary artery bypass grafting.

On April 30 2013 The Medicines Company submitted an NDA seeking approval to market cangrelor for two indications:

1. Reduction in the rate of thrombotic events (including stent thrombosis) in patients with coronary artery disease undergoing PCI 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 when oral $P2Y_{12}$ therapy is interrupted due to surgery (hereafter referred to as the "Bridging indication").

The Office of Drug Evaluation 1 sent a letter to the applicant on April 30 2014 declining to approve either indication.

The applicant has submitted a complete response to address the Office's concerns about the first indication. (b) (4)

2. Background

The applicant conducted three trials that were intended to provide substantial evidence of efficacy and safety to support approval for the first 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 PCI to cangrelor followed by a 600 mg dose of clopidogrel, or to clopidogrel alone. The endpoints for all three were composites of death plus various peri-procedural thrombotic events. The first two trials, PCI and PLATFORM, were conducted concurrently and were both stopped early and at the same time for futility. The third trial, PHOENIX, was designed with knowledge of the results of the first two trials. It differed from the first two trials in several important ways:

1. A higher proportion of patients with stable angina could be enrolled. Elevations in post-procedural biomarkers of cardiac myonecrosis are more readily detected in these patients because they have normal levels of biomarkers at baseline. Patients with MI have elevated biomarkers at baseline making it harder to detect further elevation and to differentiate elevations resulting from the procedure than those caused by the MI.
2. A more specific definition for ascertaining peri-procedural myocardial infarction (MI) was used.
3. On average, the subjects were less intensively treated with anti-platelet agents. The eligibility criteria for PHOENIX excluded subjects requiring glycoprotein 2b/3a inhibitors

(GPIs) or who had been pretreated with an oral platelet P2Y12 inhibitor. Investigators could administer 300 or 600 mg of clopidogrel during or after PCI to subjects in the clopidogrel arm.

The sum effect of these changes was to make it easier to detect a beneficial effect of cangrelor in PHOENIX compared to the two previous trials.

The applicant prospectively consulted the Division about the ability of PHOENIX as a single trial to provide sufficient evidence of efficacy to support approval of an NDA. The Division agreed that if successful at a low p-value (< 0.01), it could be sufficient. The Division viewed PHOENIX as sufficiently different from the first two trials so that their failure would not be viewed as impugning a positive result from PHOENIX. Also, the Division did not request two trials successful at $p < 0.05$ because 1) the pharmacology and clinical profile of the drug class is well understood (the first P2Y12 inhibitor was approved for marketing well over two decades ago) and so provides independent evidence of efficacy and 2) clopidogrel reduces the risk of stent thrombosis and superiority to an active control provides strong evidence that a drug is effective. It should be noted that the clopidogrel PI does not include a claim for reduction in the risk of stent thrombosis. However, its pharmacology is sufficiently similar to ticlopidine, which was proven in the Stent Anticoagulation Restenosis Study to substantially reduce the risk of stent thrombosis compared to aspirin alone (OR 0.15, 95% CI 0.03, 0.51), that it has been used for this purpose since the time of its approval in 1997. The Division has previously implicitly accepted that clopidogrel is useful for reducing the risk of stent thrombosis in approving ticagrelor for this indication.

PHOENIX was successful on its prespecified primary endpoint at a p-value of ~ 0.005 but the Office declined to approve because it doubted the clinical relevance. The issues listed in the complete response letter included:

1. Concern that two subcomponents of the primary endpoint, intraprocedural stent thrombosis (IPST) and small post-procedural myocardial infarctions (MIs) identified solely by increases in serum biomarkers of myocardial necrosis, were not events whose avoidance were clinical benefits.
2. Concern about an apparent difference in the outcome of PHOENIX if site-reported events are used for the primary analysis instead of adjudicated events.
3. Concern about the classification of subjects' clinical presentation as ST-elevation MI (STEMI), non-ST elevation acute coronary syndrome (NSTE-ACS), or stable coronary disease and the effect of cangrelor in each presentation type.
4. Concern about the appropriateness of using cangrelor in patients with stable angina. In particular, there was concern about delaying administration of clopidogrel until the time of PCI when it could be given much earlier, which would avoid a 2-hour or more period immediately after PCI of minimal anti-platelet activity.
5. Concern about unlocking of the PHOENIX data base after unblinding.
6. Concern about whether the over-encapsulated clopidogrel administered to clopidogrel subjects in PHOENIX was bioequivalent to clopidogrel approved in the USA.

3. CMC

There were no unresolved CMC issues related to cangrelor remaining from the first review of this NDA but the resubmission included an update to some CMC information. The chemistry reviewers concluded cangrelor continues to be approvable with a 24 month drug product shelf-life. All facility inspections are complete and all are acceptable from a cGMP perspective.

4. Biopharmaceutics

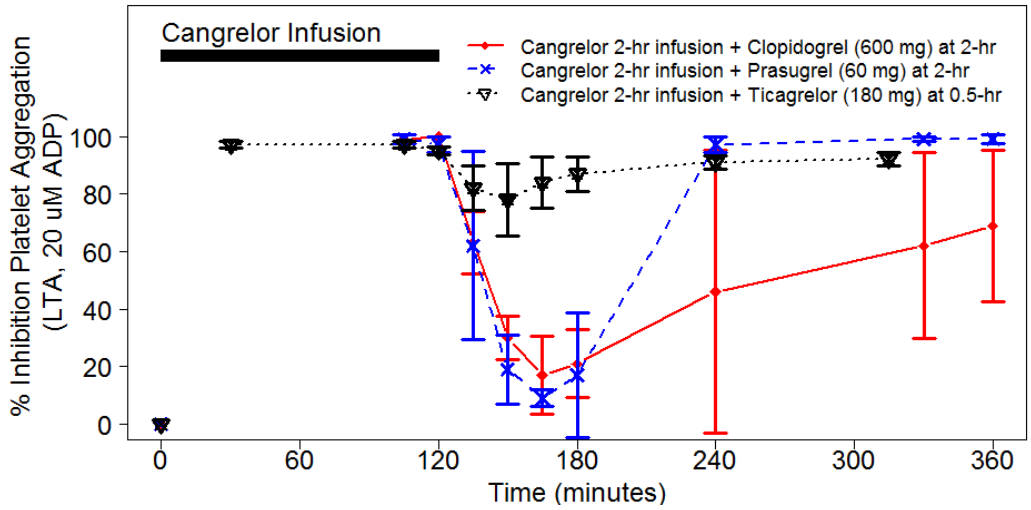
One of the approvability issues identified in the 30 April 2014 CR letter was lack of documentation of bioequivalence of the over-encapsulated clopidogrel administered in CHAMPION-PHOENIX to the US approved clopidogrel product. Dr. Eradiri's review references an earlier review that concluded "This study confirms the validity of using over-encapsulated clopidogrel tablets in other studies to comply with blinding studies requirement."

5. Nonclinical Pharmacology/Toxicology

There were no remaining unresolved pharmacology-toxicology issues remaining from the first review of this NDA and no reviews were performed during this review cycle.

6. Clinical Pharmacology

Dr. Sabarinath performed an addendum clinical pharmacology review. In it he discusses the transition from cangrelor to ticagrelor, prasugrel, and clopidogrel, the currently available oral P2Y12 inhibitors. In PHOENIX all subjects were transitioned to clopidogrel at the end of the cangrelor infusion, which results in a period of a few hours during which platelet activity is minimally inhibited. The pharmacology of clopidogrel as well as prasugrel prevents them from having an effect if administered during infusion of cangrelor and therefore there is an unavoidable increase in platelet aggregation for a few hours if patients are transitioned to either of these drugs after discontinuation of cangrelor. Avoidance of a decrease in platelet inhibition after immediately after discontinuing cangrelor is preferable because there continues to be a significant risk of thrombus formation on the stent. Dr. Sabarinath provides the following figure in his review that nicely summarizes the situation (the horizontal black bar indicates 2 hour-infusion duration for cangrelor and the error bars represent 90 % confidence intervals):



Cangrelor does not interfere with the antiplatelet activity of ticagrelor and so ticagrelor can be administered at any time during administration of cangrelor. Administering ticagrelor prior to discontinuing cangrelor results in the least loss of anti-platelet effect and so should generally be the preferred strategy. Perhaps in a few patients at high risk of bleeding, the risk-benefit favors less inhibition of platelet aggregation in the few hours after discontinuation of cangrelor and so one of the other drugs might be considered. The antiplatelet effect of clopidogrel is less potent and more variable than the other two drugs and has been demonstrated inferior in outcome trials to the other two agents, so it is hard to imagine that is the preferred strategy for any patients except for those at very high risk of bleeding.

I also concur with Dr. Sabarinath's conclusion in the addendum review that the pharmacology of cangrelor and glycoprotein 2b/3a inhibitors (GPIs) suggest that administering cangrelor with a GPI will not add to the effect of the GPI. In PHOENIX subjects who had received a GPI prior to PCI or for whom administration of a GPI was planned based on clinical characteristics and/or coronary anatomy ("upfront" administration) were not eligible to enroll and so there is no outcome data about the utility of co-administration.

7. Clinical Microbiology

There were no remaining unresolved clinical microbiology issues remaining from the first review of this NDA and no reviews were performed during this review cycle.

8. Clinical/Statistical-Efficacy

I generally agree with the assessments of Drs. Beasley, Senatore, and Zhang. I will make a few additional comments about the clinical/statistical issues in the complete response letter

A. Composition 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 two subcomponents, IPST and small peri-procedural MIs detected solely by increases by markers of myocardial necrosis, is unclear.

First, the applicant definition of stent thrombosis included "intraprocedural stent thrombosis" (IPST), which represents an angiographic finding identified during PCI. Stent thrombosis is generally considered to be an event that occurs after completion of PCI. The Division has not previously considered a similar claim and the applicant did not seek the Division's concurrence to its inclusion as a subcomponent of the primary endpoint.[1] The clinical benefit of avoidance of a cath lab event detectable solely by angiography that does not result in any permanent sequelae is unclear.

Second, the clinical import of peri-procedural MIs identified solely by increases in serum biomarkers of myocardial necrosis continues to be controversial in the cardiology community.

[1] Interestingly, one component of the primary endpoint of the ESPRIT trial of eptifibatide in PCI conducted in the late 1990's was need for thrombotic bailout (TBO) with open label eptifibatide for a thrombotic complication of PCI. This trial is mentioned in the eptifibatide label so clearly avoidance of thrombotic complications of PCI has been considered useful by the Division at least one time. It should be noted however that there is no specific claim in section 1 of the eptifibatide label for avoidance of TBO or even stent thrombosis.

The current assays for troponin are so sensitive that up to 30% of patients have elevations after PCI. While increases in post-procedural biomarkers are associated with some increase in risk for subsequent CV events, it is unclear if the minimal amounts of myocardial damage detected by small increases in post-procedural biomarkers cause an increase in subsequent significant CV events (such as heart failure) or are simply a marker for the likelihood of subsequent events.

There were two concerns about the inclusion of IPST and small peri-procedural MIs detected solely by increases in biomarkers in the primary efficacy endpoint. The first concern was the possibility that the positive outcome in PHOENIX was driven by an effect on these events so that the trial would not have established a real clinical benefit for cangrelor. The second concern was about the use of events with little or no clinical import for benefit-risk analysis.

To address these concerns, the Division asked the applicant to perform a sensitivity analysis excluding IPST and small peri-procedural MIs detected solely by increases in biomarkers. The results adapted from the clinical review are shown below:

Endpoint components	**Cangrelor** N=5470	**Clopidogrel** N=5469	**OR (95% CI)**	**p-value**
Death, MI, IDR, ST (primary endpoint)	257 (4.7%)	322 (5.9%)	0.78 (0.66-0.93)	0.005
Death, 'SCAI MI', IDR, ARC-ST (primary endpoint excluding IPST and MI not meeting SCAI criteria)	79 (1.4%)	114 (2.1%)	0.69 (0.52-0.92)	0.011 (nominal)

The sensitivity analysis is quite reassuring that cangrelor has an impact on events whose clinical meaningfulness is not disputed. It excludes 386 events considered not to be important clinical events (about 2/3 of the total primary endpoint events), which would greatly decrease the power to find an effect. Nonetheless the nominal p-value is about 0.01, good enough to have met the Division's prespecified threshold for adequate evidence of efficacy. And the apparent risk reduction as measured by the odds ratio is somewhat greater when including in the analysis only events whose clinical meaningfulness is not disputed, 0.69 vs. 0.78, suggesting that cangrelor's effect on events whose clinical consequences are not disputed is not likely to be smaller than its effect on IPST and small peri-procedural MIs detected solely by increases in biomarkers.

B. Site-reported events vs adjudicated events

The CDTL for the review of this NDA during the first review cycle, Dr. Thomas Marciniak, stated in one of his reviews that performing the primary analysis using the site-reported events of MI and unplanned revascularization in the ITT population (based on checkboxes on the CRF) resulted in a significantly different outcome from the prespsecified primary analysis of adjudicated primary endpoint events (page 5 of his review dated 13 January 2014). His rationale for the utility of this analysis was that investigators would observe and report only the most clinically meaningful events, such as large MIs and acute stent thrombosis resulting in revascularization and so the effect of cangrelor on clinically meaningful events could be more clearly discerned. Further, he asserted that although the protocol specified use of the mITT population (defined as all randomized subjects who received at least one dose of study drug and who underwent PCI) he believed analysis of the ITT population was a better measure of the drug's utility. Dr. Marciniak did not assert that the adjudication process was flawed. He reports that there were 241 "site-reported" events and the analysis of them results in an odds ratio (OR)

of 0.91 with a nominal p-value of 0.5. He concludes that the results of PHOENIX are not "robust."

Reviewer's comment: The difference in odds ratio between the prespsecified primary analysis (0.78) and Dr. Marciniak's analysis (0.91) is not so large that as a single sensitivity analysis among many possible reasonable sensitivity analyses, it seriously impugns the results of the primary analysis. The 95% confidence interval for the prespsecified primary endpoint (0.66, 0.93) includes the point estimate from Dr. Marciniak's analysis. Further, the large nominal p-value reported by Dr. Marciniak is the result of loss of power caused by removal of many of the events included in the primary analysis (p-values for exploratory analyses should always be termed nominal to indicate they are not the result of a prespsecified analysis). Finally, in this trial use of either mITT or ITT for the primary analysis is acceptable. While ITT clearly preserves randomization, very few subjects are excluded from the mITT analysis and most of those did not receive drug and did not undergo PCI because they had no significant coronary stenosis, i.e. exclusion of these subjects did not importantly bias the result.

The Division requested that the applicant perform a sensitivity analysis of the primary endpoint using site-reported events in the ITT population. The applicant's sensitivity analysis of site-reported events in the ITT population resulted in an OR of 0.82 with 95% confidence interval of (0.63, 1.07); similar to the results of the prespsecified primary analysis. The applicant's sensitivity analysis includes 223 events whereas Dr. Marciniak's analysis includes 241 events. Drs. Beasley, Senatore, and Zhang identified and examined the 18 additional events that were included in Dr. Marciniak analysis. For nine events, the CRF boxes for MI and unplanned revascularization were blank because the subjects had withdrawn consent; Dr. Marciniak's includes each in his analysis as a primary endpoint event at 48 hours and death at 30 days. For two more events, the CRF boxes for MI and unplanned revascularization were checked 'no' but the site could not contact them; Dr. Marciniak includes each in his analysis as a primary endpoint event at 48 hours and death at 30 days. Six of the events included Dr. Marciniak's analysis occurred after 48 hours and so did not occur within the timeframe stipulated for the primary analysis. For the final event, the CRF boxes for MI and unplanned revascularization were checked 'no' but the subject was adjudicated as having an event.

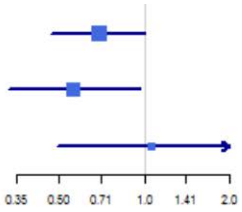
Reviewer's comment: Dr. Marciniak appears to have included events in his analysis that failed to meet his definition of a site-reported event. I conclude there is no demonstrated discrepancy between the prespsecified primary analysis and appropriately conducted sensitivity analyses of site-reported events.

C. Classification of clinical presentation and effect of in STEMI

In the original NDA submission the applicant used information additional to that entered in IVRS at the time of randomization for the purpose of classifying subjects as undergoing PCI for stable coronary disease, NSTE-ACS, or STEMI. This *post hoc* process used some information that was not determined at baseline. The Division objected, believing practitioners at the time they were deciding whether to use cangrelor would have about the same information as did PHOENIX investigators had when the decision was made to enroll the patient. If true, then the classification based on the investigators' assessments, while not necessarily more accurate, was more useful. The applicant eventually concurred with the Division.

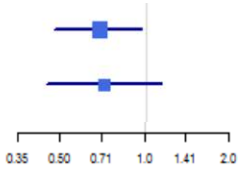
Outcomes in PHOENIX in clinical presentation subgroups classified on information entered in the IVRS are shown below:

Clinical Presentation	Cangrelor	Clopidogrel	HR (95% CI)
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)



The observed outcomes in patients with STEMI are neutral, raising a question about the benefit of cangrelor in this subgroup. In general the best estimate of the treatment effect is in the overall group and not in subgroups and so such analyses should be viewed with a certain amount of suspicion. I conclude that the information available makes it unlikely the effect in cangrelor is different in STEMI patients. First there are relatively few events in the STEMI subgroup so the confidence intervals are wide and overlap the point estimates for the other two groups. Second, the subgroup analysis suggests that the effect is largest in NSTE-ACS, intermediate in stable coronary disease, and minimal in STEMI. However both NSTE-ACS and STEMI share a similar pathophysiology in that both result from coronary thrombosis so it is unlikely the effect of cangrelor in one subgroup would be markedly different from that in the other. Finally, subjects were classified as normal and abnormal for stratification during randomization. To be classified as abnormal a subject had to have ischemic ECG changes or symptoms of cardiac ischemia or elevated biomarkers of cardiac ischemia and so all STEMI and most NSTE-ACS patients were classified as abnormal. That analysis (shown below) demonstrates no heterogeneity and so provides further reassurance.

Subject stratum	Cangrelor	Clopidogrel	HR (95% CI)
Normal	50/3549	73/3524	0.68 (0.47, 0.97)
Abnormal	29/1921	41/1945	0.71 (0.44, 1.15)



D. Utility in Stable Angina

During the first review cycle, the review team questioned whether cangrelor should be used in patients undergoing PCI for reasons other than ACS. As is discussed in the clinical pharmacology reviews of this NDA (and above in this review), the anti-platelet effect of clopidogrel (and prasugrel) is blocked if given while cangrelor is being infused. Therefore clopidogrel (and prasugrel) cannot be given until cangrelor is discontinued, which results in a period of a few hours during which platelet aggregation is minimally inhibited. In stable patients, clopidogrel or prasugrel can be given prior to PCI, achieving maximal platelet inhibition at the time of PCI, avoiding a few hours of minimal anti-platelet activity after cangrelor is stopped.

Nonetheless, I agree with the clinical review team that cangrelor may be useful in the treatment of stable patients undergoing PCI. For a variety of reasons, stable patients in the USA not taking any platelet P2Y12 inhibitor frequently undergo PCI immediately after undergoing coronary angiography. PHOENIX demonstrates that in this situation cangrelor may be useful. The applicant provides an analysis of the occurrence of primary endpoint events during the first few hours of PHOENIX in their advisory committee presentation (CE-53), which is copied below.

Although there are nine more events in the cangrelor subjects compared to clopidogrel subjects for a few hours immediately after discontinuation of cangrelor, there are 59 fewer events during the two hours that cangrelor is being infused. Finally, it is possible to avoid a period of reduced anti-platelet activity immediately after stopping cangrelor by administering ticagrelor during while cangrelor is being infused.

9. Safety

For the PCI indication the only relevant safety issue identified by the clinical reviewers was bleeding. The applicant and the clinical reviewers concur on the following description of the risk of bleeding:

Non-CABG Bleeding up to 48 hours in PHOENIX

	Cangrelor N=5529	Clopidogrel N=5527
Non-CABG bleeds	857 (15.5%)	602 (10.9%)
GUSTO severe or moderate	32 (0.6%)	20 (0.4%)
GUSTO severe	11 (0.2%)	6 (0.1%)
GUSTO moderate	21 (0.4%)	14 (0.6%)
GUSTO mild	825 (14.9%)	582 (10.5%)
TIMI Major or Minor	45 (0.8%)	17 (0.3%)
TIMI Major	12 (0.2%)	6 (0.1%)
TIMI Minor	33 (0.6%)	11 (0.2%)

10. Advisory Committee Meeting

This application was discussed for a second time by the Cardiovascular and Renal Advisory Committee on April 15 2015. The Committee voted 9-2 with one abstention for approval. Committee members who voted against approval expressed a number of concerns:

- PLATFORM and PCI should not be viewed as hypothesis generating but rather as trials similar to PHOENIX; their lack of success should therefore be viewed as weakening the conclusions of PHOENIX
- PHOENIX did not provide strong enough support for efficacy to support approval on the basis of a single trial.
- Because cangrelor was compared to clopidogrel given around the time of PCI, PHOENIX did not provide enough information to inform prescribers in how to use cangrelor. In particular, it left unresolved whether patients would be better served by being preloaded with clopidogrel prior to undergoing coronary angiography or by use of ticagrelor or prasugrel at the time of PCI, as these P2Y12 platelet inhibitors are more potent and work more rapidly than clopidogrel.

Reviewer's comment: I have discussed the first two concerns elsewhere in this memo. The third concern is correct but not determinative. There is inadequate comparative information to make data-driven decisions about which anti-platelets drugs to use and when to administer them for prevention of thrombotic complications of PCI and so, not surprisingly, practice is variable. As a general matter, the Agency recognizes and accepts diverse practices even if there are 'concerns' that one or more might be superior. The Agency does not have the authority to require a sponsor to resolve as part of the development of their drug uncertainties about the use of other drugs approved for the same or a similar indication. The reality is that clopidogrel is not regularly given before PCI, which would make cangrelor unnecessary, and GPIs, which would also make cangrelor unnecessary, are used in a limited number of patients. There are no definitive data that these practices are harmful.

11. Pediatrics

DCaRP previously 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 indication sought by the applicant would not be feasible.

12. Other Relevant Regulatory Issues - Unlocking of PHOENIX Database after Unblinding

The database for PHOENIX was initially locked and unblinded on January 4 2013. It was then discovered that 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 generated paper CRFs for these subjects and distributed them to the 84 sites. These were returned, the database was unlocked from February 1 2013 to February 18 2013 to allow entry of these data, and the database was again locked. The applicant indicated in the original NDA

submission that this process was conducted in accordance with a "documented agreement among the Sponsor's data management team, biostatistician, and study management team."

The Division requested documentation that the unlocking of the database did not result in any other changes to the database. Both OSI and clinical reviewers examined the applicant's response in the resubmission and concluded that the integrity of data is well documented and so reliable enough to be used to support the application

13. Labeling

A. Indication

Cangrelor should be indicated solely for patients who have not been administered either a loading dose of, or who are not chronically taking an oral $P2Y_{12}$ receptor inhibitor. It should also not be indicated for patients who have been administered a glycoprotein 2b/3a receptor inhibitor (so-called upstream use) (b) (4) because co-administration of cangrelor is unlikely to add an important increment to the anti-platelet effects of a GPI.

B. Dosing

The label should stipulate the time of administration and expected time course of platelet inhibition when any of the three widely-used oral P2Y12 platelet inhibitors are administered after cangrelor. In particular, the label should instruct that use of either thienopyridine should be delayed until termination of cangrelor infusion and therefore there will a period of two hours during which there will be minimal anti-platelet activity. Use of ticagrelor obviates this period of little anti-platelet activity.

C. Pharmacokinetics

The label should provide prescribers information to help them choose an appropriate oral P2Y12 platelet inhibitor to administer after cangrelor is terminated. A figure with the expected time course of inhibition of platelet aggregation after administration of ticagrelor, prasugrel, or clopidogrel should be included.

D. Clinical Studies

The label should disclose the results of the primary endpoint of PHOENIX but should not include the sensitivity analyses submitted by the applicant in the re-submission. These *post hoc* sensitivity analyses were useful to support the primary analysis, but should not be used to supplant it

14. Decision /Risk Benefit Assessment

A. Risk Benefit Assessment

I concur with the clinical reviewers' benefit-risk assessment, which compares the number of large MIs, ischemia driven coronary revascularizations, and conventionally-defined stent thromboses prevented (35) by cangrelor in PHOENIX with the number of GUSTO severe and moderate bleeds caused (12). Simply subtracting the latter from the former results in a positive number (23). The benefit in a trial of over 10000 subjects is not large but is positive.

B. Recommended Regulatory Action

Approval.

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

/s/

STEPHEN M GRANT
06/19/2015