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January 7, 2016

J. Thomas Puglisi, Ph.D.
Chief Officer
Office of Research Oversight (10R)
Veterans Health Administration
Department of Veterans Affairs
810 Vermont Avenue, NW
Washington, DC 20420

RE: A Clinical Trial Comparing Cangrelor to Clopidogrel Standard Therapy in Subjects Who Require Percutaneous Coronary Intervention (PCI) (CHAMPION PHOENIX)
Sponsor: The Medicines Company
ClinicalTrials.gov Identifier: NCT01156571

Dear Dr. Puglisi:

Public Citizen, a consumer advocacy organization with more than 400,000 members and supporters nationwide, hereby requests that the Office of Research Oversight (ORO) promptly conduct a compliance oversight investigation of the CHAMPION PHOENIX trial, which was conducted, in part, at Department of Veterans Affairs (VA) health care facilities.

The trial, as conducted at three VA health care facilities (Dallas VA Medical Center, Jesse Brown VA Medical Center, and VA Boston Healthcare System[1]), was unethical and failed to satisfy the requirements of VA human subjects protection regulations at 38 C.F.R. Part 16. In particular:

(1) The CHAMPION PHOENIX research protocol failed to mandate appropriately timed antiplatelet therapy in control group subjects undergoing percutaneous coronary intervention (PCI). As a result, appropriate antiplatelet therapy with clopidogrel was delayed in the vast majority of control group subjects enrolled at VA medical centers — as well as in a significant minority of control group subjects at other trial sites — until *after* the subjects had undergone their PCI procedures. Such delays represented substandard antiplatelet therapy and unnecessarily exposed subjects to risk of serious complications related to coronary stent thrombosis during and immediately after their PCI procedures. Therefore, the design and conduct of the trial failed to ensure that risks

[1] Bhatt DL, Stone GW, Mahaffey KW, et al. Effect of platelet inhibition with cangrelor during PCI on ischemic events. *N Engl J Med*. 2013;368(14):1303-1313. Supplementary Appendix. http://www.nejm.org/action/showSupplements?doi=10.1056%2FNEJMoa1300815&viewType=Popup&viewClass=Suppl. Accessed January 4, 2016. PDF page 5.

to control group subjects were minimized, as required by VA human subjects protection regulations at 38 C.F.R. §16.111(a)(1).

(2) We also are concerned that when informed consent of the subjects was sought, the investigators failed to provide:

(a) an accurate description of the procedures to be followed for subjects randomized to the control group, as required by VA human subjects protection regulations at 38 C.F.R. §16.116(a)(1);

(b) an adequate description of the reasonably foreseeable risks to subjects randomized to the control group, as required by VA human subjects protection regulations at 38 C.F.R. §16.116(a)(2); and

(c) a complete disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subjects, as required by VA human subjects protection regulations at 38 C.F.R. §16.116(a)(4).

The following detailed discussion explains the basis for our complaint.

Overview of the CHAMPION PHOENIX trial

Trial rationale and primary objective

PCI with stent implantation is commonly used to treat patients with atherosclerotic coronary artery disease. Thrombotic complications during and after PCI have been a long-standing major concern. Prior to the initiation of the CHAMPION PHOENIX trial, substantial evidence supported the benefit of pre-procedure antiplatelet therapy with $P2Y_{12}$-receptor inhibitors in patients undergoing PCI to reduce the risk of ischemic events such as myocardial infarction, acute stent thrombosis, and cardiovascular death.[2]

When the trial was designed, only oral $P2Y_{12}$-receptor inhibitors were available, with clopidogrel being the most frequently used member of this drug class. However, clopidogrel has several limitations, including a delayed onset of action, variable on-treatment effect, and irreversible platelet inhibition.[3] In addition, some patients with acute coronary syndromes have nausea,

[2] The Medicines Company. 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. September 28, 2010. See online Supplementary Material for: Bhatt DL, Stone GW, Mahaffey KW, et al. Effect of platelet inhibition with cangrelor during PCI on ischemic events. *N Engl J Med*. 2013;368(14):1303-1313. http://www.nejm.org/doi/suppl/10.1056/NEJMoa1300815/suppl_file/nejmoa1300815_protocol.pdf. Accessed January 4, 2016. PDF page 76 .

[3] *Ibid*. PDF page 76.

impaired drug absorption, or an inability to swallow oral medications, all of which limit the usefulness of oral clopidogrel as an antiplatelet agent.[4]

Cangrelor was developed in an effort to overcome the limitations of oral $P2Y_{12}$-receptor inhibitors. It is an intravenous, rapidly acting, potent, and direct-acting platelet $P2Y_{12}$-receptor inhibitor.[5] Cangrelor's antiplatelet effect is immediate and can be maintained with a continuous infusion.[6] The effects of cangrelor are rapidly reversible, with platelet function being restored within one hour of stopping the infusion.[7]

The CHAMPION PHOENIX trial was the third phase III randomized clinical trial comparing cangrelor with clopidogrel in patients undergoing PCI. The first two — the CHAMPION PCI and CHAMPION PLATFORM trials — failed to show that cangrelor was superior to clopidogrel,[8] despite the fact that the timing of clopidogrel dosing in the control group subjects was suboptimal. The CHAMPION PHOENIX trial represented the third attempt by The Medicines Company, the manufacturer of cangrelor, to obtain evidence to support Food and Drug Administration (FDA) approval of the drug for use in patients undergoing PCI. The primary objective of the CHAMPION PHOENIX trial, as stated in the protocol, was to demonstrate that in patients requiring PCI, cangrelor provides superior efficacy to clopidogrel "standard of care."[9]

Trial design

The CHAMPION PHOENIX trial was a randomized, controlled, double-blind, double-dummy, multicenter clinical trial.[10,11] Patients eligible for enrollment in the trial were adult men or nonpregnant women with coronary atherosclerosis who required PCI for one of three conditions:

- stable angina, with diagnostic coronary angiography within 90 days prior to randomization demonstrating atherosclerosis;

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[4] Bhatt DL, Stone GW, Mahaffey KW, et al. Effect of platelet inhibition with cangrelor during PCI on ischemic events. *N Engl J Med.* 2013;368(14):1303-1313.
[5] *Ibid*.
[6] *Ibid*.
[7] *Ibid*.
[8] 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 January 4, 2016. PDF page A1.
[9] The Medicines Company. 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. September 28, 2010. See online Supplementary Material for: Bhatt DL, Stone GW, Mahaffey KW, et al. Effect of platelet inhibition with cangrelor during PCI on ischemic events. *N Engl J Med*. 2013;368(14):1303-1313. http://www.nejm.org/doi/suppl/10.1056/NEJMoa1300815/suppl_file/nejmoa1300815_protocol.pdf. January 4, 2016. PDF page 62.
[10] *Ibid*. PDF page 62.
[11] Bhatt DL, Stone GW, Mahaffey KW, et al. Effect of platelet inhibition with cangrelor during PCI on ischemic events. *N Engl J Med*. 2013;368(14):1303-1313.

- a non-ST-segment-elevation acute coronary syndrome (NSTE-ACS), with diagnostic coronary angiography within72 hours prior to randomization demonstrating atherosclerosis; or
- ST-segment-elevation myocardial infarction (STEMI), with no requirement for a diagnostic angiograpy.[12]

Patients who had received recent treatment with any of the following antiplatelet agents prior to randomization were excluded: a $P2Y_{12}$-receptor inhibitor or a glycoprotein IIb/IIIa inhibitor.[13]

According to the study protocol, subjects randomly assigned to the experimental group were to receive an intravenous bolus of cangrelor (30 micrograms [µg]/kilogram), followed immediately by a continuous infusion of 4 µg/kilogram/minute. The infusion was to begin as soon as possible following randomization but only after completion of an initial diagnostic coronary angiogram and confirmation of suitability for PCI. The protocol required that the infusion begin before the PCI procedure, but not more than 30 minutes prior. The infusion then continued for at least two hours or until the end of the PCI procedure, whichever was longer. The experimental subjects also were to receive placebo clopidogrel capsules (matching a 300 or 600 milligram [mg] dose) "administered as soon as possible following randomization as directed by the investigator." Immediately following the cangrelor infusion, the subjects were to be given clopidogrel capsules (600 mg).[14]

Subjects randomly assigned to the control group were to receive a matching cangrelor placebo bolus and continuous infusion, according to the same time frame as the experimental group, and clopidogrel capsules (300 or 600 mg dose) to be "administered as soon as possible following randomization as directed by the investigator." Immediately following the placebo cangrelor infusion, the subjects also were to be given placebo clopidogrel capsules (matching a 600 mg dose).[15]

Subjects in both groups also were to be given aspirin (75 to 325 mg) starting any time on the day of the PCI procedure and daily thereafter for at least 30 days, another dose of clopidogrel (75 mg) within 48 hours of the PCI procedure, and clopidogrel or another $P2Y_{12}$-receptor inhibitor thereafter at the discretion of the investigator.[16,17]

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[12] The Medicines Company. 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. September 28, 2010. See online Supplementary Material for: Bhatt DL, Stone GW, Mahaffey KW, et al. Effect of platelet inhibition with cangrelor during PCI on ischemic events. *N Engl J Med*. 2013;368(14):1303-1313. http://www.nejm.org/doi/suppl/10.1056/NEJMoa1300815/suppl_file/nejmoa1300815_protocol.pdf. Accessed January 4, 2016. PDF page 82.

[13] *Ibid*. PDF page 82.

[14] *Ibid*. PDF pages 81 and 85.

[15] *Ibid*. PDF pages 81 and 85.

[16] *Ibid*. PDF page 81 and 86.

[17] Bhatt DL, Stone GW, Mahaffey KW, et al. Effect of platelet inhibition with cangrelor during PCI on ischemic events. *N Engl J Med*. 2013;368(14):1303-1313.

The primary efficacy endpoint was a composite of all-cause mortality, myocardial infarction, ischemia-driven revascularization, and stent thrombosis in the 48 hours after randomization in the modified intention-to-treat population, which comprised patients who actually underwent PCI and received at least one dose of a study drug.[18]

Appropriate timing of clopidogrel in the setting of PCI to prevent serious adverse outcomes

The CHAMPION PHOENIX trial investigators enrolled 11,145 subjects from September 30, 2010, to October 3, 2012.[19] While the ideal timing for administration of clopidogrel in the context of a PCI procedure had not been precisely defined, several pieces of evidence, multiple expert clinical practice guidelines, and other observations available to the investigators before the beginning of the trial established that delaying administration of clopidogrel in patients undergoing PCI — particularly those presenting with STEMI or NSTE-ACS — until *after* the procedure constituted substandard antiplatelet therapy. Even administration as early as *5 to 15 minutes before* the PCI procedure was probably insufficient, given the pharmacokinetics and pharmacodynamics of the drug: As the drug label for clopidogrel noted in August 2010, "Dose-dependent inhibition of platelet aggregation can be seen 2 hours after single oral doses" of the drug.[20]

Analysis of CHAMPION PCI and CHAMPION PLATFORM trials

An analysis of data from the CHAMPION PCI[21] and CHAMPION PLATFORM[22] trials — which were completed in 2009, before the CHAMPION PHOENIX trial began, and conducted by many of the same investigators who subsequently conducted the CHAMPION PHOENIX trial — strongly suggested that administration of clopidogrel after PCI results in worse patient outcomes than administration before PCI.

The CHAMPION PCI trial was a large randomized, double-blind, double-dummy, multicenter clinical trial that enrolled 8,877 subjects requiring PCI for stable angina (15%), unstable angina (25%), myocardial infarction without ST-segment elevation (49%), or myocardial infarction with

[18] The Medicines Company. 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. September 28, 2010. See online Supplementary Material for: Bhatt DL, Stone GW, Mahaffey KW, et al. Effect of platelet inhibition with cangrelor during PCI on ischemic events. *N Engl J Med*. 2013;368(14):1303-1313. http://www.nejm.org/doi/suppl/10.1056/NEJMoa1300815/suppl_file/nejmoa1300815_protocol.pdf. Accessed January 4, 2016. PDF pages 105,106, and 143.

[19] Bhatt DL, Stone GW, Mahaffey KW, et al. Effect of platelet inhibition with cangrelor during PCI on ischemic events. *N Engl J Med*. 2013;368(14):1303-1313.

[20] Sanofi Aventis and Bristol-Myers Squibb. Product label for Plavix. August 2010. http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020839s048lbl.pdf. Accessed January 4, 2016.

[21] 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.

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

ST-segment elevation (11%).[23] Subjects randomized to the experimental group received a cangrelor infusion that was initiated before the PCI procedure, followed by a 600 mg loading dose of clopidogrel. Subject randomized to the control group received a 600 mg oral dose of clopidogrel administered within 30 minutes *before* the PCI procedure.[24]

The CHAMPION PLATFORM trial, conducted concurrently with the CHAMPION PCI trial, was also a large randomized, double-blind, double-dummy, multicenter clinical trial. This trial enrolled 5,362 subjects requiring PCI for stable angina (5%), unstable angina (35%), or STEMI (60%).[25] Subjects randomized to the experimental group received a cangrelor infusion that was initiated before the PCI procedure, followed by a 600 mg loading dose of clopidogrel. In stark contrast to the CHAMPION PCI trial, subjects randomized to the control group in the CHAMPION PLATFORM trial received a 600 mg oral dose of clopidogrel administered *after* the PCI procedure.[26]

The FDA's cross-discipline team leader for the clinical review of the initial new drug application for cangrelor summarized the key results of the CHAMPION PCI and PLATFORM trials in the following table:[27]

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

[23] 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.
[24] *Ibid*.
[25] Bhatt DL, Lincoff M, Gibson CM, et al. Intravenous platelet blockade with cangrelor during PCI. *N Engl J Med*. 2009;361(24):2330-2341.
[26] *Ibid*.
[27] 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 January 4, 2016. See PDF page A4.

The sponsor terminated both trials after a second planned interim analysis (at 70 percent planned enrollment), allegedly for futility.[28] Both trials failed to meet their primary efficacy endpoint, which was a composite of death, myocardial infarction, or ischemia-driven revascularization at 48 hours.[29,30]

Strikingly, for the primary efficacy endpoint, deaths, and stent thrombosis, the event rates were substantially higher in the CHAMPION PLATFORM control group compared with the other three groups (i.e., the CHAMPION PLATFORM experimental group and the CHAMPION PCI experimental and control groups). For the CHAMPION PLATFORM study, the event rates for both deaths and stent thrombosis were statistically significantly higher in the control group, in which clopidogrel was delayed until after the PCI procedure. For the CHAMPION PCI trial, in which control subjects received clopidogrel immediately before the PCI procedure — which was still suboptimal — the point estimates for the primary efficacy endpoint and deaths actually favored the control group, although these differences were not statistically significant. These differing effects in the CHAMPION PCI trial compared with the CHAMPION PLATFORM trial likely were due to the delayed administration of clopidogrel in the latter trial.

In 2009, CHAMPION PHOENIX co-principal investigator stated that experts recommended clopidogrel before PCI

In a November 15, 2009, interview with *Heartwire from Medscape*, Dr. Deepak Bhatt — one of the two co-principal investigators for the CHAMPION PHOENIX trial and a cardiologist affiliated with the VA Boston Healthcare System — made the following statements regarding the timing of clopidogrel dosing in the setting of PCI based on his assessment of the data from the CHAMPION PCI and CHAMPION PLATFORM trials:[31]

- "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 endpoints 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]

[28] *Ibid*. See PDF page A3.
[29] 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.
[30] Bhatt DL, Lincoff M, Gibson CM, et al. Intravenous platelet blockade with cangrelor during PCI. *N Engl J Med*. 2009;361(24):2330-2341.
[31] Hughes S. CHAMPION: Negative trials but some positive angles for cangrelor? *Heartwire from Medscape*. November 15, 2009. http://www.medscape.com/viewarticle/712388. Accessed January 4, 2016.

- 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]

As co-principal investigator of the CHAMPION PHOENIX trial, Dr. Bhatt had a responsibility to ensure that the timing of the clopidogrel loading dose in the control group subjects was consistent with what experts in the cardiology field, including him, considered best clinical care.

Discussion of the timing of clopidogrel dosing in the CHAMPION PHOENIX trial protocol

Section 1.3 (STUDY RATIONALE) of the initial final version of the CHAMPION PHOENIX trial protocol, dated June 15, 2010, included the following discussion indicating that clopidogrel should be administered as soon as possible after subject randomization:[32]

> 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 given as soon as possible after randomization.** [Emphasis added]

Expert clinical practice guidelines

Consistent with the above statements made by Dr. Bhatt, expert clinical practice guidelines issued before the PHOENIX CHAMPION trial was initiated generally recommended earlier use of clopidogrel (i.e., before PCI) in a variety of clinical scenarios:

The European Society of Cardiology's (ESC's) 2007 guidelines for management of NSTE-ACS stated the following:[33]

> 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 increased bleeding risk

[32] The Medicines Company. 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. June 15, 2010. See online Supplementary Material for: Bhatt DL, Stone GW, Mahaffey KW, et al. Effect of platelet inhibition with cangrelor during PCI on ischemic events. *N Engl J Med*. 2013;368(14):1303-1313. http://www.nejm.org/doi/suppl/10.1056/NEJMoa1300815/suppl_file/nejmoa1300815_protocol.pdf. Accessed January 4, 2016. PDF page 18.

[33] Bassand JP, Hamm CW, Ardissino D, et al. (2007). Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. *Eur Heart J*. 2007; 28(13):1598-1660.

> 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. In patients who cannot be given clopidogrel before PCI, [glycoprotein] IIb/IIIa inhibitors should be administered.

The American College of Cardiology/American Health Association's (ACC/AHA's) 2007 guidelines for management of unstable angina (UA)/non-ST-segment-elevation myocardial infarction (NSTEMI) recommended early treatment with clopidogrel or a glycoprotein IIb/IIIa inhibitor:[34]

> 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)

The ACC/AHA's 2007 guidelines on PCI stated the following regarding clopidogrel dosing:[35]

> A loading dose of clopidogrel, generally 600 mg, should be administered before or when PCI is performed. (Level of Evidence: C) In patients 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) …
>
> 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 ESC's 2008 guidelines for management of STEMI recommended immediate treatment with clopidogrel:[36]

> Although clopidogrel is less studied in patients with STEMI treated with primary PCI, there is abundant evidence on its usefulness as an adjunctive antiplatelet therapy on top of aspirin in patients undergoing PCI. Based on these data, clopidogrel should be given as

[34] Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non ST-elevation myocardial infarction: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non ST-Elevation Myocardial Infarction). *Circulation.* 2007;116(7):e148-304.

[35] King SB, Smith SC, Hirshfeld JW, et al. 2007 Focused Update of the ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2008;117(2):261-295.

[36] Van de Werf F, Bax J, Betriu A, et al. Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation. *Eur Heart J*. 2008;29(23): 2909-2945.

> soon as possible to all patients with STEMI undergoing PCI. It is started with a loading dose of at least 300 mg, but a 600 mg loading dose achieves a more rapid and stronger inhibition of platelet aggregation.

The American College of Chest Physicians' (ACCP's) 2008 guidelines for management of NSTE-ACS recommended upstream (i.e., early) administration of clopidogrel:[37]

> 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 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).

The ACCP's 2008 guidelines for management of STEMI recommended immediate administration of clopidogrel for such patients:[38]

> 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.

The ESC and European Association for Cardio-Thoracic Surgery's 2010 guidelines on myocardial revascularization stated the following regarding elective percutaneous coronary intervention:[39]

> 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. If this is not possible, a loading dose of 600 mg should be administered at least 2 h before PCI.

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[37] Harrington RA, Becker RC, Cannon CP, et al. (2008). Antithrombotic therapy for non-ST segment elevation acute coronary syndromes: American College of Chest Physicians evidence-based clinical practice guidelines (8th Edition). *Chest*. 2008;133(6 Suppl):670S-707S.

[38] Goodman SG, Menon V, Cannon CP, et al. (2008). Acute ST-segment elevation myocardial infarction: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest*. 2008;133(6 Suppl): 708S-775S.

[39] Wijns W, Kolh P, Danchin N, et al. (2010). Guidelines on myocardial revascularization. *Eur Heart J*. 2010;31(20): 2501-2555. (Published online August 29, 2010)

Finally, the ACA/AHA's 2009 updated guidelines for management of STEMI and for PCI included the following complicated recommendations:[40]

> 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)

Notably, Dr. Robert Harrington, the other co-principal investigator for the CHAMPION PHOENIX trial, was a co-author of the above-referenced ACCP guidelines.[41] Other PHOENIX investigators also wrote or helped develop several of the above-referenced ESC guidelines.[42]

These expert clinical practice guidelines, particularly those written by CHAMPION PHOENIX investigators, overall strongly endorsed early use of clopidogrel in patients undergoing PCI procedures in a variety of clinical circumstances. When combined with the data from the CHAMPION PCI and CHAMPION PLATFORM trials, it was clear before the initiation of the CHAMPION PHOENIX trial that administration of clopidogrel prior to the start of PCI was clearly preferable to administration after PCI, particularly in patients presenting with STEMI or NSTE-ACS.

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[40] Kushner FG, Hand M, Smith SC, et al. 2009 focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update): A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2009;120(22):2271-2306.

[41] 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 January 4, 2016. See PDF page E7.

[42] *Ibid* . See PDF page E6.

The CHAMPION PHOENIX protocol: Ambiguity on timing of clopidogrel administration

The trial protocol failed to clearly mandate that, whenever possible, investigators administer clopidogrel pre-PCI to control group subjects.

The initial version of the final CHAMPION PHOENIX trial protocol, dated June 15, 2010 (before any subjects were enrolled),[43] included the following statements and stipulations regarding administration of clopidogrel to control subjects:

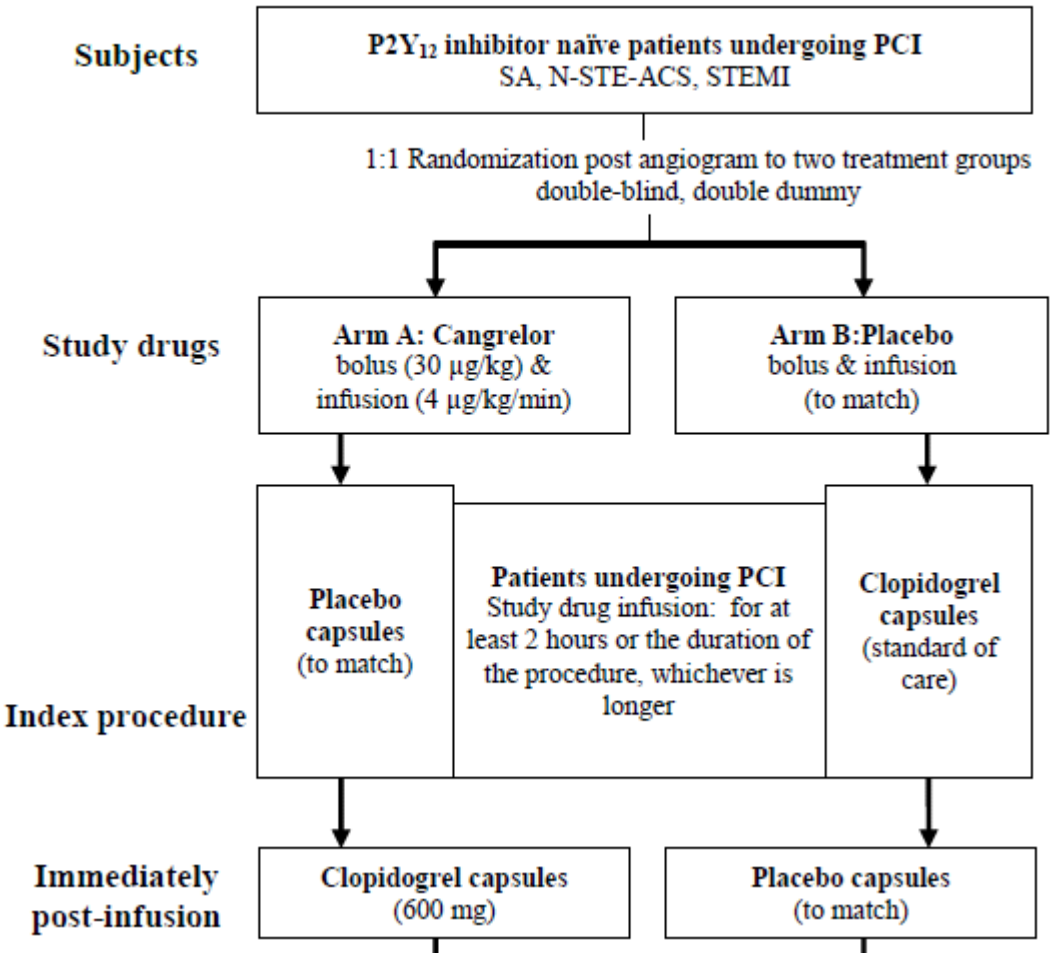
- PROTOCOL SYNOPSIS: … **Reference Therapy, Dose and Mode of Administration:** Clopidogrel standard of care: Clopidogrel loading dose administered at the time of PCI as by standard of care at the participating site.[44]

- **1.3. STUDY RATIONALE** … 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 given as soon as possible after randomization. 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 in line with institution standard of care.[45]

- **3.5. TYPE/DESIGN OF TRIAL** … At the time of PCI, as by contemporary standard of care at the participating site, patients will receive their first set of capsules containing either clopidogrel (Arm B) or matching placebo (Arm A).[46]

- **Figure 2: Trial Design**[47]

[43] The Medicines Company. 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. June 15, 2010. See online Supplementary Material for: Bhatt DL, Stone GW, Mahaffey KW, et al. Effect of platelet inhibition with cangrelor during PCI on ischemic events. *N Engl J Med*. 2013;368(14):1303-1313. http://www.nejm.org/doi/suppl/10.1056/NEJMoa1300815/suppl_file/nejmoa1300815_protocol.pdf. Accessed January 4, 2016. PDF pages 3-59.
[44] *Ibid*. PDF page 4.
[45] *Ibid*. PDF page 18.
[46] *Ibid*. PDF page 22.
[47] *Ibid*. PDF page 23.



- **5.1. STUDY MEDICATIONS** … **5.1.2. Clopidogrel** Clopidogrel will be provided in the study drug kit in an over-encapsulated form. In the control arm (Arm B), kits will contain 300 mg or 600 mg of clopidogrel to be administered at the time of PCI as per institutional standard.[48]

- ***7.2.1.3. Timing of study drug administration*** … The first set of [clopidogrel] capsules may be given at the time of PCI as by standard of care at the participating site.[49]

Although the June 15, 2010, version of the protocol noted in the Study Rationale section that the majority of patients were expected to receive a 600 mg clopidogrel dose as soon as possible after randomization and before the PCI procedure, the other descriptions of study procedures referenced above were ambiguous regarding the protocol-stipulated timing of the initial clopidogrel loading dose in the control group subjects.

[48] *Ibid*. PDF page 27.
[49] *Ibid*. PDF page 35.

Presumably because of concerns about this ambiguity regarding the timing of clopidogrel administration, the FDA sent a protocol advice letter to the sponsor, dated September 9, 2010, requesting the following revisions to the protocol:[50]

> 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 FDA's intent in requesting the above revision undoubtedly was to ensure that clopidogrel was administered to control group subjects as soon as possible before PCI and to allow administration of the drug on presentation in STEMI subjects, rather than waiting for angiography.[51] However, the FDA's proposed clarifying edit, "to allow the investigator to determine the timing of clopidogrel administration," itself lacked clarity on this critical issue.

In response to the FDA's letter, the following pertinent revisions were incorporated into the September 28, 2010, version of the protocol, which was in effect for the conduct of the entire trial (deletions in strikeout and insertions underlined):

- **PROTOCOL SYNOPSIS:** … **Reference Therapy, Dose and Mode of Administration:** Clopidogrel standard of care: Clopidogrel loading dose administered in patients undergoing PCI ~~at the time of PCI as by standard of care at the participating site~~ as soon as possible following randomization as directed by the investigator.[52]

- **1.3. STUDY RATIONALE** … 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. 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

[50] 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 January 4, 2016. PDF page E26.

[51] *Ibid.* PDF page E26.

[52] The Medicines Company. 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. September 28, 2010. See online Supplementary Material for: Bhatt DL, Stone GW, Mahaffey KW, et al. Effect of platelet inhibition with cangrelor during PCI on ischemic events. *N Engl J Med*. 2013;368(14):1303-1313. http://www.nejm.org/doi/suppl/10.1056/NEJMoa1300815/suppl_file/nejmoa1300815_protocol.pdf. Accessed January 4, 2016. PDF page 122.

treating physician. In these clinical settings, the administration of 600 mg clopidogrel following PCI is allowed ~~in line with institution standard of care~~per investigator's discretion.[53]

- **3.5. TYPE/DESIGN OF TRIAL** … ~~At the time of PCI, as by contemporary standard of care at the participating site,~~After randomization and as directed by investigator, patients will receive their first set of capsules containing either clopidogrel (Arm B) or matching placebo (Arm A).[54]

- **Figure 2: Trial Design** [for subject randomized to Arm B, control group]: **Clopidogrel capsules** (per ~~standard of care~~investigator's discretion).[55]

- **5.1. STUDY MEDICATIONS** … **5.1.2. 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 mg or 600 mg of clopidogrel ~~to be administered at the time of PCI as per institutional standard~~.[56]

- ***7.2.1.3. Timing of study drug administration*** … The first set of [clopidogrel] capsules ~~may~~must be given ~~at the time of PCI as by standard of care at the participating site~~ after randomization per investigator's discretion.[57]

Disturbingly, the above revisions made by the investigators to the final CHAMPION PHOENIX trial protocol — particularly the insertions of the phrases "at the discretion of the investigator" and "as directed by the investigator" and the multiple deletions of "standard of care" — created more, not less, ambiguity regarding the protocol-stipulated timing of the initial loading dose of clopidogrel in the control group subjects and left the door wide open to inappropriate, hazardous delays in the administration of clopidogrel to these subjects.

Thus, the trial design, as described in the final protocol, failed to ensure that risks to subjects were minimized.

Implementation of the CHAMPION PHOENIX protocol: VA health care facilities versus other trial sites

Data on the actual timing of clopidogrel administration in subjects enrolled in the CHAMPION PHOENIX trial at the three participating VA health care facilities compared with other

[53] *Ibid.* PDF page 122.
[54] *Ibid.* PDF page 124.
[55] *Ibid.* PDF page 124.
[56] *Ibid.* PDF page 125.
[57] *Ibid.* PDF pages 127-128.

participating trial sites is presented in the following table prepared by the FDA's cross-discipline team leader for the clinical review of the initial new drug application for cangrelor:[58]

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)

Strikingly, 89 percent of subjects enrolled in the trial at the VA trial sites received their initial clopidogrel dose (active drug capsules in the control group or placebo capsules in the experimental cangrelor group) *after* the completion of the PCI procedure. By comparison, 30 percent of subjects enrolled at non-VA trial sites had administration of the initial clopidogrel dose after completion of the PCI procedure, a rate that in our view was still unacceptably high.

Predictably, the delay in clopidogrel administration likely resulted in preventable harms to some subjects enrolled at VA trial sites: As shown in the above table, the primary efficacy endpoint (i.e., all-cause mortality, myocardial infarction, ischemia-driven revascularization, and stent thrombosis in the 48 hours after randomization) occurred in 9.8 percent of control group subjects at VA trial sites versus 5.8 percent of control subjects at non-VA sites. In contrast, VA subjects and non-VA subjects in the cangrelor group had comparable rates of these events (4.7 percent for both). Thus, subjects enrolled at VA trial sites fared much worse with the greatly delayed clopidogrel than the non-VA subjects with lesser delays or than VA and non-VA patients assigned to the cangrelor group.

The FDA's cross-discipline team leader correctly concluded that the CHAMPION PHOENIX trial was unethical for several reasons, including the delayed use of clopidogrel in control group subjects that was permitted under the trial protocol.[59] Commenting on the rate of such delays for the entire study, he stated: [60]

> *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*

[58] Marciniak TA. Cross-discipline team leader review memo for NDA 204-958, Kengreal/cangrelor. March 23, 2014 http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/204958Orig1s000MedR.pdf. Accessed January 4, 2016. PDF page 151.

[59] 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 January 4, 2016. PDF page E1.

[60] *Ibid*. PDF pages E28-E29.

> *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 of PCI. The control arm did not represent clopidogrel standard of care even by the protocol expectations, much less by the guidelines.* [Italics in original]

Concluding remarks about the failure to minimize risks in the CHAMPION PHOENIX trial

In summary, as the above documentation indicates, the design and conduct of the CHAMPION PHOENIX trial with respect to the timing of clopidogrel administration in control group subjects failed to ensure that risks to control subjects were minimized, as required by VA human subjects protection regulations at 38 C.F.R. §16.111(a)(1).

To minimize risks to subjects, the CHAMPION PHOENIX trial protocol should have explicitly mandated that all trial site investigators administer the initial clopidogrel dose to subjects at least two hours prior to PCI, unless the subject needed to undergo the PCI procedure sooner for urgent clinical reasons. Furthermore, for circumstances in which the PCI procedure could not be delayed until at least two hours after the initial clopidogrel dose, the protocol should have mandated that the initial clopidogrel dose be administered immediately after randomization and as soon as possible before the PCI procedure, unless the subject was unable to swallow the clopidogrel study capsules. For prospective subjects who could not safely swallow clopidogrel capsules prior to the PCI procedure, the protocol should have either excluded such patients from the trial or allowed administration of alternative antiplatelet agents.

The failure of the trial protocol to include such stipulations paved the way for inappropriate delays in antiplatelet therapy for subjects enrolled in the control group. Inexplicably, the rate of such delays was exceptionally high at the VA trial sites, making participation in the trial even more hazardous for subjects randomized to the control group at those sites compared with non-VA trial sites.

The investigators who wrote the CHAMPION PHOENIX trial protocol no doubt understood that administration of antiplatelet therapy with cangrelor prior to the PCI procedure was likely to result in better clinical outcomes than administration after the PCI procedure. 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 the PCI procedure, and earlier administration could only have improved the chances for better clinical outcomes for these patients. By designing the trial to allow investigators to routinely delay administration of clopidogrel until after the PCI procedure, control group subjects were placed at a significant disadvantage relative to the cangrelor group subjects, which ultimately increased the chances that the cangrelor intervention would appear to be superior to the clopidogrel intervention.

Finally, while our complaint regarding the failure to minimize risk in the CHAMPION PHOENIX trial has focused on the timing of clopidogrel administration, we note that the FDA's

cross-discipline team leader also highlighted several other problems with the trial's design that resulted in additional failures to minimize risk and contributed to the trial being unethical.[61]

Concerns about the adequacy of the informed-consent process

Based on our review of the sample consent form for the CHAMPION PHOENIX trial, which is available on the FDA's website,[62] we also are concerned that the consent forms used when investigators enrolled subjects at the VA clinical trial sites failed to satisfy the requirements of VA human subjects protection regulations at 38 C.F.R. 16.116(a) regarding three basic elements of informed consent:

(1) The description in the sample consent form of the study procedures for the control group stated that "Per your institutions' standard of care, you will receive 2 - 4 150 mg capsules of [clopidogrel] at the time of the PCI."[63] This statement was misleading given that nearly 90 percent of subjects enrolled at the VA clinical trial sites received their initial dose of clopidogrel *after* the PCI procedure, not at the time of the procedure. Therefore, this description failed to satisfy the requirements of VA human subjects protection regulations at 38 C.F.R. 16.116(a)(1).

(2) The sample consent form provided no mention of the reasonably foreseeable risks to subjects randomized to the control group related to delaying the initial dose of clopidogrel until the start of, or even after, the PCI procedure.[64] As a result of this omission, the description of risks failed to satisfy the requirements of VA human subjects protection regulations at 38 C.F.R. 16.116(a)(2).

(3) The sample consent form included the following uninformative disclosure of appropriate alternative procedures or courses of treatment that may have been advantageous to the subjects: "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."[65] This statement failed to disclose the following antiplatelet treatments that may have been advantageous to the subjects: treatment with clopidogrel at least two hours prior to the PCI procedure, treatment with a glycoprotein IIb/IIIa inhibitor prior to the PCI procedure, and treatment with ticagrelor prior to the PCI procedure. Therefore, this disclosure of alternative procedures or courses of treatment failed to satisfy the requirements of VA human subjects protection regulations at 38 C.F.R. §§16.116(a)(4).

We therefore urge ORO, as part of its investigation of the CHAMPION PHOENIX trial, to inspect the institutional review board–approved consent forms signed by subjects enrolled in the

[61] 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 January 4, 2016. PDF pages E1-E37.
[62] *Ibid*. PDF pages H1-H7.
[63] *Ibid*. PDF page H2.
[64] *Ibid*. PDF pages H3-H4.
[65] *Ibid*. PDF page H4.

CHAMPION PHOENIX trial at VA sites and determine whether any of these forms had the same deficiencies as those found in the sample consent form for the trial.

Please note that the ORO may share our complaint letter, with identifiers, with anyone. We will be posting a copy on our website as well.

We look forward to ORO's thorough and careful investigation of our allegations. We would be happy to meet with you to answer questions and provide additional information.

Sincerely,

Michael A. Carome, M.D.
Director
Public Citizen Health Research Group

Sidney M. Wolfe, M.D.
Founder and Senior Adviser
Public Citizen Health Research Group

cc: The Honorable Dr. David J. Shulkin, Under Secretary for Health, VA
The Honorable Linda A. Halliday**,** Deputy Inspector General, VA
The Honorable Jeff Miller, Chairman, House Committee on Veterans' Affairs
The Honorable Corrine Brown, Ranking Member, House Committee on Veterans' Affairs
The Honorable Johnny Isakson, Chairman, Senate Committee on Veterans' Affairs
The Honorable Richard Blumenthal, Ranking Member, Senate Committee on Veterans' Affairs