



FDA Briefing Document Addendum for the Cardiovascular and Renal Drugs Advisory Committee (CRDAC)

Meeting Date: 12 February 2014

NDA: 204958

Applicant: The Medicines Company

Drug: Cangrelor Injection

Proposed Indications: **PCI** - Cangrelor is a P2Y₁₂ 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)

Bridging - Cangrelor is indicated to 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

Title of Studies: **PHOENIX** - A randomized, double-blind, parallel group, superiority study comparing cangrelor to clopidogrel in subjects who require PCI. The primary objective was to demonstrate that cangrelor reduces the risk of a composite of all-cause mortality, myocardial infarction, ischemia driven revascularization, and stent thrombosis compared to clopidogrel.

BRIDGE – A randomized, double-blind, placebo-controlled study comparing administration of cangrelor to placebo in patients who had discontinued clopidogrel prior to coronary artery bypass grafting (CABG), attempting to maintain platelet inhibition until shortly before CABG. The primary efficacy endpoint was the proportion of subjects with P2Y₁₂ Reaction Units (PRU) < 240 measured by the VerifyNow P2Y₁₂ Test device during the entire period prior to CABG. The trial demonstrated that intravenous cangrelor at a dose of 0.75 µg/kg/min for several days consistently maintained platelet P2Y₁₂ inhibition at PRU < 240.

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the cangrelor New Drug Application (NDA) to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

This document is based on the applicant's information as submitted up to 10 January 2014.

Table of Contents

Draft Points to Consider

Addenda to the FDA CRDAC Briefing Book

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research

Meeting of the Cardiovascular and Renal Drugs Advisory Committee (CRDAC)

FDA White Oak Campus, Building 31, the Great Room (Rm. 1503)
White Oak Conference Center, Silver Spring, Maryland
February 12, 2014

DRAFT POINTS TO CONSIDER

The Advisory Committee will consider the approvability of cangrelor, an intravenous antagonist of the platelet P2Y₁₂ receptor, for two uses: (1) the reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with coronary artery disease undergoing percutaneous coronary intervention (PCI) and (2) to 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 for surgery (the “bridging” indication). Cangrelor and clopidogrel have similar platelet antagonist activities. Cangrelor works promptly; clopidogrel’s action is more delayed. Cangrelor’s inhibitory activity disappears rapidly when it is stopped; in contrast, clopidogrel’s activity is prolonged after its discontinuation.

The applicant conducted three large outcome trials relevant to the PCI indication: CHAMPION PCI, CHAMPION PLATFORM, and CHAMPION PHOENIX. These differed in the population studied and the timing and precise nature of treatments. The CHAMPION PLATFORM trial compared cangrelor to placebo during PCI, and the CHAMPION PCI trial compared cangrelor to clopidogrel during PCI. The primary efficacy endpoint in both of these trials was the composite of all-cause mortality, myocardial infarction (MI), and ischemic driven revascularization (IDR) at 48 hours. These two trials failed to demonstrate superior efficacy against their respective control arms. Post-hoc analyses of these two trials generated a hypothesis that the efficacy of cangrelor was manifested during PCI, but this was masked by evolving pre-PCI biomarker MIs. The post-hoc analysis also noted that cangrelor appeared to be effective in reducing the incidence of stent thrombosis (ST). Consequently, the CHAMPION PHOENIX trial, comparing cangrelor to clopidogrel (loading dose either 300 mg or 600 mg), was designed to evaluate MIs and ST during PCI in subjects who did not have pre-PCI evolving biomarker MIs and had not been treated with oral P2Y₁₂ inhibitor therapy for at least 7 days prior to randomization. The primary endpoint in PHOENIX was the composite of all-cause mortality, MI, IDR, and ST at 48 hours post-PCI. In this trial, the MI component of the primary endpoint was based on the Universal Definition of MI (UDMI). PHOENIX did show superior efficacy of the cangrelor regimen compared to the clopidogrel regimen by the applicant’s adjudicated endpoint (odds ratio 0.78; 95% confidence interval 0.66-0.93, p=0.005). All three trials showed increased bleeding rates with the cangrelor regimen.

The applicant submitted one pharmacodynamic study specifically supporting the bridging indication: the BRIDGE trial. The BRIDGE trial demonstrated that a cangrelor infusion could maintain platelet inhibition similar to that achieved with clopidogrel. BRIDGE was too small (210 subjects) to assess an efficacy benefit.

Regarding the PCI indication

1. Concern with the CHAMPION study results does not relate primarily to whether the study demonstrated the effect claimed, but to whether the results suggest an actual benefit in any defined population. In particular, the review team questions whether CHAMPION studies demonstrated anything beyond that delaying clopidogrel administration is disadvantageous. In PLATFORM, where clopidogrel administration was delayed until after PCI, deaths and stent thrombosis were significantly greater in the clopidogrel arm. The efficacy endpoints in all three trials appear to correlate with the timing of clopidogrel administration relative to start of PCI. In PHOENIX, earlier administration of clopidogrel is associated with better efficacy. Given the reasons for using cangrelor and the recognized delayed effect of clopidogrel, the question is whether such delayed use of clopidogrel is reasonable. It will be important to look at current recommendations about when to start clopidogrel.

FOOD AND DRUG ADMINISTRATION
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DRAFT POINTS TO CONSIDER (cont.)

2. The review team notes the discrepant results for different types of MI. The primary endpoint rate at 48 hours in the stable angina subgroup of PHOENIX was about 6 percent. The results of the PHOENIX trial were driven by Type 4a MI (primarily small increases in biomarker) and intraprocedural stent thrombosis.
3. The review team questions to whom the PCI results apply. The results were driven by subjects presenting with stable angina while the clinical need is greatest in STEMI.

Regarding the Bridging Indication

4. The review team questions whether the demonstrated effect on the surrogate is persuasive support for the bridging indication. The BRIDGE study used platelet activity units measured using VerifyNow[®], although the applicant has also studied cangrelor using other platelet aggregation inhibition assays.
5. A critical question is whether available data adequately define the risks and benefits in the bridging indication. BRIDGE had more bleeds in the cangrelor group than in the placebo group pre-CABG (about 2% vs. 1% for GUSTO severe/life-threatening bleeds and 10% vs. 4% for GUSTO moderate bleeds.) On the other hand, BRIDGE had fewer ischemic events (death/MI/ischemia driven revascularization/stroke) in the cangrelor group than in the placebo group pre-CABG (about 3% vs. 4%).



DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

NDA: 204958
Drug: Cangrelor
Applicant: The Medicines Company
Proposed Indication: PCI

Cangrelor for injection is an intravenous (IV) P2Y₁₂ 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 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 [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*

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

Benefit-risk of Cangrelor

- 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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