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Testimony before the FDA's Cardiovascular and Renal Drugs Advisory Committee Regarding New Drug Application (NDA) 204958 for KENGREAL (Cangrelor) for Injection

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I am Dr. Michael Carome, Director of Public Citizen's Health Research Group. I have no financial conflicts of interest.

Public Citizen strongly opposes approval of the NDA for cangrelor injection for reduction of thrombotic cardiovascular events in patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI) who have not received an oral $P2Y_{12}$ inhibitor prior to the PCI procedure and in whom oral therapy with $P2Y_{12}$ inhibitors is not feasible or desirable. We oppose approval because many subjects in the active-comparator control group for the CHAMPION PHOENIX trial (PHOENIX trial) — the lone trial upon which approval would be based — received substandard antiplatelet management, and as a result, the trial failed to provide substantial evidence that cangrelor is superior, or even noninferior, to clopidogrel, appropriately administered, in patients undergoing PCI.

The fact that the proposed PCI indication for cangrelor has been narrowed substantially from the one considered by this committee in February 2014 represents a tacit acknowledgement by the sponsor that the PHOENIX trial failed to demonstrate superiority to appropriately administered clopidogrel.

We also remain disturbed by the apparent ethical lapses that occurred in the conduct of the CHAMPION trials. Given the study design, there was a failure to ensure that risks to control subjects were minimized and the consent forms for the trial appear to have failed to adequately describe the nature and risks of the control group interventions relative to usual or recommended antiplatelet care.

Failure to Demonstrate Effectiveness of Cangrelor for PCI

The sponsor initially conducted, concurrently, two large, randomized, double-blind, "active-controlled" trials comparing cangrelor infusion initiated before PCI followed by clopidogrel 600 mg loading to clopidogrel 600 mg bolus administered either before (CHAMPION PCI) or after the PCI procedure (CHAMPION PLATFORM). CHAMPION PCI enrolled predominantly subjects with acute coronary syndromes (ACS), including non-ST elevation MI or unstable angina (74%) or ST elevation MI (11%).[1] CHAMPION PLATFORM enrolled almost exclusively subjects with non-ST elevation ACS (95%).[2] Both trials failed to meet their primary efficacy endpoints (composite of death from any cause, MI, or ischemia-driven revascularization at 48 hours). (See tables 1 and 2 below.)

[1] Harrington RA, Stone GW, McNulty S, et al. Platelet inhibition with cangrelor in patients undergoing PCI. *N Engl J Med*. 2009;361(24):2318-2329.
[2] Bhatt DL, Lincoff M, Gibson CM, et al. Intravenous platelet blockade with cangrelor during PCI. *N Engl J Med*. 2009;361(24):2330-2341.

Table 1. CHAMPION PCI Primary Endpoint Data (mITT)[3]

Cangrelor N=3889	Clopidogrel N=3865	Odds Ratio (95% CI)	P value
290 (7.5%)	276 (7.1%)	1.05 (0.88-1.24)	0.59

Table 2. CHAMPION PLATFORM Primary Endpoint Data (mITT)[4]

Cangrelor N=2654	Clopidogrel N=2641	Odds Ratio (95% CI)	P value
185 (7.0%)	210 (8.0%)	0.87 (0.71-1.07)	0.17

While the ideal time for administration of clopidogrel in the context of a PCI procedure has not been precisely defined, an analysis of the CHAMPION PCI and PLATFORM trials by the FDA Medical Team Leader for the prior NDA submission strongly suggests that administration of clopidogrel after PCI is worse than administration before PCI.[5]

The PHOENIX trial was conducted from September 2010 to November 2012. The subjects for the PHOENIX trial included 11,145 adults undergoing PCI for stable angina (58%), non-ST-segment-elevation ACS (26%), or ST-segment-elevation myocardial infarction (MI) (16%).[6] Although this trial met the sponsor's primary efficacy endpoint, the conduct of the trial was seriously flawed because of deficiencies in the delivery of control group interventions, including:

- inappropriate timing of clopidogrel administration;
- inappropriate dosing of clopidogrel;
- protocol-specified prohibition against use of other antiplatelet drugs known to be superior to clopidogrel for patients with ACS undergoing PCI (prasugrel and ticagrelor); and
- protocol-specified restriction on the use of glycoprotein IIb/IIIa inhibitors to bailout use only.

As a result of these deficiencies, a substantial number of control subjects received either substandard or no antiplatelet interventions with a $P2Y_{12}$ inhibitor during the PCI procedure itself.

There was also an imbalance in the loading dose of clopidogrel between the two study groups.

None of the sensitivity analyses presented in the resubmitted NDA for cangrelor make these flaws in the timing and dosing of clopidogrel in the control group subjects go away.

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[3] Harrington RA, Stone GW, McNulty S, et al. Platelet inhibition with cangrelor in patients undergoing PCI. *N Engl J Med*. 2009;361(24):2318-2329.

[4] Bhatt DL, Lincoff M, Gibson CM, et al. Intravenous platelet blockade with cangrelor during PCI. *N Engl J Med*. 2009;361(24):2330-2341.

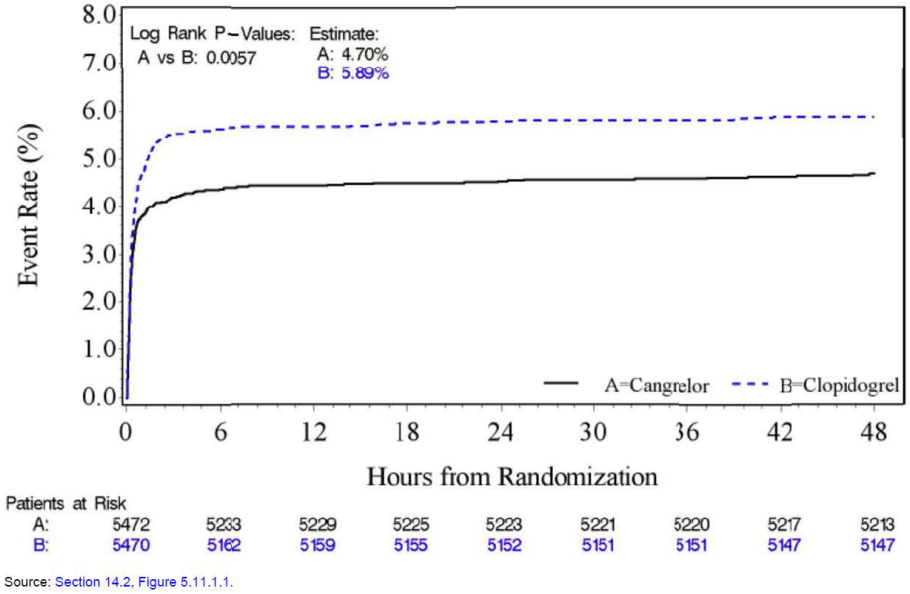
[5] Food and Drug Administration. FDA Briefing document for the Cardiovascular and Renal Drugs Advisory Committee meeting on February 12, 2014. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM385234.pdf. Accessed April 14, 2014. PDF pages 21-23.

[6] Food and Drug Administration. FDA Briefing document for the Cardiovascular and Renal Drugs Advisory Committee meeting on February 12, 2014. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM385234.pdf. Accessed April 14, 2014. PDF page 78.

Timing of study drug interventions

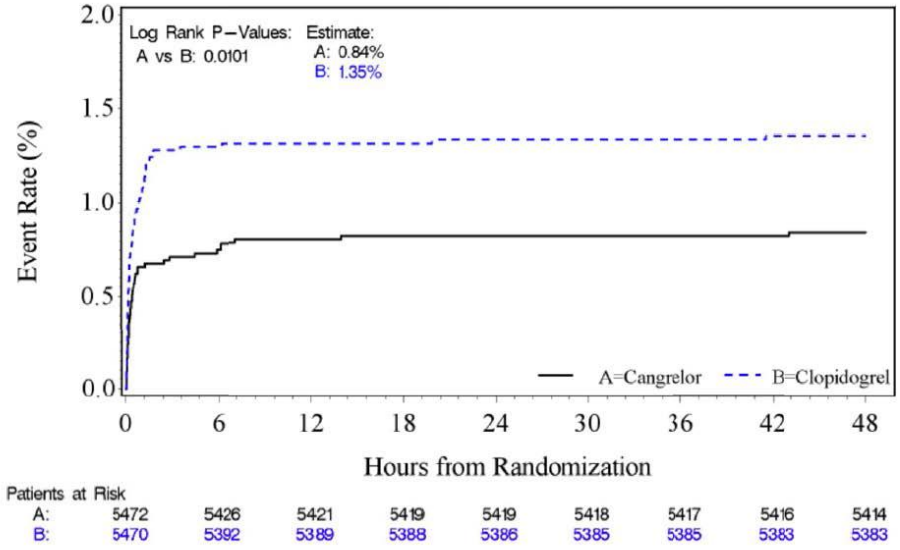
The Kaplan-Meier plots to first occurrence of the primary efficacy endpoint (composite of death from any cause, MI, ischemia-driven revascularization, or stent thrombosis) within 48 hours (Figure 1) and to the first occurrence of the key secondary endpoint, stent thrombosis (ST) within 48 hours (Figure 2) in the modified intention-to-treat (mITT) population demonstrate that the divergence between the curves for the cangrelor and control subjects occurs within one to two hours post randomization. This is a time period when PCI occurred and when many control subjects had not received adequate anti-platelet intervention.

Figure 1. CHAMPION PHOENIX Kaplan-Meier Plot to first occurrence of the primary efficacy endpoint within 48 hours (mITT Population)[7]



Source: Section 14.2, Figure 5.11.1.1.

Figure 2: CHAMPION PHOENIX Kaplan-Meier Plot to first occurrence of ST within 48 hours (mITT Population) [8]



Source: Section 14.2, Figure 5.51.1.1.

[7] *Ibid*. PDF page 87.
[8] *Ibid*. PDF page 87.

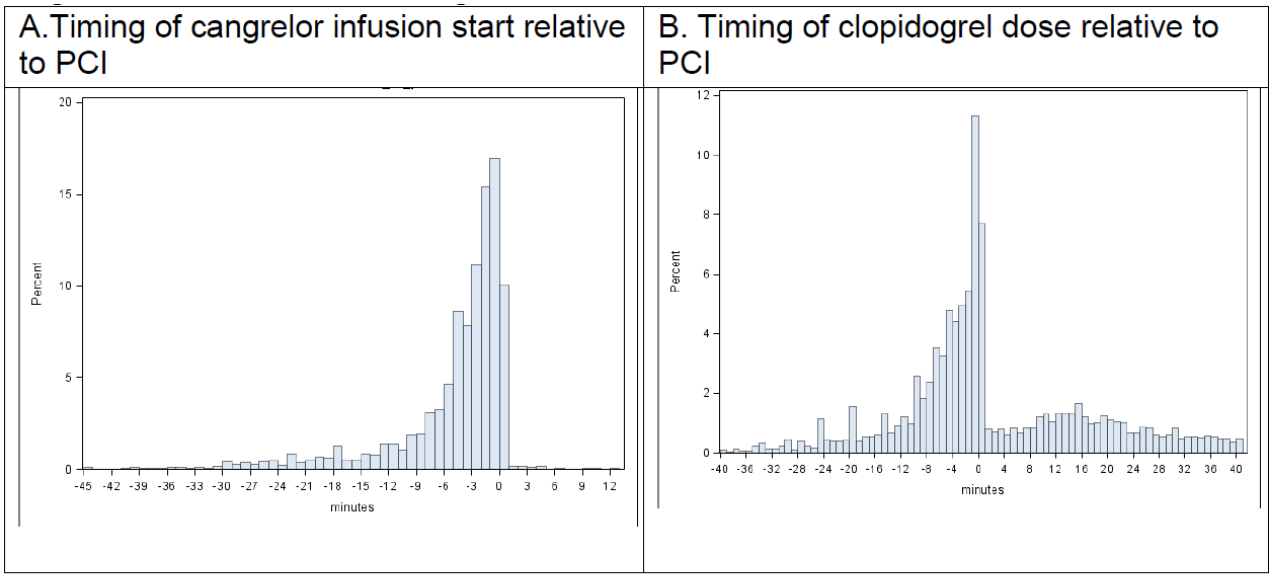
These observations highlight the importance of assessing the adequacy of the anti-platelet interventions in the PHOENIX trial during and immediately after the PCI procedure, a time when most of the primary endpoint events occurred.

The FDA Medical Team Leader who conducted the review of the prior NDA submission noted the following regarding the administration of clopidogrel to control subjects:[9]

> For about 32% of the patients the first oral study drug was administered **after the completion of the PCI**. [Emphasis added]
>
> *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.* [Emphasis in original]

Data comparing timing of active drug administration to cangrelor subjects and control (clopidogrel) subjects overall and for each subject subgroup based on presenting clinical syndrome are shown in Figures 3-6.

Figure 3. Start to active drug relative to PCI, all subjects[10]



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.

[9] *Ibid*. PDF page 15.
[10] *Ibid*. PDF page 121.

Figure 4. Start to active drug relative to PCI, stable angina subjects[11]

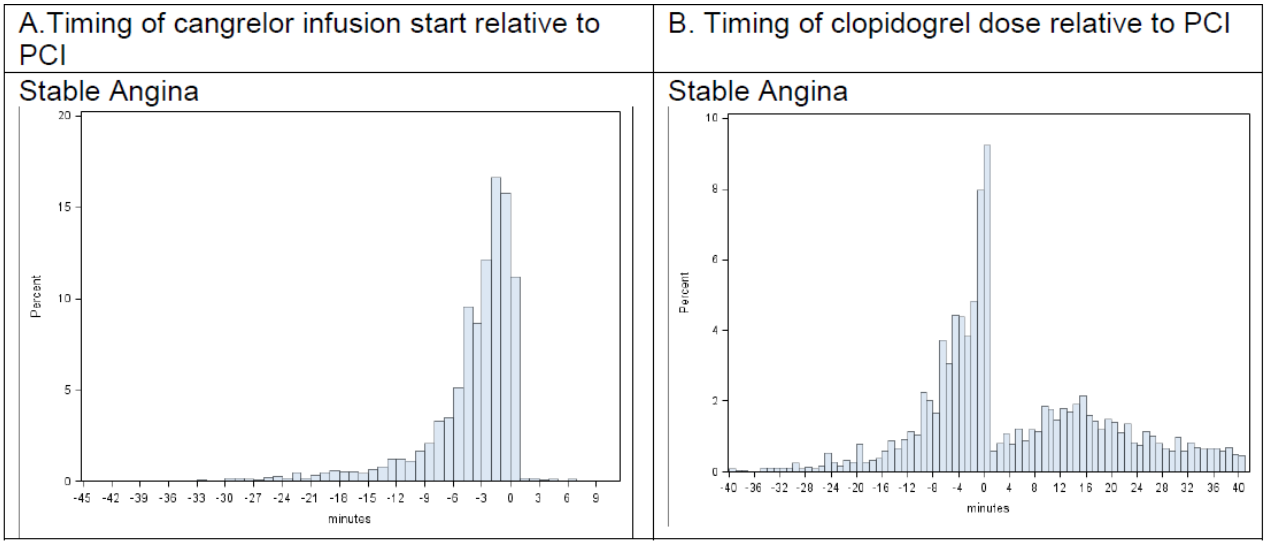
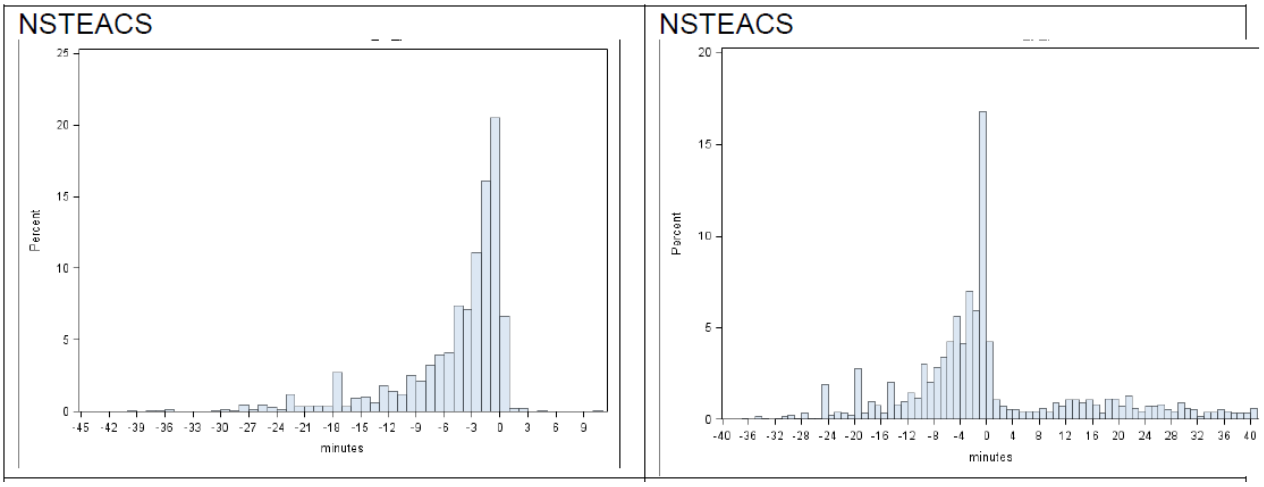
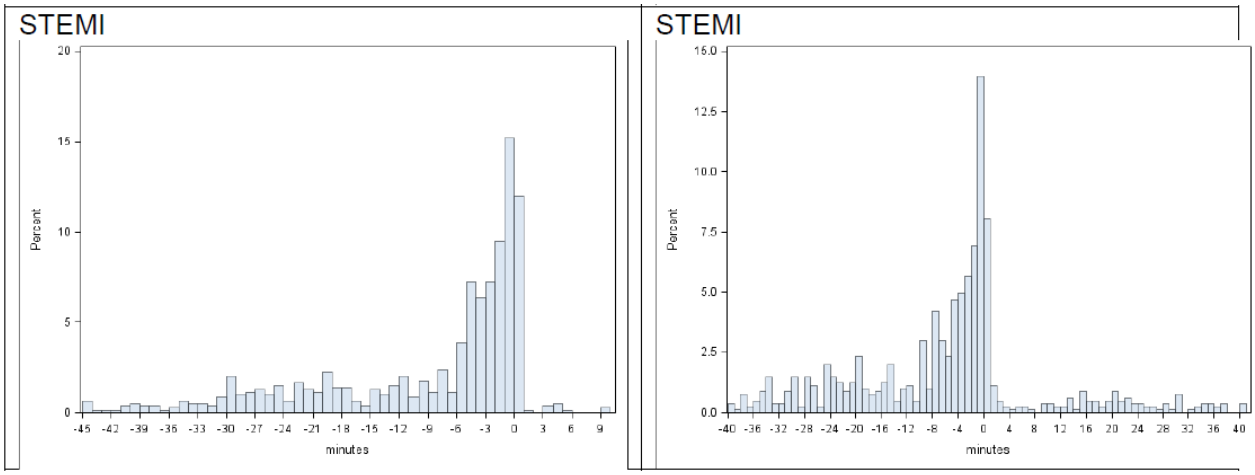


Figure 5. Start to active drug relative to PCI, non-ST-segment elevation acute coronary syndrome subjects[12]



[11] *Ibid*. PDF page 121.
[12] *Ibid*. PDF page 122.

Figure 6. Start to active drug relative to PCI, ST-segment elevation myocardial infarction subjects[13]



Thus, disturbingly, the cangrelor-group subjects received a rapidly acting $P2Y_{12}$ inhibitor at an earlier time point on average — in almost all cases prior to the start of PCI — whereas the control subjects received an oral, delayed-onset $P2Y_{12}$ inhibitor at a later time point on average and, in many cases, after the PCI procedure.

Why did the site investigators not have discretion on the timing of starting the cangrelor infusion, before versus after the start of the PCI procedure? The investigators no doubt understood that earlier anti-platelet therapy with cangrelor would provide the most benefit. There is no reason to believe that giving clopidogrel as early as possible pre-PCI would have been more harmful compared to giving it after PCI, and earlier administration could only have improved the chances for benefit. Thus, the delay in administration of clopidogrel until after the PCI disadvantaged many control group subjects.

The FDA clinical reviewers for the prior NDA submission made the following comments regarding the timing of active drug administration:[14]

> *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.* [Emphasis in original]

Given the difference in the pharmacodynamics and the timing of the administration of the initial active agent given to the cangrelor and control subjects, it is highly plausible that the differences in study outcomes can be explained by the inadequate antiplatelet intervention provided to the control subjects.

Dosing of clopidogrel

Regarding the dosing of initial loading dose of clopidogrel in both groups, nearly all of the cangrelor subjects received a 600 mg dose of clopidogrel as a transition dose, whereas as only 74 percent of control

[13] *Ibid*. PDF page 122.
[14] *Ibid*. PDF page 122.

subjects received such an initial dose, with 26 percent receiving a lower, 300 mg dose.[15] The FDA statistical reviewer for the prior NDA submission noted the following regarding this difference:[16]

> [T]here was an imbalance on the actual loading dose between two treatment groups in the study. … If the intended loading dose in the primary analysis was replaced by the actual loading dose in the model, the treatment effect would not be statistically significant anymore. The p-value increased from 0.005 to 0.088. Although the treatment effect of cangrelor was still trending in the right direction when compared with clopidogrel patients who had 600 mg loading dose, the results seemed to be driven by the comparison with the patients given 300 mg clopidogrel loading dose.

The FDA in its briefing document for this meeting attempts to discount the notion that clopidogrel should have be given before PCI rather than after in the PHOENIX trial. The FDA claims that "there are no firm guidelines regarding the optimal timing of $P2Y_{12}$ therapy relative to PCI, and the timing of clopidogrel in the PHOENIX trial was within the variability of the treatment paradigm."[17] Three points should be considered when weighing this claim:

First, the FDA was fully aware of the PHOENIX trial design and allowed it to proceed and, therefore, has an interest in defending that the trial design was ethical.

Second, some contemporaneous guidelines at the time the trial was conducted recommended administration of $P2Y_{12}$ therapy as soon as possible in patients with non-ST-elevation ACS.[18]

Third, the FDA offers the results of the ACCOAST trial as evidence that a pretreatment strategy with a $P2Y_{12}$ inhibitor may not be optimal. The ACCOAST trial randomized 4,033 non-ST-segment elevation MI patients to pretreatment with prasugrel 30 mg before angiography versus placebo. The pretreatment arm received an additional 30 mg and the placebo arm received 60 mg at the time PCI was performed. Pretreatment was not superior to post-angiography, pre-PCI treatment for the primary composite endpoint at day 7 of death, MI, stroke, urgent revascularization, or glycoprotein IIb/IIIa inhibitor rescue therapy (HR with pretreatment 1.02, 95% CI 0.84-1.25; p=0.81).[19] Importantly, the ACCOAST trial findings cannot be extrapolated to the timing of clopidogrel dosing because prasugrel is a faster, better platelet inhibitor than clopidogrel.

Contemporaneous statements by PHOENIX co-principal investigators about clopidogrel timing and dosing

Comments made by Drs. Deepak Bhatt and Robert Harrington, the co-principal investigators for the PHOENIX trial, about clopidogrel dosing before the start of the trial are quite revealing.

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[15] *Ibid*. PDF page 122.
[16] *Ibid*. PDF page 211.
[17] Food and Drug Administration. FDA Briefing document for the Cardiovascular and Renal Drugs Advisory Committee meeting on April 15, 2015. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM442199.pdf. Accessed April 14, 2015. PDF page 32.
[18] Food and Drug Administration. FDA Briefing document for the Cardiovascular and Renal Drugs Advisory Committee meeting on February 12, 2014. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM385234.pdf. Accessed April 14, 2014. PDF pages 271-273.
[19] Montalescot G, Bolognese L, Dudek D, et al. Pretreatment with prasugrel in non-ST-segment elevation acute coronary syndromes. *N Engl J Med*. 2013;369:999-1010.

In a November 15, 2009 interview with *Heartwire from Medscape*, Dr. Bhatt was quoted as follows regarding the CHAMPION-PCI and CHAMPION-PLATFORM trials:[20]

> "CHAMPION-PCI was testing cangrelor vs clopidogrel with both being given up front, whereas CHAMPION-PLATFORM was testing cangrelor up front vs delayed clopidogrel."
>
> Bhatt noted that there was a "more robust" effect of cangrelor on secondary end points in the CHAMPION-PLATFORM trial, where the new IV drug was being compared with placebo up front, than in the CHAMPION-PCI, where it was pitted against clopidogrel up front. "Although these observations must be thought of as hypothesis-generating, **there were significant reductions in death and stent thrombosis in the cangrelor group vs the placebo group in CHAMPION-PLATFORM that I believe are real. This strongly supports the strategy of earlier antiplatelet therapy. It confirms that such therapy should be given before the procedure rather than after.**" [Emphasis added]
>
> Asked if anyone was still actually waiting until after PCI to give antiplatelet agents, Bhatt said he believed some people were. "If you ask the experts, they will all tell you to give antiplatelet therapy up front before the PCI procedure. But if you look at what is actually going on, many interventionalists are giving clopidogrel after the procedure, even now in 2009, in ACS patients. This is probably just for practical reasons--the patient is flat on his back in the cath lab or may be sedated and groggy, so it is difficult to give pills at the beginning. **But for me, the CHAMPION-PLATFORM trial reinforces that we need to get the antiplatelet therapy on board as soon as possible.**" [Emphasis added]

Dr. Harrington, at the July 28, 2010, meeting of the Cardiovascular and Renal Drugs Advisory Committee regarding the NDA for ticagrelor, stated the following regarding the design of the phase 3 PLATO study, which compared ticagrelor to clopidogrel in patients with ACS:[21]

> "Unlike some other trials, which identified patients in the cath lab, in a more PCI-oriented approach, we were interested in studying ticagrelor at the point of entry, when they met up with their clinicians and decisions were being made about how to employ dual anti-platelet therapy. …
>
> "[D]ual anti-platelet therapy in all settings of acute coronary syndrome has been given a Class I weight of evidence A by both the American and European professional societies in our guidelines. We, therefore, were interested in understanding the role of ticagrelor upstream, if you will, before decisions had been made to proceed to the cath lab, before decisions had been made to proceed to revascularization based on a knowledge of coronary anatomy. …
>
> "The second important point that I'd like to highlight on this slide is that this is an active-control trial. The clopidogrel, as you've heard, has been given a 1A recommendation, and so we wanted to compare ticagrelor with the standard. And if we were going to compare it with the standard, the steering committee felt very strongly that we needed to give the standard the best chance possible.

[20] Hughes S. CHAMPION: Negative trials but some positive angles for cangrelor? *Heartwire from Medscape*. November 15, 2009. http://www.medscape.com/viewarticle/712388. Accessed April 13, 2015.
[21] Food and Drug Administration. Transcript of the July 28, 2010, meeting of the Cardiovascular and Renal Drugs Advisory Committee. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM223579.pdf. Accessed April 14, 2015. PDF pages 36-38.

> "So we did a couple of things which were different in PLATO than some other contemporary trials. First off, we allowed patients into the trial who had been on chronic clopidogrel. Secondly, we allowed patients to have received clopidogrel prior to randomization, because in many hospitals, that's part of the algorithm of care. They see their emergency room physician, they have acute chest pain, they receive clopidogrel in the emergency room. We did not want to exclude those patients. We allowed those patients in the trial; much different than some other contemporary trials.
>
> "Third, we wanted to give the comparator the best chance in terms of dosing. Now, the recommendation in the label for clopidogrel dosing is a 300 milligram loading dose, but **the guidelines in both the United States and Europe for the use of clopidogrel in the peri-PCI period includes an additional loading dose, where patients may get 600 or even 900 milligrams of clopidogrel prior to percutaneous revascularization. We designed the trial to incorporate all of that, again, to give the comparator a fair test.**" [Emphasis added]

In contrast to the PLATO trial, the clopidogrel comparator in the PHOENIX trial was not given a fair test.

Protocol-specified restriction on the use of glycoprotein IIb/IIIa inhibitors

Another flaw in the design of the PHOENIX trial was the protocol-specified restriction on the use of glycoprotein IIb/IIIa inhibitors.

The FDA reviewers in their briefing document for this meeting noted the following regarding the use of glycoprotein (GP) IIb/IIIa inhibitors:[22]

> 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. …
>
> **The data from the antecedent CHAMPION trials suggest that common practice would deploy [GP IIb/IIIa inhibitors] at a much higher incidence than that seen in PHOENIX**, as well as in the PCI and PLATFORM trials post-amendment. …[Emphasis added]
>
> 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 [GP IIb/IIIa inhibitors] were enrolled in PHOENIX, the rate of use probably would have been much higher and the outcome of the trial might have been different.** [Emphasis added]

The problems regarding the design of the CHAMPION PHOENIX trial were recognized by the authors of an editorial in the *New England Journal of Medicine* that accompanied the initial publication of the study results on April 4, 2013. In their editorial, Drs. Richard Lange and L. David Hillis noted the following:[23]

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[22] Food and Drug Administration. FDA Briefing document for the Cardiovascular and Renal Drugs Advisory Committee meeting on April 15, 2015. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM442199.pdf. Accessed April 14, 2015.. PDF pages 36-37.

[23] Lange RA, Hillis LD. The duel between dual antiplatelet therapies. *N Engl J Med*. 2013;368(14):1356-1357.

> Where does cangrelor fit in the armamentarium of dual antiplatelet therapy? Unfortunately, the study by Bhatt et al. does not answer this question definitively. In the patients given cangrelor, a maximal antiplatelet effect was operative before and during PCI; this was not true in the case of the patients treated with clopidogrel. Approximately one fourth of the patients who were randomly assigned to clopidogrel received a 300-mg loading dose, which is inferior to a dose of 600 mg in achieving platelet inhibition and preventing periprocedural ischemic events. Furthermore, 37% of the patients in the clopidogrel group received the drug during or after PCI; as a result, the antiplatelet effects of clopidogrel were suboptimal at the time of PCI. …Finally, in many centers, patients with an acute coronary syndrome (which was the diagnosis at presentation in 44% of the patients in this study) receive ticagrelor or prasugrel, since these drugs are superior to clopidogrel at reducing PCI-related complications. Studies comparing cangrelor with these agents are lacking.

The FDA Medical Team Leader for the prior NDA submission made the following overall assessment of the three CHAMPION trials:[24]

> 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 [CHAMPION] PCI to horribly (after PCI) in [CHAMPION] 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.** [Emphasis added]

CHAMPION Clinical Trials: Apparent Ethical Lapses

We agree with the assessment of the FDA Medical Team Leader for the prior NDA submission that in all three CHAMPION trials evaluating cangrelor, many subjects randomized to the control groups received substandard antiplatelet therapy, particularly with respect to timing, and in many cases dosing, of clopidogrel, given existing published clinical guidelines and usual clinical practice at the participating hospitals. As a result, risks to control subjects were not minimized. These disturbing ethical lapses were most prominent in the CHAMPION PLATFORM trial in which all control subjects received their first dose of clopidogrel 600 mg after undergoing PCI. However, the lapses were also quite significant in the PHOENIX trial and to a lesser degree in the CHAMPION PCI trial.

It also appears that the at least some, and perhaps many, of the consent forms used to enroll subjects in the PHOENIX trial failed to adequately describe the nature and risks posed by the control group antiplatelet intervention relative to guideline-recommended care provided to subjects undergoing PCI, and alternative courses of treatment that may have been advantageous to the subjects.

Conclusions

The Medicines Company obviously is desperate to obtain FDA approval for cangrelor for any indication, knowing that once approved, the drug will no doubt be used extensively off-label. However, because the development plan for cangrelor was poorly conceived and implemented, we have no idea where cangrelor fits in the armamentarium of antiplatelet therapies for the range of patients undergoing PCI or whether it as

[24] Food and Drug Administration. FDA Briefing document for the Cardiovascular and Renal Drugs Advisory Committee meeting on February 12, 2014. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM385234.pdf. Accessed April 14, 2014. PDF page 25.

safe and effective as existing antiplatelet therapies, including prasugrel, ticagrelor, and GP IIb/IIIa inhibitors. Approving the drug now given the great uncertainty of its benefit-risk profile relative to other products on the market would do a great disservice to public health.

Therefore, Public Citizen urges the advisory committee to recommend that the FDA not approve the NDA for cangrelor for the proposed narrowed PCI indication.