

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

Meeting Date: 12 February 2014

NDA: 204958

Applicant: The Medicines Company

Drug: Cangrelor Injection

Proposed **PCI**

Indications: 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

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CLINICAL REVIEW

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: January 13, 2014

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

NDA: 204-958
Drug: cangrelor

Indication: For the reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with coronary artery disease undergoing percutaneous coronary intervention (PCI)

Subject: Benefit-risk of cangrelor

Summary and Recommendation

Cangrelor is an intravenously (IV) administered P2Y₁₂ platelet inhibitor studied in three large clinical outcomes trial in patients undergoing percutaneous coronary intervention (PCI). (The sponsor has also submitted a pharmacokinetic/pharmacodynamic study for an indication in transitioning patients on oral P2Y₁₂ platelet inhibitors to discontinuation prior to CABG, but I do not address that indication in this review.) The two earlier trials, PCI and PLATFORM, failed to show superiority of a cangrelor regimen to a clopidogrel regimen.¹ The sponsor alleges that the failure of these latter two trials was the result of problems with adjudicating new myocardial infarctions (MIs) in patients having baseline biomarker elevations. A third trial, PHOENIX, allegedly corrected this flaw and demonstrated superiority of the cangrelor regimen to a clopidogrel regimen.

I conclude that the CHAMPION trials did not show superiority or noninferiority of a cangrelor regimen to a clopidogrel regimen or to standard of care for the following reasons:

¹ In this review for brevity I refer to the “cangrelor” regimen or arm and the “clopidogrel” regimen or arm. The more complete references are the “cangrelor infusion followed by clopidogrel” regimen or arm and the “clopidogrel alone” regimen or arm.

- Clopidogrel administration was delayed inappropriately in all of the trials. The trials themselves provide evidence that earlier administration of clopidogrel was better both by cross-trial comparisons and by logistic regressions of the PHOENIX data. Clopidogrel was never consistently administered early enough such that we can not even conclude that cangrelor is noninferior to clopidogrel.
- The cangrelor regimen was only statistically significantly superior for the sponsor's primary endpoint including predominantly "chemical" MIs. The difference in site-reported events has a higher odds ratio and is not statistically significant.
- In PHOENIX use of a 300 mg loading dose was only allowed in the clopidogrel arm. The exclusive use of the 600 mg loading dose in the cangrelor arm may explain some of the "superiority" of that arm.
- The "superiority" is only statistically significant in the stable angina subgroup. Yet stable angina is the condition for which cangrelor offers minimal advantages if any: We can easily load clopidogrel in stable angina patients at any desired interval before PCI and we can delay CABG for days to washout the clopidogrel effects if the anatomy elucidated at angiography is unsuitable for PCI and CABG is preferred.
- The data suggest the possibility of harm with cangrelor for ST segment elevation MI (STEMI) patients.
- While the trials did not demonstrate convincingly superiority of cangrelor for efficacy, they do demonstrate an increased risk of bleeding with it.

There are other reasons for rejecting approval besides uncertain noninferiority to clopidogrel. Both prasugrel and ticagrelor have demonstrated superior efficacy to clopidogrel. We do not know whether cangrelor affects this superiority so we do not know whether to use cangrelor with or instead of prasugrel and ticagrelor—or prasugrel or ticagrelor instead of cangrelor. Because the superiority involves irreversible harm, i.e., deaths and MIs, we should understand the tradeoffs among these agents.

Finally, I document in a parallel review that the CHAMPION trials were conducted unethically. (Marciniak 2014) We can refuse approval of cangrelor based on that fact alone.

I recommend not approving cangrelor at this time for the PCI indication. I recommend not approving cangrelor until another trial succeeds in correcting the flaws that I have documented in this review and in my parallel review on the ethicalness of the cangrelor development program.

Background

Cangrelor is a new platelet inhibitor studied for use with PCI for the treatment of stable angina or acute coronary syndromes (ACS, or myocardial infarction (MI) and unstable angina (UA)). Cangrelor is a platelet P2Y₁₂ receptor inhibitor like clopidogrel, the first approved P2Y₁₂ inhibitor. Cangrelor, unlike orally-administered clopidogrel, is administered intravenously and is a reversible rather than an irreversible inhibitor. Cangrelor has a quick onset and offset and short half-life compared to clopidogrel and other approved P2Y₁₂ inhibitors, potentially making it very useful in situations in which these qualities are desirable, such as recent onset ACS.

The PHOENIX trial was a randomized, double-blind, active-controlled trial comparing a bolus and infusion of cangrelor followed by clopidogrel 600 mg to clopidogrel 300 or 600 mg alone. (Bhatt, Stone et al. 2013) The trial was conducted from September 30, 2010, to October 3, 2012, in 11,145 patients who were undergoing either urgent or elective PCI, i.e., in both stable angina and ACS patients, and who did not receive pretreatment with platelet inhibitors (except aspirin). The trial was an international trial conducted in the US, Europe (including Austria, Germany, and the Czech Republic), Brazil, New Zealand, and Thailand. The primary endpoint was the composite of death, MI, ischemia-driven revascularization, or stent thrombosis at 48 hours. The rate of this endpoint was significantly lower in the cangrelor group than in the clopidogrel group² (4.7% vs. 5.9%; odds ratio [OR], 0.78; 95% confidence interval [CI] 0.66 to 0.93; P = 0.005) in the sponsor's "modified ITT" subgroup. The sponsor in its integrated summary of efficacy introduces the PHOENIX results as follows: "Data from the CHAMPION PHOENIX (N=11,145 mITT) [TMC-CAN-10-01] trial are presented to demonstrate that cangrelor significantly reduces thrombotic events (including death/MI/IDR/ST and ST) superior to clopidogrel in patients who require PCI."

PHOENIX was not the first clinical outcomes trial of cangrelor. Two similar trials preceded it: CHAMPION PCI and CHAMPION PLATFORM. (Bhatt, Lincoff et al. 2009; Harrington, Stone et al. 2009) Both were conducted in patients undergoing PCI, both used clopidogrel with a 600 mg loading dose, and both had a primary endpoint of death, MI, or ischemia-driven revascularization at 48 hours. The major difference was that in CHAMPION PCI clopidogrel was given prior to the PCI (but after angiography except early use was allowed in STEMI) while in PLATFORM clopidogrel administration was delayed until after the PCI. CHAMPION PCI included ST segment elevation MI (STEMI) patients while PLATFORM excluded them; both included 5-15% stable angina. At second planned interim analyses (at 70% enrollment) the sponsor terminated both trials early allegedly because the estimated conditional power to demonstrate superiority was low, i.e., for futility. I summarize relevant results in Table 1.

² In this review for brevity I refer to the "cangrelor group" and the "clopidogrel group". The more complete references are the "cangrelor infusion followed by clopidogrel group" and the "clopidogrel alone" group.

Table 1: Cangrelor CHAMPION Trials Results at 48 Hours

		PCI	PLATFORM
N		8877	5301
clopidogrel within 5 days		34%	0%
study clopidogrel timing		immediately prior to PCI	after PCI
primary endpoint	cangrelor	7.5%	7.0%
	clopidogrel	7.1%	8.0%
efficacy OR*		1.05 NS†	0.87 NS†
deaths	cangrelor	0.2%	0.2%
	clopidogrel	0.1%	0.7%
death OR*		1.59 NS†	0.33 (p=0.02)
stent thrombosis	cangrelor	0.2%	0.2%
	clopidogrel	0.3%	0.6%
stent thrombosis OR*		0.63 NS†	0.31 (p=0.02)
bleeding ORs*		1.2-1.4	1.3-1.6

* OR = odds ratio cangrelor:clopidogrel; †NS = not significant

For all three CV endpoints the rate that is substantially higher than those in the other three arms is the one in the clopidogrel arm of PLATFORM. In that latter arm clopidogrel initiation was delayed until after PCI. For the PCI trial in which clopidogrel was given earlier—although still not optimally—the point estimates for the primary endpoint and death actually favor clopidogrel. The CHAMPION trials confirmed that delaying clopidogrel initiation is bad.

Is the PHOENIX Cangrelor Regimen Superior to Delayed Clopidogrel?

ITT vs. “Modified ITT”

As I noted above, PHOENIX was successful for the sponsor’s primary adjudicated endpoint of death, MI, ischemia-driven revascularization, or stent thrombosis at 48 hours, with an OR of 0.78 (95% CI 0.66 to 0.93, $p = 0.005$) in the sponsor’s “modified ITT” subgroup. For “modified ITT” the sponsor excluded 203 (94 clopidogrel and 109 cangrelor) patients who were not treated or did not undergo a PCI. I assert that true ITT analyses that preserve the randomization are the appropriate ones for valid statistics. Hence I will use true ITT analyses for the rest of this review. The true ITT analyses are very slightly less favorable for cangrelor than the sponsor’s “modified ITT”. For the sponsor’s primary endpoint at 48 hours there is little difference: the true ITT OR is 0.79 (95% CI 0.67 to 0.93, $p = 0.005$). I explore the robustness of these results below.

Sponsor’s Endpoint Rates at 48 Hours by Index Event Type

Examining the sponsor’s endpoint results by the type of index event (stable angina, unstable angina (UA)/NSTEMI, STEMI) suggests a potential problem with the sponsor’s definition of endpoints. I show the sponsor’s endpoint rates at 48 hours by index event type in Table 2.

Table 2: Sponsor's Endpoint Rates at 48 Hours by Index Event Type in PHOENIX

index event	primary endpoint		adjudicated MI		death	
	clopidogrel	cangrelor	clopidogrel	cangrelor	clopidogrel	cangrelor
stable angina	6.8%	5.7%	6.3%	5.3%	0.0%	0.2%
UA/NSTEMI	5.7%	3.6%	3.3%	2.4%	0.7%	0.3%
STEMI	2.8%	2.8%	0.4%	0.1%	1.2%	1.3%
all	5.8%	4.7%	4.6%	3.7%	0.4%	0.4%

Note that the primary endpoint and adjudicated MI rates in the stable angina patients (58% of randomized subjects) are about 6%, higher for clopidogrel than for cangrelor. On the other hand, there appears to be little benefit in the STEMI subgroup and no overall benefit regarding mortality.

COMMENT: Event rates of 6% in stable angina patients at 48 hours seem high. The endpoints counted by the sponsor must not be clinically overt events but biomarker rises, e.g., "chemical" MIs, associated with the PCIs. The sponsor has explained the lower rates of MI endpoints in the UA/NSTEMI and particularly in the STEMI subgroups as the result of the difficulties of adjudicating MIs in these patients because of problems with establishing stable or falling biomarkers pre-randomization and with distinguishing new biomarker increases from the biomarker rises from the index event. I believe examining the site-reported events should be informative regarding the real benefit or detriment of cangrelor..

Site-Reported Event Rates at 48 Hours by Index Event Type

The CRFs for the 48-hour and 30-day follow-ups included a MI CRF with a yes/no checkbox labeled "Did patient experience an MI?" I counted the yes responses from these checkboxes as site-reported MIs. There was a similar CRF checkbox for revascularizations and an additional CRF for indicating whether the revascularization was planned; I counted unplanned revascularizations. I show the site-reported event rates at 48 hours by index event type in PHOENIX in Table 3.

Table 3: Site-Reported Event Rates at 48 Hours by Index Event Type in PHOENIX

index event	primary endpoint		MI event	
	clopidogrel	cangrelor	clopidogrel	cangrelor
angina	2.1%	1.8%	1.7%	1.2%
UA/NSTEMI	2.6%	2.2%	1.3%	1.3%
STEMI	2.3%	2.8%	1.2%	0.5%
all	2.3%	2.1%	1.5%	1.1%

The site-reported event rates for stable angina are more believable than the sponsor's, although they still seem high for stable angina. One possible explanation is that sites may not have recorded index events accurately because about 4.4% of "stable angina" patients had an elevated CKMB on the baseline measurement (drawn between randomization and study drug administration.) Regardless, overall the cangrelor regimen was not statistically significantly better than the clopidogrel regimen in PHOENIX for a site-reported primary endpoint event rate, with OR 0.91 (95% CI 0.7 to 1.2, $p = 0.5$).

The point estimates for the site-reported primary endpoint results in STEMI favor clopidogrel, as did the point estimates for all cause mortality. However, the site-reported new MI point estimates favor cangrelor. None of the interactions between treatment and STEMI are statistically significant.

COMMENT: The site-reported results at 48 hours suggest that the adjudicated results are not robust, particularly in STEMI patients. There are other analyses that should help to clarify the robustness or lack thereof. One is whether the difference in clopidogrel dosing in the two PHOENIX arms (the sponsor forced clopidogrel dosing to 600 mg in the cangrelor arm) affected the results. A second is whether the speed with which PCI was done represents optimal practice. However, the greatest limitation precluding concluding that cangrelor is superior to, or even as effective as, clopidogrel is the fact that the sponsor delayed clopidogrel dosing in PHOENIX. I present data elucidating all of these factors below.

Event Rates by Clopidogrel Loading Dose

The NEJM article (Bhatt, Stone et al. 2013) has the following tabulation for the “loading dose” of clopidogrel:

Table 1. (Continued.)		
Characteristic	Cangrelor (N=5472)	Clopidogrel (N=5470)
Periprocedural medications — no./total no. (%)		
Clopidogrel, 300-mg loading dose	1405/5472 (25.7)	1401/5470 (25.6)
Clopidogrel, 600-mg loading dose	4067/5472 (74.3)	4069/5470 (74.4)

The Results section presents the following subgroup analysis regarding the “loading dose”:

“Similarly, there was no significant difference in the effect of cangrelor on the primary end point between patients who received a 600-mg loading dose of clopidogrel (74.4% of the population) and those who received a 300-mg loading dose (25.6% of the population): the odds ratio for the primary end point with cangrelor was 0.77 (95% CI, 0.63 to 0.94) with the 600-mg loading dose and 0.84 (95% CI, 0.62 to 1.14) with the 300-mg loading dose (P = 0.62 for interaction).”

The Discussion section alleges the following:

“There are some limitations of the current study. A 600-mg loading dose of clopidogrel is known to be superior to a 300-mg dose in some, though not all, patients undergoing PCI. However, the results of the CHAMPION PHOENIX trial were similar after adjustment for loading dose and in each loading-dose subgroup.”

The PHOENIX study report has a corresponding table for results by “loading dose”:

Table 25: 48-hour composite efficacy endpoint based on CEC-adjudicated results, by clopidogrel loading dose (mITT)

	n (%) of patients		OR and 95% CI	P value ^a
	Cangrelor (N=5472)	Clopidogrel (N=5470)		
Death/MI/IDR/ST by assigned clopidogrel loading dose	(Placebo)			
600 mg	176/4065 (4.3)	227/4068 (5.6)	0.77 (0.63, 0.94)	0.009
300 mg	81/1405 (5.8)	95/1401 (6.8)	0.84 (0.62, 1.14)	0.267

COMMENT: The above results are incorrect and misleading. About 26% of patients in each arm did not receive a 300 mg loading dose of clopidogrel. Recall that, by protocol, ALL patients in the cangrelor arm were to receive a 600 mg loading dose. As I document below, adherence to this protocol specification was virtually 100%. The analyses presented are not for the “loading dose” but for the “intended loading dose”—only valid for the clopidogrel arm. Given the protocol specification summarized in the NEJM article’s Methods Study Treatment section regarding the 600 mg loading dose in the cangrelor group, the NEJM reviewers and editors should have caught this blatant misrepresentation.

By the study drug administration records 26% of the patients in the clopidogrel arm received two capsules (clopidogrel 300 mg) and all but 6 of the rest received four capsules (clopidogrel 600 mg) at the first oral study drug administration immediately following randomization. About 26% of the patients in the cangrelor arm also received two clopidogrel dummy capsules at the first oral study drug administration. At the second oral study drug administration after completion of the cangrelor or dummy infusion 99.85% of the patients in the cangrelor arm received four capsules (clopidogrel 600 mg) and 99.71% of patients in the clopidogrel arm received four capsules (dummy).

Clopidogrel dosing in the clopidogrel arm was highly consistent by site. I show the counts of sites and numbers of patients studied by clopidogrel dosing in Table 4.

Table 4: Loading Doses in Clopidogrel Arm by Site in PHOENIX

loading dose	# of sites	patients	% of study
300 mg only	5	1,170	10.5%
600 mg only	113	4,269	38.3%
both	35	5,706	51.2%

While the majority of the sites used only a 600 mg loading dose, the 35 sites using both randomized the majority of patients. Because only patients at these latter sites had the opportunity for receiving either loading dose, I analyzed the patients at these sites by loading dose used. I show the endpoint and bleed rates at 48 hours by loading dose at these latter sites in Table 5.

Table 5: Endpoint Rates at 48 Hours by Loading Dose at Sites Using Both Loading Doses in PHOENIX

arm	sponsor's endpoint		site-reported endpoint		any GUSTO bleed		deaths	
	300 mg	600 mg	300 mg	600 mg	300 mg	600 mg	300 mg	600 mg
clopidogrel	7.1%	4.8%	2.6%	1.5%	0.6%	1.3%	0.95%	0.25%
cangrelor		4.5%		1.9%		1.9%		0.35%

The rates in Table 5 suggest that both efficacy and bleeding are higher with the higher loading dose in the clopidogrel arm while bleeding, but not efficacy, is higher in the cangrelor arm compared to the clopidogrel patients loaded with 600 mg. Site-reported primary endpoints and deaths were greater in the cangrelor arm than for patients in the clopidogrel arm loaded with 600 mg.

Because clopidogrel loading did not vary in the cangrelor arm and at some sites, we should only test the effects of the loading dose in the clopidogrel arm at the sites using both loading doses. I show the endpoint odds ratios comparing 600 mg to 300 mg loading in the clopidogrel arm at those sites in Table 6.

Table 6: Endpoint Odds Ratios at 48 Hours Comparing 600 mg to 300 mg Loading in the Clopidogrel Arm of PHOENIX at Sites Using Both Loading Doses

endpoint	OR	95% LCL	95% UCL	P
sponsor's endpoint	0.66	0.47	0.92	0.014
site-reported endpoint	0.57	0.33	0.99	0.047
any GUSTO bleed	2.2	0.84	5.8	0.105
deaths	0.26	0.09	0.80	0.019

OR = odds ratio 600mg/300mg; LCL = lower confidence limit (of OR)

UCL = upper confidence limit; P = P value

The 600 mg loading dose appears to be more effective perhaps at the expense of more bleeding. However, patients were not randomized to the 300 mg or 600 mg loading dose and we do not know how the dosages were selected. Examining baseline characteristics may help elucidate how loading doses were determined so I show selected baseline characteristics in Table 7.

Table 7: Baseline Characteristics by Loading Dose at Sites Using Both Loading Doses in PHOENIX

arm	mean age		diabetic		stable angina		minutes to PCI*	
	300 mg	600 mg	300 mg	600 mg	300 mg	600 mg	300 mg	600 mg
clopidogrel	61.8	64.1	17.8%	28.7%	40.8%	60.2%	10.8	-6.3
cangrelor		63.6		24.0%		54.5%		-1.4

*mean minutes from loading dose to PCI start; negative values indicate loading dose after PCI start

While older diabetic patients, i.e., higher risk, more frequently received a 600 mg loading dose, the patients loaded with 600 mg more frequently had an index event of stable angina. The major factor determining loading dose may have been the clopidogrel

loading timing relative to the PCI start, with the 600 mg dose used more frequently when the oral study drug was to be administered after PCI start. This greater delayed administration of the 600 mg loading dose should favor the 300 mg loading dose regarding outcomes. Loading dose remains a significant predictor of outcomes after adjustment for these factors as I show in Table 8 with a logistic regression of the sponsor's primary endpoint at 48 hours.

Table 8: Logistic Regression of Sponsor's Primary Endpoint at 48 Hours in the Clopidogrel Arm of PHOENIX at Sites Using Both Loading Doses

Logistic regression	Number of obs	=	2788
	LR chi2(5)	=	25.39
	Prob > chi2	=	0.0001
Log likelihood = -582.97334	Pseudo R2	=	0.0213

pep48h	Odds Ratio	Std. Err.	z	P> z	[95% Conf. Interval]
600 mg load	.485656	.0924904	-3.79	0.000	.3343662 .7053995
age	1.014637	.0077365	1.91	0.057	.9995861 1.029914
diabetes	.8780803	.1746731	-0.65	0.513	.5945769 1.296762
angina	1.617155	.2927221	2.66	0.008	1.134162 2.305834
hrs to PCI	.5881325	.164602	-1.90	0.058	.3398189 1.017895
_cons	.0281376	.0144412	-6.96	0.000	.0102901 .07694

The use of the 600 mg loading dose is the most significant predictor of outcome. The timing of clopidogrel (hrs to PCI) is almost a significant predictor and it is (p = 0.012) if angina is omitted from the analysis (and see the next section below.)

Loading dose may also have an effect upon bleeding as shown by the logistic regression of any GUSTO bleed by 48 hours in Table 9.

Table 9: Logistic Regression of Any GUSTO Bleed by 48 Hours in the Clopidogrel Arm of PHOENIX at Sites Using Both Loading Doses

Logistic regression	Number of obs	=	2788
	LR chi2(5)	=	7.07
	Prob > chi2	=	0.2157
Log likelihood = -162.26119	Pseudo R2	=	0.0213

any GUSTO bld	Odds Ratio	Std. Err.	z	P> z	[95% Conf. Interval]
600 mg load	2.772517	1.57514	1.79	0.073	.9105088 8.442367
age	1.0233	.0179589	1.31	0.189	.9887 1.059111
male	1.354659	.6023627	0.68	0.495	.566676 3.238361
weight	.9927052	.0121671	-0.60	0.550	.9691423 1.016841
hrs to PCI	1.275293	.853462	0.36	0.716	.3435281 4.734324
_cons	.0016133	.0028174	-3.68	0.000	.0000526 .0494567

While higher loading dose may be a risk factor for bleeding, the timing of clopidogrel appears to be unimportant, at least within the timings in PHOENIX.

The second largest subgroup by loading dose used is the subgroup of sites that used only a 600 mg loading dose. For this subgroup efficacy was greater in the cangrelor arm for

the sponsor's primary endpoint, OR 0.69 (95% CI 0.52 to 0.90, $p = 0.007$). The timing of clopidogrel administration was also later and more variable in this subgroup (mean about 9 minutes after PCI start, 41% after completion of PCI) than in the subgroup of sites using both loading doses.

COMMENT: The results in the subgroup of sites using both loading doses suggest that the 600 mg clopidogrel loading dose was more effective than the 300 mg loading dose, at least with the delayed administration of clopidogrel forced in PHOENIX. In this subgroup cangrelor appears less effective and less safe than delayed clopidogrel. The results in the subgroup of sites using the 600 mg dose suggest that the cangrelor regimen was more effective than a delayed 600 mg loading dose. A limitation of all of these analyses of sites by loading doses is that they are non-randomized subgroup analyses that we must interpret cautiously.

Event Rates by Timing of Clopidogrel

The timing of clopidogrel varied by the index event as I show in Table 10.

Table 10: Minutes from Clopidogrel Administration to PCI by Index Event in the Clopidogrel Arm of PHOENIX

index event	mean	SD*	median	IQR†
stable angina	-6.1	40.3	0	-17, 5
UA/NSTEMI	-1.8	19.6	2	-7, 7
STEMI	6.0	20.7	4	1,16

*SD = standard deviation; †IQR = interquartile range

The timings in Table 10 are for the clopidogrel arm only, although the timings for dummy clopidogrel administration in the cangrelor arm are virtually identical. The greatest variability for clopidogrel timing is in the patients with stable angina.

COMMENT: While there was variability in clopidogrel timing, it is less than what we would want to resolve definitively how clopidogrel timing affects efficacy: Clopidogrel requires about two hours to achieve near maximal pharmacodynamic effects and the European guidelines suggest that efficacy is improved by administration six to 24 hours prior to PCI. The variability in clopidogrel timing in PHOENIX is measured in minutes rather than hours. Also, we do not know the reasons for the variability, although I attempt to explore some reasons below.

Note also that clopidogrel was administered minutes before PCI in the patients presenting with STEMI. This delayed administration does not appear consistent with the protocol specification to allow immediate administration without waiting for angiography and with the concept that “time is myocardium” in STEMI patients. That care for STEMI patients may not have been optimal in PHOENIX I discuss in the next section.

Timing of clopidogrel also varied by the site loading doses as I show in Table 11.

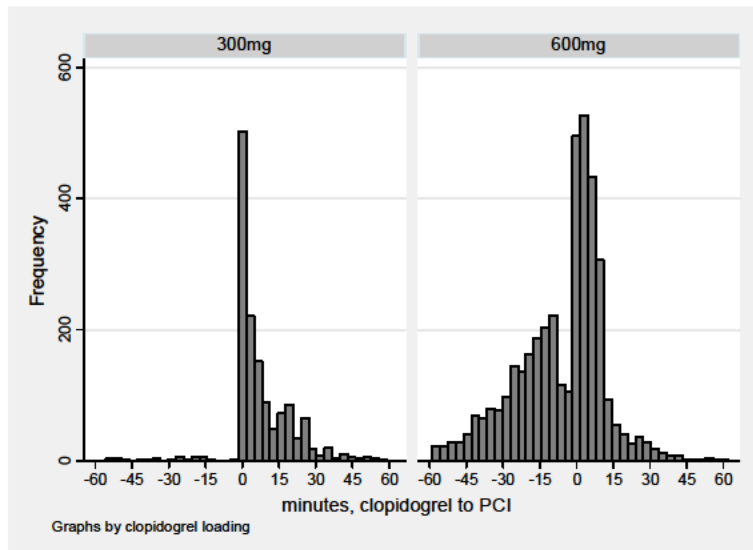
Table 11: Minutes from Clopidogrel Administration to PCI by Index Event and Site Loading Dose in the Clopidogrel Arm of PHOENIX

site loading dose:	300 mg only		600 mg only		both			
					300 mg		600 mg	
index event	mean	SD*	mean	SD*	mean	SD*	mean	SD*
stable angina	22.8	121.7	-10.8	30.0	5.5	12.4	-9.1	16.5
UA/NSTEMI	3.0	13.5	-9.4	23.0	11.7	10.8	-4.7	17.5
STEMI	2.0	5.0	3.6	25.0	18.5	22.6	1.6	17.3

*SD = standard deviation

As shown in Table 11, the 300 mg loading dose was typically administered prior to PCI. The distributions of clopidogrel timings varied by loading dose as I show in Figure 1.

Figure 1: Timing of Clopidogrel Administration by Loading Dose in the Clopidogrel Arm of PHOENIX



(outliers <-60 and >60 minutes not shown)

While the 300 mg loading dose was predominantly administered prior to PCI, the 600 mg loading dose has a bimodal distribution with modes both prior to start and after the PCI end. For about 32% of the patients the first oral study drug was administered after the completion of the PCI.

COMMENT: Given the PLATFORM results, I find it very disturbing that PHOENIX sites delayed clopidogrel administration until after PCI in a substantial number of patients.

Because of the associations of clopidogrel timing with the index event and loading doses and likely other factors, sorting out timing effects from other effects is difficult. A multivariate analysis seems appropriate. Hence I show the results of a logistic regression of the sponsor's primary endpoint at 48 hours in the clopidogrel arm of PHOENIX in Table 12.

Table 12: Logistic Regression of the Sponsor’s Primary Endpoint at 48 Hours in the Clopidogrel Arm of PHOENIX

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

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

Both the use of a 600 mg loading dose and earlier timing of clopidogrel administration are associated with better outcomes, although the association is stronger for the 600 mg loading dose.

COMMENT: Because the loading doses and their timing were not randomized it is difficult to sort out their effects from whatever investigator decision factors motivated them. However, the data do suggest that both the 600 mg loading dose and earlier timing are associated with better outcomes. We can not assume that any benefit shown by the cangrelor arm in PHOENIX is the result of a simple superiority of cangrelor over clopidogrel—the regimen (including delayed clopidogrel dosing, differential clopidogrel loading dose between the arms) likely plays a role. Both the delayed clopidogrel dosing and the differential clopidogrel loading dose between the arms could easily have—and should have—been avoided for ethical reasons and to enable PHOENIX to demonstrate the comparability of a cangrelor regimen to standard clopidogrel use.

Timing in STEMI Patients and Quality of Care

The NEJM article does not present statistics on symptom-to-balloon (PCI) times or door-to-balloon times for the STEMI patients. The sponsor’s study report makes this claim:

“Patient arrival at the catheterization laboratory was fast, with a median time from hospital admission to PCI of 4.4 hours for both cangrelor and clopidogrel treatment groups. In the STEMI subgroup, the median time from admission to PCI was faster, at 1.3 hours for both treatment groups.”

What the sponsor fails to mention is that the hospital admission time was AFTER the PCI time for 1128 patients. The sites apparently did not collect a “door” time but some or all must have collected an administrative hospital admission time.

COMMENT: The statistics based on hospital admission time are worthless. The statistics most informative regarding timing in STEMI patients are the times from symptom onset to PCI and the times from clopidogrel administration to angiography and to PCI, which I present below.

About 5% of the STEMI patients did not have an initial ischemia onset time recorded and another 5% lack a PCI time. For the STEMI patients with both recorded the median time from symptom onset to PCI was 4.9 hours and the mean time was 10.1 hours. If we assume the intent was primary PCI for patients who went to PCI within the first 24 hours, then the median time was 4.5 hours and the mean time was 6.2 hours. Fewer than 8% of STEMI patients had a PCI within 2 hours of symptom onset and about 58% had a PCI within 6 hours of symptom onset.

COMMENT: These statistics are substantially worse than the ideal of performing primary PCI in STEMI patients within 2 hours of symptom onset. Whether the study requirements affected the speed of angioplasty is impossible to determine.

While when the first angiography was done varied widely by the index event, the mean and median timings of administration of oral study drug relative to PCI varied little in PHOENIX as I show in Table 13.

Table 13: Minutes from Oral Study Drug Administration to Angiography and PCI by Intended Loading Dose in PHOENIX

index event	300mg intended loading dose				600mg intended loading dose			
	oral to angio		oral to PCI		oral to angio		oral to PCI	
	mean	median	mean	median	mean	median	mean	median
angina	-2350	-27	11.4	3	-1506	-41	-9.7	-6
UA/NSTEMI	-350	-25	7.3	2	-152	-37	-7.3	1
STEMI	-34	-2	12.7	8	-44	-17	1.4	4

The times above are for both arms but they differ minimally for each arm. In the STEMI subgroup oral study drug was administered after angiography in the majority of patients, i.e., about 68%.

COMMENT: Despite the clinical concept that “time is myocardium” in STEMI, administration of study drug was typically delayed until after angiography. I question whether this is the standard of care at the sites or whether some sites tended to treat all study patients similarly, administering study drug after angiography regardless of index event.

Event Rates at Days 3 to 30 by Index Event Type

Event rates from days 3 to 30 did not vary greatly between the two arms as I show in Table 14 and Table 15.

Table 14: Sponsor’s Endpoint Rates Days 3 to 30 by Index Event Type in PHOENIX

index event	primary endpoint		adjudicated MI		death	
	clopidogrel	cangrelor	clopidogrel	cangrelor	clopidogrel	cangrelor
stable angina	1.2%	1.1%	0.3%	0.1%	0.4%	0.3%
UA/NSTEMI	2.2%	2.4%	0.3%	0.7%	1.0%	1.0%
STEMI	2.3%	2.9%	0.2%	0.5%	1.0%	2.2%

index event	primary endpoint		adjudicated MI		death	
	clopidogrel	cangrelor	clopidogrel	cangrelor	clopidogrel	cangrelor
all	1.6%	1.7%	0.3%	0.3%	0.7%	0.8%

Table 15: Site-Reported Event Rates Days 3 to 30 by Index Event Type in PHOENIX

index event	primary endpoint		MI event	
	clopidogrel	cangrelor	clopidogrel	cangrelor
stable angina	1.7%	1.4%	0.3%	0.1%
UA/NSTEMI	2.7%	2.4%	0.6%	0.9%
STEMI	3.6%	4.6%	0.4%	0.8%
all	2.3%	2.2%	0.4%	0.4%

COMMENT: The one noteworthy variation is that STEMI patients fared slightly, but not usually statistically significantly, worse on cangrelor for days 3 to 30. For deaths days 3 to 30 the difference is nominally statistically significant (19 vs. 9, $p = 0.043$). While this may be a random subgroup variation, it seems strange to me that the group with the greatest need for good antiplatelet effect has the worst outcomes on cangrelor. Furthermore, for short term outcomes this variation is also true for another reversible P2Y₁₂ inhibitor, ticagrelor. I question whether there is a biological explanation for this variation.

The event rates from days 3 to 30 seemed low to me, so another issue regarding them is whether the reporting at day 30 was complete in this study. I address that issue next.

I show the MI and death rates from days 3 to 30 for the control arms of recent ACS trials for the UA/NSTEMI subgroups in Table 16 and for the STEMI subgroups in Table 17.

Table 16: MI and Death Rates from Days 3 to 30 for the UA/NSTEMI Subgroups in the Control Arms of Recent P2Y₁₂ Inhibitor ACS Trials

study	mean age	adjudicated MI	site-reported MI	deaths
PHOENIX	63.2	0.3%	0.6%	1.0%
PCI	62.1	0.6%	0.8%	0.6%
PLATO invasive	63.2	1.9%	1.1%	1.5%
TRITON	61.3	1.0%	0.8%	0.6%

Table 17: MI and Death Rates from Days 3 to 30 for the STEMI Subgroups in the Control Arms of Recent P2Y₁₂ Inhibitor ACS Trials

study	mean age	adjudicated MI	site-reported MI	deaths
PHOENIX	60.8	0.2%	0.4%	1.0%
PCI	61.0	1.2%	2.0%	1.8%
PLATO invasive	59.3	1.6%	1.7%	1.7%
TRITON	59.7	1.9%	1.3%	1.9%

For the ticagrelor PLATO trial I have included only the statistics for the subgroup of patients who were managed invasively. In the prasugrel TRITON trial all patients were to

undergo PCI as in the CHAMPION trials. I have included the mean ages to show that there is good consistency among the trials at least for that demographic statistic. While deaths and site-reported MIs in the UA/NSTEMI group of PHOENIX appear comparable to those in the other studies, the rest of the endpoints are substantially lower in PHOENIX.

COMMENT: There appears to be underreporting of events at 30 days in PHOENIX. The underreporting is present in both arms, so per se it is not evidence of bias. However, it does raise questions about the quality of conduct of PHOENIX. I am also concerned that the negative lean in events in the STEMI subgroup for cangrelor may be worse than reported and may be associated with worse outcomes with cangrelor in the other subgroups if reporting was complete.

CHAMPION Study Comparisons

Reasons for Not Pooling CHAMPION Studies

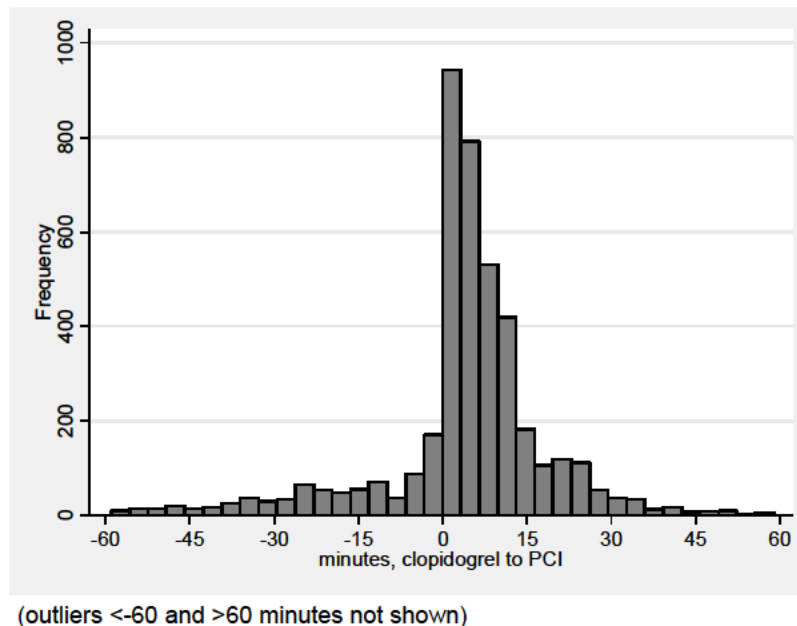
The CHAMPION Investigators recently published in Lancet a pooled analysis of all three of the CHAMPION studies (PCI, PLATFORM, and PHOENIX). (Steg, Bhatt et al. 2013) The sponsor's integrated summary of efficacy also includes such a pooled analysis. I assert that such a traditional pooled analysis of all three studies is inappropriate because the administration of clopidogrel in the control arm of PLATFORM was consistently by protocol inappropriately delayed until after the completion of PCI. I document the problems with PLATFORM in a parallel review regarding the ethicalness of the cangrelor development program. (Marciniak 2014) I will not repeat the descriptions of the many problems and my analyses of PLATFORM from that review in this review.

COMMENT: PLATFORM had nominally statistically significantly greater rates of deaths and stent thromboses at 48 hours in its clopidogrel arm. (See Table 1 above.) Its DSMB was considering stopping the trial for these findings when the sponsor convened another committee that recommended stopping the trial for futility. PLATFORM demonstrated that delaying clopidogrel administration until after PCI is inappropriate and hazardous to the patient.

PHOENIX and PCI are more similar such that we might consider combining them. However, there were five major differences in their design and conduct:

1. PHOENIX allowed a clopidogrel 300 mg loading dose in the clopidogrel arm while the PCI protocol specified a 600 mg loading dose in both arms.
2. The PCI protocol was more explicit regarding administering oral study drug after angiography so oral dosing was typically earlier in PCI than in PHOENIX (median 5 minutes to 1 minute). For example, about 11% of PCI patients received oral study drug after PCI completion compared to 32% of PHOENIX patients. I show the distribution of timing of clopidogrel administration in the clopidogrel arm of PCI in Figure 2.

Figure 2: Timing of Clopidogrel Administration in the Clopidogrel Arm of PCI



PCI does not show the bimodality of the distribution seen with the 600 mg loading dose in PHOENIX.

3. PCI enrolled patients already taking a thienopyridine while PHOENIX excluded such patients.
4. The endpoint definition was different in PCI than in PHOENIX. The pre-specified primary endpoint for PCI did not include stent thrombosis. The sponsor also alleges that in PCI and PLATFORM “The protocol definition of MI was not specific enough to differentiate between evolving pre-procedural biomarker MIs (especially as only one baseline biomarker sample was collected) and MI events that developed during PCI, when the study drug could have an effect.”
5. The index event distributions were substantially different. PHOENIX was predominantly stable angina (58%) while PCI was predominantly UA/NSTEMI (74%). The STEMI subgroup in PCI is small enough (996 patients in both arms) that any inferences based on STEMI results from PCI alone are uncertain.

COMMENT: I judge that there are sufficient differences between PCI and PHOENIX such that we should not combine their results in a traditional pooled analysis. Two of the major differences between PCI and PHOENIX (the allowance of the 300 mg loading dose and the greater delay in clopidogrel timing in PHOENIX) were discretionary changes that would be expected to increase the likelihood that the cangrelor regimen appears superior to the clopidogrel regimen—although not because of any superiority of cangrelor itself. The delay in clopidogrel loading is inappropriate particularly in view of the PLATFORM results.

While I would not combine the studies in a traditional meta-analysis, there are two special topics for which cross-study comparisons are informative (effects by index event type and by delay in clopidogrel loading) and another unique to the PCI study (effects in patients already taking clopidogrel.) I address these three topics below.

Comparison of the CHAMPION Studies by Index Event Type

I show the odds ratios for the primary endpoints in the three CHAMPION studies by index event type in Table 18.

Table 18: Odds Ratios (cangrelor/clopidogrel) for the Primary Endpoints in the CHAMPION Studies by Index Event Type

	stable angina	UA/NSTEMI	STEMI
PLATFORM	0.60	0.88	
PHOENIX	0.83	0.61-0.84*	1.00
PCI	0.88	1.09	1.05

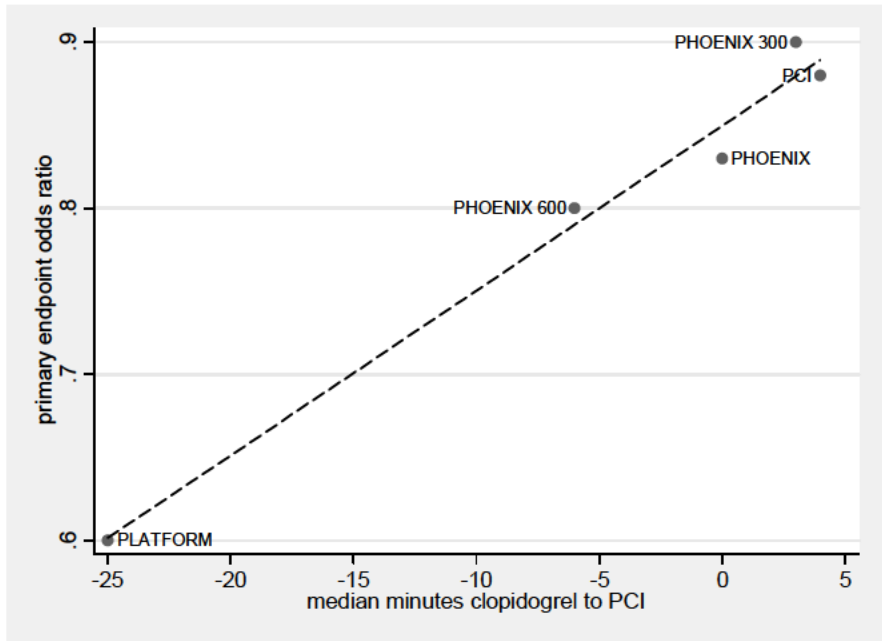
*0.84 for the site-reported primary endpoint

COMMENT: With the exception of the low odds ratio for the sponsor's UA/NSTEMI group of PHOENIX—which is not low for the site-reported primary endpoint—there is a pattern to the odds ratios. The odds ratios for the stable angina group are the most favorable. They sort in the same order as the speed of clopidogrel administration, with the lowest odds ratio in PLATFORM with the greatest delay. The odds ratios are neutral to unfavorable for the STEMI subgroups. As I mentioned earlier, ticagrelor showed unfavorable short term results for the STEMI subgroup of PLATO, so I wonder whether there is a biological explanation rather than a chance subgroup variation.

Comparison of the CHAMPION Studies by Clopidogrel Timing

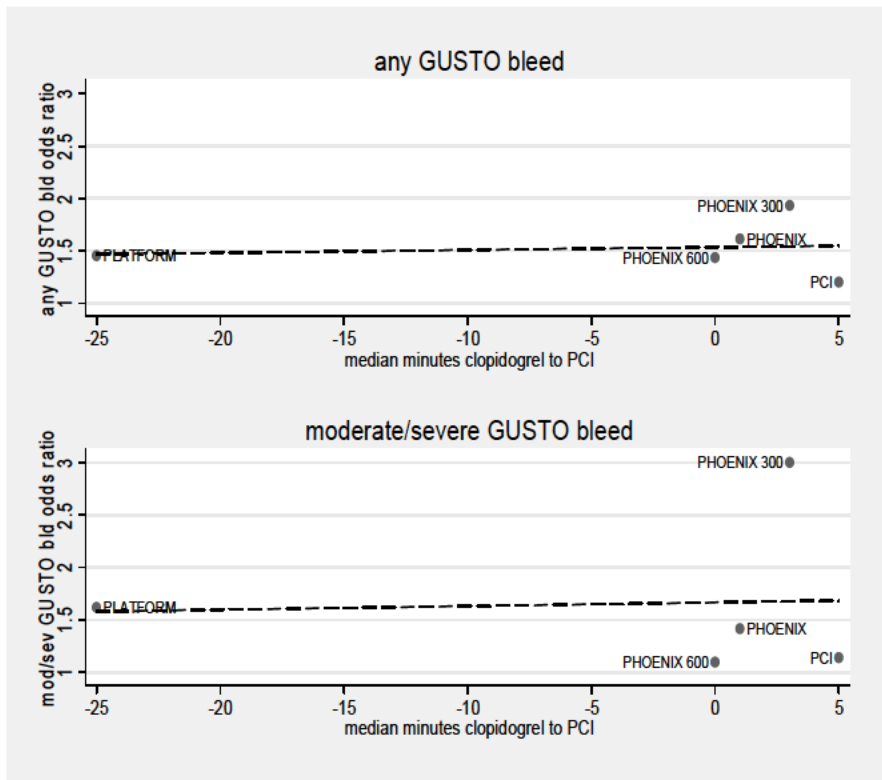
As I mentioned earlier, the sponsor has alleged that efficacy endpoint determinations were problematic in PLATFORM and PCI in the ACS subgroups. Hence the most valid cross-trial comparisons for efficacy should be for the stable angina subgroups. For bleeding the type of index event should be unimportant and, because moderate and severe bleeding events were less frequent than the efficacy endpoints, restricting to the stable angina groups is not necessary. I show a scatter plot of the odds ratios of the primary endpoints in the stable angina groups of the three trials vs. the median minutes from clopidogrel administration to PCI in Figure 3 and the odds ratios of GUSTO bleeding rates for the entire studies vs. the median minutes from clopidogrel administration to PCI in Figure 4. I have also included in the figures the results for the PHOENIX subgroups by intended loading dose because the sites consistently administered the 300 mg loading dose earlier than the 600 mg as I showed in Figure 1Figure 2 above.

Figure 3: Odds Ratios of the Primary Endpoints in the Stable Angina Groups of the CHAMPION Trials vs. Median Minutes from Clopidogrel Administration to PCI



(PHOENIX 300 and 600 are the PHOENIX subgroups by intended loading dose)

Figure 4: Odds Ratios of GUSTO Bleeding Rates in the CHAMPION Trials vs. Median Minutes from Clopidogrel Administration to PCI



COMMENT: The greater the delay in administering clopidogrel the better cangrelor looked for efficacy. The relative risk of bleeding did not vary greatly by clopidogrel timing. While I did not include error bars or confidence limits in Figure 3, what is striking to me is the pattern of the point estimates. I also find it convincing that the pattern is real because PLATFORM showed more deaths and stent thromboses in the clopidogrel arm with the long delay in administration, the logistic regressions of the PHOENIX data suggest the same pattern, and there is biological plausibility based on the clopidogrel PK/PD data.

The various delays of clopidogrel administration likely explain the differing results from the three trials and all of the “superiority” of cangrelor: In PLATFORM, with clopidogrel delayed until after PCI, the clopidogrel regimen performed poorly as also evidenced by its greater death and stent thrombosis rates. In PCI, with the earliest but still not optimal timing for clopidogrel administration, there is no clear evidence for superiority of the cangrelor regimen. In PHOENIX, with intermediate timing, the results for the overall trial are also intermediate and segregate for the different timings in the two intended loading dose groups consistent with the cross-trial comparisons—timing of clopidogrel appears to be the more significant factor than the magnitude of the loading dose.

Note that the data do not suggest that administering clopidogrel five minutes before PCI is optimal. There is no suggestion that the diminishing relative efficacy with increasing time of clopidogrel administration before PCI is plateauing at the right of Figure 3. If we extrapolate the line the predicted time at which the odds ratio is 1.0 is about 15 minutes prior to PCI. The data are biologically plausible and consistent with clopidogrel PK and PD that, if the critical time for antiplatelet effect is the start of PCI when plaques and endothelium are eroded, more than five minutes is needed for optimal clopidogrel antiplatelet effect. While we do not know how the cangrelor regimen would compare to clopidogrel administered earlier than 5 or 15 minutes prior to PCI, our expectation based on these data is that the “superiority” of cangrelor would erode more and possibly clopidogrel would be superior to cangrelor. The European guidelines, based on similar analyses of non-randomized timings of clopidogrel in the clopidogrel trials, suggest that administering clopidogrel 6 to 24 hours prior to PCI is advantageous.

For prasugrel, the results of the ACCOAST trial suggest that loading prasugrel prior to angiography produced more bleeding but not greater efficacy than loading prasugrel after angiography at the time of PCI. (Montalescot, Bolognese et al. 2013) However, prasugrel is a faster, better platelet inhibitor than clopidogrel so I do not think that the ACCOAST results can be extrapolated to clopidogrel. Furthermore, prasugrel may offer the same advantage of cangrelor (delaying administration until after angiography) plus possibly a mortality benefit early in STEMI.

Finally, ticagrelor also may offer advantages over clopidogrel but we do not know whether use with cangrelor affects these advantage. Hence we don’t know whether to use ticagrelor with cangrelor or instead of cangrelor.

Cangrelor in Added to Background Clopidogrel in the PCI Study

PCI was the only one of the CHAMPION trials that allowed patients already taking a thienopyridine to be randomized. In PCI 34% of patients had taken a thienopyridine (clopidogrel in all but a handful) within the five days prior to randomization. I show the primary endpoint rates by arm and prior clopidogrel use in Table 19.

Table 19: Primary Endpoint and Bleed Rates by Prior Clopidogrel Use in PCI

	primary endpoint		GUSTO mod/sev		any GUSTO bld	
	clopidogrel	cangrelor	clopidogrel	cangrelor	clopidogrel	cangrelor
no prior clopidogrel	6.6%	7.3%	0.9%	1.2%	17.0%	21.3%
prior clopidogrel	6.8%	6.5%	1.3%	1.0%	18.3%	18.4%

The point estimate for the primary endpoint rate in the cangrelor arm in patients without prior clopidogrel use is slightly higher than those for the other subgroups. However, the interaction between treatment and prior clopidogrel use is not statistically significant. The bleeding rates were also higher in the cangrelor arm in patients without prior clopidogrel use. The interaction between bleeding and cangrelor use is nominally statistically significant as shown in the logistic regression in Table 20.

Table 20: Logistic Regression of Any GUSTO Bleed in the PCI Study

Logistic regression	Number of obs	=	8880
	LR chi2(6)	=	43.85
	Prob > chi2	=	0.0000
Log likelihood = -4279.4506	Pseudo R2	=	0.0051

any GUSTO bld	Odds Ratio	Std. Err.	z	P> z	[95% Conf. Interval]
cangrelor	1.325022	.0886596	4.21	0.000	1.162164 1.5107
prior clop.	1.094032	.0905058	1.09	0.277	.9302779 1.286611
interaction	.7651691	.0883201	-2.32	0.020	.6102488 .959418
age	.9997847	.0024814	-0.09	0.931	.994933 1.00466
weight	.999617	.0015198	-0.25	0.801	.9966428 1.0026
male	.7421594	.0462227	-4.79	0.000	.6568758 .8385157
_cons	.2646358	.0605331	-5.81	0.000	.1690222 .4143367

COMMENT: I do not have a clinical explanation for cangrelor use in patients on clopidogrel leading to both greater efficacy and lower bleeding than cangrelor use in patients not on clopidogrel but nearly identical to clopidogrel use in patients on clopidogrel. There is no strong evidence for an interaction between prior clopidogrel use and cangrelor effect but neither do the data rule one out.

Benefit-Risk of Cangrelor

My interpretation of the CHAMPION trials is that they demonstrated that a cangrelor regimen including a clopidogrel 600 mg loading dose is slightly more efficacious than a bad clopidogrel regimen with delayed clopidogrel loading. The major limitation of any perceived greater efficacy is that clopidogrel was loaded badly ranging from questionably (after angiography) in PCI to horribly (after PCI) in PLATFORM. The CHAMPION trials provide evidence that earlier administration of clopidogrel is better by both the cross-trial comparisons and by logistic regressions of the PHOENIX data. If clopidogrel had been administered consistently earlier in the CHAMPION trials it is possible that clopidogrel would be shown superior to cangrelor.

There are several other limitations of the cangrelor “superior” efficacy:

- The cangrelor regimen was only statistically significantly superior for the sponsor’s primary endpoint including predominantly “chemical” MIs. The fact that the primary endpoint rates in PHOENIX in the stable angina arm were about 6% at 48 hours illustrates that the PHOENIX endpoint was not a typical MACE endpoint. For benefit-risk evaluations I favor using the site-reported endpoints which reflect events rather than troponin increases. There is no cangrelor superiority for site-reported events.
- We can’t even be confident that the “superiority” is related to cangrelor: The only successful trial was PHOENIX, in which both 300 mg and 600 mg loading doses were used in the clopidogrel arm while only 600 mg was used in the cangrelor arm. In PCI and PLATFORM 600 mg was used in both arms and the cangrelor regimen was not superior to the clopidogrel alone regimen. PHOENIX provides some evidence that the 600 mg loading dose was more effective than the 300 mg loading dose for the sponsor’s primary endpoint in the clopidogrel arm. However, it also provides some evidence that the cangrelor regimen with 600 mg loading was superior to the delayed 600 mg loading alone. We don’t know whether clopidogrel 600 mg is the optimal loading dose for cangrelor—but the more important question is whether prasugrel or ticagrelor should be used with cangrelor rather than clopidogrel.
- The “superiority” is only statistically significant in the stable angina subgroup. While there are no statistically significant interactions between index event type and treatment in PHOENIX, the point estimate for the odds ratio for the primary endpoint is neutral at 48 hours and unfavorable for cangrelor at 30 days—with mortality unfavorable at 30 days. The PCI and PLATFORM results also suggest that the cangrelor benefit is predominantly for stable angina. Yet stable angina is the condition for which cangrelor offers minimal advantages if any: We can easily load stable angina patients with clopidogrel 24 hours before PCI (as the ESC guidelines recommend) and we can delay CABG for days if the anatomy elucidated at angiography is unsuitable for PCI.

- Both prasugrel and ticagrelor are superior to clopidogrel for efficacy. We don't know how a cangrelor regimen compares to a prasugrel or ticagrelor regimen. We don't know whether there is any advantage to using cangrelor at all.

There does not appear to be any real superiority for efficacy of the cangrelor regimen over a clopidogrel regimen with clopidogrel administered sufficiently prior to PCI. Furthermore, even the alleged efficacy "superiority" shown in PHOENIX is further limited by the facts that the superiority is predominantly based on "chemical" MIs and not events, is marginal in the UA/NSTEMI subgroup and nonexistent in the STEMI subgroup, and is completely uncertain compared to ticagrelor and prasugrel. For the STEMI subgroup in PHOENIX the 30 day data even provide some evidence of concerning inferiority, i.e., more deaths. The UA/NSTEMI and STEMI subgroups, and not the stable angina subgroup, are the ones for which a rapid onset and offset of platelet inhibition would be clinically useful.

Against this lack of substantial evidence of superiority or even noninferiority regarding efficacy there is consistent evidence that the cangrelor regimen caused more bleeding in all three CHAMPION trials. I will not review all of the bleeding data here but suggest reading the safety section of the primary clinical review. Figure 4 above shows that the odds ratios for GUSTO bleeding, both any and severe, were typically about 1.5 for the CHAMPION trials. Moderate or severe bleeding was uncommon so that the absolute difference in moderate or severe bleeds within 48 hours in PHOENIX was about 0.2%, rising to 0.4% if one considers any transfusion to convey an increased thrombotic risk. Relative bleeding risk did not increase with earlier administration of clopidogrel, so the net clinical "benefit" of the cangrelor regimen compared to an appropriately timed clopidogrel only regimen is a net clinical detriment of an increased net event rate of about 0.2% to 0.4%.

Our laws do not require a new drug to be superior to older drugs in order to be approved. Our laws require substantial evidence of safety and effectiveness. One could argue that the CHAMPION trials provide such evidence despite the lack of clear superiority. I would argue that, for irreversible outcomes such as mortality and MIs, we should not approve a drug if we do not have substantial evidence that such outcomes are not adversely affected. For STEMI patients with cangrelor we lack such substantial evidence and one could argue that the evidence for noninferiority is not substantial for the UA/NSTEMI patients either.

Finally, there is another reason for denying approval of cangrelor: the ethicalness of the cangrelor trials. I discuss that reason in detail in a parallel review. (Marciniak 2014)

References

- Bhatt, D. L., A. M. Lincoff, et al. (2009). "Intravenous platelet blockade with cangrelor during PCI." N Engl J Med **361**(24): 2330-41.
- Bhatt, D. L., G. W. Stone, et al. (2013). "Effect of Platelet Inhibition with Cangrelor during PCI on Ischemic Events." New England Journal of Medicine **368**(14): 1303-1313.
- Harrington, R. A., G. W. Stone, et al. (2009). "Platelet inhibition with cangrelor in patients undergoing PCI." N Engl J Med **361**(24): 2318-29.
- Marciniak, T. A. (2014). Clinical Review: Ethicalness of the cangrelor development program, FDA.
- Montalescot, G., L. Bolognese, et al. (2013). "Pretreatment with Prasugrel in Non- ST -Segment Elevation Acute Coronary Syndromes." New England Journal of Medicine **369**(11): 999-1010.
- Steg, P. G., D. L. Bhatt, et al. (2013). "Effect of cangrelor on periprocedural outcomes in percutaneous coronary interventions: a pooled analysis of patient-level data." Lancet **382**(9909): 1981-92.

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/s/

THOMAS A MARCINIAK
01/13/2014

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	204958
Priority or Standard	Standard
Submit Date	01 May 2013
Received Date	02 May 2013
PDUFA Goal Date	30 Apr 2014
Division / Office	DCaRP/ODE I
Reviewer Names	Fred Senatore MD, PhD, FACC B. Nhi Beasley Pharm.D.
Review Completion Date	13 January 2014
Established Name	To be determined
(Proposed) Trade Name	To be determined
Therapeutic Class	P2Y ₁₂ receptor antagonist
Applicant	The Medicines Company
Formulation(s)	intravenous

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

Template Version: March 6, 2009

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List of Abbreviations

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

Clinical Review

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NDA 204958

Cangrelor

NPV	Negative Predictive Value
NSTEACS	Non-ST segment elevation acute coronary syndrome
NSTEMI	Non-ST segment elevation myocardial infarction
OR	Odds Ratio
P (int)	P value of interaction using Breslow-Day test
PAD	Peripheral Arterial Disease
PCI	Percutaneous Coronary Intervention
PD	Pharmacodynamic
PK	Pharmacokinetic
PP	Per Protocol population
PPI	Percent Platelet Inhibition
PPV	Positive Predictive Value
PRU	P2Y ₁₂ or Platelet Reactivity Unit (interchangeable)
QC	Quality Control
QD	Once a day (i.e. scheduled administration of drug)
QWMI	Q-wave Myocardial Infarction
RCA	Right Coronary Artery
RCT	Randomized Clinical Trial
ROC	Receiver Operator Characteristic
RPR	Residual Platelet Reactivity
RR	Risk Reduction
SA	Stable Angina
SAP	Statistical Analysis Plan
SIHD	Stable Ischemic Heart Disease
ST	Stent Thrombosis
STEMI	ST segment elevation myocardial infarction
TEAE	Treatment-emergent adverse event
TIA	Transient Ischemic Attack
TIMI	Thrombolysis in Myocardial Infarction
TLR	Target Vessel Revascularization
TVR	Target Lesion Revascularization
UA	Unstable Angina
UDMI	Universal Definition Myocardial Infarction
URL	Upper Reference Limit

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

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

The basis of this recommendation is:

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

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

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

Bridge to Surgery Indication: We recommend a Complete Response to the proposed separate indication to maintain P2Y₁₂ inhibition in patients with acute coronary syndrome or with stents who are at increased risk for thrombotic events (such as stent thrombosis) when oral P2Y₁₂ Inhibitor therapy is interrupted due to surgery.

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

- Lack of clinical data from BRIDGE to support the PD effect at the proposed Bridging dose.
- The clinical efficacy observed in the PHOENIX trial is not applicable to the Bridging indication because of the five-fold lower dose used in BRIDGE.
- Literature-based evidence suggesting no relationship between the PD effect from the VerifyNow PRU data and clinical outcome as well as inconsistent and conflicting results regarding pre-CABG P2Y₁₂ inhibition therapy.

1.2 Risk Benefit Assessment

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

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

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

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

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Postmarket Requirements and Commitments

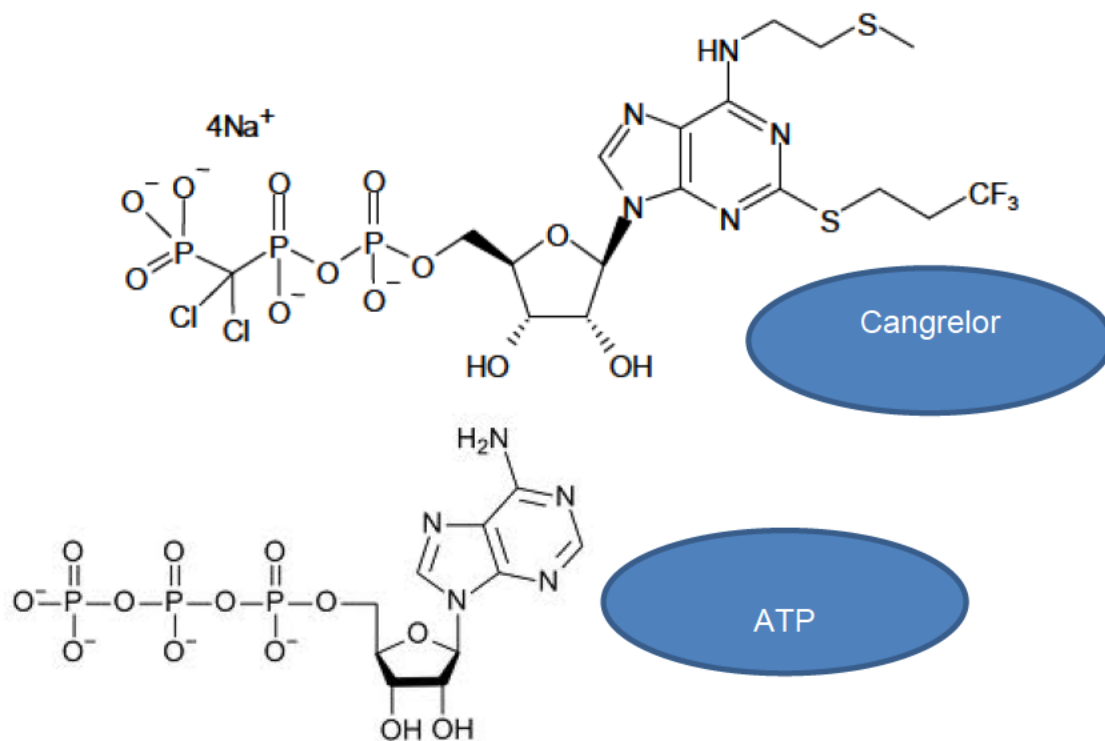
None

2 Introduction and Regulatory Background

2.1 Product Information

Cangrelor is an intravenous (IV), direct acting, reversible competitive inhibitor of P2Y₁₂ receptor that blocks adenosine diphosphate (ADP)-induced platelet activation and aggregation. Cangrelor has been identified as FPL-69931MX, ARL-69931MX, AR-C69931MX, The chemical name of cangrelor is tetrasodium salt of N6-[2-(methylthio)ethyl]-2-[(3, 3, 3 trifluoropropyl) thio]-5'-adenylic acid, monoanhydride with (dichloromethylene) bisphosphonic acid. Cangrelor is an ATP analogue ([Figure 1](#)).

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



2.2 Tables of Currently Available Treatments for Proposed Indications

The five classes of approved anti-platelet drugs are described in [Table 1](#). Prasugrel is the only agent which explicitly includes “stent thrombosis” in its indication. There are no drugs approved as a bridge to surgery.

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

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

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

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

2.3 Availability of Proposed Active Ingredient in the United States

N/A

2.4 Important Safety Issues with Consideration to Related Drugs

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

Elinogrel, a P2Y₁₂ inhibitor, was being developed for the treatment of acute coronary syndrome and prevention of secondary thrombotic events. Elinogrel showed rapid inhibition of ADP-mediated platelet response and complete reversal within 24 hours of discontinuation. A randomized, double-blind dose ranging Phase 2b trial (Welsh, R, et al., 2012, INNOVATE-PCI) was conducted where 652 subjects received either oral clopidogrel load + maintenance, or IV Elinogrel load plus oral elinogrel maintenance.

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

2.5 Summary of Presubmission Regulatory Activity Related to Submission

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

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

- CHAMPION PHOENIX focused on P2Y₁₂ naïve subjects. Patients undergoing PCI should be pretreated with clopidogrel as the standard of care.
- One clinical trial similar to the CHAMPION trials (i.e. PCI, PLATFORM) demonstrating a decrease in death/Q-MI/acute stent thrombosis is likely to be sufficient for a NDA submission.
- A priority review request would require evidence that cangrelor is superior to all available therapies. There is no data comparing cangrelor to either prasugrel or ticagrelor, both of which are superior to clopidogrel.
- BRIDGE and PHOENIX would be viewed as two separate indications.
- CHAMPION studies should be presented as individual trials and analyzed as specified in each protocol.
- The Division understood that neither thrombotic nor bleeding events were adjudicated in BRIDGE and requested the BRIDGE adjudication committee charter, all adjudication packages, and an adjudication data file.
- The Division requested that the Applicant review the value of using Verify-Now results for determining the type and dose of thienopyridine and other platelet P2Y₁₂ inhibitors. The Applicant agreed to provide relevant data in the dossier.
- The Division requested the Applicant calculate the actual event rate of stent thrombosis in those patients who discontinued clopidogrel and include information on whether the stent was a drug eluting stent (DES) or bare metal stent (BMS) as well as stent characteristics (diameter, length).
- From the GRAVITAS trial, post-PCI patients randomized to high or standard doses of clopidogrel had identical proportions of patients with death, MI, or stent thrombosis. Furthermore, the proportion of patients with GUSTO severe or major bleeding was higher in the group randomized to the standard dose of clopidogrel which had a higher level of PRU. This suggested that treatment-driven changes in Verify-Now based PRU results may not be useful in predicting the risk of either CV events or bleeding complications.

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

2.6 Other Relevant Background Information

No other relevant clinical background.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

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

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

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

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

3.2 Compliance with Good Clinical Practices

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

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

3.3 Financial Disclosures

The Applicant has certified that there was no financial arrangement with investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). The Applicant also certified that no investigator disclosed any proprietary interest in the drug or significant equity in the Applicant as defined in 21CFR54.2(b), and that no investigator was the recipient of significant payments of other sorts as defined in 21CFR 54.2(f).

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Based on the ONDQA Review, the recommendation and conclusion on approvability was to “recommend approval from CMC perspective on receipt of an overall acceptable recommendation from CDER Office of Compliance”. The review listed all but one evaluation as adequate. One evaluation assessed as inadequate concluded that the “ability of cangrelor to meet its related substance acceptance criteria while being stored in the diluents has not been demonstrated”. Data will have been requested from the Applicant and this was conveyed to the Applicant on 18 OCT 2013.

Based on this review, there does not appear to be any clinically impactful issues.

4.2 Clinical Microbiology

The Applicant stated that cangrelor injection is a preservative free sterile product which is aseptically filtered, filled under sterile nitrogen in a sterile area, and lyophilized in an aseptic environment. The Applicant also stated that the primary container (glass vial and stopper) provides adequate barrier to microbial ingress (CTD section 3.2.P.2.5). Review by Microbiology specified that the conclusions of the growth promotion study are not reflected in product labeling. Product labeling indicates that the drug product diluted in either diluent may be stored at room temperature for 24 hours whereas the growth promotion submitted on 09 October 2013 concluded that product diluted in 5% Dextrose may be stored at room temperature for only 12 hours. The suggested hold period for saline, at 24 hours, was supported by the study and was therefore acceptable.

4.3 Preclinical Pharmacology/Toxicology

Salient features from the finalized Pharmacology/toxicology review include the following:

- Cangrelor was evaluated in a series of toxicity studies in-vitro and in dogs and rats which were considered appropriate models for humans due to pharmacological similarity between dogs, rats, and humans. The primary adverse effects of cangrelor in rats and dogs consisted of injury to renal tubules, renal pelvis, and ureter (caused by the parent molecule). Anatomic changes correlated with increased plasma creatinine and urea, and increased albumin and red blood cells in urine. The changes in the kidney tubules and ureter tended to reverse upon cessation of treatment.

- Based on in-vitro and in-vivo genetic toxicity studies involving bacterial mutagenicity, mouse lymphoma tyrosine kinase, in-vitro human peripheral lymphocyte chromosome aberration, and mouse bone marrow micronucleus assays, there was no evidence of genotoxicity.
- In the rat EFD study, cangrelor produced dose-related fetal growth retardation characterized by incidences of incomplete ossification and ossified hind limb metatarsals. In the rabbit EFD study, cangrelor was associated with increased incidences of abortion and intrauterine losses. There was no additional teratogenicity in either the rat or rabbit EFD studies, respectively.
- The exposure safety margin for the BRIDGE setting at the NOAEL doses in the 1 month toxicity studies ranged from 4 to 5 fold for cangrelor and 3 to 5 fold for the metabolite AE-C69712CXX, and were several-fold higher in regard to exposure at doses that were not associated with histological changes to the kidney and urinary tract.
- The proposed dose of 30 ug/kg followed by 4 ug/kg/min for 2 hours (in the PCI setting) exceeds the NOAEL in dogs (AUC_{0-28d} 53957 ng*h/ml) by ~8-fold.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Cangrelor is an intravenous direct-acting P2Y₁₂ receptor antagonist that blocks adenosine diphosphate (ADP)-induced platelet activation and aggregation.

4.4.2 Pharmacodynamics

Key points in the pharmacodynamic studies as described by the Applicant were:

- Cangrelor is a reversible competitive inhibitor with a half-life of 3-6 minutes.
- Pre-clinical studies showed a concentration-dependent (in-vitro) inhibition of ADP-induced platelet aggregation and a dose-related (in-vivo dog model) inhibition of thrombosis with little effect on bleeding time.
- Based on two clinical studies (SC-931-5058 and SC-931-5129), the Applicant identified the highest infusion tested (4ug/kg/min) as the dose maintaining steady-state lowest platelet reactivity to 3uM ADP within 15-30 minutes of initiating infusion.
- In order to achieve rapid reduction in ADP-mediated platelet reactivity, study TMC-CAN-04-02 was performed and showed that the highest bolus of 30ug/kg antecedent to the highest infusion of 4ug/kg/min produced complete IPA measured by blood impedance aggregometry within 2 minutes.

- The dosing regimen for the BRIDGE indication was based on Stage 1 of the BRIDGE study (0.75ug/kg/min infusion). The Applicant opined that from a population PK/PD model based on several studies (TMC-CAN-05-02-S1, TMC-CAN-05-03-S1, TMC-CAN-08-02 {BRIDGE study}) there was a lower probability of achieving a PRU threshold in the PCI population compared to the BRIDGE population. Therefore, the Applicant felt that the dosing regimen for the PCI population should be higher than that for the BRIDGE population. Based on TMC-CAN-04-02, the selected dosing regimen for the PCI indication was 30ug/kg bolus and 4ug/kg/min infusion.

4.4.3 Pharmacokinetics

The plasma pharmacokinetic properties of cangrelor were linear and dose-proportional at a dose range from 4.8 to 60ug/kg/min (Table 2.6.4.3-2 CTD-Pharmacokinetic Written Summary). Steady-state plasma levels of cangrelor were attained 10-60 minutes following initiation of infusion. Elimination was rapid and biphasic with an initial $t_{1/2}$ of 1-2 minutes and a terminal half-life of 1-4 hours. Approximately 90% of the total cangrelor dose was cleared from plasma during the initial elimination phase.

Cangrelor was rapidly inactivated via de-phosphorylation to metabolic byproducts which were eliminated mainly through the biliary route (80% in 48 hours) with 15% of the total dose recovered in the urine within 24-48 hours post-dose.

5 Sources of Clinical Data

Cangrelor has been evaluated in 16 clinical trials, including four pivotal trials ([Table 2 and Table 3](#)). Doses of cangrelor have included a range of IV boluses up to 60ug/kg, and an IV infusion ranging from 0.01 to 8ug/kg/min. The four pivotal trials described in [Table 2](#) support efficacy and safety: CHAMPION-PCI (TMC-CAN-05-02), CHAMPION-PLATFORM (TMC-CAN-05-03), CHAMPION PHOENIX (TMC-CAN-10-01), and BRIDGE (TMC-CAN-08-02).

5.1 Tables of Studies/Clinical Trials

See [Table 2](#) for a description of the four pivotal trials conducted for the proposed indications.

CHAMPION-PCI and CHAMPION-PLATFORM failed to meet their respective primary endpoints. Post-hoc analyses of PLATFORM and PCI led to the PHOENIX hypothesis and development of new primary endpoints. Therefore, the PHOENIX trial was the sole trial supporting the PCI claim.

The BRIDGE trial is the sole trial for evaluation of the proposed claim to maintain P2Y₁₂ inhibition in patients who are at increased risk of thrombotic events (such as stent

thrombosis) when oral P2Y₁₂ therapy is interrupted due to surgery. The BRIDGE trial was a PD study evaluating platelet reactivity of cangrelor vs. placebo. The Applicant provided published literature of clinical data designed to demonstrate three key items pursuant to their program hypothesis: 1) high association between platelet reactivity and thrombotic events (POPULAR trial and ADAPT-DES trial); 2) risk of thrombosis if oral P2Y₁₂ therapy is discontinued 5-7 days prior to CABG (Dutch Stent Thrombosis Registry Registry); and 3) risk of bleeding if oral P2Y₁₂ therapy is discontinued too close to CABG (two meta-analyses and one review article).

In the Dutch Stent Registry Study (Van Werkum, JW, et al., 2009), a total of 21,009 patients were reviewed from which two cohorts were selected. A total of 437 patients with angiographically demonstrated ST and 866 matched control patients were selected for analysis. The control group did not have angiographically demonstrated ST but were matched for PCI indication, same date of index PCI, and same intervention center. The median follow-up time was 30.9 months (25th percentile: 23.6 months; 75th percentile 41.9 months).

Table 2. Pivotal Trials

TRIAL	Study Design	ITT Sample Size	Subject Description	Primary objective	Primary End Point
CHAMPION-PCI (TMC-CAN-05-02)	Prospective, randomized (1:1), double-blind, double-dummy, active-control, parallel-group Active control: clopidogrel 600 mg	8,877 Cangrelor: 4,433 Clopidogrel: 4,444	UA/NSTEACS/STEMI patients amenable to PCI	To demonstrate that the efficacy of cangrelor was superior to that of clopidogrel 600 mg in patients requiring percutaneous coronary intervention (PCI) as measured by a composite of all-cause mortality, myocardial infarction (MI), and ischemia-driven revascularization (IDR) at 48 hours	Composite of all-cause mortality, MI, and IDR 48 hours after randomization
CHAMPION-PLATFORM (TMC-CAN-05-03)	Prospective, randomized (1:1), double-blind, double-dummy, placebo-control, parallel-group over standard of care: including clopidogrel 600mg	5,364 Cangrelor: 2,695 Placebo: 2,669	UA/NSTEACS patients amenable to PCI	To demonstrate that the efficacy of cangrelor (combined with usual care) was superior to that of usual care, in subjects requiring percutaneous coronary intervention (PCI) as measured by a composite of all-cause mortality, myocardial infarction (MI), and ischemia-driven revascularization (IDR)	Composite of all-cause mortality, MI, and IDR 48 hours after randomization
CHAMPION-PHOENIX (TMC-CAN-10-01)	Prospective, randomized (1:1), double-blind, double-dummy, active-control, parallel-group Active control: clopidogrel 300 mg or 600 mg	11,145 Cangrelor: 5,581 Clopidogrel: 5,564	UA/NSTEACS patients amenable to PCI	To demonstrate that in patients requiring percutaneous coronary intervention (PCI), cangrelor provides superior efficacy to clopidogrel standard of care, as measured by a composite of all-cause mortality, myocardial infarction (MI), ischemia-driven revascularization (IDR) and stent thrombosis	Composite of all-cause mortality, MI, IDR and ST 48 hours after randomization: MI: as per UDMI ST: as per ARC
BRIDGE (TMC-CAN-08-02)	Stage 1: Prospective, open label, dose-finding, multi-center. Stage 2: Prospective, double-blind, placebo-controlled, randomized, multi-center.	Stage 1: 11 Stage 2: 207 (n=106 cangrelor; n=101 placebo)	Patients requiring bridging from oral thienopyridine therapy prior to cardiac surgery	To demonstrate that intravenous (IV) cangrelor, compared to standard of care (SOC) provides effective and consistent P2Y ₁₂ inhibition below levels known to be associated with a low risk of thrombotic events up to the time of surgery, without increasing surgical bleeding	Stage 1: Maintenance of platelet inhibition > 60% in at least 80% patient samples by VerifyNow P2Y ₁₂ point of care assay. Stage 2: percentage of patients with PRU < 240 as determined by VerifyNow P2Y ₁₂ point of care assay measured during study drug infusion pre-surgery.

Cangrelor Dose: CHAMPION trials: 30ug/kg IV bolus + 4ug/kg/min IV infusion x 2-4 hours;
BRIDGE: Stage 1: 0.5ug/kg/min or 0.75ug/kg/min or 1.0ug/kg/min or 1.5ug/kg/min IV infusion,
Stage 2: 0.75ug/kg/min IV infusion 48 hours or more;

Table 3. Additional 12 trials included in the ISS

Trial	Study design	Subjects treated (cangrelor treated) Subject type	Objectives	Cangrelor max infusion (ug/kg/min)	Max duration
SC-931-5014	DB, PC	40 (28) HV	PK, PD [†]	0.0005 – 4	≤ 24 h
SC-931-9017	OL	4 (4) HV	ADME cangrelor & metabolite	2	2 h
SC-931-5037	DB, PC, XO	12 (12) HV	Effects of aspirin, heparin, and nitroglycerin on safety, PK, PD	2	3 h 45 min
SC-931-5036	DB, PC	23 (15) HV	PK, PD	0.1 – 4	≤ 24 h
TMC-CAN-04-02	OL	42 (42) HV	PK, PD transition to /from clopidogrel	1.5 – 4.2 [‡]	2 h
TMC-CAN-08-01	DB, PC, moxifloxacin control, XO	71 (71) HV	cardiac repolarization	3.7 – 8*	3 h
SC-931-5109	OL	24 (24) HV renal impaired	PK, PD	1.6 – 3.2	5 h
SC-931-5058	OL, stepped dose titration	39 (39) UA/NQWMI BRIDGE indication	PK, PD [†]	2 - 4	72 h
SC-931-5060	DB, PC	91 (45) UA/NQWMI BRIDGE indication	PK	4	72 h
SC-931-5129Pt1	DB, PC	200 (149) Not STEMI; PCI	PK, PD [†]	1 - 4	24 h
SC-931-5129Pt2	OL, abciximab control	199 (105) Not STEMI; PCI	PD [†]	4	24 h
SC-931-5135**	OL, alteplase control	92 (85) STEMI	Compare coronary artery patency	0.3 – 5.2	72 h

Reviewer's analysis: exposure\indose, Applicant datasets: iss disp, isd

ADME=absorption, distribution, metabolism, excretion, DB=double-blind, h=hour, HV=healthy volunteers, OL=open label, PC=placebo-controlled, PD=pharmacodynamics, PK=pharmacokinetic, XO=crossover

[†] ADP-induced platelet aggregation

[‡] 15 or 30 ug/kg IV bolus prior to infusion

* 30 or 60 ug/kg IV bolus prior to infusion

**prematurely terminated because of "reprioritization of drug development candidates by Astra Zeneca"

5.2 Review Strategy

Dr. Senatore reviewed efficacy. The review strategy to evaluate efficacy to support the PCI claim focused on the CHAMPION PHOENIX trial as the sole basis of a regulatory recommendation. This strategy was based on the fact that the uniquely crafted PHOENIX primary efficacy endpoint was derived from post-hoc analyses of the previous CHAMPION trials and was distinct from the endpoints of those trials. Key items of the review strategy included:

- Evaluation of the adjudication process leading to the diagnosis of IPST, considered a biomarker and its prognostic significance from the PHOENIX data. This was considered a strategic action item because IPST drove the ST endpoint which subsequently drove the composite primary efficacy endpoint.
- Evaluation of the adjudication process leading to the diagnosis of UDMI type 4a, as opposed to type 4b, the former which was a co-driver of the primary endpoint and the latter which was associated with ST.

The review strategy to evaluate efficacy data to support the Bridge claim associated with surgery included:

- Evaluation of the Verify-Now P2Y₁₂ assay as a prognostic indicator for clinical events.
- Evaluation of thrombotic events from BRIDGE and the Dutch Registry.
- Evaluation of P2Y₁₂ therapeutic impact on bleeding risk from the meta-analyses and literature review provided by the Applicant which addressed this risk.

Dr. Beasley reviewed safety. The review strategy for safety focused on the primary safety concern, bleeding, in the PHOENIX trial since PHOENIX contained substantive data to support safety; the other CHAMPION trials were stopped for futility, not for safety. Data from the other CHAMPION trials were examined to aid with interpretation of subgroup analyses. Other safety analyses included analyses of the ISS dataset (16 trials) for AEs, SAEs, and clinically significant laboratory findings.

Drs. Senatore and Beasley reviewed the risk benefit. The risk benefit analysis was approached from the perspective of evaluating the degree of benefit relative to the degree of risk. The degree of clinical benefit was small (e.g. driven by subjects with stable angina who were thienopyridine naïve, evidence of effectiveness only in the PCI setting, loss of efficacy beyond 48 hours when subtracting IPST from the primary endpoint). Consequently, there was less tolerance for bleeding. The safety review incorporated many bleed classifications in order to ensure a comprehensive and balanced approach to evaluating safety.

The four pivotal trials are discussed in Section 5.3.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 CHAMPION PCI

The objective of CHAMPION PCI was to demonstrate that the efficacy of cangrelor was superior to that of clopidogrel in subjects requiring PCI as measured by the primary efficacy endpoint: composite of all-cause mortality, MI, and IDR assessed 48 hours after randomization.

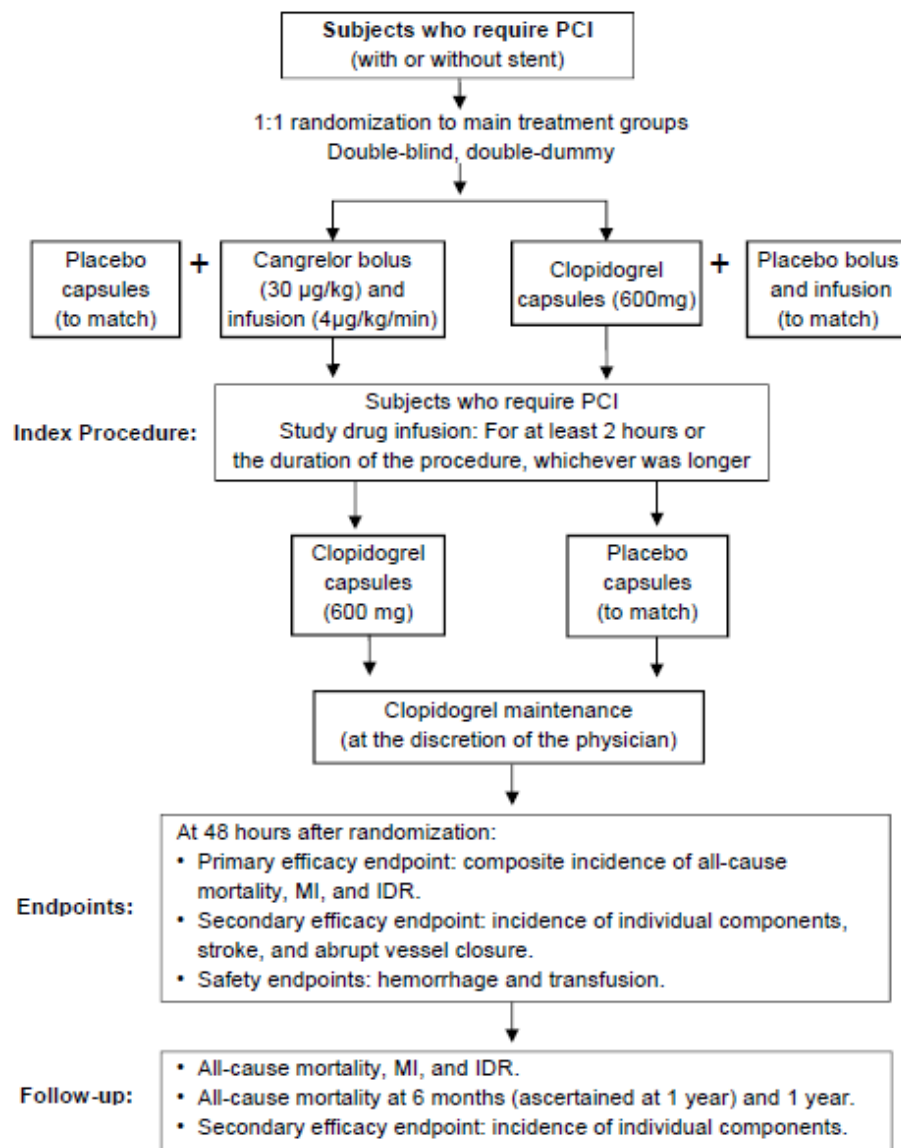
CHAMPION PCI was a prospective, randomized (1:1), double-blind, active-control, parallel-group trial that compared cangrelor (30ug/kg bolus plus 4ug/kg/min infusion) to oral clopidogrel 600mg in patients with coronary atherosclerosis requiring PCI. Subjects were randomized to receive an IV bolus / infusion of cangrelor and placebo capsules vs. Clopidogrel capsules (600mg) / IV bolus and infusion of placebo. After infusion of at least 2 hours or the duration of the procedure (whichever was longer), subjects in the IV cangrelor + placebo capsule arm received clopidogrel capsules (600mg), and subjects in the clopidogrel capsule (600mg) +IV placebo arm received placebo capsules. All subjects subsequently received clopidogrel maintenance as per physician discretion. See [Figure 2](#) for a schematic of the trial design.

The original subject population mirrored that of CHAMPION PLATFORM. Following a protocol amendment on 08 May 2007 (same date as the protocol amendment of CHAMPION PLATFORM), subjects were required to demonstrate one of the two same criteria described in CHAMPION PLATFORM trial.

The sample size was based on the assumption that the primary endpoint in the SA /UA/ NSTEMI population would be 7.0% in the clopidogrel arm and 5.4% in the cangrelor arm (22.9% relative risk reduction). A sample of 4000 subjects in each arm (total 8000) was estimated to provide a power of 82.3% to detect this difference at a two-sided significance level of 0.05. In addition, up to 1000 STEMI subjects were planned to be enrolled, resulting in a total sample size of 9000 SA/UA/NSTEMI/STEMI subjects. The Applicant planned a group sequential method, allowing for the possibility of sample-size re-estimation based on interim data.

The timeline for the CHAMPION PCI trial spanned from FPI March 2006 to LPO (30 days) June 2009. Study enrollment was terminated on 13 May 2009 at 98.7% enrollment following a recommendation from the IARC (i.e. Cyrus Mehta, Christian Hamm, Robert Califf, Carl Pepine, and James Ware) where at a meeting (closed and open session) on 22 September 2008, it was determined that there was a low likelihood of achieving the primary endpoint.

Figure 2. CHAMPION PCI trial design



At this IARC meeting and similar to CHAMPION PLATFORM, Dr. Mehta reviewed his steps leading to his determination that the IARC should recommend terminating the trial due to futility. He described the G0 (mITT /ex-STEMI population), G1 (subset of G0 containing only diabetic or baseline cardiac marker positive patients), and G2 (subset of G1 consisting of patients that are clopidogrel-naïve at baseline). He showed that for each population, increasing the sample size to the limit of 15,000 (maximum sample size specified by the Applicant if there was a need to re-estimate sample size in the PCI trial) would not produce sufficient power to detect a treatment effect.

PCI had a planned enrollment of 9000 subjects. At the time of trial termination, 8882 subjects were randomized (4435 to cangrelor; 4447 to clopidogrel 600mg). The incidence of the primary endpoint (composite of all-cause mortality, MI, and IDR at 48 hours after randomization) for the ITT populations was 292/3933 (7.4%) in the cangrelor arm and 277/3924 (7.1%) in the clopidogrel arm (OR 1.06, 95% CI [0.89, 1.25], $p=0.5323$ -Table 5.1.2.1 PCI CSR). The incidence of the all-cause mortality component was 8/3933 (0.2%) in the cangrelor arm and 6/3924 (0.2%) in the clopidogrel arm (OR 1.33, 95% CI [0.46, 3.84], $p=0.5969$ -Table 5.1.2.1 PCI CSR). The incidence of ST was 7/3933 (0.2%) in the cangrelor arm and 11/3924 (0.3%) in the clopidogrel arm (OR 0.63, 95% CI [0.25, 1.64], $p=0.3469$ -Table 5.1.2.1 PCI CSR). The incidence of Acute ST was 5/3933 (0.1%) in the cangrelor arm and 9/3924 (0.2%) in the clopidogrel arm (OR 0.55, 95% CI [0.19, 1.65], $p=0.2987$ -Table 5.1.2.1 PCI CSR). The incidence of adjudicated MI was 278/3933 (7.1%) in the cangrelor arm and 256/3924 (6.5%) in the clopidogrel arm (OR 1.09, 95% CI [0.91, 1.30], $p=0.3378$). The incidence of adjudicated IDR was 15/3933 (0.4%) in the cangrelor arm and 23/3924 (0.6%) in the clopidogrel arm (OR 0.65, 95% CI [0.34, 1.25], $p=0.1943$).

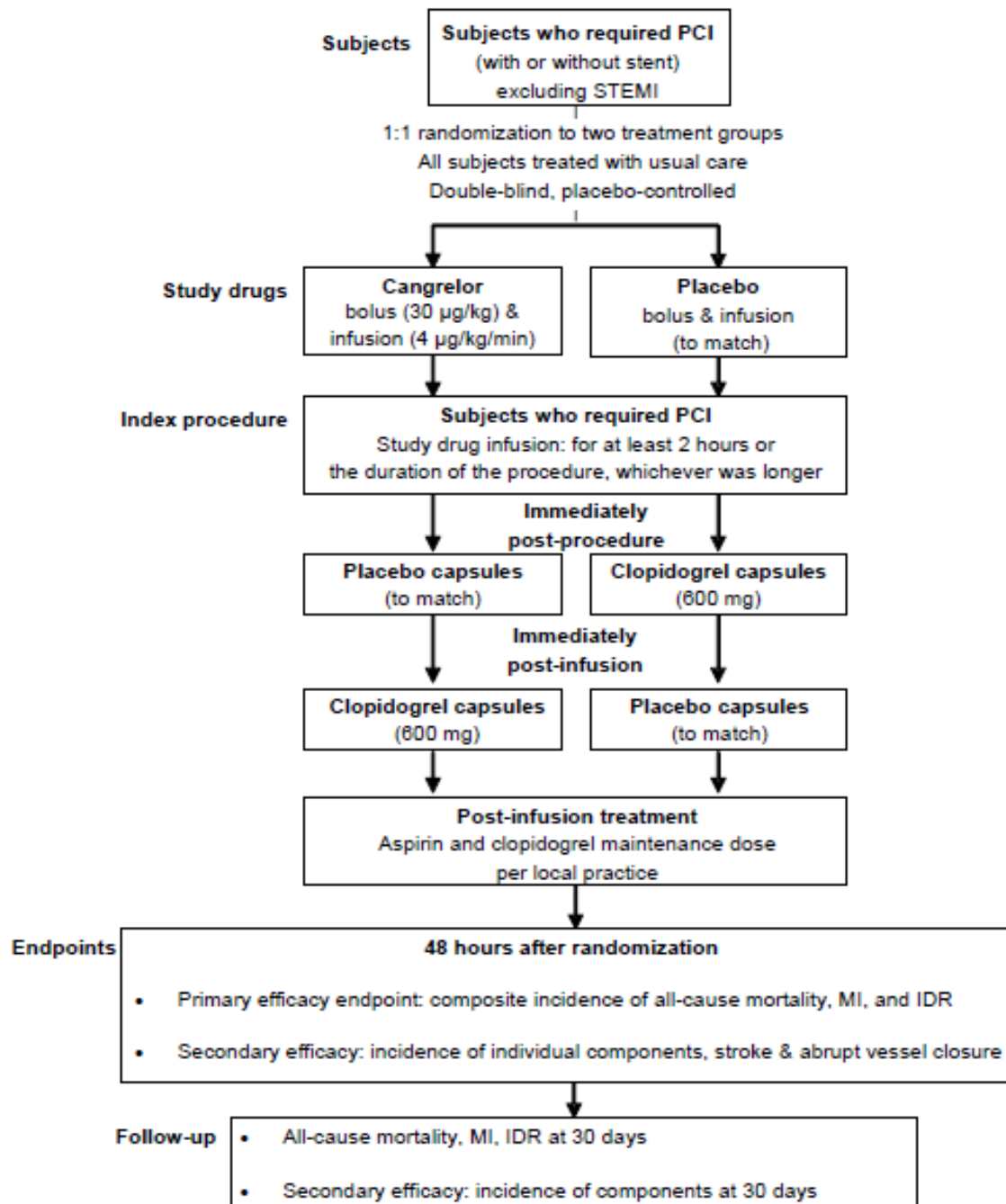
Contrary to the CHAMPION PLATFORM trial, there was no difference between the cangrelor and clopidogrel arm for any of the components of the composite efficacy endpoint. This efficacy issue is discussed in section 6.1.1.10 of this review.

5.3.2 CHAMPION PLATFORM

The objective of CHAMPION PLATFORM was to demonstrate that the efficacy of cangrelor (combined with usual care) was superior to that of usual care, in subjects requiring PCI as measured by the primary efficacy endpoint: composite of all-cause mortality, MI, and IDR assessed 48 hours after randomization.

CHAMPION PLATFORM was a prospective, randomized (1:1), double-blind, placebo-control, parallel-group trial that compared IV cangrelor (30ug/kg bolus plus 4ug/kg/min infusion) to IV placebo in patients with coronary atherosclerosis requiring PCI. Subjects were randomized to receive an IV bolus and infusion of study drug (cangrelor or placebo). Immediately post-procedure, subjects in the IV cangrelor arm received placebo capsules, and subjects in the IV placebo arm received clopidogrel capsules (600mg). Immediately following the infusion period of at least 2 hours or the duration of the procedure (whichever was longer), those having received cangrelor infusion and post-procedure placebo capsules were also given clopidogrel capsules (600mg); and those subjects having received placebo infusion and post-procedure clopidogrel capsules (600mg) were also given placebo capsules. Post-infusion maintenance therapy included aspirin and clopidogrel as per local practice (see [Figure 3](#)).

Figure 3. CHAMPION PLATFORM trial design



The original subject population included patients with a diagnostic coronary angiography demonstrating atherosclerosis amenable to treatment by PCI with or without stent implantation regardless of disease severity. Following a protocol amendment (08 May 2007), in addition to the diagnostic coronary angiography demonstrating atherosclerosis amenable to PCI, one of the following criteria was required to be satisfied: NSTEMI

based on troponin I or T or CK-MB > upper limit of normal, or UA defined as ischemic chest discomfort \geq 10 minutes duration and dynamic ECG changes.

The sample size was based on the assumption that the primary endpoint in the SA /UA/ NSTEMI population would be 7.70% in the placebo arm and 5.78% in the cangrelor arm (25% relative risk reduction). A sample of 3200 subjects in each arm (total 6400) was estimated to provide 85% power to detect this difference at a one-sided significance level of 0.025. The Applicant planned a group sequential method, allowing for the possibility of sample-size re-estimation based on interim data.

The timeline for the CHAMPION PLATFORM trial spanned from FPI October 2006 to LPO (30 days) July 2009. Study enrollment was terminated on 13 May 2009 at 84% enrollment following a recommendation from an Interim Analysis Review Committee (IARC) (i.e. Cyrus Mehta, Christian Hamm, Robert Califf, Carl Pepine, and James Ware) where at a closed meeting on 1 May 2009, it was determined that there was a low likelihood of achieving the primary endpoint.

At this IARC closed meeting, Dr. Mehta reviewed his steps leading to his determination that the IARC should recommend terminating the trial due to futility. He described the G0 (mITT population) and G1 (subset of G0 containing only diabetic or baseline cardiac marker positive patients) and showed that for each population, increasing the sample size to the limit of 15,000 (maximum sample size specified by the Applicant if there was a need to re-estimate sample size in the PLATFORM trial) would not produce sufficient power to detect a treatment effect.

CHAMPION PLATFORM had a planned enrollment of 6400 subjects. At the time of trial termination, 5364 subjects were randomized (2695 to cangrelor→placebo capsules; 2669 to IV placebo→oral clopidogrel 600mg). The incidence of the primary endpoint for the ITT population was 187/2691 (6.9%) in the cangrelor arm and 210/2641 (8.0%) in the clopidogrel arm (OR 0.86, 95% CI [0.70, 1.05], $p=0.1456$ -Table 13 PLATFORM CSR). The incidence of the all-cause mortality component was 8/2691 (0.3%) in the cangrelor arm and 19/2664 (0.7%) in the clopidogrel arm (OR 0.42, 95% CI [0.18, 0.95], $p=0.0374$ -Table 5.1.2.1 PLATFORM CSR). The incidence of ST was 5/2691 (0.2%) in the cangrelor arm and 16/2664 (0.6%) in the clopidogrel arm (OR 0.31, 95% CI [0.11, 0.84], $p=0.0217$ -Table 5.1.2.1 PLATFORM CSR). The ST results were driven by Acute ST: 5/2691 (0.2%) in the cangrelor arm and 14/2664 (0.5%) in the clopidogrel arm (OR 0.35, 95% CI [0.13, 0.98], $p=0.0456$ -Table 5.1.2.1 PLATFORM CSR). There were no differences in the rate of adjudicated MI (cangrelor: 177/2691 (6.6%); clopidogrel: 192/2664 (7.2%); OR 0.91, 95% CI (0.73, 1.12), $p=0.3632$) or in the rate of adjudicated IDR (cangrelor: 19/2691 (0.7%); clopidogrel: 26/2664 (1.0%); OR 0.72, 95% CI (0.40, 1.31), $p=0.2814$).

Although there was no difference between the arms of the CHAMPION PLATFORM trial for the primary efficacy endpoint, a significant mortality signal was empirically evident

against clopidogrel. There was also a significantly higher incidence of acute stent thrombosis in the clopidogrel arm. See section 6.1.1.10 for a review analysis of the results from CHAMPION PLATFORM and CHAMPION PCI – latter shown in section 5.3.1.

5.3.3 POOLED ANALYSIS of CHAMPION PCI and CHAMPION PLATFORM

In a post-hoc analysis of the pooled data from CHAMPION PCI and CHAMPION PLATFORM published by White, H, et al., 2012, substitution of the original CEC adjudicated MI with the UDMI type 4a definition of MI resulted in a significant decrease in the incidence of the composite endpoint of death, UDMI-type 4a, and IDR for cangrelor over comparator (placebo or clopidogrel) (OR 0.82, 95%CI [0.68-0.99], $p=0.0374$). Similarly, cangrelor was observed to have a significantly lower incidence of the post-hoc composite of death, UDMI type 4a, and ARC-ST (OR 0.82, 95%CI [0.67-1.00], $p=0.0458$) and the composite of death, QWMI and IDR (OR 0.61, 95%CI [0.42-0.88], $p=0.0080$) over comparator (placebo or clopidogrel).

In a study by Leonardi, S, et al., 2013, substitution of the originally defined CEC-adjudicated MI with the UDMI type 4a, using criteria 5x ULN and 10x ULN but not 3x ULN, into the primary composite endpoint, yielded a significant difference for the revised composite endpoint favoring cangrelor over placebo.

Based on these post-hoc analyses (CHAMPION PLATFORM and pooled analysis of CHAMPION PLATFORM and PCI), CHAMPION PHOENIX was designed for a composite endpoint of all-cause mortality, MI, IDR, and ST assessed at 48 hours after randomization. MI was defined as per UDMI and ST was defined as per ARC.

5.3.4 CHAMPION PHOENIX

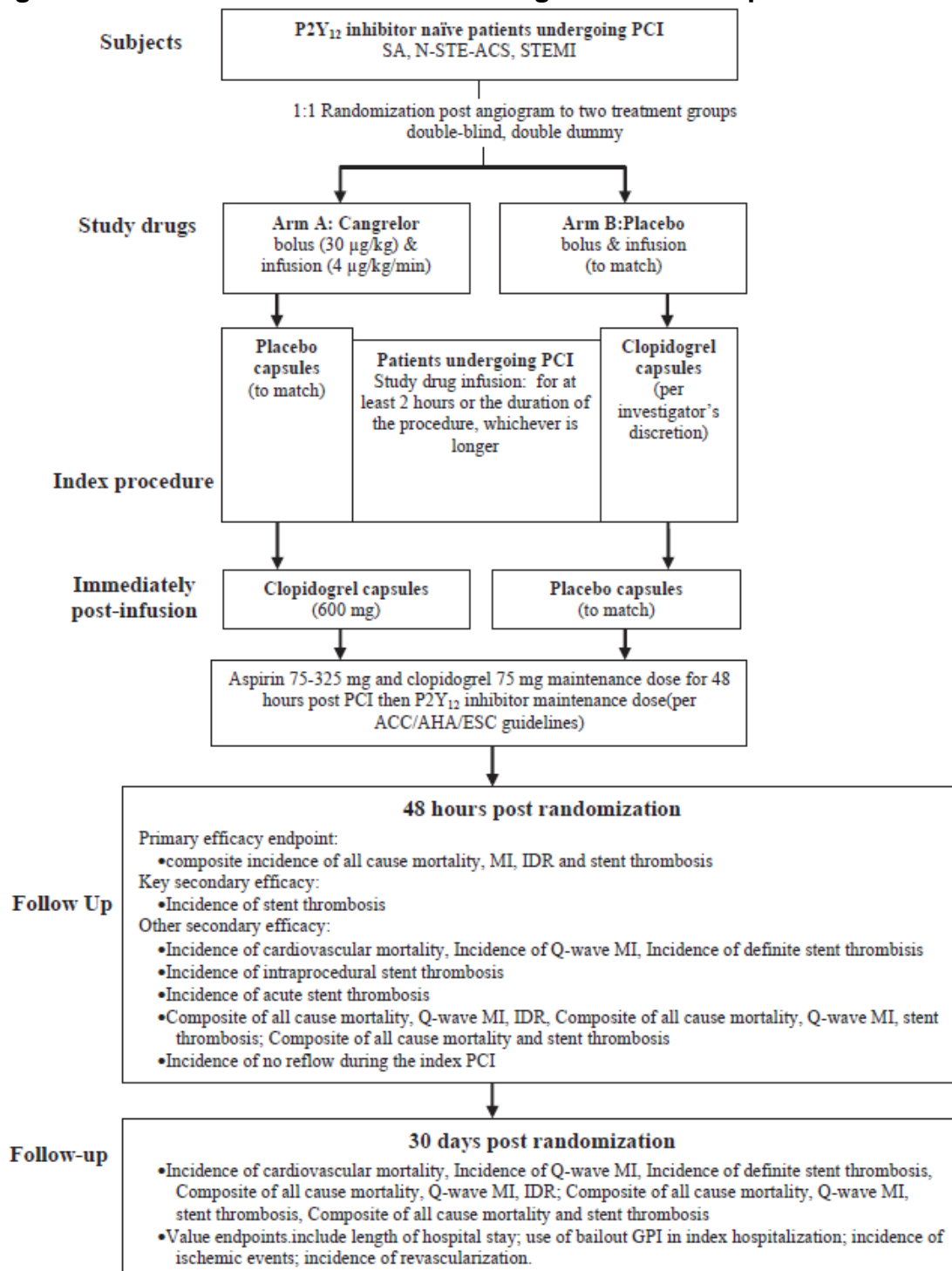
In support of the proposed indication, the Applicant conducted “A clinical trial comparing cangrelor to clopidogrel standard of care therapy in subjects who require percutaneous coronary intervention: CHAMPION PHOENIX (Cangrelor versus standard therapy to achieve optimal management of platelet inhibition)”. An overview of the final protocol (and only amendment which was dated prior to the first patient being enrolled) dated 28 September 2010 is described in this section.

5.3.4.1 Study Design

The CHAMPION PHOENIX trial was a phase III, randomized, double-blind, double-dummy, active comparator, controlled trial comparing cangrelor IV + placebo PO to placebo IV + clopidogrel PO (300mg or 600mg) in patients presenting either with stable angina (SA), non-ST-segment elevation acute coronary syndrome (NSTEMI), or ST-segment elevation myocardial infarction (STEMI) who are planned to undergo either

elective or urgent PCI. The trial design, key efficacy endpoints and follow-up are shown in **Figure 4**.

Figure 4: CHAMPION PHOENIX Trial Design and Follow-up



5.3.4.2 Study Duration/Dates

The first subject was enrolled on 30 September 2010. The last patient completed on 14 November 2012.

5.3.4.3 Study Population

Main inclusion criteria required that subjects be at least 18 years of age with SA, NSTEMI, or STEMI who required PCI and had not previously received a P2Y₁₂ inhibitor within 7 days.

Notable exclusion criteria were related to bleeding including ischemic stroke within the last year, any previous hemorrhagic stroke, and trauma or major surgery within the last month.

5.3.4.4 Study Procedures

Randomization occurred once eligibility was confirmed and prior to commencement of the index PCI. To be eligible, coronary anatomy and suitability for PCI was assessed via angiography in SA and NSTEMI patients.¹ STEMI patients could be randomized on diagnosis prior to angiography based on ECG (e.g., in the Emergency Room), provided there was no impediment to PCI. Subjects were randomized by IV/WRS with stratification based on site, baseline status² and intended clopidogrel loading dose.

Reviewer comment: The protocol did not provide guidance on clopidogrel loading dose strength. It is unclear what criteria the investigator used to choose the intended clopidogrel loading dose. Moreover, it was also unclear why all subjects randomized to cangrelor received only clopidogrel 600 mg loading dose whereas subjects randomized to clopidogrel could receive either 300 mg or 600 mg. So while the blinded investigator declared an “intended dose” (300 mg or 600 mg), subjects randomized to cangrelor only received clopidogrel 600 mg. The “intended dose” was used in the Applicant’s regression analysis of the primary efficacy endpoint.

Subjects received a study drug kit containing IV drug and two sets of capsules (pink and blue). Intravenous study drug was to be administered as soon as possible following randomization but not more than 30 minutes prior to PCI (defined as time of guidewire

¹ Angiography within 90 days of index PCI for SA patients and within 72 hours prior to randomization for NSTEMI patients.

² The CEC classified “baseline status” using troponin levels, ischemic symptoms and ECG changes to designate subjects as “baseline normal” or “baseline abnormal.” The purpose was to assess peri-procedural MI at 48 hours.

insertion).³ In STEMI patients, this would be prior to or immediately after angiography. For others this would be after angiography confirmation of suitability for PCI.

The first set of oral over-encapsulated capsules (pink) was to be ingested as soon as possible following randomization per the investigator's discretion.⁴ For subjects randomized to cangrelor, these capsules were placebo. For subjects randomized to clopidogrel, this was clopidogrel at a dose of either 300 mg or 600 mg (at investigator discretion).

The second set of oral over-encapsulated capsules (blue) was the transition dose and was to be taken immediately following infusion cessation. For subjects randomized to cangrelor, these capsules were clopidogrel 600 mg. For subjects randomized to clopidogrel, this was placebo.

Aspirin 75-325 mg and clopidogrel 75 mg were prescribed for 48 hours post PCI then a P2Y12 inhibitor maintenance dose per ACC/AHA/ESC guidelines.

Pertinent tests included the following:

- Within 72 hours prior to randomization: 12-lead ECG, hemoglobin, hematocrit, platelets, PT/INR, Troponin I or T (at least one, ideally two or more).
- Immediately following randomization prior to study drug initiation: Troponin I or T and CK-MB mass
- Following drug infusion cessation through hospital discharge or 48 hours, whichever occurs sooner: 12-lead ECG within 1 hour after the index PCI and on the morning after the procedure (or at hospital discharge, whichever occurs sooner), CK-MB mass every 6 hours post PCI (minimum of 3 samples), Troponin I or T and CK-MB according to hospital standard of care, hemoglobin, hematocrit, and platelet count on the day after the index PCI (or at hospital discharge, whichever occurs first)

Concomitant medications

Glycoprotein IIb/IIIa inhibitors were allowed during the index PCI as bailout therapy. Antithrombin therapy (heparin, fondaparinux, and bivalirudin) was also allowed.

CYP2C19 inhibitors (e.g. omeprazole) were prohibited for the first 48 hours post randomization.

³ In cases where intravascular ultrasound (IVUS) was used during the diagnostic angiogram, study drug infusion was to begin prior to the IVUS catheter crossing the target lesion.

⁴ Each capsule contained two clopidogrel 75 mg tablets.

48 hour follow-up

All patients were contacted either by telephone (if already discharged from the hospital), evaluated during an office visit, or evaluated as an in-patient for the following assessments:

- Concomitant medications (i.e., ticlopidine, aspirin, clopidogrel, prasugrel)
- Clinical endpoints: Death, MI, IDR, stent thrombosis, no reflow
- Value endpoints: length of hospital stay, use of bailout GPI during index hospitalization, incidence of ischemic events, incidence of revascularization.
- AEs and hemorrhage assessment occurring through 48 hours after randomization

The patient could be contacted up to 72 hours after the 48-hour time point in order to determine patient status at 48 hours (48 hours [+ 72 hours]). If there was a delay of more than 12 hours between time of randomization and start of study drug, AEs were to be collected from time of randomization through 48 hours after study drug initiation.

Reviewer comment: Concomitant and discharge medications were assessed post procedure/discharge. These did not appear to be assessed on the 48 hour follow-up eCRF.

30 day follow-up

All patients were to be contacted 30 days (+5 days) after randomization for efficacy endpoints. The following was ascertained: occurrence of ischemia, MI, angiography, revascularization, and death. Patients were to be questioned regarding their use of maintenance thienopyridines and aspirin.

Reviewer comment: Although the protocol specified that subjects would be questioned regarding thienopyridine and aspirin use, the CRF did not collect this information at the 30 day follow-up visit.

5.3.4.5 Efficacy Endpoints

The primary efficacy endpoint was a composite of all-cause mortality, Myocardial Infarction (MI), Ischemic Driven Revascularization (IDR) and Stent Thrombosis (ST) at 48 hours. The MI component was based on the Universal Definition of Myocardial Infarction (UDMI) as part of the Applicant's strategy to re-define this endpoint from the previous CHAMPION studies pursuant to optimizing the probability of a successful PHOENIX trial. The assessment of acute MI followed satisfying at least one of the following diagnostic criteria:

a) Rise and fall of cardiac biomarkers above the 99th percentile of the upper reference limit (URL) with evidence of at least one of the following: ischemic symptoms, ECG changes indicative of new ischemia, development of pathological Q waves in the ECG, imaging evidence of new loss of viable myocardium or new regional wall motion abnormality;

- b) Sudden, unexpected cardiac death involving cardiac arrest with signs or symptoms of myocardial ischemia;
- c) For PCI in patients with normal baseline troponin values, elevation of cardiac biomarkers greater than the 99th percentile of the URL is indicative of peri-procedural myocardial necrosis. Conventionally, increases in biomarkers greater than 3 x 99th percentile URL have been designated as defining PCI-related MI;
- d) For CABG in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of myocardial necrosis. Conventionally, increases of biomarkers greater than 5 x 99th percentile URL plus either new pathological Q waves or new left bundle branch block (LBBB), or angiographically documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium, have been designated as defining CABG-related myocardial infarction;
- e) Pathological findings of an acute MI.

The UDMI was classified according to 5 types ([see section 9.2 Universal Definition of Myocardial Infarction](#)). The Applicant's program objective focused on the re-defined hypothesis, compared to the original CHAMPION program, that the benefit of cangrelor would be made manifest by decreasing the incidence of peri-procedural MI compared to clopidogrel. Therefore, the trial design focused on Type 4a and Type 4b MI where baseline cardiac biomarkers were normal.

The ST component was a combination of Academic Research Consortium (ARC) defined ST (see section [9.3 Stent Thrombosis](#)) and Intra-Procedural Stent Thrombosis (IPST). ARC defined ST (ARC-ST) was developed in order to harmonize endpoint definitions (see section [6.1.1.5 Analysis of Secondary Endpoints\(s\)](#)). ARC-ST was defined by time and by probability.⁵ The key feature of ARC-ST was the association of angiographically demonstrated thrombosis and clinical signs or symptoms. IPST was introduced by Brener, S, et al. in 2013 (see section [6.1.1.5 Analysis of Secondary Endpoints\(s\)](#)) as a variable postulated to not be included in the ARC definitions of ST. The ARC defined acute ST, which began at time 0 immediately after stent implantation, was argued by Brenner et al. to not consider thrombosis which occur while the stent is being implanted (e.g. a discreet time period prior to "time 0"). Because of the post-hoc derived prognostic significance for major adverse cardiac events, the Applicant included IPST into the ARC-ST component of the primary endpoint. The CEC Charter defined IPST for adjudication purposes and as such, rendered challenging the distinction between IPST and ARC-acute ST. The difference between ARC-acute ST and IPST was the lack of requisite clinical signs or symptoms when adjudicating IPST. As pointed out in section 6.1.1.5, the combination of IPST and ARC-ST in defining ST as a component of the primary efficacy endpoint was analogous to combining a clinically

⁵ Time (acute: 0-24 hours after stent implantation; subacute: > 24 hours to 30 days after stent implantation; late: > 30 days to 1 year after stent implantation; very late: > 1 year after stent implantation); probability (definite, probable, possible-see section 9.2).

meaningful angiographic parameter with a biomarker which has not undergone a validation or harmonization process.

IDR (see section **9.4 Ischemic Driven Revascularization**) was defined as repeat PCI or CABG due to signs or symptoms of ischemia. The episode of ischemia leading to repeat PCI or CABG will have been required to have occurred following completion of the index procedure.

A protocol defined key secondary endpoint was ST at 48 hours. Other secondary endpoints were: individual incidences of all-cause mortality, MI, and IDR at 48 hours; cardiovascular mortality at 48 hours and 30 days; QWMI at 48 hours and 30 days; Definite ST at 48 hours; IPST; Acute ST (ARC-defined); the composite of all-cause mortality, QWMI and IDR at 48 hours and 30 days; the composite of all-cause mortality, QWMI, and ST 48 hours and 30 days; the composite of all-cause mortality and ST at 48 hours and 30 days; no-reflow during PCI; and value endpoints (i.e. length of hospital stay, bailout GPI).

5.3.4.6 Safety Endpoints and Definitions

The primary safety endpoint was the incidence of GUSTO severe bleeding. This was stated in the SAP which was finalized just prior to the last patient completing the trial. The Applicant chose this bleeding classification because of its common use in coronary artery disease and anti-platelet studies. Other bleeding scales defined in the SAP are shown in Table 4.

Reviewer comment: The final protocol and SAP did not distinguish between CABG and non-CABG bleeding. However, the synopsis in the original protocol and amended protocol stated that one of the safety endpoints was “the incidence of major/minor non-CABG related hemorrhage by clinically relevant criteria at 48 hours after randomization.”

Bleeding was assessed from the time of randomization through 48 hours after study drug initiation. The protocol specified that the following safety endpoints would be evaluated (although not adjudicated):

- Incidence of hemorrhage by clinically relevant criteria (GUSTO, TIMI, other major bleeding scales) up through 48 hours, and
- The incidence of blood product transfusion up through 48 hours, categorized according to relationship with CABG surgery.

Table 4. Bleeding definitions in PHOENIX SAP

Bleed Classification	Definition
GUSTO severe	<ul style="list-style-type: none"> • Intracranial bleeding or • Resulting in hemodynamic compromise requiring treatment (includes fatal bleeding)
GUSTO moderate	<ul style="list-style-type: none"> • Requiring blood transfusion
GUSTO mild	<ul style="list-style-type: none"> • Other bleeding requiring intervention, but not requiring transfusion or causing hemodynamic compromise
TIMI major [†]	<ul style="list-style-type: none"> • Intracranial bleeding or • Any bleeding associated with clinically overt signs associated with a drop in hemoglobin of > 5 g/dL (or when hemoglobin is not available, an absolute drop in hematocrit > 15%)
TIMI minor [†]	<ul style="list-style-type: none"> • Clinically overt sign of bleeding (including observations by imaging techniques) that is associated with a fall in hemoglobin of ≥3 g/dL and ≤5 g/dL (or when hemoglobin is not available, an absolute drop in hematocrit ≥9% and ≤15%)
ACUITY major [†]	<ul style="list-style-type: none"> • Intracranial bleeding or • Intraocular bleeding or • Retroperitoneal or • Access site hemorrhage requiring intervention or • ≥ 5 cm diameter hematoma or • Reduction in Hg ≥ 4 g/dL without an overt source of bleeding or • Reduction in Hg ≥ 3 g/dL with an overt source of bleeding or • Reoperation for bleeding or • Use of any blood product transfusion
ACUITY minor	<ul style="list-style-type: none"> • All other bleeding not listed as major
BARC Type 0	<ul style="list-style-type: none"> • No evidence of bleeding
BARC Type 1	<ul style="list-style-type: none"> • Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional
BARC Type 2	<ul style="list-style-type: none"> • Clinically overt sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that is actionable but does not meet criteria for type 3, 4, or 5.
BARC Type 3	<ul style="list-style-type: none"> • Clinical, laboratory, and/or imaging evidence of bleeding with specific healthcare provider responses as listed below:
BARC Type 3a [†]	<ul style="list-style-type: none"> • Any transfusion with overt bleeding or • Overt bleeding plus hemoglobin drop of ≥3 g/dL to <5 g/dL (provided hemoglobin drop is related to bleeding)

Bleed Classification	Definition
BARC Type 3b [†]	<ul style="list-style-type: none"> • Overt bleeding plus hemoglobin drop ≥ 5 g/dL (provided hemoglobin drop is related to bleeding) or • Cardiac tamponade or • Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid) or • Bleeding requiring intravenous vasoactive drugs
BARC Type 3c	<ul style="list-style-type: none"> • Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation; does include intraspinal); or • Subcategories confirmed by autopsy, imaging, or lumbar puncture or • Intraocular bleed compromising vision
BARC Type 4	CABG related bleeding: <ul style="list-style-type: none"> • Perioperative intracranial bleeding within 48 hours or • Reoperation after closure of sternotomy for the purpose of controlling bleeding or • Transfusion of ≥ 5 U whole blood or packed red blood cells within a 48-hour period (only allogenic transfusions are considered transfusion for CABG-related bleeds) • Chest tube output ≥ 2 L within a 24-hour period
BARC Type 5	<ul style="list-style-type: none"> • Fatal bleeding, bleeding that directly causes death with no other explainable cause:
BARC Type 5a	<ul style="list-style-type: none"> • Probable fatal bleeding: clinically suspicious as the cause of death, but the bleeding is not directly observed and there is no autopsy or confirmatory imaging
BARC Type 5b	<ul style="list-style-type: none"> • Definite fatal bleeding: bleeding that is directly observed (by either clinical specimen [blood, emesis, stool, etc.] or imaging) or confirmed on autopsy.

Bleed Classification	Definition
“clinically overt” or “overt source”	<p>Used for all of the above bleeding classifications: AT LEAST ONE of the following checked on eCRF:</p> <ul style="list-style-type: none"> • Requiring intervention: health care professional-guided medical treatment or percutaneous intervention • Leading to hospitalization or an increased level of care: prolonged hospitalization or hospital transfer • Prompting evaluation: an unscheduled visit to healthcare professional resulting in diagnostic testing <p>AND ANY of the following checked on eCRF:</p> <ul style="list-style-type: none"> • Clinically overt bleed • Intracranial hemorrhage • Intraocular • Cardiac tamponade • Retroperitoneal • Access site bleeding requiring radiologic or surgical intervention • Reoperation for bleeding • Hemodynamic compromise • Epistaxis • Gross hematuria • Hematemesis • Hematoma ≥ 5 cm at puncture site
Non-CABG related bleeding	Any bleeding, unless it is marked as “associated with CABG” on eCRF

† Hemoglobin and hematocrit drop adjusted for packed red blood cells or whole blood transfusion based on the following formula:

$\Delta \text{Hg} = \text{baseline Hg} - \text{post transfusion Hg} + \text{number of units transfused}$

$\Delta \text{Hct} = \text{baseline Hct} - \text{post transfusion Hct} + (\text{number of units transfused} \times 3)$

GUSTO= the Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries (The GUSTO Investigators, 1993)

TIMI=Thrombolysis in Myocardial Infarction (Antman et al, 2005)

ACUITY=Acute Catheterization and urgent intervention triage strategy (Stone et al, 2004)

BARC=Bleeding Academic Research Consortium scale (Mehran et al, 2011)

Reviewer comment: Applicant’s definition of GUSTO mild appears different from that published in 1993 which states that GUSTO mild was “other bleeding, not requiring transfusion or causing hemodynamic compromise.” See also [Section 7.1.2](#) for how bleeds were classified.

The Stone et al 2004 and 2006 publication do not specify a retroperitoneal bleed to be an ACUITY major bleed but it does appear as a subcategory under major bleeding in a table in the 2006 publication.

Bleeding events were also classified as instrumented (direct result of an invasive procedure) or spontaneous and as access-site or non-access site.

Treatment emergent AEs (TEAE) was defined as an adverse event occurring at or after study drug start up to 48 hours after initiation of study drug administration. All AEs were coded using the dictionary terms from the MedDRA Adverse Reaction Dictionary (version 13.1).

5.3.4.7 Statistical Plan

The sample size calculation was based on the observed results from CHAMPION-PCI and CHAMPION-PLATFORM. A composite event rate of 5.1% in the clopidogrel arm and 3.9% in the cangrelor arm (24.5% reduction in odds ratio) was assumed. The sample size of 10,900 (i.e. 5450 subjects per arm) was estimated to provide a power of 85% to detect this difference at the one-sided significance level of 0.025.

The primary and secondary efficacy analyses were to be based on the Modified Intent-to-treat population (MITT), defined as randomized subjects receiving at least one dose of study drug and who underwent the index PCI procedure. Analyses based on the Intent to Treat (ITT) and Per Protocol (PP)⁶ were secondary and confirmatory.

The primary endpoint was analyzed using a logistic regression model adjusted for baseline status and *intended* clopidogrel loading dose.⁷ The CEC classified “baseline status” using troponin levels, ischemic symptoms and ECG changes to designate subjects as “baseline normal” or “baseline abnormal.” The purpose was to assess peri-procedural MI at 48 hours. The results of logistic regression analysis were presented with proportions by treatment group with adjusted odds ratio, p-value and 95% confidence interval.

The SAP was finalized on 25 October 2012, just shortly before the last patient completed the trial on 14 November 2012.

5.3.4.8 Adjudication and Core Lab

A centralized CEC adjudicated the cause of death, occurrence of MI, IDR, and stent thrombosis in a blinded fashion. The angiography core lab was to provide independent,

⁶ Per Protocol defined as randomized subjects who received the assigned study drug and underwent the index PCI.

⁷ The SAP noted that the primary analysis would also be adjusted for intended clopidogrel dose if more than 15% of the patient population were observed to receive clopidogrel 300 mg loading dose at the time of randomization. The SAP notes that at the time of writing, the patient population receiving 300 mg clopidogrel loading dose had exceeded 15%.

blinded evaluation of stent thrombosis events according to ARC criteria before CEC adjudication.

5.3.4.9 Data Safety and Monitoring Board

The DSMB planned to meet after every 2000 subjects were enrolled. An independent Statistical Reporting Organization at Duke Clinical Research Institute (DCRI) provided study data for DSMB review. A planned 70% interim efficacy analysis occurred on June 27, 2012.

5.3.5 BRIDGE

The BRIDGE trial was a phase II prospective, two stage study. The primary objective of this trial was to demonstrate that compared to placebo, discontinuation of oral P2Y₁₂ inhibitors followed by institution of IV cangrelor provided effective and consistent P2Y₁₂ inhibition up to the time of surgery without increasing surgical bleeding. Furthermore, discontinuation of IV cangrelor would result in rapid return of platelet reactivity to baseline and to levels indistinguishable from placebo.

Stage I was a dose-finding open label study (no reference therapy) with the objective of identifying a dose of cangrelor that achieved a level of IPA after discontinuation of oral P2Y₁₂, equivalent to that expected to be maintained if oral P2Y₁₂ inhibition had not been discontinued. The primary efficacy endpoint for Stage I was the maintenance of IPA during cangrelor infusion at levels above 60% in at least 80% of patient samples as reported by the *VerifyNow*TM P2Y₁₂ point of care assay. This endpoint was selected as an approximation of the antiplatelet effect expected to meet the stated objective.

Cangrelor was administered as an IV infusion to cohorts of 5 subjects in a stepwise fashion at predetermined doses: 0.5ug/kg/min, 0.75ug/kg/min, 1.0ug/kg/min, 1.5ug/kg/min, until the primary endpoint was met. If the primary endpoint were not met, then the dose would have been increased to a maximum of 2.0ug/kg/min. After each dose-specific cohort of open-label subjects completed their treatment, an interim analysis was performed and results were reviewed by an Applicant Executive Committee prior to dose advancement.

Stage II was a double-blind, placebo controlled, randomized study comparing IV cangrelor to IV placebo with the objective of demonstrating that cangrelor, at the dose identified in Stage 1, maintained levels of platelet reactivity below a threshold for the duration of infusion, which was identified to be associated with a low-risk of thrombotic events (PRU < 240) as measured by the Accumetrics *VerifyNow*TM P2Y₁₂ assay. The primary efficacy endpoint for Stage II was the percentage of patients with PRU < 240, as determined by the *VerifyNow*TM P2Y₁₂ point of care assay, measured during study drug infusion pre-surgery. Based on the assumption that 30% of placebo-treated subjects and at least 60% of cangrelor treated subjects would maintain platelet inhibition

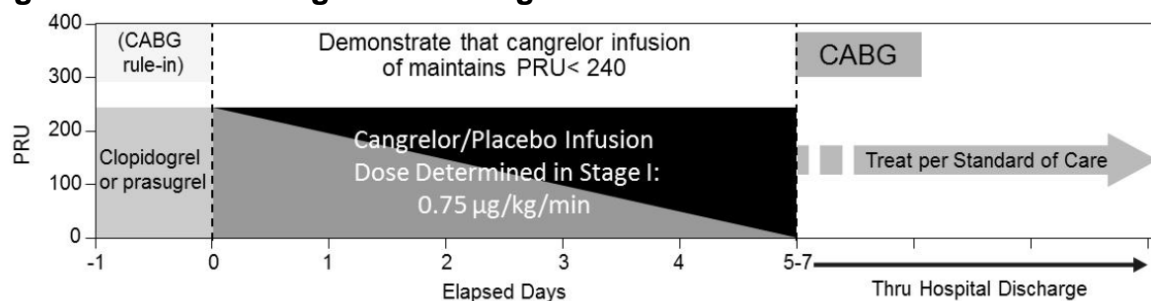
below PRU < 240, a sample size of 106 (53/arm) was calculated to provide 90% power and a significance level of 0.05.

Secondary efficacy endpoints from Stage II included:

- percentage of total patient samples with at least 60% IPA as determined by *VerifyNow*TM P2Y₁₂ point of care assay measured during study drug infusion prior to surgery
- percentage of total patient samples with PRU < 240 as determined by *VerifyNow*TM P2Y₁₂ point of care assay measured during study drug infusion prior to surgery
- percentage of patients with PRU < 240 during their last on-treatment sample prior to surgery
- percentage of patients in whom all PRU evaluations during study drug infusion prior to surgery were less than or equal to baseline PRU
- CABG-related bleeding (i.e. fatal, peri-operative ICH, re-operation after sternotomy closure to control bleeding, transfusion of ≥ 5 units of whole blood or packed red blood cells within a 48 hour period after CABG, chest tube output ≥ 2 L within a 24 hour period after CABG), pre-operative bleeding (TIMI, GUSTO, ACUTY).

Approximately 200 subjects (100 subjects per arm) were randomized. The per-protocol population included 70 subjects randomized to the cangrelor arm and 77 subjects randomized to the placebo arm. The trial design of Stage II is illustrated in **Figure 5**.

Figure 5. BRIDGE Stage II trial design schematics



Source: BRIDGE CSR, Section 9.1, Figure 1

Subjects included in the BRIDGE trial were those who anticipated non-emergent CABG, either on-pump or off-pump, no sooner than 48 hours from randomization but no longer than 7 days from randomization, with the subject hospitalized until planned CABG. Subjects presented with either ACS or elective PCI with stent deployment where subsequent planned CABG was not based on ACS. Subjects enrolled in the BRIDGE trial received a stent approximately 6 months prior to surgery and were stratified by the

number of days to surgery (< 3 days or > 3 days). Subjects also have received a thienopyridine within 72 hours prior to enrollment for either the treatment of ACS regardless of time from ACS and/or long term preventative therapy following DES or BMS treatment. Study drug infusion (cangrelor or placebo) was initiated immediately after randomization (within 72 hours of the last dose of oral P2Y₁₂ inhibitor) and maintained throughout the pre-operative period for a minimum of 48 hours. Infusion durations of up to 7 days were allowed. Sites were instructed to discontinue the infusion 1 to 6 hours prior to surgical incision. Study drug was not administered during or after cardiac surgery. **Figure 6** details the operational schematics applicable to both Stage 1 and Stage 2.

Figure 6. BRIDGE Schedule of Assessments (Stage I and II)

Study Assessment	Screening/Randomization		Pre-Operative		Intra-Operative	Post-Operative Through Discharge				Follow-Up
	Pretreatment / Screening ^a	Randomization	Days 1-7	Pre-Surgery	During Surgery ^b	Immediately Post-Surgery ^c	4 h (± 1 h) Post-Surgery	24 h (± 1 h) Post-Surgery	Discharge	30-Day (+5 days)
Informed consent	X									
Medical history	X									
Inclusion/ exclusion criteria	X									
Pregnancy test (serum or urine), if applicable	X									
PT/INR	X									
Previous medications	X									
Hematology (Hgb, Hct, WBC, platelets)	X		X ^d					X		
Serum creatinine and LFTs	X				X ^e					
12-lead ECG	X							X		
CK, CK-MB	X									
IVRS randomization		X ^f								
VerifyNow™ P2Y12 Assay		X ^g	X ^h	X ⁱ	X ^j	X		X		
Study drug administration		X	X	X ^k						
Concomitant medications		X								
Clinical endpoint assessments		X								
Adverse event reporting		X								
Serious adverse event reporting		X								

- a Screening period tests were conducted within 24 hours prior to randomization
b Surgery start was defined as time of first incision; surgery stop was defined as last suture placed
c Immediately was defined as within 1 hour post end of CABG surgery unless otherwise defined
d Hematology tests were drawn daily during the infusion period, at approximately the same time each day
e Presurgery serum creatinine and LFTs were drawn following the discontinuation of study drug infusion, but prior to CABG surgery
f IVRS randomization not applicable to Stage I. Patients were enrolled via a manual process
g VerifyNow™ P2Y12 assay sample was drawn just prior to initiation of study drug
h VerifyNow™ P2Y12 assay samples were taken daily during infusion period and at approximately the same time each day, in conjunction with daily labs if possible
i Pre-surgery VerifyNow™ P2Y12 assay testing was done before discontinuation of study drug infusion. Patients had to have at least 48 hours on cangrelor infusion before termination. If the last on-infusion VerifyNow™ sample was within 12 hours of study drug discontinuation, an additional sample was not required before cangrelor termination
j VerifyNow™ P2Y12 assay samples drawn just prior to surgical incision
k Study drug infusion was stopped at no less than 1 and no more than 6 hours prior to anesthesia for surgery
PT = prothrombin time; h = hour(s); INR = International Normalized Ratio; Hgb = hemoglobin; Hct = hematocrit; WBC = white blood cells; LFT = liver function tests; ECG = electrocardiogram; CK = creatine kinase; CK-MB = creatine kinase-myocardial isoenzyme band; IVRS = interactive voice response system

Source: BRIDGE CSR, Section 9.5.1, Table 2

Subjects were enrolled at 35 centers in 5 countries: Austria, Czech Republic, Netherlands, United Kingdom, and USA. The FPI (Stage 1) occurred on 02 January 2009. The FPI (Stage II) occurred 14 October 2009, and the LPO (Stage II) occurred 07 June 2011. The CSR was finalized on 29 March 2013.

6 Review of Efficacy

Efficacy Summary

CHAMPION-PHOENIX:

The CHAMPION-PHOENIX trial showed that in the ITT population, including subjects with SA, NSTEMI and STEMI, cangrelor reduced the incidence of the composite primary endpoint of death, MI, IDR, and ST to a greater degree than clopidogrel (OR 0.79, 95%CI [0.67-0.93], p=0.0053) at 48 hours. The results were driven by MI (OR 0.80, 95%CI [0.67-0.97], p=0.0212) and ST (OR 0.62, 95%CI [0.43-0.89], p=0.0098). There was no significant difference between cangrelor and clopidogrel for death (OR 0.95, 95%CI [0.51-1.75], p=0.8702), and IDR (OR 0.76, 95%CI [0.47-1.23], p=0.2663). The MI component of the composite primary endpoint was driven by UDMI-type 4a (i.e. associated with PCI). There were no other significant differences between cangrelor and clopidogrel for other MI definitions (i.e. QWMI, types 1, 2, 3, 4b, and 5). The ST component of the composite primary endpoint was driven by IPST (OR 0.64, 95%CI [0.42-0.99], p=0.0421). There was no difference between cangrelor and clopidogrel for Definite ST (OR 0.54, 95%CI [0.27-1.10], p=0.0847) and Acute ST (OR 0.52, 95%CI [0.25-1.08], p=0.0757). Probable and Possible ST were not evaluated at 48 hours. Results for the composite primary endpoint were similar for the ITT and PP populations.

The incidence of the composite of death, QWMI, and ST was significantly lower in the cangrelor group (69/5573{1.2%}) compared to the clopidogrel group (100/5561{1.8%}), OR 0.68, 95% CI [0.50, 0.93], p=0.0156. The Agency told the Applicant that this composite from PHOENIX would be sufficient for an NDA submission.

At 30 days, the composite endpoint of death, MI, IDR and ST for the ITT population was also significantly reduced in the cangrelor cohort compared to the clopidogrel cohort (OR 0.85, 95%CI [0.73-0.99], p=0.0326). These results were also driven by MI (OR 0.82, 95%CI [0.68-0.98], p=0.0281) and ST (OR 0.68, 95%CI [0.50-0.92], p=0.0122). There was no significant difference between cangrelor and clopidogrel for death (OR 1.10, 95%CI [0.77-1.57], p=0.5980). As the OR indicates, however, there was a numerical increase in the death rate for cangrelor (64/5564: 1.2%) compared to clopidogrel (58/5545: 1.0%). There was no significant difference between cangrelor and clopidogrel in the rate of IDR (OR 0.85, 95%CI [0.59-1.21], p=0.3564). The ST results were driven by IPST (OR 0.64, 95%CI [0.42-0.99], p=0.0415). There was no difference between cangrelor and clopidogrel for Definite ST (OR 0.71, 95%CI [0.43-1.16], p=0.1669), Subacute ST (OR 0.87, 95%CI [0.52-1.45], p=0.5954) and Probable ST (OR 0.80, 95%CI [0.37-1.70], p=0.5572). Possible ST was not evaluated at 30 days. Results for the composite primary endpoint were similar for the ITT and PP populations.

The efficacy endpoint of death, MI, IDR and ARC-ST, devoid of IPST, maintained a significant difference favoring cangrelor over clopidogrel (OR 0.80, 95%CI [0.67-0.95], $p=0.0112$) at 48 hours, but not at 30 days (OR 0.87, 95%CI [0.75-1.01], $p=0.0752$).

The overall CEC-adjudicated results were driven by the SA population, as well as those overall subjects (SA, NSTEACS, and STEMI) who did not have an elevated baseline biomarker associated with myocardial injury. There were no regional variations between the US and non-US populations.

Issues supportive of efficacy included:

- The primary endpoint (death, MI, IDR, and ST at 48 hours) was satisfied and sustained for 30 days.
- The primary endpoint following removal of IPST (e.g. death, MI, IDR, and ARC-ST) was still satisfied.

Issues not supportive of efficacy included:

- The primary endpoint following removal of IPST, although satisfied at the pre-specified 48 hour time point, was not sustained at 30 days.
- The endpoints which were used in the CHAMPION PLATFORM and PCI trials (death, MI, and IDR) were not significantly different between the cangrelor and clopidogrel arms of PHOENIX.

BRIDGE:

The Stage I (open-label, dose finding) study identified the cangrelor dose of 0.75ug/kg/min as having satisfied the Stage 1 primary efficacy endpoint (i.e. >60% IPA in at least 80% of subject samples) by maintaining platelet inhibition above 60% in 94.4% (17/18) of subject samples. Results for the lower dose of 0.5ug/kg/min showed that platelet inhibition remained above 60% in 76.5% (13/17) of subject samples, thereby not satisfying the primary efficacy endpoint. Doses higher than 0.75ug/kg/min were not evaluated.

The Stage II (double-blind placebo controlled randomized) study showed that cangrelor infusion of 0.75ug/kg/min maintained a PRU < 240 for all time points measured in 98.8% of subjects, compared to 19.9% of placebo subjects (RR 5.2 [95%CI, 3.3-8.1] $p<0.001$). These results satisfied the Stage II primary efficacy endpoint. After discontinuation of the infusion (1-6 hours before surgery), platelet function prior to surgery for subjects in the cangrelor arm was similar to that for subjects in the placebo arm.

Death, MI, stroke, and IDR prior to surgery in Stage II occurred at a rate of 2.8% (3/106) and 4.0% (4/101) in the cangrelor and placebo subjects, respectively. The number of

deaths was numerically lower in the cangrelor group (1) compared to the placebo group (3) during the pre-surgery period. Cangrelor was associated with a numerical increase in non-CABG related bleeding during the 5-day bridge period.

6.1 Indication

6.1.1 PCI Indication

The Applicant's proposed indication is "Platelex IV is an intravenous P2Y₁₂ platelet inhibitor indicated for the reduction of thrombotic events (including stent thrombosis) in patients with coronary artery disease undergoing percutaneous coronary intervention (PCI)."

6.1.1.1 Methods

As described in section 5.3.3, the Applicant's method was to design the CHAMPION PHOENIX trial where the primary efficacy endpoint was based on post-hoc analyses of the CHAMPION PLATFORM and PCI trials. This resulted in the introduction of the UDMI type 4a and ARC-ST as two components of the PHOENIX primary efficacy endpoint.

Pursuant to the review strategy described in section 5.2, the review methodology focused on:

- Evaluating the overall results based on the primary efficacy endpoint from the PHOENIX trial.
- Evaluating components of the composite endpoint and their impact on the primary efficacy analysis.
- Verifying that ARC-defined ST criteria were satisfied by reviewing adjudication packages.
- Determining if the prognostic significance of IPST as outlined by Brener et al. (2013) from the ACUTY and HORIZONS-AMI trials was also evident in the PHOENIX database.
- Evaluating subgroup results by clinical presentation (i.e. STEMI, NSTEMI, and SA), baseline biomarker status, region (US vs. non-US), clopidogrel loading dose in the comparator arm, and other general subgroups.

6.1.1.2 Demographics

Table 5 and **Table 6** show the CHAMPION PHOENIX subject demographic and baseline characteristics of the ITT population. The mean age was 64 years with equal distribution above and below the mean age. Seventy two percent of the subjects were male and approximately 94% were white, 3% black/African American, 3% Asian. An overall 3.6% were of Hispanic/Latino ethnicity. The approximate average weight was

85kg with an average BMI of 29. Approximately 58% of the subjects presented with SA, 27% with NSTEMI, and 16% with STEMI (Table 7). Demographic and baseline characteristics were similar between the two arms of the study.

Table 5. CHAMPION PHOENIX ITT Subject Demographics and Baseline Characteristics-1

Parameter, Statistic Category	Cangrelor (N=5581)	Clopidogrel (N=5564)	Overall (N=11,145)
Age, years			
N	5581	5564	11,145
Mean \pm SD	64.0 \pm 11.0	63.8 \pm 11.0	63.9 \pm 11.0
Median (Q1, Q3)	64.0 (56, 72)	64.0 (56, 72)	64.0 (56, 72)
Age group, years			
<65, n (%)	2892 (51.8)	2902 (52.2)	5794 (52.0)
\geq 65, n (%)	2689 (48.2)	2662 (47.8)	5351 (48.0)
Male, n (%)	3982 (71.3)	4042 (72.6)	8024 (72.0)
Race			
N	5578	5557	11,135
White, n (%)	5231 (93.8)	5206 (93.7)	10,437 (93.7)
Asian, n (%)	173 (3.1)	177 (3.2)	350 (3.1)
Black/African American, n (%)	156 (2.8)	152 (2.7)	308 (2.8)
Native Hawaiian/Pacific Islander, n (%)	13 (0.2)	16 (0.3)	29 (0.3)
American Indian/Alaskan native, n (%)	5 (0.1)	6 (0.1)	11 (0.1)
Ethnicity			
N	5581	5564	11,145

Table 6. CHAMPION PHOENIX ITT Subject Demographics and Baseline Characteristics-2

Parameter, Statistic Category	Cangrelor (N=5581)	Clopidogrel (N=5564)	Overall (N=11,145)
Hispanic/Latino, n (%)	196 (3.5)	202 (3.6)	398 (3.6)
Weight, kg			
N	5580	5564	11,144
Mean ± SD	85.2 ± 17.8	85.6 ± 17.9	85.4 ± 17.8
Median (Q1, Q3)	84.0 (73, 95)	84.0 (74, 96)	84.0 (73, 96)
BMI, kg/m ²			
N	5577	5561	11,138
Mean ± SD	28.96 ± 5.22	29.01 ± 5.14	28.99 ± 5.18
Median (Q1, Q3)	28.37 (25.5, 31.8)	28.37 (25.6, 31.8)	28.37 (25.6, 31.8)
Patient types, n (%) ^a			
N	5581	5564	11,145
SA	3158 (56.6)	3059 (55.0)	6217 (55.8)
NSTEMI	1401 (25.1)	1424 (25.6)	2825 (25.3)
STEMI	1022 (18.3)	1081 (19.4)	2103 (18.9)
Cardiac markers >ULN			
Troponin I/T	1885/5534 (34.1)	1947/5520 (35.3)	3832/11,054 (34.7)
CK-MB	1190/5270 (22.6)	1230/5280 (23.3)	2420/10,550 (22.9)

Source: Section 14.1, Table 1.1, Table 2.1.2.1 and Table 2.2.2.1.

^a As determined by statistical analysis, taking into account clinical study data available after time of randomization.
Q1 = first quartile; Q3 = third quartile; SD = standard deviation.

Table 7. Investigator declared patient type

	Cangrelor		Clopidogrel	
Treated	N=5581	(%)	N=5564	(%)
Stable Angina	3220	(57.7)	3208	(57.7)
NSTEMI	1479	(26.5)	1435	(25.8)
STEMI	882	(15.8)	921	(16.6)

Reviewer's analysis: time/time tx relative. Dataset raw\dem (pttype)

Table 8 and **Table 9** show the medical history of the ITT population. Approximately 28% had diabetes mellitus of which 71% were non-insulin dependent. Approximately 29% were current smokers, 80% had hypertension, 69% had hyperlipidemia, 5% had a cerebrovascular event, 21% had a previous MI, 10% had congestive heart failure, and

8% had peripheral artery disease. Approximately 24% had a previous PCI and 10% had a previous CABG. Medical histories were similar between the two arms of the study.

Table 8. CHAMPION PHOENIX ITT Subject Medical History-1

Parameter Category	n/N (%)		
	Cangrelor (N=5581)	Clopidogrel (N=5564)	Overall (N=11,145)
Diabetes Mellitus	1546/5571 (27.8)	1559/5555 (28.1)	3105/11126 (27.9)
Insulin-dependent	464/5571 (8.3)	412/5555 (7.4)	876/11126 (7.9)
Non-insulin-dependent	1040/1504 (69.1)	1121/1533 (73.1)	2161/3037 (71.2)
Unknown	42/5571 (0.8)	25/5555 (0.5)	67/11126 (0.6)
Current smoker within past 30 days	1533/5444 (28.2)	1573/5428 (29.0)	3106/10872 (28.6)
Hypertension	4460/5566 (80.1)	4406/5546 (79.4)	8866/11112 (79.8)
Hyperlipidemia	3412/4942 (69.0)	3380/4908 (68.9)	6792/9850 (69.0)

Table 9. CHAMPION PHOENIX ITT Subject Medical History-2

Parameter Category	n/N (%)		
	Cangrelor (N=5581)	Clopidogrel (N=5564)	Overall (N=11,145)
Cerebrovascular event	276/5559 (5.0)	252/5543 (4.5)	528/11102 (4.8)
Family history of coronary artery disease	2121/5214 (40.7)	2108/5195 (40.6)	4229/10409 (40.6)
Previous MI	1111/5547 (20.0)	1191/5517 (21.6)	2302/11064 (20.8)
≤30 days before enrollment	55/5547 (1.0)	54/5517 (1.0)	109/11064 (1.0)
Previous PCI	1281/5569 (23.0)	1344/5550 (24.2)	2625/11119 (23.6)
≤30 days before enrollment	13/5569 (0.2)	19/5550 (0.3)	32/11119 (0.3)
Previous CABG	581/5574 (10.4)	509/5553 (9.2)	1090/11127 (9.8)
≤30 days before enrollment	581/5574 (10.4)	509/5553 (9.2)	1090/11127 (9.8)
Congestive heart failure	565/5567 (10.1)	592/5546 (10.7)	1157/11113 (10.4)
Peripheral artery disease	449/5513 (8.1)	390/5509 (7.1)	839/11022 (7.6)

Source: [Section 14.1](#), [Table 2.3.2.1](#).

CABG = coronary artery bypass graft; MI = myocardial infarction; PCI = percutaneous coronary intervention.

6.1.1.3 Subject Disposition

Table 10 shows the subject disposition. A total of 11,145 ITT subjects were randomized (5581 to the cangrelor arm and 5564 to the clopidogrel arm). A total of 109 subjects in the cangrelor arm and 94 subjects in the clopidogrel arm were reported to either not

have received study drug or not have undergone the index procedure. Of the resulting mITT population (98.0% of the ITT cangrelor arm and 98.3% of the ITT clopidogrel arm), 232 subjects in the cangrelor arm and 225 subjects in the clopidogrel arm had protocol violations, the majority of which were deviations from inclusion/exclusion criteria or incorrect administration of IV or oral study drug. The Applicant also reported that in the ITT population, a total of 341/5581 (6.1%) cangrelor subjects and 319/5564 (5.7%) clopidogrel subjects had a protocol “major deviation” also described as incorrect study drug administration (see CSR Table 7). The per-protocol population included 5240 in the cangrelor arm (93.9% of the ITT cangrelor population) and 5245 in the clopidogrel arm (94.3% off the ITT clopidogrel population). A total of 5498 of the 5581 (98.5%) cangrelor ITT subjects completed the study, and a total of 5482 of the 5564 (98.5%) clopidogrel ITT subjects completed the study. Of the 83 subjects in the cangrelor arm who discontinued from the study, 64 died, 1 had an adverse event leading to discontinuation, 5 withdrew consent, 1 was discontinued as per physician discretion, 10 were lost to follow-up, and 2 were classified as “other”. Of the 82 subjects in the clopidogrel arm who discontinued from the study, 57 died, 0 had an adverse event leading to discontinuation, 7 withdrew consent, 4 were discontinued as per physician discretion, 12 were lost to follow-up, and 2 were classified as “other”.

Table 11 shows the subject stratification for the ITT population. Approximately 75% of the subjects were administered clopidogrel 600mg (active drug or placebo image) loading dose as specified by the investigator at the time of randomization. Approximately 69% of the subjects were reported to be non-ischemic and 73% of the subjects were reported to not have any ECG changes.

Table 10. CHAMPION PHOENIX Subject Disposition

Category	Stat	Cangrelor	Clopidogrel	Overall
Number of Subjects Randomized	N	5581	5564	11,145
ITT Population	n/N (%)	5581/5581(100)	5564/5564(100)	11145/11145(100)
mITT Population	n/N (%)	5472/5581(98.0)	5470/5564(98.3)	10942/11145(98.2)
PP Population	n/N (%)	5240/5581(93.9)	5245/5564(94.3)	10485/11145(94.1)
Safety Population	n/N (%)	5529/5581(99.1)	5527/5564(99.3)	11056/11145(99.2)
Number of Subjects Completing Study	n/N (%)	5498/5581(98.5)	5482/5564(98.5)	10980/11145(98.5)
Number of Subjects Discontinued	n/N (%)	83/5581 (1.5)	82/5564(1.5)	165/11145 (1.5)
• Death	n/N (%)	64/5581 (1.1)	57/5564 (1.0)	121/11145 (1.1)
• AE	n/N (%)	1/5581 (0.0)	0/5564 (0.0)	1/11145 (0.0)
• Withdrew Consent	n/N (%)	5/5581 (0.1)	7/5564 (0.1)	12/11145 (0.1)
• Physician Decision	n/N (%)	1/5581 (0.0)	4/5564 (0.1)	5/11145 (0.0)
• Lost to Follow-Up	n/N (%)	10/5581 (0.2)	12/5564 (0.2)	22/11145 (0.2)
• Other	n/N (%)	2/5581 (0.0)	2/5564 (0.0)	4/11145 (0.0)

Source: CSR section 14.1.1 (Table 1.0)

Table 11. CHAMPION PHOENIX ITT Subject Stratification

Stratum	Number (%) of patients		
	Cangrelor (N=5581)	Clopidogrel (N=5564)	Overall (N=11,145)
Patient Type ^a			
Stable angina	3220 (57.7)	3208 (57.7)	6428 (57.7)
NSTE-ACS	1479 (26.5)	1435 (25.8)	2914 (26.1)
STEMI	882 (15.8)	921 (16.6)	1803 (16.2)
Clopidogrel Loading Dose ^b	(Placebo)	(Clopidogrel)	
600 mg	4148 (74.3)	4136 (74.3)	8284 (74.3)
300 mg	1433 (25.7)	1428 (25.7)	2861 (25.7)
NSTE-ACS patients ^a	N=1479	N=1435	N=2914
Patient Baseline Status ^a			
Abnormal	1994 (35.7)	2000 (35.9)	3994 (35.8)
Normal	3587 (64.3)	3564 (64.1)	7151 (64.2)
Ischemia Status			
Yes	467 (31.6)	439 (30.6)	906 (31.1)
No	1012 (68.4)	996 (69.4)	2008 (68.9)
ECG Changes			
Yes	408 (27.6)	374 (26.1)	782 (26.8)
No	1071 (72.4)	1061 (73.9)	2132 (73.2)

Source: Section 14.1, Table 1.4.2.

^a As determined by investigator at the time of randomization (does not take into account clinical data available after time of randomization).

^b As specified by investigator at the time of randomization.

ITT = intent-to-treat; NSTE-ACS = non-ST-segment elevation acute coronary syndrome;
STEMI = ST-segment elevation myocardial infarction; ECG = electrocardiogram.

Reviewer comment: Note that the clopidogrel loading dose in the above table is the investigator “declared/intended” dose at randomization. Nearly all subjects in the cangrelor arm actually received clopidogrel 600 mg as a transition dose.

6.1.1.4 Analysis of Primary Endpoint(s)

Table 12 shows that the incidence of the primary composite efficacy endpoint of all-cause mortality, MI, IDR and ST at 48 hours was significantly lower in the cohort randomized to cangrelor compared to clopidogrel (RR 0.80, 95%CI [0.68, 0.94]; OR 0.79, 95%CI [0.67, 0.93], p=0.0053) for the ITT population. This result was consistent across the mITT and PP populations. **Table 13** summarizes the results of the trial for the primary composite efficacy endpoint, as well as individual components of the

composite endpoint, for the ITT population. The results favoring cangrelor over clopidogrel were driven by ST (OR 0.62, 95%CI [0.43, 0.89], $p=0.0098$) and MI (OR 0.80, 95%CI [0.67, 0.97], $p=0.0212$). There was no difference between cangrelor and clopidogrel for the component endpoints of all-cause mortality, and IDR.

The ST component of the primary composite endpoint was driven by IPST (OR 0.64, 95%CI [0.42, 0.99], $p=0.0421$). There was no difference between cangrelor and clopidogrel for Definite ST (OR 0.54, 95%CI [0.27-1.10], $p=0.0847$) and Acute ST (OR 0.52, 95%CI [0.25-1.08], $p=0.0757$). Probable and Possible ST were not analyzed at 48 hours.

The MI component of the composite primary endpoint was driven by UDML-type 4a (OR 0.80, 95%CI [0.66, 0.97], $p=0.0258$). There were no other significant differences between cangrelor and clopidogrel for other MI definitions (i.e. QWMI, types 1, 2, 3, 4b, and 5). Results for the composite primary endpoint were similar in the ITT and PP populations.

The incidence of the composite of death, QWMI, and ST was significantly lower in the cangrelor group (69/5573{1.2%}) compared to the clopidogrel group (100/5561{1.8%}), OR 0.68, 95% CI [0.50, 0.93], $p=0.0156$. The Agency told the Applicant that this composite from PHOENIX would be sufficient for an NDA submission.

As indicated in section 5.3.3, the sample size estimation was based on a presumed composite event rate of 5.1% in the clopidogrel arm and 3.9% in the cangrelor arm (24.5% reduction in odds ratio). A sample size of 10,900 was estimated to provide 85% power to detect this difference at the one-sided alpha of 0.025. The actual data ($n=11,145$) showed a clopidogrel event rate of 5.8% and a cangrelor event rate of 4.7%. (21% reduction in odds ratio).

Figure 7 shows the Kaplan-Meier plot to first occurrence of the primary efficacy endpoint within 48 hours post- randomization (mITT population). The separation between the arms occurred within the initial 2 hours after randomization, after which the difference between the arms remained the same. **Figure 8** shows the Kaplan-Meier plot to first occurrence of ST within 48 hours post- randomization (mITT population). The time course for ST was similar to that for the primary efficacy endpoint.

Figure 9 shows the results of an exploratory landmark analysis of first occurrence of the composite efficacy endpoint of death, MI, IDR, and ST at 48 hours for the mITT population. The landmark analysis was originally designed to minimize bias in estimating time to event probabilities in each group conditional on the group characteristics at a specific time-point (Dafni, U, 2011). The original premise of the landmark analysis regarding clopidogrel studies was to explore the association of extended clopidogrel use and long-term outcomes of patients receiving DES and BMS for the treatment of CAD. This analysis was performed by the Applicant in order to

investigate the effect of transitioning from cangrelor to clopidogrel on clinical outcomes between 2 time periods: early treatment (0 →6 hours) and extended treatment (6 →48 hours). The results showed an early protective benefit of cangrelor over clopidogrel in the early treatment time period. After the transition to the extended treatment period, there was no difference in the estimated event rate for the primary endpoint between “clopidogrel and clopidogrel”. The data showed that the transition from cangrelor to clopidogrel did not result in a differential benefit for any arm of the study. This suggested no harm due to the transition process. The Applicant’s interpretation, considered acceptable in this review, was that there was no gap in the effectiveness of P2Y₁₂ inhibitor therapy when transitioning from IV cangrelor to oral clopidogrel.

Table 12. CHAMPION PHOENIX 48 hour Composite Results in various Populations

	n (%) of patients		RR and 95% CI	OR and 95% CI	P-value ^a
	Cangrelor	Clopidogrel			
mITT (primary), N	5470	5469			
Death/MI/IDR/ST	257 (4.7)	322 (5.9)	0.80 (0.68, 0.94)	0.79 (0.67, 0.93)	0.006
mITT all-subjects ^b , N	5472	5470			
Death/MI/IDR/ST	257 (4.7)	322 (5.9)	0.80 (0.68,0.94)	0.79 (0.67,0.93)	0.005
ITT, N	5573	5561			
Death/MI/IDR/ST	260 (4.7)	325 (5.8)	0.80 (0.68,0.94)	0.79 (0.67,0.93)	0.005
ITT all-subjects ^b , N	5581	5564			
Death/MI/IDR/ST	260 (4.7)	325 (5.8)	0.80 (0.68,0.93)	0.79 (0.67,0.93)	0.005
PP, N	5240	5245			
Death/MI/IDR/ST	233 (4.4)	290 (5.5)	0.80 (0.68,0.95)	0.80 (0.67,0.95)	0.011
PP all-subjects ^b , N	5240	5245			
Death/MI/IDR/ST	233 (4.4)	290 (5.5)	0.80 (0.68,0.95)	0.80 (0.67,0.95)	0.011

Source: [Section 14.1](#), [Table 5.1.1.1](#), [Table 5.1.2.1](#), [Table 5.1.3.1](#), [Table 5.4.1.1](#), [Table 5.4.2.1](#), [Table 5.4.3.1](#).

^a P-value for the odds ratio comparing cangrelor versus clopidogrel.

^b Analysis of the specified population in which patients who did not complete follow-up were counted in the denominator as having had no event.

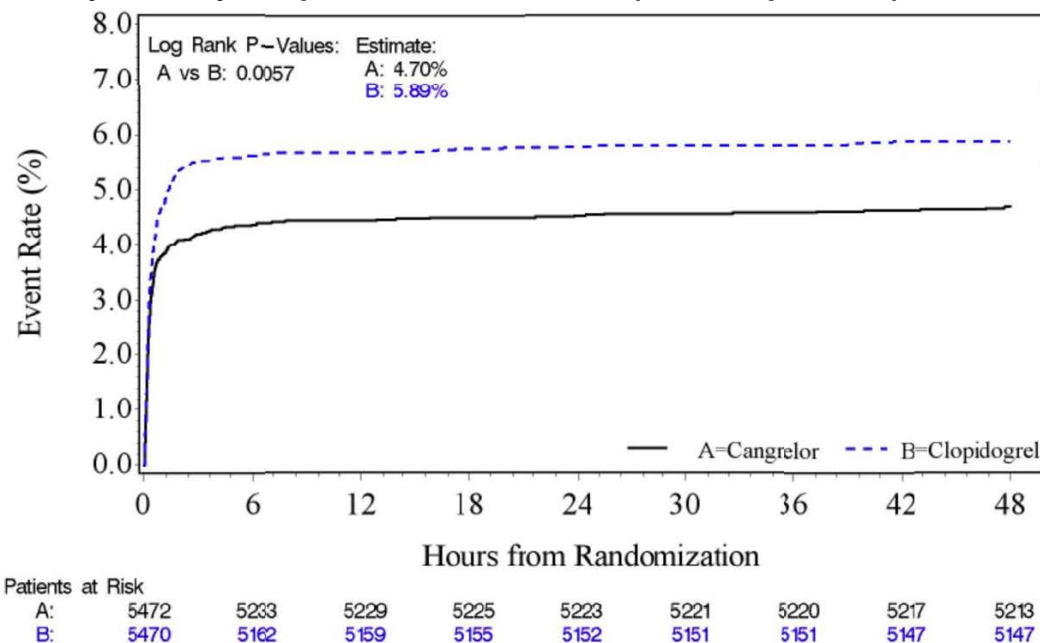
Table 13. CHAMPION PHOENIX 48 hour CEC Adjudicated Efficacy Endpoint (ITT)

			Cangrelor vs. Clopidogrel		
	Cangrelor (N=5581)	Clopidogrel (N=5564)	RR and 95%CI	OR and 95%CI	P- value for OR
48 hours post randomization					
Death/MI/IDR/ST (primary end point)	260/5573(4.7%)	325/5561(5.8%)	0.80(0.68,0.94)	0.79(0.67,0.93)	0.0053
ST	46/5573(0.8%)	74/5561(1.3%)	0.62(0.43,0.89)	0.62(0.43,0.89)	0.0098
-IPST	35/5573(0.6%)	54/5561(1.0%)	0.65(0.42,0.99)	0.64(0.42,0.99)	0.0421
-Def. ST	12/5573(0.2%)	22/5561(0.4%)	0.54(0.27,1.10)	0.54(0.27,1.10)	0.0847
-Prob. ST	0/5573(0.0%)	0/5561(0.0%)	----(----)	----(----)	
-Poss. ST	0/5573(0.0%)	0/5561(0.0%)	----(----)	----(----)	
Acute ST	11/5573(0.2%)	21/5561(0.4%)	0.52(0.25,1.08)	0.52(0.25,1.08)	0.0757
Death	20/5573(0.4%)	21/5561(0.4%)	0.95(0.52,1.75)	0.95(0.51,1.75)	0.8702
-CV Death	20/5573(0.4%)	21/5561(0.4%)	0.95(0.52,1.75)	0.95(0.51,1.75)	0.8702
MI	207/5573(3.7%)	255/5561(4.6%)	0.81(0.68,0.97)	0.80(0.67,0.97)	0.0212
-Q MI	11/5573(0.2%)	18/5561(0.3%)	0.61(0.29,1.29)	0.61(0.29,1.29)	0.1911
-Type 1	1/5573(0.0%)	1/5561(0.0%)	1.00(0.06,15.95)	1.00(0.06,15.96)	0.9988
-Type 2	0/5573(0.0%)	0/5561(0.0%)	----(----)	----(----)	
-Type 3	3/5573(0.1%)	0/5561(0.0%)	----(----)	----(----)	0.0836
-Type 4a	194/5573(3.5%)	239/5561(4.3%)	0.81(0.67,0.98)	0.80(0.66,0.97)	0.0258
-Type 4b	9/5573(0.2%)	15/5561(0.3%)	0.60(0.26,1.37)	0.60(0.26,1.37)	0.2182
-Type 5	0/5573(0.0%)	0/5561(0.0%)	----(----)	----(----)	
IDR	29/5573(0.5%)	38/5561(0.7%)	0.76(0.47,1.23)	0.76(0.47,1.23)	0.2663
-PCI	22/5573(0.4%)	33/5561(0.6%)	0.67(0.39,1.14)	0.66(0.39,1.14)	0.1349

-CABG	7/5573(0.1%)	5/5561(0.1%)	1.40(0.44,4.40)	1.40(0.44,4.41)	0.5660
Death/MI/IDR/ARC-ST	233/5573(4.2%)	289/5561(5.2%)	0.80(0.68,0.95)	0.80(0.67,0.95)	0.0112
Death/Q MI/IDR/ST	83/5573(1.5%)	115/5561(2.1%)	0.72(0.54,0.95)	0.72(0.54,0.95)	0.0209
Death/MI/IDR	233/5573(4.2%)	289/5561(5.2%)	0.80(0.68,0.95)	0.80(0.67,0.95)	0.0112
Death/Q MI/IDR	52/5573(0.9%)	67/5561(1.2%)	0.77(0.54,1.11)	0.77(0.54,1.11)	0.1632
Death/MI/ST	251/5573(4.5%)	315/5561(5.7%)	0.80(0.68,0.93)	0.79(0.66,0.93)	0.0053
Death/MI/ARC-ST	224/5573(4.0%)	279/5561(5.0%)	0.80(0.67,0.95)	0.79(0.66,0.95)	0.0113
Death/Q MI/ST	69/5573(1.2%)	100/5561(1.8%)	0.69(0.51,0.93)	0.68(0.50,0.93)	0.0156
Death/MI	222/5573(4.0%)	275/5561(4.9%)	0.81(0.68,0.96)	0.80(0.67,0.96)	0.0140
Death/Q MI	30/5573(0.5%)	39/5561(0.7%)	0.77(0.48,1.23)	0.77(0.48,1.24)	0.2732
Death/IDR	46/5573(0.8%)	57/5561(1.0%)	0.81(0.55,1.19)	0.80(0.54,1.19)	0.2714
Death/ST	61/5573(1.1%)	90/5561(1.6%)	0.68(0.49,0.93)	0.67(0.49,0.93)	0.0169

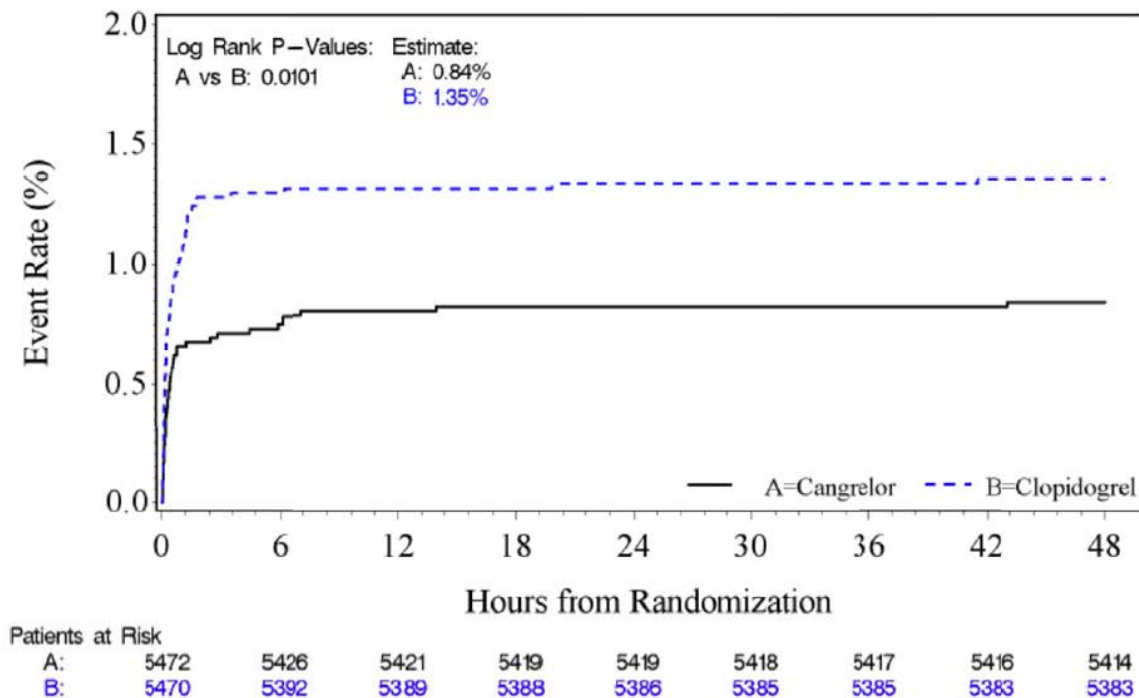
Source: PHOENIX CSR, Table 5.1.2.1, generated by T_ENDPT51.SAS 21MAR13 17:08

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



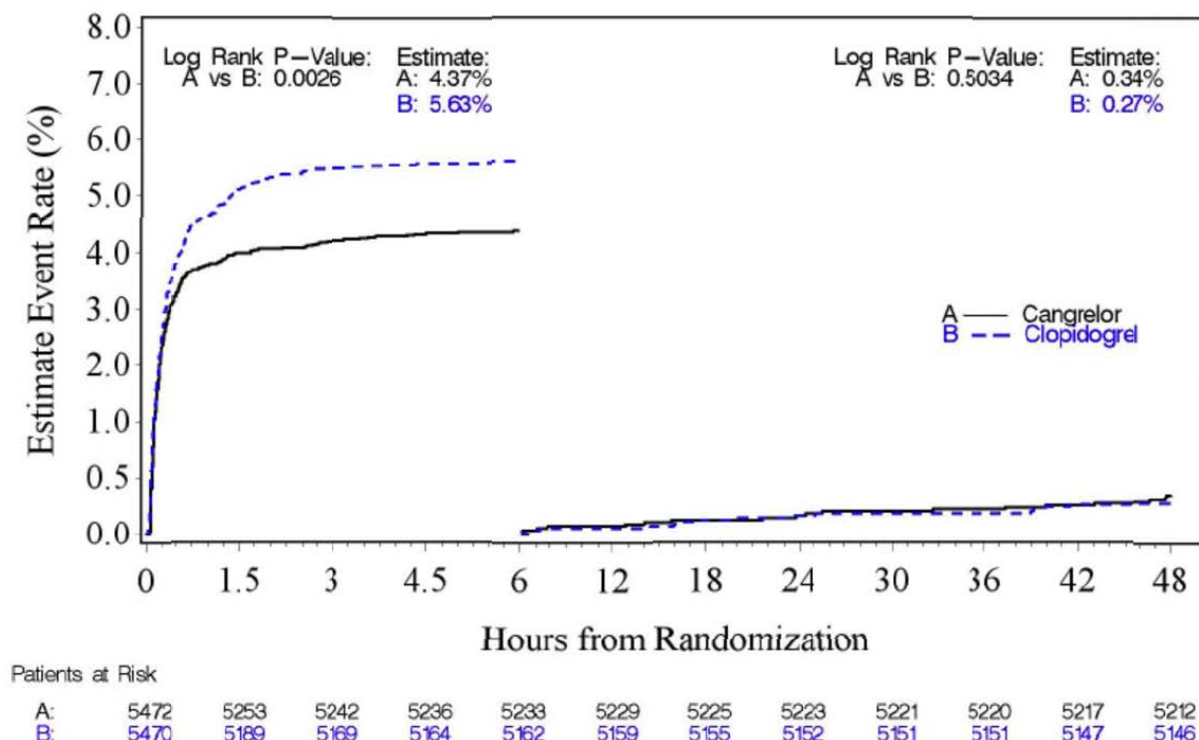
Source: Section 14.2, Figure 5.11.1.1.

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



Source: Section 14.2, Figure 5.51.1.1.

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



Source: Section 14.2, Figure 5.26.1.1.

Table 14 summarizes the 30 day efficacy (composite and components) dataset for the ITT population. The results favored cangrelor over clopidogrel for the composite primary efficacy endpoint (OR 0.85, 95%CI [0.73, 0.99], $p=0.0326$). As with the 48 hour data, the results at 30 days were driven by ST (OR 0.68, 95%CI [0.50, 0.92], $p=0.0112$) and MI (OR 0.82, 95%CI [0.68, 0.98], $p=0.0281$). There was no difference between cangrelor and clopidogrel for the component endpoints of all-cause mortality, and IDR at 30 days.

The ST component of the 30 day composite endpoint was driven by IPST (OR 0.64, 95%CI [0.42, 0.99], $p=0.0415$). There was no difference between cangrelor and clopidogrel for Definite ST (OR 0.71, 95%CI [0.43-1.16], $p=0.1669$), Subacute ST (OR 0.87, 95%CI [0.52-1.45], $p=0.5954$) and Probable ST (OR 0.80, 95%CI [0.37-1.70], $p=0.5572$). Possible ST was not evaluated at 48 hours.

The MI component of the composite primary endpoint was driven by UDML-type 4a (OR 0.81, 95%CI [0.66, 0.98], $p=0.0285$). There were no other significant differences between cangrelor and clopidogrel for other MI definitions (i.e. QWMI, types 1, 2, 4b, and 5). Results for the primary composite endpoint were similar for the ITT and PP populations.

There was a numerical difference in UDMI type 3 disfavoring cangrelor vs. clopidogrel at 30 days (4 events vs. 0 events, $p=0.0458$) in the mITT and ITT, but not the PP populations where in the latter, there was no difference for UDMI type 3.

The composite endpoint of death, MI, IDR and ARC-ST, devoid of IPST, maintained a significant difference favoring cangrelor over clopidogrel (OR 0.80, 95%CI [0.67-0.95], $p=0.0112$) at 48 hours ([Table 13](#)), but not at 30 days (OR 0.87, 95%CI [0.74-1.01], $p=0.0752$) ([Table 14](#)).

[Figure 10](#) shows the Kaplan-Meier plot to first occurrence of death, MI, IDR, or ST within 30 days post randomization (mITT population). Using the time-scale measured in days, the separation between the arms occurred early within the first day, consistent with the initial 2 hours after randomization, after which the difference between the arms remained the same. The Kaplan-Meier plot ([Figure 11](#)) to first occurrence of ST within 30 days post-randomization (mITT population) showed a similar profile to that of the composite endpoint. These results are consistent with the benefit of cangrelor occurring peri-procedurally.

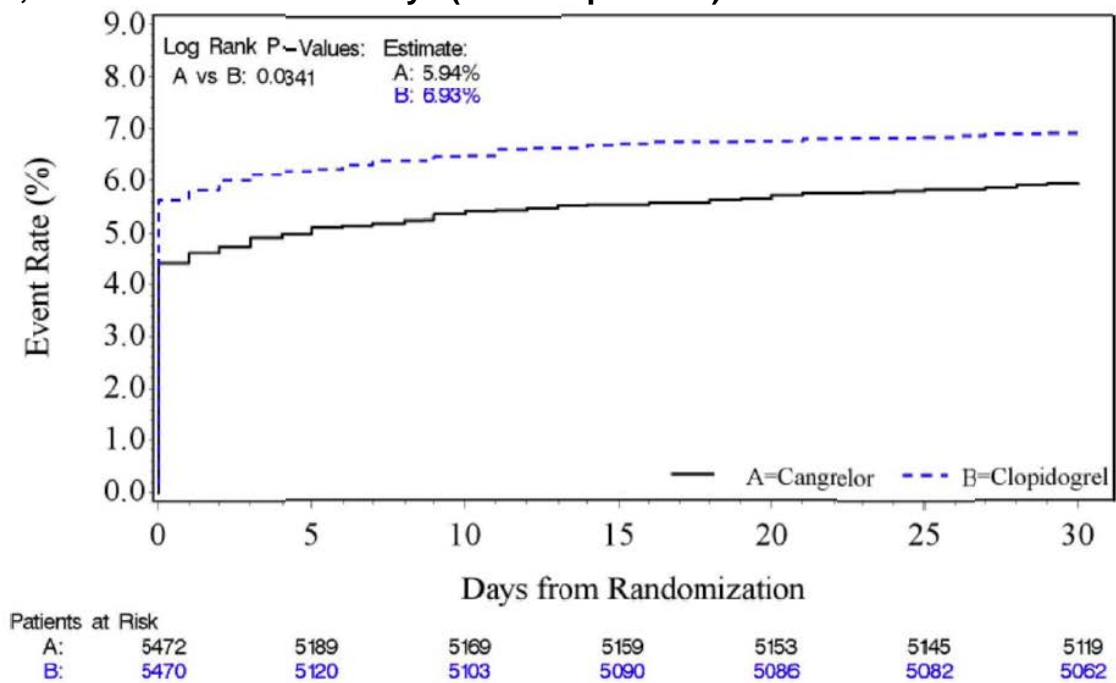
Table 14. CHAMPION PHOENIX: 30 Day CEC Adjudicated Efficacy Endpoint (ITT)

			Cangrelor vs. Clopidogrel		
	Cangrelor (N=5581)	Clopidogrel (N=5564)	RR and 95%CI	OR and 95%CI	P-value for OR
30 days post randomization					
Death/MI/IDR/ST (primary end point)	330/5564(5.9%)	384/5545(6.9%)	0.86(0.74,0.99)	0.85(0.73,0.99)	0.0326
ST	71/5564(1.3%)	104/5545(1.9%)	0.68(0.50,0.92)	0.68(0.50,0.92)	0.0112
-IPST	35/5564(0.6%)	54/5545(1.0%)	0.65(0.42,0.99)	0.64(0.42,0.99)	0.0415
-Def. ST	27/5564(0.5%)	38/5545(0.7%)	0.71(0.43,1.16)	0.71(0.43,1.16)	0.1669
-Prob. ST	12/5564(0.2%)	15/5545(0.3%)	0.80(0.37,1.70)	0.80(0.37,1.70)	0.5572
-Poss. ST	0/5564(0.0%)	0/5545(0.0%)	----(----)	----(----)	
Subacute ST	28/5564(0.5%)	32/5545(0.6%)	0.87(0.53,1.45)	0.87(0.52,1.45)	0.5954
Death	64/5564(1.2%)	58/5545(1.0%)	1.10(0.77,1.57)	1.10(0.77,1.57)	0.5980
-CV Death	51/5564(0.9%)	49/5545(0.9%)	1.04(0.70,1.53)	1.04(0.70,1.54)	0.8542
MI	225/5564(4.0%)	272/5545(4.9%)	0.82(0.69,0.98)	0.82(0.68,0.98)	0.0281
-Q MI	14/5564(0.3%)	22/5545(0.4%)	0.63(0.32,1.24)	0.63(0.32,1.24)	0.1784
-Type 1	5/5564(0.1%)	9/5545(0.2%)	0.55(0.19,1.65)	0.55(0.19,1.65)	0.2819
-Type 2	0/5564(0.0%)	1/5545(0.0%)	----(----)	----(----)	0.3165
-Type 3	4/5564(0.1%)	0/5545(0.0%)	----(----)	----(----)	0.0458
-Type 4a	195/5564(3.5%)	239/5545(4.3%)	0.81(0.68,0.98)	0.81(0.66,0.98)	0.0285
-Type 4b	21/5564(0.4%)	27/5545(0.5%)	0.78(0.44,1.37)	0.77(0.44,1.37)	0.3790
-Type 5	0/5564(0.0%)	0/5545(0.0%)	----(----)	----(----)	
IDR	57/5564(1.0%)	67/5545(1.2%)	0.85(0.60,1.20)	0.85(0.59,1.21)	0.3564
-PCI	49/5564(0.9%)	62/5545(1.1%)	0.79(0.54,1.14)	0.79(0.54,1.14)	0.2083

-CABG	8/5564(0.1%)	5/5545(0.1%)	1.59(0.52,4.87)	1.60(0.52,4.88)	0.4086
Death/MI/IDR/ARC-ST	305/5564(5.5%)	348/5545(6.3%)	0.87(0.75,1.01)	0.87(0.74,1.01)	0.0752
Death/Q MI/IDR/ST	152/5564(2.7%)	176/5545(3.2%)	0.86(0.70,1.07)	0.86(0.69,1.07)	0.1686
Death/MI/IDR	304/5564(5.5%)	346/5545(6.2%)	0.88(0.75,1.02)	0.87(0.74,1.02)	0.0814
Death/Q MI/IDR	121/5564(2.2%)	128/5545(2.3%)	0.94(0.74,1.20)	0.94(0.73,1.21)	0.6341
Death/MI/ST	307/5564(5.5%)	362/5545(6.5%)	0.85(0.73,0.98)	0.84(0.71,0.98)	0.0251
Death/MI/ARC-ST	282/5564(5.1%)	326/5545(5.9%)	0.86(0.74,1.01)	0.85(0.73,1.01)	0.0603
Death/Q MI/ST	122/5564(2.2%)	147/5545(2.7%)	0.83(0.65,1.05)	0.82(0.65,1.05)	0.1161
Death/MI	278/5564(5.0%)	319/5545(5.8%)	0.87(0.74,1.02)	0.86(0.73,1.02)	0.0771
Death/Q MI	75/5564(1.3%)	78/5545(1.4%)	0.96(0.70,1.31)	0.96(0.70,1.32)	0.7906
Death/IDR	115/5564(2.1%)	118/5545(2.1%)	0.97(0.75,1.25)	0.97(0.75,1.26)	0.8220
Death/ST	114/5564(2.0%)	137/5545(2.5%)	0.83(0.65,1.06)	0.83(0.64,1.06)	0.1347

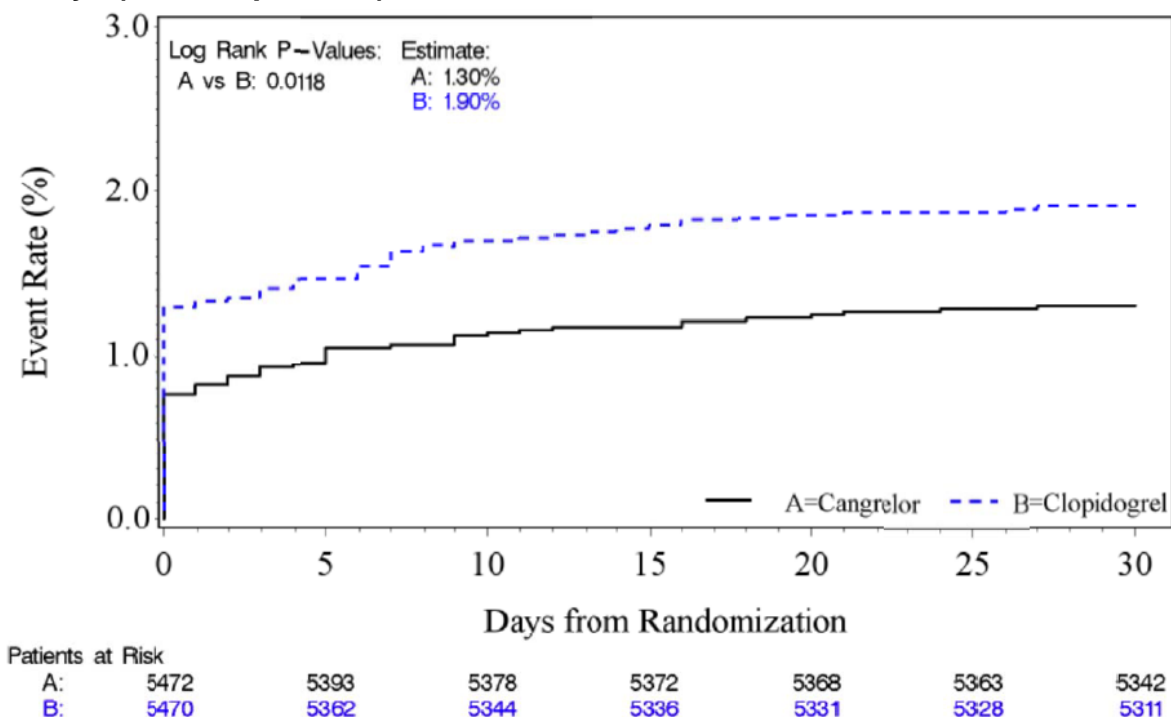
Source: PHOENIX CSR, Table 5.2.1.1, generated by T_ENDPT52.SAS 21MAR13 17:17

Figure 10. CHAMPION PHOENIX Kaplan-Meier Plot to first occurrence of death, MI, IDR and ST within 30-Days (mITT Population)



Source: Section 14.2, Figure 5.14.1.1.

Figure 11. CHAMPION PHOENIX Kaplan-Meier Plot to first occurrence of ST within 30-Days (mITT Population)



Source: Section 14.2, Figure 5.52.1.1.

6.1.1.5 Analysis of Secondary Endpoints(s)

Stent Thrombosis

ST was developed as a novel tool by the ARC as part of an informal collaborative effort to establish a broad-based consensus on endpoint definitions involving coronary stent clinical trials (Cutlip, D, et al., 2007). Although it was recognized by the ARC that consensus criteria would include some arbitrary features, consistency of endpoints across studies was postulated to facilitate the evaluation of safety and efficacy of stents and therefore foster recognition for regulatory purposes.

The definition of ARC-ST included accompanying clinical signs or symptoms as described in Appendix 9.2. The apparent rationale underlying the definition of ARC-ST was to ensure clinical significance to an angiographically based visual biomarker. The ARC-ST was sub-defined in relation to timing (i.e. Acute ST: 0-24 hours after stent implantation, Subacute ST: > 24 hours-30 days after stent implantation, Late ST: > 30 days-1 year after stent implantation, and Very Late ST: > 1 year after stent implantation) and likelihood of event (i.e. Definite ST, Probable ST, Possible ST).

The Applicant's use of ARC-ST was based on the hypothesis generated from the post-hoc analyses of the CHAMPION PCI and CHAMPION PLATFORM trials. The data from PHOENIX indicated that in the cangrelor arm (n=5472, mITT population), 3061 (55.9%) received a DES and 2308 (42.2%) received a non-DES. Similarly in the clopidogrel arm (n=5470, mITT population), 3020 (55.2%) received a DES and 2344 (42.9%) received a non-DES (see Table 4.2.1.1 CHAMPION PHOENIX CSR). Therefore, 98.1% of the mITT subject population received a stent. As Tables 9 and 10 respectively indicated, the results significantly favoring cangrelor over clopidogrel in the reduction of the primary composite endpoint was driven by ST thereby confirming the Applicant's hypothesis generated by the CHAMPION PCI and PLATFORM post-hoc analyses. The ST results were driven by IPST (see below). The data also suggested no difference in the incidence of the primary composite efficacy endpoint between those subjects given a DES and those given a non-DES (see Figure 6 CHAMPION PHOENIX CSR).

The Applicant's definition of ARC-ST required that the event occurred after the subject will have departed from the catheterization lab. Based on Cutlip, D, et al. (2007), it is this reviewer's opinion that "time 0" occurred immediately after stent deployment, whereby the subject is still located in the catheterization lab. Therefore, events which could have been adjudicated as an acute ARC-ST were adjudicated as an IPST (see next section below on IPST).

A random sampling of cangrelor treated subjects (n=13/122) adjudicated to have sustained an ARC-ST is shown in [Table 15](#). Similarly, a sampling of clopidogrel treated subjects (n=13/140) adjudicated to have sustained an ARC-ST is shown in [Table 16](#). Under the column titled "Reviewer Comments", the ECG and Ischemia symptoms were defined at baseline. The presence of MI occurred after randomization. Based on the approximate 10% sampling from both arms of the PHOENIX trial, the following features were observed:

- There was a tendency to align the timing of the ARC-ST to the time of chest pain, as per comments from the adjudicators located in the comment field of individual adjudication packages.
- The average time from PCI to ARC-ST was 5.1 days (range 0 days → 21 days) for subjects in the cangrelor arm and 3.7 days (range 0 days → 30 days) for subjects in the clopidogrel arm.
- Of the 13 ARC-ST in the cangrelor arm ([Table 15](#)), 10 were definite ST and 3 were probable ST. Of the 13 ARC-ST in the clopidogrel arm ([Table 16](#)), 11 were definite ST and 2 were probable ST.
- In the cangrelor arm, 9 of the 10 definite ST were associated with an MI (usually STEMI), 6 of which had an abnormal baseline ECG and 3 of which had a normal baseline ECG. None of the probable ST subjects were associated with an MI. In the clopidogrel arm, all 11 of the definite ST were associated with an MI (approximately 50% STEMI and 50% NSTEMI), 7 of which had an abnormal baseline ECG and 4 of which had a normal baseline ECG. Both of the probable ST subjects were associated with an MI (ECG

characteristics not identified due to lack of available ECG at the time of MI in each case).

- In both arms, the timing of the MI and the timing of the definite ST were identical.

Based on the observed features of the randomly sampled subjects who were adjudicated to have sustained an ARC-ST, these events occurred several days post PCI, were associated with an MI, and were similar in characteristics between each arm. The adjudication of ARC-ST was consistent with the analysis description in the CEC Charter.

Table 15. Cangrelor-treated Subjects Adjudicated to have sustained ARC-ST

Cangrelor-treated Subjects Adjudicated to have sustained ARC-ST (random sampling n= 13/122)					
Patient ID	Angiography: Date(Time)	PCI: Date(Time start, end)	ARC-Stent Thrombosis Date(Time)	CEC Comments	Reviewer Comments
401001027	(b) (6)	(b) (6)	Def. ST (b) (6)	Timed to CP	ECG: ABN no criteria entered MI: yes. STEMI (b) (6) Isch: yes
401091342	(b) (6)	(b) (6)	Prob. ST (b) (6)	Timed by Clinical Scenario not death. Death at (b) (6)	ECG: ABN no criteria applies MI: no Isch: no
401091647	(b) (6)	(b) (6)	Prob. ST (b) (6)	-----	ECG: ABN no criteria applies MI: no Isch: yes
407005010	(b) (6)	(b) (6)	Def. ST (b) (6)	Autopsy report confirmed ST. Death (b) (6)	ECG: ABN STE and ST-dep MI: yes by autopsy report Isch: yes
407007014	(b) (6)	(b) (6)	Def. ST (b) (6)	-----	ECG: ABN STE MI: yes (b) (6) not ECG specified Isch: yes
420005054	(b) (6)	(b) (6)	Prob. ST	Death 20	ECG: N

	(b) (6)	(b) (6)	(b) (6) (-)	days after PCI, unknown cause	MI: no Isch: no
420009271	(b) (6)	(b) (6)	Def. ST (b) (6)	Timed to onset of angina (b) (6)	ECG: N MI: yes, STEMI (b) (6) Isch: yes
439004225	(b) (6)	(b) (6)	Def. ST (b) (6)	----	ECG: ABN STE MI: no Isch: yes
448001321	(b) (6)	(b) (6)	Def. ST (b) (6)	----	ECG: N MI: yes STEMI (b) (6) Isch: no
448001378	(b) (6)	(b) (6)	Def. ST (b) (6)	Per core lab	ECG: N MI: yes STEMI (b) (6) Isch: no
449005020	(b) (6)	(b) (6)	Def. ST (b) (6)	----	ECG: ABN no criteria applies MI: yes STEMI (b) (6) Isch: no
459002020	(b) (6)	(b) (6)	Def. ST (b) (6)	Timed to onset of recurrent symptoms	ECG: ABN no criteria applies MI: yes STEMI (b) (6) Isch: no
466001076	(b) (6)	(b) (6)	Def. ST (b) (6)	----	ECG: ABN STE, new QW MI: yes unknown ECG (b) (6) Isch: yes

Date and Time: month/day/year; 24-hour clock. CP = Chest Pain; ABN = abnormal; N= Normal; Rem-ABN = Remains abnormal; ECG=electrocardiogram performed at baseline; STE = ST-segment elevation; ST-dep = ST-segment depression; Isch = ischemic symptoms at baseline; TWI = T wave inversion; Def ST = Definite ARC-Stent

Thrombosis; Prob ST – Probable ARC-Stent Thrombosis; MI = Myocardial Infarction;
QW= Q-wave

Table 16. Clopidogrel-treated Subjects Adjudicated to have sustained ARC-ST

Clopidogrel-treated Subjects Adjudicated to have sustained ARC-ST (random sampling n= 13/140)					
Patient ID	Angiography: Date(Time)	PCI: Date(Time start, end)	ARC-Stent Thrombosis Date(Time)	CEC Comments	Reviewer Comments
401001119	(b) (6)	(b) (6)	Def.ST (b) (6)	----	ECG: N MI: yes STEMI (b) (6) Isch: No
401015011	(b) (6)	(b) (6)	Def. ST (b) (6)	-----	ECG: ABN no criteria applies MI: yes STEMI (b) (6) Isch: No
401030335	(b) (6)	(b) (6)	Prob. ST (b) (6)	-----	ECG: ABN no criteria applies MI: yes, no ECG (b) (6) Isch: yes
401032015	(b) (6)	(b) (6)	Def. ST (b) (6)	Core lab assessment confirmed in-stent thrombosis	ECG: N MI: yes STEMI (b) (6) Isch: no
401058008	(b) (6)	(b) (6)	Def. ST (b) (6)	Symptoms with angio→ST	ECG: ABN no criteria applies MI: yes NSTEMI (b) (6) Isch: not at baseline
401070012	(b) (6)	(b) (6)	Def. ST (b) (6)	-----	ECG: ABN no criteria applies MI: yes STEMI (b) (6) Isch: no
401077030	(b) (6)	(b) (6)	Def. ST (b) (6)	Timed to onset of	ECG: ABN, SB

		(b) (6)	(b) (6)	chest pain after end of index PCI	MI: yes, NSTEMI (b) (6) Isch: yes
401079204	(b) (6)	(b) (6)	Prob. ST (b) (6)	-----	ECG: ABN no criteria applies MI: yes, no ECG available (b) (6) Isch: no
401084003	(b) (6)	(b) (6)	Def. ST (b) (6)	Timed to recurrence of ischemic symptoms. No source documents available	ECG: ABN, possible septal infarct (b) (6) MI: yes, NSTEMI (b) (6) Isch: yes
401091451	(b) (6)	(b) (6)	Def. ST (b) (6)	New symptoms plus abrupt closure of LAD and some STE	ECG: N MI: yes NSTEMI (b) (6) Isch: no
401109073	(b) (6)	(b) (6)	Def. ST (b) (6)	In stent thrombosis (core lab report)	ECG: N MI: yes STEMI (b) (6) Isch: yes
407005206	(b) (6)	(b) (6)	Def. ST (b) (6)		ECG: ABN ST-dep and new QW MI: yes STEMI (b) (6) Isch: yes
420009100	(b) (6)	(b) (6)	Def. ST (b) (6)	-----	ECG: ABN STE MI: yes STEMI (b) (6) Isch: yes

Date and Time: month/day/year; 24-hour clock. CP = Chest Pain; ABN = abnormal; N= Normal; Rem-ABN = Remains abnormal; ECG=electrocardiogram performed at baseline; STE = ST-segment elevation; ST-dep = ST-segment depression; Isch = ischemic symptoms at baseline; TWI = T wave inversion; Def ST = Definite ARC-Stent

Thrombosis; Prob ST – Probable ARC-Stent Thrombosis; MI = Myocardial Infarction;
QW= Q-wave; SB = Sinus Bradycardia

Intra-Procedural Stent Thrombosis

A total of 89 subjects in the PHOENIX trial were adjudicated to have sustained an IPST. A random sampling of cangrelor treated subjects (n=13/35) adjudicated to have sustained an IPST is shown in [Table 17](#). Similarly, a sampling of clopidogrel treated subjects (n=13/54) adjudicated to have sustained an IPST is shown in [Table 18](#). Under the column titled “Reviewer Comments”, the ECG and Ischemia symptoms were defined at baseline. The presence of MI occurred after randomization. Based on the approximate 30% sampling from both arms of the PHOENIX trial, the following features were observed:

- The adjudicated timing of the IPST was precisely the same as the adjudicated timing of the start of PCI for each of the sampled subjects.
- Of the 13 IPST in the cangrelor arm, 2 were associated with MI, of which 1 had a baseline abnormal ECG. Of the 11 IPST not associated with an MI, 7 had a baseline abnormal ECG, 3 had a baseline normal ECG, and 1 ECG was not performed.
- Of the 13 IPST in the clopidogrel arm, 3 were associated with MI, of which 2 had a baseline abnormal ECG and 1 had a baseline normal ECG. Of the 10 IPST not associated with an MI, 5 had a baseline abnormal ECG, 4 had a baseline normal ECG, and 1 ECG was not performed.

The precise coincidence of the timing of the adjudicated IPST with the timing of the start of PCI raised a question about whether or not the specified timing in the adjudication package was an arbitrary artifact of “in-cath-lab” thrombosis, which was observed during angiography and which occurred prior to or at the start of PCI. This raised an additional question about whether or not the thrombotic event was truly intra-procedural. Unlike ARC-ST, the event of an IPST was usually not associated with an MI, thereby raising a further question on the clinical significance of this angiographic-driven endpoint based on the PHOENIX data.

Brener, S et al., 2013, postulated that IPST was a rare but serious complication of PCI and that the ARC-ST definition excluded events occurring during PCI. The term Intra-Procedural Stent Thrombosis (IPST) was coined to incorporate stent thrombotic events during stent deployment, compared to after the stent was deployed. In a post-hoc analysis of angiographic data from the ACUTY and HORIZONS-AMI trial, a frame-by-frame review by an independent core laboratory sought to identify patients with the occurrence of an IPST. Patients with versus without IPST were compared to each other in order to identify baseline characteristics associated with IPST and demonstrate the independent association between IPST and adjudicated events at 30 days and 1 year.

[Table 19](#) shows that IPST was associated with baseline STEMI, bailout GPI, TIMI-

grade 0/1 flow, lesions with thrombus treated, bifurcation lesions, and BMS deployment (compared to DES). **Table 20** shows that IPST was also associated with 30 day and 1 year clinical events: death, MI, ARC-ST (definite or probable), ARC-ST definite, TVR, and TIMI Major Bleed (non-CABG). Brenner, S, et al. concluded that IPST was a relatively rare complication of PCI in ACS but was strongly associated with subsequent out-of-lab ST and mortality. It was opined that IPST should be considered as a distinct category of ST and routinely reported, particularly for ACS patients.

Key to the Applicant's application was their position that IPST was an important parameter based on the work of Brenner, S, et al., and consequently justified including this parameter as an expansion of the ARC-ST definition. The inclusion of IPST was consistent with the Applicant's program hypothesis of benefit in the peri-procedural domain based on the "fast on—fast off" property of cangrelor.

As a consequence of queries dispatched to the Applicant, the Applicant explored the prognostic significance of IPST from the PHOENIX data. The results at 48 hours shown in **Table 21** and at 30 days shown in **Table 22** revealed a similar pattern to that observed in the ACUITY and HORIZONS-AMI post-hoc analysis by Brenner et al., 2013. The presence of an IPST was significantly associated with the composite primary endpoint of death, MI, IDR, and ARC-ST as well as with each component of the composite primary endpoint both at 48 hours and at 30 days. Because this was an exploratory analysis, the Applicant performed a propensity score adjusted analysis in order to evaluate whether or not IPST as a predictor of MACE was independent of potential confounders (i.e. patient type, worst pre-procedure TIMI Score, stent type, bifurcation treatment). Adjustments for these potential confounders demonstrated that the effect of IPST remained an independent predictor of clinical outcomes (OR and 95%CI on death, MI, IDR, ARC-ST: 10.11[6.29, 16.23], $p<0.0001$). The addition of other covariates (i.e. age ≥ 65 years, biomarker status, previous PCI, previous CABG, aspirin, PAD, US region, race, weight, smoking, number of vessels, clopidogrel loading dose, infusion duration ≥ 129 minutes, previous MI, use of bivalirudin) did not attenuate the independent predictor status of IPST for the composite of death, MI, IDR, ARC-ST (OR and 95% CI: 11.85 [7.08, 19.84], $p<0.0001$). These same adjustments also did not affect the difference between cangrelor and clopidogrel (Applicant response to 74 day letter, appendix 4, Table 5.15.1.1).

It is unclear whether or not Acute ARC-ST, if subjected to a similar post-hoc analysis as was IPST, would have yielded a similar prognostic indication of clinical outcome. The strong correlation between IPST and ARC-ST suggested that the presence of ARC-ST would be of similar prognostic significance for MACE.

The inter-reader variability of IPST was estimated to be Kappa 0.7125. **Table 23** describes the measurement of observer agreement for categorical data (Landis, JR, et al., 1977) and represented this value as "substantial" (i.e. between "moderate" and "almost perfect" which is the highest score). Alternatively, in an expert opinion (Byrt, T,

1996) which challenged this categorical assessment, a revised categorical description was offered and shown in **Table 24**. Under this revision, the estimated Kappa of 0.7125 has been represented as “good” (i.e. above “fair” but below “very good”, which is one level below the highest score of “excellent”). Therefore, scale categories might reflect differences in the confidence of data accuracy. The Applicant has recognized that inter-reader variability by the Angiography Core Lab was “not considered perfect”, and have argued that this level of variability was consistent with that of many diagnostic tests in widespread use, as illustrated in **Table 25**. Based on this evaluation, the inter-reader variability was considered to be acceptable.

Distinguishing IPST from Acute ARC-ST appeared to have been dependent on timing relative to stent deployment. From the definitions (see Appendix 9.2), an ARC-ST would be diagnosed starting from the time immediately after the stent will have been deployed unless other requisite diagnostic criteria (i.e. clinical signs and/or symptoms) were not present. IPST would presumably be diagnosed while the stent was still being deployed (i.e. after crossing the lesion to the deployment of stent). In the index publication by Brener, S, et al. (2013), IPST was defined “as new or increasing (compared with baseline) thrombus within or adjacent to a deployed stent occurring during the index PCI procedure, whether occlusive or non-occlusive. IPST was also deemed present when the baseline level of thrombus was decreasing or resolved after balloon angioplasty or thrombus aspiration but then increased any time after stent implantation (including stent post-dilation)”. This published definition of IPST overlaps with acute ARC-ST from the angiographic perspective. The definitions of IPST as provided by the CEC Charter and the Angiographic Core Laboratory Charter (i.e. ST occurring while the subject is still in the catheterization lab) also overlaps with that of acute ARC-ST from the angiographic perspective. This overlap, in addition to the issues which were raised in section 3.1 (i.e. IPST is a biomarker devoid of associated requisite clinical signs/symptoms), has caused IPST to become a questionable entity.

Based on the efficacy data, IPST drove the primary endpoint whereby its removal from the ST component of the primary endpoint caused loss of sustained benefit for cangrelor at 30 days.

Table 17. Cangrelor-treated Subjects Adjudicated to have sustained IPST

Cangrelor-treated Subjects Adjudicated to have sustained IPST (random sampling n= 13/35)					
Patient ID	Angiography: Date(Time)	PCI: Date(Time start, end)	IPST Date(Time)	CEC Comments	Reviewer Comments
401010006	(b) (6)	(b) (6)	IPST (b) (6)	-----	ECG: ABN, SB with occasional PVC MI: no Isch: no
401017066	(b) (6)	(b) (6)	IPST (b) (6)	Core lab report = IPST	ECG: not done- protocol violation MI: no Isch: no
401023002	(b) (6)	(b) (6)	IPST (b) (6)	-----	ECG: N MI: no Isch: yes
401029071	(b) (6)	(b) (6)	IPST (b) (6)	-----	ECG: ABN no criteria applies MI: no Isch: no
401079059	(b) (6)	(b) (6)	IPST (b) (6)	-----	ECG: ABN no criteria applies MI: no Isch: no
420009476	(b) (6)	(b) (6)	IPST (b) (6)	-----	ECG: N MI: no Isch: yes
420009638	(b) (6)	(b) (6)	IPST (b) (6)	-----	ECG: N MI: no Isch: yes
420019004	(b) (6)	(b) (6)	IPST (b) (6)	-----	ECG: ABN, STE, new QW MI: no (no entry) Isch: yes

					Note: troponin-I 11.74
439004216	(b) (6)	(b) (6)	IPST (b) (6)	-----	ECG: not done- protocol violation MI: yes, NSTEMI, NQWMI, CKMB 22.5, (b) (6) Isch: no
448019001	(b) (6)	(b) (6)	IPST (b) (6)	-----	ECG: ABN, STE, new QW MI: no (no audit trial) Isch: yes Note: troponin-T 0.148. Patient considered to have had STEMI upon entry.
449001025	(b) (6)	(b) (6)	IPST (b) (6)	-----	ECG: ABN, TWI MI: no Isch: no
495002003	(b) (6)	(b) (6)	IPST (b) (6)	-----	ECG: ABN, ST-dep and STE MI: no Isch: yes
495005595	(b) (6)	(b) (6)	IPST (b) (6)	Thrombosis detected during, not after PCI	ECG: ABN, old QW MI: yes, type 3 associated with death on (b) (6) Cardiac

Clinical Review

Fred Senatore MD, PhD, FACC; Nhi Beasley Pharm D.

NDA 204958

Cangrelor

					markers not increased. No ECG available. Isch: no
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Date and Time: month/day/year; 24-hour clock. CP = Chest Pain; ABN = abnormal; N= Normal; ECG=electrocardiogram performed at baseline; SB = Sinus Bradycardia; STE = ST-segment elevation; ST-dep = ST-segment depression; Isch = ischemic symptoms at baseline; TWI = T wave inversion; MI = Myocardial Infarction; QW= Q-wave; ULN = upper limit of normal; PVC = premature ventricular contraction; CKMB ULN 5.09

Table 18. Clopidogrel-treated Subjects Adjudicated to have sustained IPST

Clopidogrel-treated Subjects Adjudicated to have sustained IPST (random sampling n= 13/54)					
Patient ID	Angiography: Date(Time)	PCI: Date(Time start, end)	IPST Date(Time)	CEC Comments	Reviewer Comments
401010011	(b) (6)	(b) (6)	IPST (b) (6)	-----	ECG: ABN no criteria applies MI: no Isch: yes
401010092	(b) (6)	(b) (6)	IPST (b) (6)	No evidence of IPST in catheterization report	ECG: ABN no criteria applies MI: yes, NSTEMI, NQWMI, (b) (6) Isch: no
401053066	(b) (6)	(b) (6)	IPST (b) (6)	Per core lab	ECG: ABN no criteria applies MI: no Isch: no
401073002	(b) (6)	(b) (6)	IPST (b) (6)	-----	ECG: not done- protocol violation MI: no Isch: no
401079061	(b) (6)	(b) (6)	IPST (b) (6)	-----	ECG: N MI: no Isch: no
401091530	(b) (6)	(b) (6)	IPST (b) (6)	-----	ECG: ABN no criteria applies MI: yes, NSTEMI (b) (6) Isch: yes
420009051	(b) (6)	(b) (6)	IPST (b) (6)	-----	ECG: N MI: no

420009318	(b) (6)	(b) (6)	IPST (b) (6)	Per core lab report	Isch: no ECG: ABN, ST-dep MI: no Isch: yes
420009566	(b) (6)	(b) (6)	IPST (b) (6)	Per core lab report	ECG: N MI: no Isch: no
420011009	(b) (6)	(b) (6)	IPST (b) (6)	-----	ECG: ABN STE, old QW MI: no Isch: yes-day before but not at baseline
443002362	(b) (6)	(b) (6)	IPST (b) (6)	Per core labs	ECG: N MI: yes STEMI, (b) (6) CKMB 17.8 Isch: no
448001092	(b) (6)	(b) (6)	IPST (b) (6)	IPST vs. definite ST	ECG: ABN, old LBBB MI: no Isch: yes
449002020	(b) (6)	(b) (6)	IPST (b) (6)	Core lab assessment confirmed IPST	ECG: N MI: no Isch: yes

Date and Time: month/day/year; 24-hour clock. CP = Chest Pain; ABN = abnormal; N= Normal; ECG=electrocardiogram performed at baseline; SB = Sinus Bradycardia; STE = ST-segment elevation; ST-dep = ST-segment depression; Isch = ischemic symptoms at baseline; TWI = T wave inversion; MI = Myocardial Infarction; QW= Q-wave; ULN = upper limit of normal; CKMB ULN 5.09

Table 19. Baseline associations with IPST from ACUTY and HORIZONS-AMI

Table 1. Baseline Clinical and Angiographic Characteristics of Patients With and Without IPST			
Variable	IPST (n = 47)	No IPST (n = 6,544)	p Value
Age	61.4 [52.4–69.5]	60.6 [52.7–70.0]	0.91
Male	74.5% (35/47)	73.5% (4,812/6,544)	1.0
Diabetes mellitus	17.0% (8/47)	24.2% (1,581/6,528)	0.31
Insulin-treated	10.0% (4/40)	10.5% (440/4,182)	1.0
Current cigarette smoker	34.0% (16/47)	39.1% (2,555/6,531)	0.55
Hypertension	57.4% (27/47)	61.1% (3,990/6,529)	0.65
Hyperlipidemia	47.8% (22/46)	52.5% (3,416/6,501)	0.56
Previous MI	14.9% (7/47)	22.7% (1,463/6,452)	0.29
Previous PCI	17.0% (8/47)	29.3% (1,913/6,525)	0.08
Previous CABG	6.4% (3/47)	12.6% (821/6,535)	0.27
Clinical presentation			
Unstable angina	4.3% (2/47)	24.3% (1,587/6,544)	0.0005
Non-STEMI	17.0% (8/47)	28.0% (1,831/6,544)	0.10
STEMI	78.7% (37/47)	47.8% (3,126/6,544)	<0.0001
Baseline creatinine clearance, ml/min	86 [64–106]	90 [69–116]	0.20
Baseline hemoglobin (g/dl)	14.3 [13.2–15.7]	14.3 [13.2–15.3]	0.58
Baseline white blood cell count ($\times 10^3$)	10.7 [8.8–13.20]	9.20 [7.2–11.8]	0.002
Baseline platelet count ($\times 10^3$)	235 [201–293]	236 [197–281]	0.66
Randomized treatment: bivalirudin alone	59.6% (28/47)	41.3% (2,701/6,544)	0.02
GPI used for bailout	64.3% (18/28)	10.8% (292/2,697)	<0.0001
Number of diseased vessels			
1	76.6% (36/47)	54.7% (3,580/6,541)	0.003
2	8.5% (4/47)	20.4% (1,335/6,541)	0.04
3	14.9% (7/47)	24.5% (1,603/6,541)	0.17
Baseline TIMI 0/1 flow	74.5% (35/47)	37.7% (2,462/6,523)	<0.0001
Number of vessels treated	1 [1,1]	1 [1,1]	0.10
Number of lesions treated	2 [2–3]	2 [2–3]	0.69
Any LM lesion intervened	0% (0/47)	0.2% (10/4,105)	1.0
Any LAD lesion intervened	38.3% (18/47)	41.1% (2,685/6,540)	0.77
Any LCX lesion intervened	21.3% (10/47)	26.5% (1,730/6,530)	0.51
Any RCA lesion intervened	38.3% (18/47)	41.5% (2,713/6,540)	0.77
Any SVG lesion intervened	4.3% (2/47)	1.5% (96/6,540)	0.15
Any lesion with thrombus treated	87.2% (41/47)	47.1% (3,074/6,529)	<0.0001
Any bifurcation lesion treated	51.1% (24/47)	28.2% (1,156/4,094)	0.001
Any stent used	100% (47/47)	99.8% (6,531/6,544)	1.0
Any drug-eluting stent used	66.0% (31/47)	80.9% (5,296/6,544)	0.015
Only bare-metal stents used	34% (16/47)	19.1% (1,248/6,544)	0.015
Values are mean (range) or % (n/N).			
CABG = coronary artery bypass grafting; GPI = glycoprotein IIb/IIIa inhibitor; IPST = Intra-procedural stent thrombosis; LAD = left anterior descending; LCX = left circumflex; LM = left main; MI = myocardial infarction; PCI = percutaneous coronary intervention; RCA = right coronary artery; STEMI = ST-segment elevation myocardial infarction; SVG = saphenous vein graft; TIMI = Thrombolysis In Myocardial Infarction flow grade.			

Table 20. Clinical Event associations with IPST from ACUTY and HORIZONS-AMI

Table 2. Clinical Events Through 30-Day and 1-Year Follow-Up				
	IPST (n = 47)	No IPST (n = 6,544)	Hazard Ratio [95% CI]	p Value
30-day events				
Death	12.9% (6)	1.4% (87)	10.39 [4.54–23.77]	<0.0001
MI	14.9% (7)	4.9% (313)	3.55 [1.68–7.52]	0.0004
Death or MI	28.0% (13)	5.9% (380)	5.49 [3.16–9.54]	<0.0001
ST, definite or probable (ARC)	17.4% (8)	1.8% (117)	10.99 [5.37–22.51]	<0.0001
Definite	15.3% (7)	1.3% (85)	12.94 [5.99–27.98]	<0.0001
Probable	2.1% (1)	0.5% (32)	4.84 [0.66–35.46]	0.09
TVR	15.1% (7)	2.2% (141)	8.09 [3.79–17.29]	<0.0001
Death, MI, or TVR	34.6% (16)	6.8% (435)	6.18 [3.75–10.18]	<0.0001
TIMI major bleeding (non-CABG)	15.4% (7)	2.0% (131)	7.95 [3.72–17.01]	<0.0001
Death, MI, TVR, or TIMI major bleeding (non-CABG)	43.1% (20)	11.7% (755)	4.49 [2.88–7.00]	<0.0001
1-yr events				
Death	12.9% (6)	3.1% (200)	4.67 [2.07–10.52]	<0.0001
MI	17.6% (8)	7.5% (472)	2.84 [1.41–5.70]	0.002
Death or MI	30.1% (14)	9.9% (627)	3.79 [2.23–6.44]	<0.0001
ST, definite or probable (ARC)	19.9% (9)	2.7% (165)	9.19 [4.70–17.98]	<0.0001
Definite	17.9% (8)	2.0% (127)	10.51 [5.14–21.48]	<0.0001
Probable	2.1% (1)	0.7% (38)	4.12 [0.57–30.04]	0.13
TVR	22.8% (10)	7.9% (483)	3.79 [2.03–7.09]	<0.0001
Death, MI, or TVR	41.1% (19)	14.5% (912)	3.93 [2.50–6.19]	<0.0001
Values are % (n). ARC – Academic Research Consortium; CI – confidence interval; ST – stent thrombosis; TVR – target vessel revascularization; other abbreviations as in Table 1.				

Table 21. CHAMPION PHOENIX 48 Hour efficacy and safety outcomes in patients with and without IPST during index PCI

48 hour endpoint	IPST	Not IPST	RR (95% CI)	p-value
Efficacy (mITT population)	(N=89)	(N=10,850*)		
Death/MI/IDR/ARC-ST	26 (29.2)	490 (4.5)	6.47 (4.63,9.04)	<0.0001
Death	5 (5.6)	31 (0.3)	19.66 (7.83,49.40)	<0.0001
ARC ST	3 (3.4)	31 (0.3)	11.80 (3.67,37.88)	<0.0001
IDR	4 (4.5)	62 (0.6)	7.87 (2.92,21.15)	<0.0001
MI	23 (25.8)	439 (4.0)	6.39 (4.44,9.19)	<0.0001
Safety (Safety population)	(N=89)	(N=10,967)		
Any TIMI bleeding	1 (1.1)	21 (0.2)	5.87 (0.80,43.15)	0.0494
Major	0 (0.0)	10 (0.1)	(,)	0.7756
Minor	1 (1.1)	11 (0.1)	11.20 (1.46,85.85)	0.0035

Source: [Appendix 4, Tables 91.5.1.1.1, 91.6.1.4.1](#)

* 3 patients have no efficacy data at 48 h – total mITT population for patients without IPST is N = 10,853

Table 22. CHAMPION PHOENIX 30-day efficacy outcomes in patients with and without IPST during index PCI

30 day endpoint	IPST	Not IPST	RR (95% CI)	p-value
Efficacy (mITT population)	(N=89)	(N=10,830*)		
Death/MI/IDR/ARC-ST	28 (31.5)	617 (5.7)	5.52 (4.03,7.57)	<0.0001
Death	9 (10.1)	106 (1.0)	10.33 (5.41,19.75)	<0.0001
ARC ST	5 (5.6)	86 (0.8)	7.07 (2.94,17.01)	<0.0001
IDR	5 (5.6)	117 (1.1)	5.20 (2.18,12.42)	<0.0001
MI	24 (27.0)	473 (4.4)	6.17 (4.34,8.79)	<0.0001

Source: [Appendix 4, Table 91.5.2.1.1](#)

* 23 patients have no efficacy data at 30 days – total mITT population for patients without IPST is N = 10,853

Table 23. Measurement of Observer Agreement for Categorical Data

Kappa Value	Agreement
< 0	Poor
0 – 0.2	Slight
0.21 – 0.4	Fair
0.41 – 0.6	Moderate
0.61 – 0.8	Substantial
0.81 - 1	Almost Perfect
Landis JR and Koch GG. The Measurement of Observer Agreement for Categorical Data. Biometrics. 1977; 33:159-174.	

Table 24. Revised quality of Observer Agreement for Categorical Data

Kappa Value	Agreement
≤ 0	No agreement
0.01 – 0.20	Poor agreement
0.21 – 0.40	Slight agreement
0.41 – 0.60	Fair agreement
0.61 – 0.80	Good agreement
0.81 – 0.92	Very good agreement
0.93 – 1.00	Excellent agreement
Byrt T: How good is that agreement? (Letter to editor) Epidemiology 1996;7:561.	

Table 25. Score reproducibility and variability in quantitative coronary measurements

Test Modality	Kappa value
Dobutamine stress test (LV contraction assessment)	0.86
Helical CT with angiography (pulmonary embolism diagnosis)	0.65
Transesophageal echocardiogram (PFO diagnostic)	0.77
Mammography (cancer present)	0.54
Mammography (cancer not present)	0.62
Lesion type ABC classification of ACC/AHA24	0.33

LV indicates left ventricle; CT, computerized tomography; PFO, patent foramen ovale; ACC, American College of Cardiology; and AHA, American Heart Association

Source: Genereux, P, et al., 2011, Circ Cardiovasc Interv, 4:553-561

MI

Based on the post-hoc analyses of the CHAMPION PLATFORM and PCI trials, the Applicant hypothesized that evolving MIs prior to PCI masked the beneficial effect of cangrelor in attenuating the rate of peri-procedural events. Therefore, baseline myocardial status was required to be within normal limits at the start of PCI.

A normal baseline in the NSTEMI population was identified as two normal troponin and/or CKMB samples taken 6 hours apart, with no new changes in 12-lead ECG and no ongoing or recent clinical symptoms since the 1st normal biomarker. A normal baseline in the SA population was identified as one normal troponin or CKMB sample, with no new ECG changes and no ACS symptoms. An abnormal baseline was identified as one sample greater than the ULN or two normal samples < 6 hours apart, or new ECG changes, or recent symptoms within the last 6 hours. A “baseline unknown” was defined as no availability of pre-PCI samples.

From the PHOENIX Executive Committee Meeting Minutes of 22 SEPT 2010 (see CSR section 16.1.4.2), the definition of MI for adjudication purposes required a normal baseline followed by CKMB elevation > 3x ULN (troponin could be used if CKMB was not available). Evidence of angiographic, ECG and ischemic symptoms were not required as qualification parameters for the adjudication of an MI. Reinfarction was defined as an abnormal but decreasing baseline or baseline unknown followed by re-elevation of CKMB \geq 50% above the nadir and 3x ULN from the last sample. This was required to be accompanied by angiographic evidence of re-occlusion, or ischemic symptoms, or new ECG changes. Patients determined to have a baseline STEMI (including patients with normal baseline cardiac markers who were confirmed by the CEC adjudication to have baseline STEMI ECG) were not reviewed by the CEC for peri-procedural MI (from PHOENIX CSR section 9.5.2.3.2).

The UDMI (see Appendix 9.1 and section 5.3.3) was used in the CHAMPION PHOENIX trial. The CEC Adjudication Review Guideline provided the definition and timing of the 5 types of UDMI. Type 1 (spontaneous MI due to plaque-mediated ischemia) and Type 2 (MI due to coronary vasospasm or embolism, anemia, arrhythmia, hypo or hyper tension) were not related to procedures and the timing of the event was defined as time to 1st qualifying criteria (symptoms, first cardiac markers, first ECG). Type 3 MI was related to sudden death and the timing of the event was defined as time of death. Type 4a MI was related to PCI and the timing of the event was defined as start of PCI. Type 4b MI was related to stent thrombosis and the timing of the event was defined as time to 1st qualifying criteria (symptoms, first cardiac markers, first ECG). Type 5 MI was related to CABG and the timing of the event was defined as CABG start-time.

The CHAMPION-PHOENIX results showed that the overall MI rate was significantly lower in the ITT cangrelor group (207/5573: 3.7%) compared to the clopidogrel group (255/5561: 4.6%), (OR 0.80, 95% CI [0.67, 0.97], p=0.0212). This result was driven by

UDMI type 4a: 194/5573 (3.5%) in the cangrelor group and 239/5561 (4.3%) in the clopidogrel group (OR 0.80 [0.66, 0.97], $p=0.0258$). There was only one adjudicated Type 1 MI reported in each group. There was no reported Type 2 MIs. There were 3 reported Type 3 MIs in the cangrelor group and none in the clopidogrel group. There were 9 / 5573 (0.2%) Type 4b MIs in the cangrelor group and 15/5561 (0.3%) Type 4b MIs in the clopidogrel group (OR 0.60, 95% CI [0.26, 1.37], $p=0.2182$). There was no reported Type 5 MIs.

Type 1 MI was required for an adjudication of Type 4a MI (associated with PCI and aligned with IPST) and Type 4b MI (associated with ST and aligned with ARC-ST). Since the Adjudication Charter restricted multiple assignments of MI (e.g. an MI assigned to type 4a would not be simultaneously assigned to type 1), the paucity of type 1 MI was an artifact of the adjudication process.

The lack of a significant difference between cangrelor and clopidogrel for Type 4b MI in the setting of a significant difference in ST between the cangrelor and clopidogrel had raised a question about how the adjudication process discriminated Type 4a from Type 4b MI. This question was communicated to the Applicant. The Applicant replied that adjudication of a Type 4b MI required spontaneous MI or re-MI in association with an ARC- ST defined by the Applicant as an ST occurring after the subject departed from the catheterization lab. An MI or re-MI in the presence of an IPST, defined as an ST occurring while the subject was still in the catheterization lab, did not qualify a patient for a Type 4b MI and therefore such an MI was adjudicated as a Type 4a. [Table 26](#) shows the subjects adjudicated to have sustained an MI, subdivided by UDMI Type. The Applicant combined the adjudicated-MI subjects from both groups and re-distributed them in accordance to whether or not they were adjudicated to have an ST or not reported to have an ST. The incidences of adjudicated-ST vs. no-reported ST were further subdivided into adjudicated-IPST vs. no-reported IPST, and adjudicated-ARC-ST vs. no-reported ARC-ST, respectively. Of the 462 ITT (same number mITT) adjudicated MI subjects (207 cangrelor and 255 clopidogrel- see [Table 13](#)), 46/120 (38.3%) subjects were adjudicated to have an ST, and 416/10,819 (3.8%) subjects were not reported to have an ST. Those ST events in MI subjects adjudicated as IPST were also adjudicated to Type 4a MI, and those ST events in MI subjects adjudicated as ARC-ST were also adjudicated to Type 4b MI. Furthermore, all cases of ST with evidence suggestive of baseline cardiac marker elevation without re-elevation, or MI antecedent to ST, were adjudicated to Type 4a MI. This resulted in a higher number of adjudicated UDMI Type 4a MIs. Also, the low Type 1 MI event rate was attributed to the CEC adjudication process of not assigning more than one type of MI to each adjudication package.

It is the opinion of this reviewer that the incidence of MI favoring cangrelor over clopidogrel was due to the requirement of a normal baseline, thereby confirming the hypothesis generated from the post-hoc analyses of CHAMPION PLATFORM and CHAMPION PCI. The CHAMPION PLATFORM and PCI trials suggested that if the MI adjudications were not filtered to exclude those experiencing an MI prior to PCI, the

results from PHOENIX likely would not have shown a difference between cangrelor and clopidogrel for MI. The higher incidence of Type 4a MI was likely due to an artifact of the adjudication process associated with the nebulous distinction between IPST and Acute ARC-ST as well as the assignment of MI occurring prior to ST as Type 4a.

A random sampling of cangrelor treated subjects (n=25/469) adjudicated to have sustained an MI is shown in [Table 27](#). Similarly, a random sampling of clopidogrel treated subjects (n=25/526) adjudicated to have sustained an MI is shown in [Table 28](#). Under the column titled “Reviewer Comments”, the ECG and Ischemia symptoms were defined at baseline. Based on the approximate 5% sampling from both arms of the PHOENIX trial, the following features were observed:

- The adjudicated MIs were mostly NSTEMIs and assessed as a Type 4a from the UDMI classification. One subject from the sampled cangrelor group and three subjects from the sampled clopidogrel group were assessed as Type 4b MIs.
- In all Type 4a MI adjudications, the adjudicated timing of the event was precisely coincident with the time of the start of PCI. Baseline status in those subjects adjudicated to have sustained a Type 4a MI were classified by the Adjudication Committee as either normal, decreasing and returning to normal.
- In the Type 4b MI diagnoses, the MI was adjudicated to have occurred 2 weeks after the PCI (subject 401030065), 27 minutes after PCI (subject 401001119), 46 minutes after PCI (subject 401070012), and 67 minutes after PCI (401084003).
- The MIs were based on laboratory measurements mostly of CKMB. The average peak CKMB in the cangrelor arm was 31.7, and the average peak CKMB in the clopidogrel arm was 89.7. The reference upper limit of normal was reported to be 5.1.
- An approximate average of 70% of the subjects was adjudicated to have an abnormal ECG at baseline; and 66% of the subjects were adjudicated to have ischemia at baseline.

The respective timing of the adjudicated MI relative to the start of PCI appeared to have guided the Clinical Endpoint Committee in classifying the type of UDMI diagnosis. This was consistent with the analysis description in the Clinical Endpoint Committee Charter. Despite the large number of abnormal baseline ECGs as well as baseline ischemia, the “normal” or “returning to normal” baseline adjudication was focused on laboratory parameters. Additionally, for those baseline ECGs recorded as abnormal, the criteria for such abnormality as specified in the Case Report Form were not met in the majority of cases. The assessment of the ECG abnormalities was based on “no criteria apply”.

Table 26. CHAMPION PHOENIX Allocation of 48 hour MI by Type in Patients with ST

mITT population	ST (N=120)	Not ST (N=10,819*)	RR (95% CI)
MI	46 (38.3)	416 (3.8)	9.97 (7.80,12.75)
Type 1	0 (0.0)	2 (0.0)	(,)
Type 2	0 (0.0)	0 (0.0)	(,)
Type 3	2 (1.7)	1 (0.0)	180.32 (16.46,1975.19)
Type 4a	20 (16.7)	413 (3.8)	4.37 (2.89,6.59)
Type 4b	24 (20.0)	0 (0.0)	(,)
Type 5	0 (0.0)	0 (0.0)	(,)

mITT population	IPST (N=89)	Not IPST (N=10,850**)	RR (95% CI)
MI	23 (25.8)	439 (4.0)	6.39 (4.44,9.19)
Type 1	0 (0.0)	2 (0.0)	(,)
Type 2	0 (0.0)	0 (0.0)	(,)
Type 3	2 (2.2)	1 (0.0)	243.82 (22.31,2664.59)
Type 4a	20 (22.5)	413 (3.8)	5.90 (3.97,8.78)
Type 4b	1 (1.1)	23 (0.2)	5.30 (0.72,38.82)
Type 5	0 (0.0)	0 (0.0)	(,)

mITT population	ARC-ST (N=34)	Not ARC-ST (N=10,905***)	RR (95% CI)
MI	25 (73.5)	437 (4.0)	18.35 (14.70,22.90)
Type 1	0 (0.0)	2 (0.0)	(,)
Type 2	0 (0.0)	0 (0.0)	(,)
Type 3	0 (0.0)	3 (0.0)	(,)
Type 4a	1 (2.9)	432 (4.0)	0.74 (0.11,5.13)
Type 4b	24 (70.6)	0 (0.0)	(,)
Type 5	0 (0.0)	0 (0.0)	(,)

Source: [Appendix 4, Tables 92.5.1.1.1; 91.5.1.1.1; 93.5.1.1.1](#)

* 3 patients have no efficacy data at 48 h – total mITT population for patients without ST is N = 10,822

** 3 patients have no efficacy data at 48 h – total mITT population for patients without IPST is N = 10,853

*** 3 patients have no efficacy data at 48 h – total mITT population for patients without ARC-ST is N = 10,908

Table 27. Cangrelor-Treated Subjects Adjudicated to have sustained MI

Patient ID	MI: Date(Time)	PCI: Date(Time)	Peak CKMB	Peak TPN	ST Class	UDMI Type	If 4a, assess baseline	CEC Comments	Reviewer Comments
401001005	(b) (6)	(b) (6)	19.3	-----	NSTEMI	4a	N/D and Rtn to N	-----	ECG: N Isch: no
401001137	(b) (6)	(b) (6)	17.8	-----	NSTEMI	4a	N/D and	-----	ECG: N

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	(b) (6)	(b) (6)					Rtn to N		Isch: yes
401001158	(b) (6)	(b) (6)	22.0	---	NSTEMI	4a	N/D and Rtn to N	---	ECG: ABN no criteria applies Isch: yes
401002034	(b) (6)	(b) (6)	33.0	---	NSTEMI	4a	N/D and Rtn to N	---	ECG: N Isch: no
401010004	(b) (6)	(b) (6)	39.3	---	NSTEMI	4a	N/D and Rtn to N	---	ECG: ABN LVH cannot r/o septal MI Isch: yes
401010067	(b) (6)	(b) (6)	16	---	NSTEMI	4a	N/D and Rtn to N	---	ECG: ABN no criteria applies Isch: no
401015010	(b) (6)	(b) (6)	20.9	---	NSTEMI	4a	N/D and Rtn to N	---	ECG: ABN no criteria applies Isch: no
401024016	(b) (6)	(b) (6)	27	---	NSTEMI	4a	N/D and Rtn to N	---	ECG: ABN no criteria applies Isch: no
401025020	(b) (6)	(b) (6)	25.8	---	NSTEMI	4a	N/D and Rtn to N	---	ECG: ABN Q-wave, not new Isch: yes
401029049	(b) (6)	(b) (6)	19.5	---	NSTEMI	4a	N/D and Rtn to N	---	ECG: ABN no criteria applies Isch: no
401030065	(b) (6)	(b) (6)	---	469.48	NSTEMI	4b	---	---	ECG: ABN atrial pacer, t-wave abn Isch: no
401030207	(b) (6)	(b) (6)	26.0	---	NSTEMI	4a	N/D and Rtn to N	---	ECG: N Isch: no
401053011	(b) (6)	(b) (6)	99.6	20.45 (ULN 0.4)	STEMI	4a	ABN/D Rem- ABN	---	ECG: ABN, new QW Isch: yes
401055063	(b) (6)	(b) (6)	15.9	7.0 (ULN 0.049)	NSTEMI	4a	ABN/D Rem- ABN	ABN/D and angio compl.	ECG: N Isch: no
401059027	(b) (6)	(b) (6)	19.0	---	NSTEMI	4a	N/D and Rtn to N	---	ECG: ABN no criteria applies Isch: yes
401079223	(b) (6)	(b) (6)	16.2	---	NSTEMI	4a	N/D and Rtn to N	---	ECG: ABN no criteria applies

401091423	(b) (6)	(b) (6)	116.2	----	NSTEMI	4a	N/D and Rtn to N	----	Isch: no ECG: ABN no criteria applies
401091615	(b) (6)	(b) (6)	43.6		NSTEMI	4a	N/D and Rtn to N	CEC: SA patient with normal baseline; MB increasing	Isch: no ECG: N Isch: yes
401093046	(b) (6)	(b) (6)	19.5	----	NSTEMI	4a	N/D and Rtn to N	Stable Angina: 1 sample sufficient to assess baseline	ECG: N Isch: no
420001052	(b) (6)	(b) (6)	23.5 (ULN 6.3)	6.17 (ULN 0.03)	Un-known	4a	N/D and Rtn to N	CEC: BBB on ECG; MB increased > 3x ULN with normal baseline	ECG: ABN, old LBBB Isch: no
420003007	(b) (6)	(b) (6)	62.2	----	STEMI	4a	N/D and Rtn to N	CEC: no baseline but post PCI ECG with stent elevated that decreased on L/V ECG	ECG: ABN no criteria applies Isch: no
420003070	(b) (6)	(b) (6)	18.9	----	NSTEMI	4a	N/D and Rtn to N	CEC: partial LBBB. SA with normal baseline	ECG: ABN, old LBBB Isch: no
420003144	(b) (6)	(b) (6)	15.9	----	NSTEMI	4a	N/D and Rtn to N	----	ECG: N Isch: no
420003191	(b) (6)	(b) (6)	16.9	----	NSTEMI	4a	N/D and Rtn to N	CEC: baseline abnormal, decreasing and returned to normal; post PCI CKMB > 3 x ULN	ECG: ABN; ST dep in at least 2 contiguous leads and TWI Isch: yes
420009187	(b) (6)	(b) (6)	27.0	----	NSTEMI	4a	N/D and Rtn to N	----	ECG: N Isch: yes

Date and Time: month/day/year; 24-hour clock. N=Normal; D=decreasing; Rtn to N= return to normal; ABN = abnormal; Rem-ABN = Remains abnormal;
ECG=electrocardiogram performed at baseline; STE = ST-segment elevation; ST-dep = ST-segment depression; CKMB upper limit of normal = 5.09; Troponin-I upper limit of normal = 0.06; compl = complications; Isch = ischemic symptoms at baseline; TWI = T wave inversion

Table 28. Clopidogrel-treated Subjects Adjudicated to have sustained MI

Patient ID	MI: Date(Time)	PCI Date (Time)	Peak CKMB	Peak TPN	ST Class	UDMI	If 4a, assess baseline	CEC Comments	Reviewer Comments
401001002	(b) (6)	(b) (6)	16.0	---	NSTEMI	4a	N/D and Rtn to N	---	ECG: N Isch: no
401001031	(b) (6)	(b) (6)	241.2	---	STEMI	4a	ABN/D and Rem-ABN	Abnormal decreasing with angiographic complication	ECG: ABN with STE Isch: yes
401001119	(b) (6)	(b) (6)	82.4	---	STEMI	4b	---	Non QW STEMI	ECG: N Isch: no
401001152	(b) (6)	(b) (6)	15.6	---	NSTEMI	4a	N/D and Rtn to N	---	ECG: ABN no criteria applies Isch: yes
401003047	(b) (6)	(b) (6)	17.8	---	Un-known	4a	N/D and Rtn to N	---	ECG: ABN no criteria applies Isch: no
401008026	(b) (6)	(b) (6)	28.1	---	NSTEMI	4a	N/D and Rtn to N	---	ECG: ABN no criteria applies Isch: no
401010033	(b) (6)	(b) (6)	17.8	---	NSTEMI	4a	N/D and Rtn to N	---	ECG: N Isch: no
401010066	(b) (6)	(b) (6)	46.0	---	NSTEMI	4a	N/D and Rtn to N	---	ECG: ABN no criteria applies Isch: no
401010117	(b) (6)	(b) (6)	17.9	---	NSTEMI	4a	N/D and Rtn to N	---	ECG: ABN no criteria applies Isch: no
401010229	(b) (6)	(b) (6)	139.5	---	NSTEMI	4a	N/D and Rtn to N	4 troponin pre-PCI nl. MB all slightly abn. PCI complications with sig MB post PCI.	ECG: ABN no criteria applies Isch: yes
401011070	(b) (6)	(b) (6)	437.7	---	STEMI	4a	N/D and Rtn to N	---	ECG: not done-protocol violation Isch: no
401012108	(b) (6)	(b) (6)	70.7	---	NSTEMI	4a	N/D and Rtn to N	No new QW	ECG: not done-protocol violation Isch: no

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401019008	(b) (6)	(b) (6)	43.5	----	NSTEMI	4a	N/D and Rtn to N	----	ECG: ABN no criteria applies Isch: yes
401024036	(b) (6)	(b) (6)	17.2	----	NSTEMI	4a	N/D and Rtn to N	----	ECG: ABN no criteria applies Isch: yes
401025016	(b) (6)	(b) (6)	298.3	----	NSTEMI	4a	N/D and Rtn to N	MB increasing at 0100, significant increase in MB at 0700 post IDR sx at 0933. Still calling index PCI MI.	ECG: ABN no criteria applies Isch: no
401027083	(b) (6)	(b) (6)	168.9	----	NSTEMI	4a	N/D and Rtn to N	----	ECG: ABN no criteria applies Isch: yes
401028004	(b) (6)	(b) (6)	69.5	10.26 (ULN 0.1)	STEMI	4a	N/D and Rtn to N	ECG post PCI with >2mm STE MI, also had IPST and dissection	ECG: N Isch: yes
401030137	(b) (6)	(b) (6)	21.8	----	NSTEMI	4a	N/D and Rtn to N	----	ECG: ABN TWA Isch: no
401045005	(b) (6)	(b) (6)	21.6	1.51	NSTEMI	4a	N/D and Rtn to N	Baseline normal	ECG: ABN no criteria applies Isch: no
401058029	(b) (6)	(b) (6)	85.6	16.36 (ULN 0.29)	NSTEMI	4a	N/D and Rtn to N	----	ECG: ABN no criteria applies Isch: no
401070012	(b) (6)	(b) (6)	73.0	----	STEMI	4b	----	----	ECG: ABN no criteria applies Isch: no
401077048	(b) (6)	(b) (6)	94.2	----	NSTEMI	4a	N/D and Rtn to N	----	ECG: ABN no criteria applies Isch: yes
401079002	(b) (6)	(b) (6)	16.0	2.638 (ULN 0.19)	NSTEMI	4a	N/D and Rtn to N	----	ECG: ABN no criteria applies Isch: no
401084003	(b) (6)	(b) (6)	185.6	4.86 (ULN 0.03)	NSTEMI	4b	----	----	ECG: ABN possible septal infarct Isch: no
401091432	(b) (6)	(b) (6)	16.1	----	NSTEMI	4a	N/D and Rtn to N	----	ECG: ABN no criteria

		(b) (6)							applies
									Isch: no

Date and Time: month/day/year; 24-hour clock. Normal=N; D=decreasing; Rtn to N= return to normal; ABN = abnormal; Rem-ABN = Remains abnormal;
ECG=electrocardiogram performed at baseline; STE = ST-segment elevation; ST-dep = ST-segment depression; CKMB upper limit of normal = 5.09; Troponin-I upper limit of normal = 0.06; compl = complications; Isch = ischemic symptoms at baseline; TWI = T wave inversion; TWA = T wave abnormality

6.1.1.6 Other Endpoints

No other endpoints.

6.1.1.7 Subpopulations

Subpopulation Summary

Subpopulations of interest included:

- Clinical presentation
- Timing of Study Drug Treatment
- Subjects with normal baseline biomarkers
- US .vs. non-US subjects
- Age
- Gender
- Body Weight
- Use of GPI Therapy
- General subgroup analyses

Analysis of subpopulations suggested that compared to clopidogrel, cangrelor significantly reduced the incidence of the primary efficacy endpoint in the SA population. There was no significant difference in efficacy between the P2Y₁₂ inhibitors for the NSTEMI and STEMI populations. These results could have been due to lack of adequate power to evaluate individual cohorts, or to a hypothetical pathophysiology-treatment-time profile. The results of the trial were also driven by those subjects who did not have a baseline elevation of biomarkers associated with myocardial injury. There were no empirical confounding effects based on regional differences between the US and non-US populations, age, gender, body weight, concomitant disease, procedures (e.g. type of stent, location of arterial access) or medications with the exception of those subjects presenting with PAD. In the PAD cohort, there was an outlying OR in favor of cangrelor.

Clinical Presentation

In the PLATFORM trial, there was no difference in the primary efficacy endpoint (all-cause mortality, MI, and IDR at 48 hours) between the cangrelor and clopidogrel cohorts for the SA population and for the UA/NSTEMI population, respectively (see Figure 7 in the CSR for the PLATFORM trial). In PLATFORM, clopidogrel therapy was delayed with respect to cangrelor therapy. In the PCI trial, where both study drugs were given at the same time, there was no difference in the composite of all-cause mortality, UDMI, and ST (not the pre-specified endpoint in PCI) at 48 hours between cangrelor and clopidogrel for any of the subgroups (SA, UA/NSTEMI, STEMI). However, the point estimates favored clopidogrel in the STEMI population, was neutral (i.e. was on the 1.0 line) in the UA/NSTEMI population, and favored cangrelor in the SA population (see Figure 11 in the CSR for the PCI trial). In the ISE which combined all the CHAMPION trials (see Figure 9, ISE), the results favored cangrelor over clopidogrel in the SA and NSTEACS populations, but did not show a significant difference between the two study drugs in the STEMI population.

The possible differential results empirically observed between the SA population and the ACS population (NSTEACS and STEMI) in the PHOENIX may have been due to chance based on lack of power for individual subgroups. However, this raises a hypothesis on the efficacy of cangrelor versus an active comparator control as a function of state of inflammation.

Timing and Load of Study Drug Treatment

Subjects randomized to clopidogrel started active treatment later than subjects randomized to cangrelor ([Table 29](#). Time (minutes) from PCI to start of active treatment by patient type, [and Figure 12](#)). The timing of active drug was more similar between treatments in STEMI patients than in SA or NSTEACS patients ([Figure 13](#)).

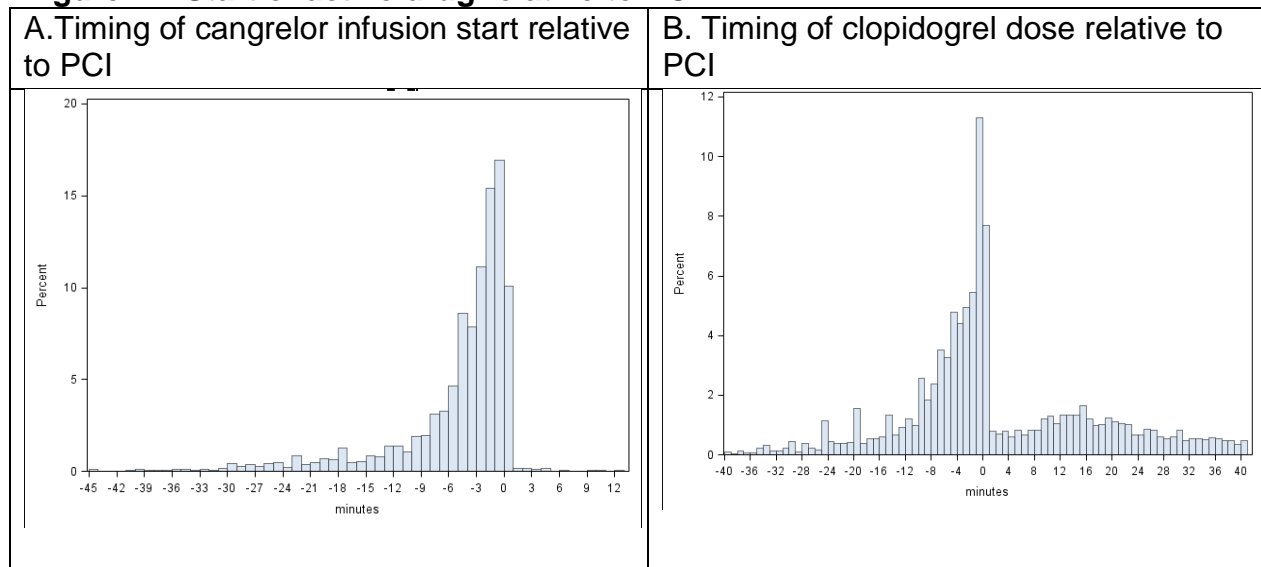
Table 29. Time (minutes) from PCI to start of active treatment by patient type

	Cangrelor Median	Cangrelor (Q1, Q3)	Clopidogrel Median	Clopidogrel (Q1, Q3)
All Subjects	-3	(-6, -1)	-1	(-6, 14)
Stable angina	-3	(-6, -1)	0	(-5, 17)
NSTEACS	-3	(-7, -1)	-2	(-7, 7)
STEMI	-4	(-17, -1)	-4	(-16, -1)

Investigator declared patient type. PCI is time 0. A negative number means the subject started drug before PCI. A positive number means the subject started drug after PCI.

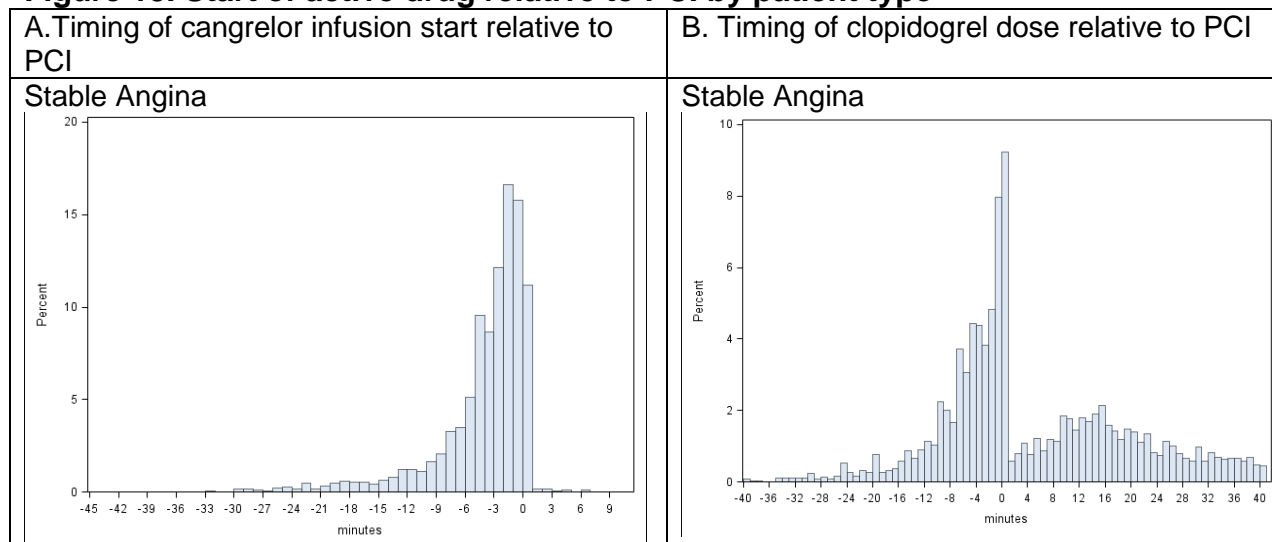
Reviewer's analysis: time|time active drug pci, Dataset isd osd dem

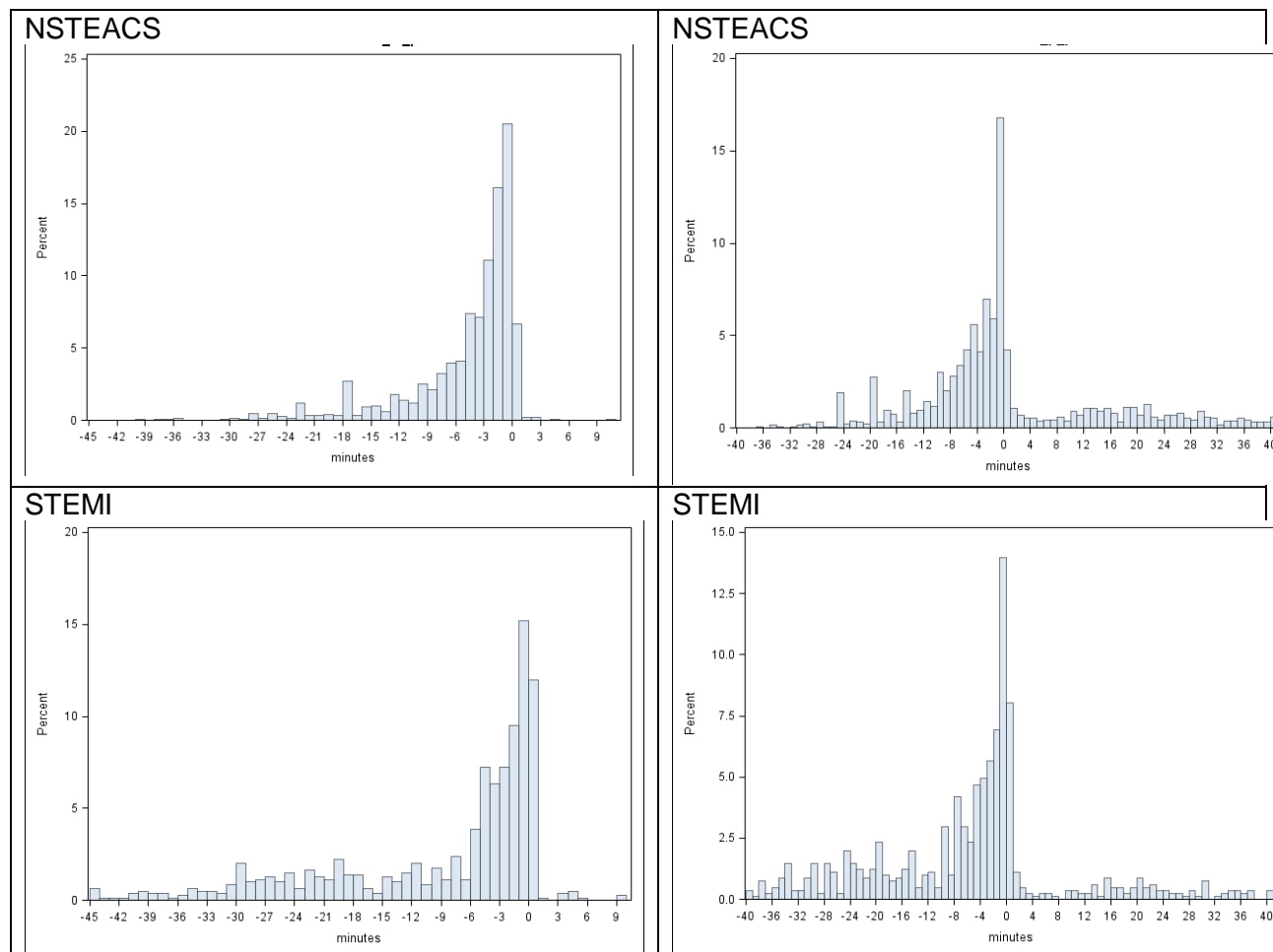
Figure 12. Start of active drug relative to PCI



PCI is at time 0. A negative number means subject received drug before PCI.
Reviewer's analysis: timetime active drug pci, Dataset isd osd dem. X-axis truncated.

Figure 13. Start of active drug relative to PCI by patient type





Investigator declared patient type. PCI is time 0. A negative number means subject received drug before PCI. Reviewer's analysis: time\time active drug pci, Dataset isd osd dem. X-axis truncated.

Reviewer comment: In the SA population a substantial number of subjects received clopidogrel after the procedure compared to the NSTEMI and STEMI populations, respectively (Figure 13). While the guidelines (page 105) for P2Y12 inhibitors (clopidogrel, ticagrelor, and prasugrel) are a Class I, Level A for PCI/stent they do not specify the precise timing of these agents relative to the start of PCI. However, practice patterns generally provide for administration before start of PCI. The primary efficacy endpoint favoring cangrelor was driven by the SA population. The data above raises speculation that the delay in clopidogrel in the SA population might have contributed to the positive results of the trial.

Table 30 shows the difference between actual clopidogrel loading dose and the investigator declared clopidogrel loading dose. Nearly all subjects in the cangrelor arm received clopidogrel 600 mg as a transition dose, whereas only 74% of subjects in the clopidogrel arm received 600 mg. It is unknown how the investigators determined which

dose to give. Analyses to determine the effect of the lower dose on endpoints was limited because few subjects in the cangrelor arm received clopidogrel 300 mg.

Table 30. Intended versus actual clopidogrel loading dose

	Cangrelor		Clopidogrel	
	N=5529	(%)	N=5527	(%)
Intended clopidogrel load of 300 mg	1428	(25.8)	1425	(25.8)
Intended clopidogrel load of 600 mg	4101	(74.2)	4102	(74.2)
Actual clopidogrel load of 300 mg	3	(0.1)	1427	(25.8)
Actual clopidogrel load of 600 mg	5442	(98.4)	4061	(73.5)

Reviewer's analysis: dose\loaddose. Dataset: raw\load, analysis\disp

Reviewer comment: Note that the numbers reported by Bhatt et al in the New England Journal of Medicine are the intended dose and not the actual clopidogrel loading dose received.

Subjects with normal baseline biomarkers

The Applicant's program hypothesis was that subjects with pre-procedural MIs as indicated by elevated baseline biomarkers might have obscured the efficacy of cangrelor in the PCI setting. Post-hoc analysis of the CHAMPION PCI and PLATFORM trials engendered this hypothesis on which the PHOENIX trial was based.

Table 31 and **Table 32** show the PHOENIX outcome data in those mITT subjects who had normal baseline cardiac biomarkers at 48 hours and at 30 days, respectively. The incidence of the primary efficacy endpoint at 48 hours (death, MI, IDR, ST) was significantly lower in the cangrelor arm vs. the clopidogrel arm (OR 0.80, 95%CI [0.66, 0.96], p=0.0199). These results were driven by IPST and MI where no specific component of MI (i.e. QWMI, type 1, 2, 3, 4a, 4b, 5) reached statistical significance. Similar results were obtained when IPST was removed from the ST component of the composite endpoint: death, MI, IDR, ARC-ST (OR 0.82, 95%CI [0.67, 0.99], p=0.0431). The outcome at 30 days for subjects with normal baseline biomarkers was similar to that at 48 hours for the efficacy endpoint of death, MI, IDR, and ST (OR 0.81, 95%CI [0.68, 0.98], p=0.0262). The results were driven by IPST and MI where no specific component of MI (i.e. QWMI, type 1, 2, 3, 4a, 4b, 5) reached statistical significance. When IPST was removed from the ST component of the composite endpoint, the 30-day benefit of cangrelor was lost (OR 0.83, 95%CI [0.69, 1.00], p=0.0537).

Table 33 shows the PHOENIX 48 hour outcome data in those mITT subjects who had abnormal baseline cardiac biomarkers. The incidence of the 48 hour primary efficacy

endpoint of death, MI, IDR and ST for cangrelor (57/1921: 3.0%) did not show a significant difference from clopidogrel (76/1945:3.9%): OR 0.75, 95%CI [0.53, 1.07], $p=0.1088$. When IPST was removed from the ST component of the composite endpoint, the results were similar: cangrelor 36/1921 (1.9%); clopidogrel 53/1945: (2.7%); OR 0.68, 95%CI [0.44, 1.05], $p=0.0778$). Similarly, there was no difference between cangrelor and clopidogrel at 30 days for the efficacy endpoint in the subgroup of subjects who had abnormal baseline cardiac markers (see table 5.2.1.7 of PHOENIX CSR).

The data suggested that the beneficial effect of cangrelor over clopidogrel appeared to have been focused on the SA population without pre-PCI myocardial injury.

Table 31. CHAMPION PHOENIX 48 hour efficacy data in subjects with normal baseline biomarkers (MITT)

			Cangrelor vs. Clopidogrel		
	Cangrelor (N=3550)	Clopidogrel (N=3525)	RR and 95%CI	OR and 95%CI	P- value for OR
48 hours post randomization					
Death/MI/IDR/ST (primary end point)	200/3549(5.6%)	246/3524(7.0%)	0.81(0.67,0.97)	0.80(0.66,0.96)	0.0199
ST	17/3549(0.5%)	34/3524(1.0%)	0.50(0.28,0.89)	0.49(0.28,0.89)	0.0158
-IPST	11/3549(0.3%)	23/3524(0.7%)	0.47(0.23,0.97)	0.47(0.23,0.97)	0.0372
-Def. ST	7/3549(0.2%)	12/3524(0.3%)	0.58(0.23,1.47)	0.58(0.23,1.47)	0.2444
-Prob. ST	0/3549(0.0%)	0/3524(0.0%)	----(----)	----(----)	
-Poss. ST	0/3549(0.0%)	0/3524(0.0%)	----(----)	----(----)	
Acute ST	6/3549(0.2%)	12/3524(0.3%)	0.50(0.19,1.32)	0.50(0.19,1.32)	0.1524
Death	5/3549(0.1%)	2/3524(0.1%)	2.48(0.48,12.79)	2.48(0.48,12.81)	0.2605
-CV Death	5/3549(0.1%)	2/3524(0.1%)	2.48(0.48,12.79)	2.48(0.48,12.81)	0.2605
MI	187/3549(5.3%)	226/3524(6.4%)	0.82(0.68,0.98)	0.81(0.66,0.99)	0.0402
-Q MI	6/3549(0.2%)	12/3524(0.3%)	0.50(0.19,1.32)	0.50(0.19,1.32)	0.1524
-Type 1	0/3549(0.0%)	0/3524(0.0%)	----(----)	----(----)	
-Type 2	0/3549(0.0%)	0/3524(0.0%)	----(----)	----(----)	
-Type 3	2/3549(0.1%)	0/3524(0.0%)	----(----)	----(----)	0.1587
-Type 4a	180/3549(5.1%)	216/3524(6.1%)	0.83(0.68,1.00)	0.82(0.67,1.00)	0.0531
-Type 4b	5/3549(0.1%)	10/3524(0.3%)	0.50(0.17,1.45)	0.50(0.17,1.45)	0.1915
-Type 5	0/3549(0.0%)	0/3524(0.0%)	----(----)	----(----)	
IDR	19/3549(0.5%)	20/3524(0.6%)	0.94(0.50,1.76)	0.94(0.50,1.77)	0.8550
-PCI	15/3549(0.4%)	18/3524(0.5%)	0.83(0.42,1.64)	0.83(0.42,1.64)	0.5866

-CABG	4/3549(0.1%)	2/3524(0.1%)	1.99(0.36,10.84)	1.99(0.36,10.86)	0.4190
Death/MI/IDR/ARC-ST	194/3549(5.5%)	233/3524(6.6%)	0.83(0.69,0.99)	0.82(0.67,0.99)	0.0431
Death/Q MI/IDR/ST	32/3549(0.9%)	50/3524(1.4%)	0.64(0.41,0.99)	0.63(0.40,0.99)	0.0422
Death/MI/IDR	194/3549(5.5%)	233/3524(6.6%)	0.83(0.69,0.99)	0.82(0.67,0.99)	0.0431
Death/Q MI/IDR	23/3549(0.6%)	30/3524(0.9%)	0.76(0.44,1.31)	0.76(0.44,1.31)	0.3217
Death/MI/ST	196/3549(5.5%)	242/3524(6.9%)	0.80(0.67,0.97)	0.79(0.65,0.96)	0.0190
Death/MI/ARC-ST	190/3549(5.4%)	229/3524(6.5%)	0.82(0.68,0.99)	0.81(0.67,0.99)	0.0415
Death/Q MI/ST	23/3549(0.6%)	42/3524(1.2%)	0.54(0.33,0.90)	0.54(0.32,0.90)	0.0166
Death/MI	189/3549(5.3%)	228/3524(6.5%)	0.82(0.68,0.99)	0.81(0.67,0.99)	0.0410
Death/Q MI	10/3549(0.3%)	14/3524(0.4%)	0.71(0.32,1.59)	0.71(0.31,1.60)	0.4036
Death/IDR	22/3549(0.6%)	22/3524(0.6%)	0.99(0.55,1.79)	0.99(0.55,1.80)	0.9812
Death/ST	20/3549(0.6%)	35/3524(2.5%)	0.57(0.33,0.98)	0.56(0.33,0.98)	0.0397

Source: Table 5.1.1.6 PHOENIX CSR

Table 32. CHAMPION PHOENIX 30 day efficacy data in subjects with normal baseline biomarkers (mITT)

			Cangrelor vs. Clopidogrel		
	Cangrelor (N=3550)	Clopidogrel (N=3525)	RR and 95%CI	OR and 95%CI	P- value for OR
30 days post randomization					
Death/MI/IDR/ST (primary end point)	226/3544(6.4%)	272/3518(7.7%)	0.82(0.70,0.98)	0.81(0.68,0.98)	0.0262
ST	26/3544(0.7%)	49/3518(1.4%)	0.53(0.33,0.85)	0.52(0.32,0.84)	0.0069
-IPST	11/3544(0.3%)	23/3518(0.7%)	0.47(0.23,0.97)	0.47(0.23,0.97)	0.0371
-Def. ST	13/3544(0.4%)	20/3518(0.6%)	0.65(0.32,1.30)	0.64(0.32,1.30)	0.2140
-Prob. ST	3/3544(0.1%)	8/3518(0.2%)	0.37(0.10,1.40)	0.37(0.10,1.40)	0.1283
-Poss. ST	0/3544(0.0%)	0/3518(0.0%)	----(----)	----(----)	
Subacute ST	10/3544(0.3%)	16/3518(0.5%)	0.62(0.28,1.37)	0.62(0.28,1.37)	0.2310
Death	17/3544(0.5%)	17/3518(0.5%)	0.99(0.51,1.94)	0.99(0.51,1.95)	0.9828
-CV Death	14/3544(0.4%)	11/3518(0.3%)	1.26(0.57,2.78)	1.26(0.57,2.79)	0.5601
MI	194/3544(5.5%)	236/3518(6.7%)	0.82(0.68,0.98)	0.81(0.66,0.98)	0.0301
-Q MI	8/3544(0.2%)	14/3518(0.4%)	0.57(0.24,1.35)	0.57(0.24,1.35)	0.1941
-Type 1	1/3544(0.0%)	6/3518(0.2%)	0.17(0.02,1.37)	0.17(0.02,1.37)	0.0574
-Type 2	0/3544(0.0%)	1/3518(0.0%)	----(----)	----(----)	0.3155
-Type 3	2/3544(0.1%)	0/3518(0.0%)	----(----)	----(----)	0.1588
-Type 4a	181/3544(5.1%)	216/3518(6.1%)	0.83(0.69,1.01)	0.82(0.67,1.01)	0.0596
-Type 4b	10/3544(0.3%)	15/3518(0.4%)	0.66(0.30,1.47)	0.66(0.30,1.47)	0.3076
-Type 5	0/3544(0.0%)	0/3518(0.0%)	----(----)	----(----)	
IDR	34/3544(1.0%)	34/3518(1.0%)	0.99(0.62,1.59)	0.99(0.62,1.60)	0.9757
-PCI	30/3544(0.8%)	32/3518(0.9%)	0.93(0.57,1.53)	0.93(0.56,1.53)	0.7762

-CABG	4/3544(0.1%)	2/3518(0.1%)	1.99(0.36,10.83)	1.99(0.36,10.85)	0.4192
Death/MI/IDR/ARC-ST	220/3544(6.2%)	259/3518(7.4%)	0.84(0.71,1.00)	0.83(0.69,1.00)	0.0537
Death/Q MI/IDR/ST	59/3544(1.7%)	77/3518(2.2%)	0.76(0.54,1.06)	0.76(0.54,1.07)	0.1092
Death/MI/IDR	219/3544(6.2%)	258/3518(7.3%)	0.84(0.71,1.00)	0.83(0.69,1.00)	0.0533
Death/Q MI/IDR	49/3544(1.4%)	56/3518(1.6%)	0.87(0.59,1.27)	0.87(0.59,1.28)	0.4677
Death/MI/ST	213/3544(6.0%)	264/3518(7.5%)	0.80(0.67,0.95)	0.79(0.65,0.95)	0.0124
Death/MI/ARC-ST	207/3544(5.8%)	251/3518(7.1%)	0.82(0.69,0.98)	0.81(0.67,0.98)	0.0273
Death/Q MI/ST	40/3544(1.1%)	64/3518(1.8%)	0.62(0.42,0.92)	0.62(0.41,0.92)	0.0160
Death/MI	205/3544(5.8%)	248/3518(7.0%)	0.82(0.69,0.98)	0.81(0.67,0.98)	0.0301
Death/Q MI	23/3544(0.6%)	30/3518(0.9%)	0.76(0.44,1.31)	0.76(0.44,1.31)	0.3212
Death/IDR	48/3544(1.4%)	48/3518(1.4%)	0.99(0.67,1.48)	0.99(0.66,1.48)	0.9710
Death/ST	37/3544(1.0%)	57/3518(1.6%)	0.64(0.43,0.97)	0.64(0.42,0.97)	0.0346

Source: Table 5.2.1.6 PHOENIX CSR

Table 33. CHAMPION PHOENIX 48 hour efficacy data in subjects with abnormal baseline biomarkers (mITT)

			Cangrelor vs. Clopidogrel		
	Cangrelor (N=1922)	Clopidogrel (N=1945)	RR and 95%CI	OR and 95%CI	P- value for OR
48 hours post randomization					
Death/MI/IDR/ST (primary end point)	57/1921(3.0%)	76/1945(3.9%)	0.76(0.54,1.06)	0.75(0.53,1.07)	0.1088
ST	29/1921(1.5%)	40/1945(2.1%)	0.73(0.46,1.18)	0.73(0.45,1.18)	0.1991
-IPST	24/1921(1.2%)	31/1945(1.6%)	0.78(0.46,1.33)	0.78(0.46,1.34)	0.3658
-Def. ST	5/1921(0.3%)	10/1945(0.5%)	0.51(0.17,1.48)	0.50(0.17,1.48)	0.2043
-Prob. ST	0/1921(0.0%)	0/1945(0.0%)	----(----)	----(----)	
-Poss. ST	0/1921(0.0%)	0/1945(0.0%)	----(----)	----(----)	
Acute ST	5/1921(0.3%)	9/1945(0.5%)	0.56(0.19,1.68)	0.56(0.19,1.68)	0.2948
Death	13/1921(0.7%)	16/1945(0.8%)	0.82(0.40,1.71)	0.82(0.39,1.71)	0.5991
-CV Death	13/1921(0.7%)	16/1945(0.8%)	0.82(0.40,1.71)	0.82(0.39,1.71)	0.5991
MI	20/1921(1.0%)	29/1945(1.5%)	0.70(0.40,1.23)	0.70(0.39,1.23)	0.2112
-Q MI	5/1921(0.3%)	6/1945(0.3%)	0.84(0.26,2.76)	0.84(0.26,2.77)	0.7785
-Type 1	1/1921(0.1%)	1/1945(0.1%)	1.01(0.06,16.18)	1.01(0.06,16.20)	0.9930
-Type 2	0/1921(0.0%)	0/1945(0.0%)	----(----)	----(----)	
-Type 3	1/1921(0.1%)	0/1945(0.0%)	----(----)	----(----)	0.3142
-Type 4a	14/1921(0.7%)	23/1945(1.2%)	0.62(0.32,1.19)	0.61(0.31,1.20)	0.1474
-Type 4b	4/1921(0.2%)	5/1945(0.3%)	0.81(0.22,3.01)	0.81(0.22,3.02)	0.7527
-Type 5	0/1921(0.0%)	0/1945(0.0%)	----(----)	----(----)	
IDR	9/1921(0.5%)	18/1945(0.9%)	0.51(0.23,1.12)	0.50(0.23,1.12)	0.0880
-PCI	6/1921(0.3%)	15/1945(0.8%)	0.40(0.16,1.04)	0.40(0.16,1.04)	0.0523

-CABG	3/1921(0.2%)	3/1945(0.2%)	1.01(0.20,5.01)	1.01(0.20,5.02)	0.9879
Death/MI/IDR/ARC-ST	36/1921(1.9%)	53/1945(2.7%)	0.69(0.45,1.05)	0.68(0.44,1.05)	0.0778
Death/Q MI/IDR/ST	48/1921(2.5%)	62/1945(3.2%)	0.78(0.54,1.14)	0.78(0.53,1.14)	0.1977
Death/MI/IDR	36/1921(1.9%)	53/1945(2.7%)	0.69(0.45,1.05)	0.68(0.44,1.05)	0.0778
Death/Q MI/IDR	26/1921(1.4%)	34/1945(1.7%)	0.77(0.47,1.29)	0.77(0.46,1.29)	0.3210
Death/MI/ST	53/1921(2.8%)	70/1945(3.6%)	0.77(0.54,1.09)	0.76(0.53,1.09)	0.1368
Death/MI/ARC-ST	32/1921(1.7%)	47/1945(2.4%)	0.69(0.44,1.08)	0.68(0.43,1.08)	0.0991
Death/Q MI/ST	44/1921(2.3%)	55/1945(2.8%)	0.81(0.55,1.20)	0.81(0.54,1.20)	0.2903
Death/MI	31/1921(1.6%)	44/1945(2.3%)	0.71(0.45,1.12)	0.71(0.45,1.13)	0.1438
Death/Q MI	18/1921(0.9%)	22/1945(1.1%)	0.83(0.45,1.54)	0.83(0.44,1.55)	0.5510
Death/IDR	21/1921(1.1%)	32/1945(1.6%)	0.66(0.38,1.15)	0.66(0.38,1.15)	0.1400
Death/ST	39/1921(2.0%)	52/1945(2.7%)	0.76(0.50,1.14)	0.75(0.50,1.15)	0.1871

Source: Table 5.1.1.7 PHOENIX CSR

US .vs. non-US subjects

There were 4097 mITT subjects in the US and 6842 mITT subjects in the rest of the world ([Table 34](#)). Cangrelor-treated subjects had a significantly lower incidence of the 48-hour primary efficacy endpoint compared to clopidogrel-treated subjects in the US population [cangrelor 93/2048{4.7%}, clopidogrel 131/2049{6.4%}; OR 0.70, 95%CI (0.53, 0.92)], and trended in favor of cangrelor in the rest of the world [cangrelor 164/3422{4.8%}, clopidogrel 191/3420{5.6%}; OR 0.85, 95%CI (0.69, 1.05)]. The regional subgroup analysis suggested no difference in the primary endpoint (P [Int] = 0.258). It was not clear how the SA, NSTEMI and STEMI populations were regionally distributed.

Age

Age was stratified (see [Table 34](#)) into subjects < 75 years (n=8931) and subjects ≥ 75 years (n=2008). In the older subgroup, there was a trend favoring the cangrelor-treated subjects for the primary efficacy endpoint: 55/1021 (5.4%) for cangrelor and 73/987 (7.4%) for clopidogrel (OR 0.71, 95% CI [0.50, 1.02]). In the younger cohort, there was a significant difference in the incidence of the primary efficacy endpoint favoring cangrelor (OR 0.81, 95% CI [0.67, 0.98]). For the ITT population (n= 11,145), the mean age of the subjects in the PHOENIX trial was 63.9 ± 11.0 years with a median of 64.0

years (1st quartile 56 years, 3rd quartile 72 years) (see CSR Table 8). The Applicant's choice of stratifying age at 75 years was very likely due to the enhanced bleeding risk in patients receiving anticoagulation or antiplatelet agents who are above age 75. The age subgroup analysis suggested no difference in the primary endpoint as a function of age (P [Int] = 0.546).

Gender

Of the ITT population, there were 8024 (72.0%) males and 3121 (28.0%) females (see CSR Table 8). The Applicant reported that in the mITT population (see [Table 34](#)), the incidence of the primary efficacy endpoint in males was 183/3913 (4.7%) in the cangrelor treated group and 219/3976 (5.5%) in the clopidogrel treated group (OR 0.84, 95% CI [0.69, 1.03]). The incidence of the primary efficacy endpoint in females was 74/1557 (4.8%) in the cangrelor treated group and 103/1493 (6.9%) in the clopidogrel treated group (OR 0.67, 95% CI [0.50, 0.92]). The gender subgroup analysis suggested no gender difference regarding efficacy of cangrelor for the primary endpoint (P [Int] = 0.234).

Body Weight

In the ITT population, the mean weight was 85.4 ± 17.8 kg with a median of 84.0 kg (1st quartile 73 kg, 3rd quartile 96 kg) (see CSR Table 8). This corresponded to a mean BMI (kg/m^2) 28.99 ± 5.18 with a median of 28.37 (1st quartile 25.6, 3rd quartile 31.8). The Applicant performed a subgroup analysis based on weight, stratified by subjects < 60 kg (n = 583) and ≥ 60 kg (n = 10,356) in the mITT population (see [Table 34](#)). Of those subjects < 60 kg, 18/315 subjects in the cangrelor arm and 20/268 subjects in the clopidogrel arm experienced a primary efficacy endpoint (OR 0.75, 95% CI [0.39, 1.45]). Of those subjects ≥ 60 kg, 239/5155 (4.6%) subjects in the cangrelor arm and 302/5201 (5.8%) subjects in the clopidogrel arm experienced a primary efficacy endpoint (OR 0.79, 95% CI [0.66, 0.94]). This subgroup analysis suggested no difference in efficacy of cangrelor vs. Clopidogrel between two subgroups stratified by weight. It is not clear why 60 kg was chosen as the boundary condition for weight stratification (P [Int] = 0.890).

Use of GPI Therapy

The use of GPI therapy: eptifibatide and tirofiban within 12 hours preceding randomization, or abciximab within 7 days preceding randomization were exclusion criteria (#2, #3 respectively) for subject selection into PHOENIX. The use of GPI, however, was permitted per protocol as bailout therapy defined when there was a new or persistent thrombus formation, slow or no reflow, side branch compromise, dissection, or distal embolization (CSR 9.4.7.2; 10.4.3).

In the cangrelor arm, 129/5581 ITT subjects (2.3%) were reportedly administered GPI as bailout. Of these 129 subjects, 76 (59%) were STEMI patients. In the clopidogrel

arm, 194/5564 (3.5%) were reportedly administered GPI as bailout, of which 102 (53%) were STEMI patients (CSR section 14.1, Table 3.4.2.1, 3.4.2.2).

Of those subjects receiving GPI inhibitors as bailout, abciximab was used in 63/5581 (1.1%) in the cangrelor arm and 62/5564 (1.1%) in the clopidogrel arm. Eptifibatide was used in 57/5581 (1.0%) subjects in the cangrelor arm and 112/5564 (2.0%) subjects in the clopidogrel arm. Tirofiban was sparingly used (8/5581 {0.1%} in the cangrelor arm and 18/5564 {0.3%} in the clopidogrel arm).

In addition to those subjects administered GPI for bailout, the Applicant reported that among the mITT patients, 26 cangrelor-treated subjects and 35 clopidogrel-treated subjects were reported by study investigators to have received GPI for reasons specified to not be bailout.

The 26 mITT cangrelor subjects administered GPI for reasons other than bailout were identified: 401009005, 401055128, 407005040, 407005041, 407005057, 407005185, 407012075, 420019004, 439001068, 439004169, 439004183, 439004186, 439004218, 439004247, 439008031, 439008037, 443002007, 443002022, 443002066, 443002234, 443002504, 448015030, 449001020, 455005005, 455005015, and 466001006. The ITT subjects included the above 26 subjects in addition to 401012030, 401012069, and 401012104.

The 35 mITT clopidogrel subjects administered GPI for reasons other than bailout were identified: 401055033, 401091247, 401091729, 401091735, 401104003, 407005012, 407005044, 407005184, 420001017, 420001084, 420005002, 420009998, 420019046, 439001014, 439004111, 439004124, 439004168, 439004175, 439004185, 439004239, 443002005, 443002010, 443002021, 443002031, 443002056, 443002186, 443002223, 443002491, 443002492, 449001009, 449003002, 449014041, 459002015, 459002017, and 459007057. The ITT subjects included the above 35 subjects in addition to subject 407005086.

The Applicant reviewed these subjects and concluded that the reasons provided by the investigators for administering GPI were not clearly distinguishable from bailout. The Applicant therefore did not classify these subjects as protocol violations. An independent review of these cases revealed that the average reason for GPI administration were “thrombus”, “continued ST elevation” (i.e. ECG ST interval), “keeping the blood fluid”, “physician discretion”, “ESC guidelines”, “in-stent thrombus”. This confirmed the Applicant’s opinion that GPI administration for reasons other than bailout were similar to bailout.

From [Table 34](#), concomitant use of peri-procedural GPI attenuated the benefit of cangrelor over clopidogrel even though the point-estimate still favored cangrelor. This might have been attributed to either a masking effect of GPI, or the relatively small sample size of those subjects receiving GPI, or a greater severity of illness in those

subjects requiring GPI which attenuated the effect of cangrelor therapy for the duration of treatment in this trial.

The use of GPI has been recognized as valuable therapeutic regimen and can serve as an alternative therapy to P2Y₁₂ platelet inhibitor therapy. Several guidelines (Anderson, J, et al., 2013; O'Gara, P, et al., 2013; Hillis, L, D, et al., 2011; Levine, G, et al., 2011) have described recommendations for GPI use in terms of a class of precision (C) and level of evidence (LOE) in various settings: C I, LOE (A) for UA/STEMI in both PCI and Medical Management; C IIa, LOE (A-B) in STEMI / primary PCI; C IIb, LOE (B) in stable ischemic heart disease (SIHD). The class and LOE is strong favoring GPI therapy in the absence of clopidogrel pre-treatment. In the setting of clopidogrel pre-treatment, the class and LOE for GPI administration is slightly weaker (C IIa, LOE (B-C)). P2Y₁₂ therapy (clopidogrel, Ticagrelor, prasugrel) generally received a C I, LOE (A) recommendation in the PCI/stent setting. Prasugrel, however, received a C III (i.e. harm), LOE (B) recommendation in patients with prior TIA / stroke.

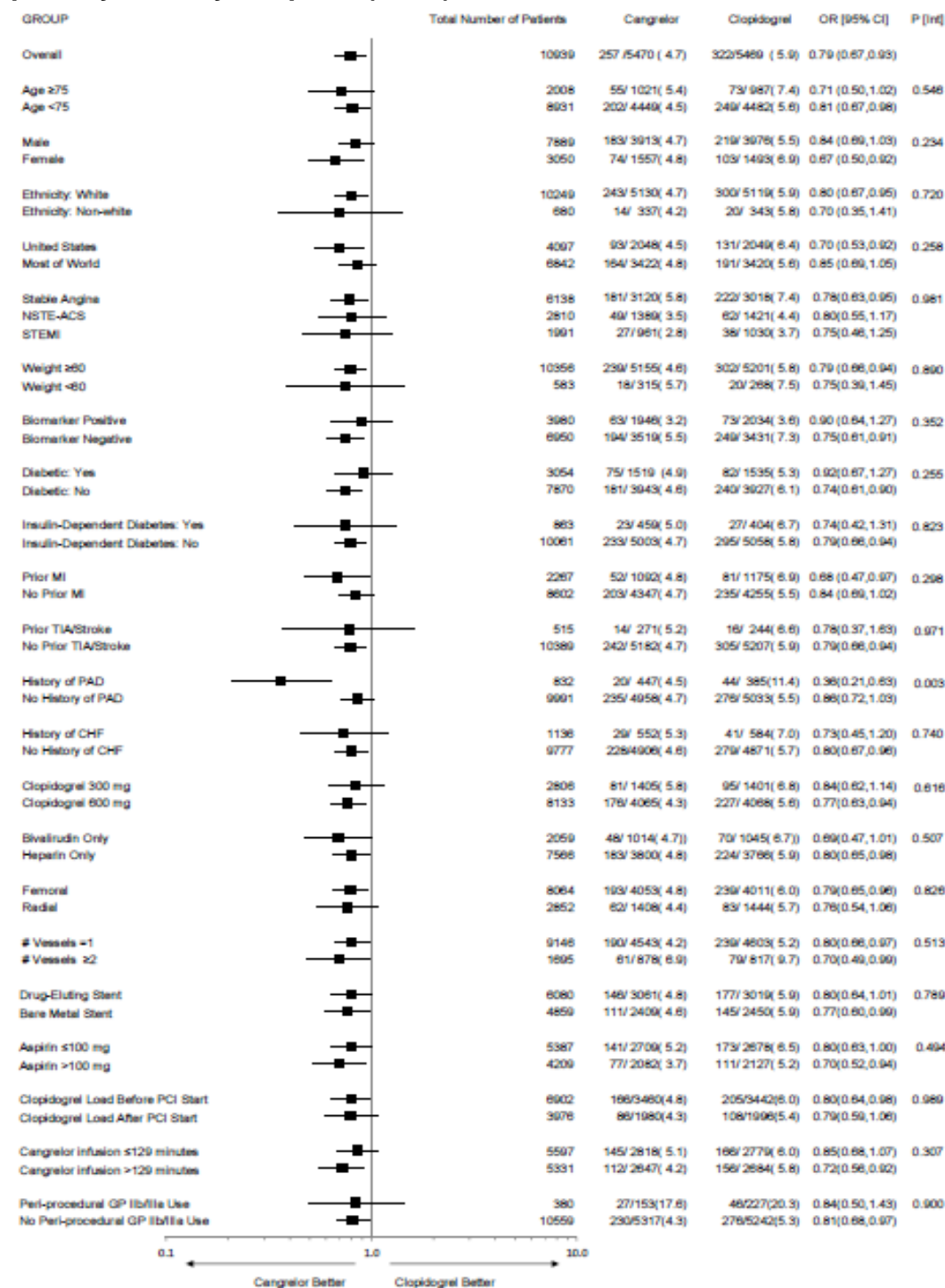
General subgroup analyses

Table 34 shows the results of various subgroup analyses for the 48 hour primary efficacy endpoint of death, MI, IDR, and ST in the mITT population.

Subjects stratified by medical histories, concomitant illnesses, concomitant medications, and protocol-based procedures (e.g. type of stent, location of arterial access) did not affect the results and generally showed point estimates either significantly favoring or trending in favor of cangrelor over clopidogrel. One outlying subgroup showed that subjects with a history of PAD significantly benefited from cangrelor over clopidogrel (cangrelor 20/447:4.5%, clopidogrel 44/385:11.4%, OR 0.36, 95%CI [0.21, 0.63]) compared to those subjects without a history of PAD (cangrelor 235/4958:4.7%, 276/5033:5.5% clopidogrel, OR 0.86, 95%CI [0.72, 1.03]), p (int) =0.003. The benefit of cangrelor over clopidogrel became significant when cangrelor infusion exceeded 129 minutes. The higher loading dose of clopidogrel (600mg) provided in the IV placebo arm during the initial 2-4 hours of the trial paradoxically favored cangrelor.

There were no subgroup cohorts favoring clopidogrel, thereby voiding concern about efficacy of cangrelor in a unique subgroup. The preponderance of the results might have been impacted by the timing of drug initiation where clopidogrel, having been initiated after the index PCI in a large number of subjects, might not have had sufficient time to manifest a clinical benefit (see section 6.1.1.10).

Table 34. CHAMPION PHOENIX general subgroup analyses for 48-hour composite primary efficacy endpoint (mITT)



Source: PHOENIX CSR, Section 11.2.5.2, Figure 8

6.1.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Dosing recommendation was based on bolus and maintenance infusion doses used in the CHAMPION PHOENIX trial.

6.1.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

No additional discussion.

6.1.1.10 Additional Efficacy Issues/Analyses

Timing of clopidogrel Administration relative to cangrelor

As shown in sections 5.3.1 and 5.3.2, the CHAMPION PLATFORM trial demonstrated a significantly higher mortality rate and acute ST rate in the clopidogrel group compared to the cangrelor group. The mortality rate was 8/2691 (0.3%) in the cangrelor group and 19/2664 (0.7%) in the clopidogrel group (OR 0.42, 95% CI [0.18, 0.95], $p=0.0374$). The rate of acute ST was 5/2691 (0.2%) in the cangrelor group and 14/2664 (0.5%) in the clopidogrel group (OR 0.35, 95% CI [0.13, 0.98], $p=0.0456$). The Interim Analysis Review Committee (IARC) attributed these differences to a cangrelor benefit. In the CHAMPION PCI trial, however, there was no difference between cangrelor and clopidogrel in the incidence of death or acute ST.

Table 35 shows a comparison of the composite primary efficacy endpoints in CHAMPION PLATFORM (death, MI, IDR at 48 hours), CHAMPION PCI (death, MI, IDR at 48 hours) and CHAMPION PHOENIX (death, UDMI, IDR, and ST at 48 hours), as well as the respective components in each of the composite primary efficacy endpoints. For comparison, the incidence of ST and acute ST were included in the table for PLATFORM and PCI although the ST variable did not comprise a component of the primary endpoint in these two trials.

In the CHAMPION PLATFORM trial, while cangrelor was initiated at the time of PCI, clopidogrel was initiated at least 2 hours after PCI. In the CHAMPION PCI trial, cangrelor and clopidogrel were both initiated at the time of PCI. The significant mortality and ST signals disfavoring clopidogrel in PLATFORM were not apparent in PCI.

Reviewer comment: This reviewer hypothesizes that the mortality and acute ST signals in PLATFORM were not due to a cangrelor efficacy benefit, as inferred by the IARC, but rather due to delayed clopidogrel therapy. There are no rigorous guidelines regarding the optimal timing of clopidogrel loading. Although the optimal timing of administration of the clopidogrel loading dose in the PCI setting could not be determined with certainty from the PCI-CURE trial, the ACCF/AHA Guidelines suggested that symptomatic patients with evidence of ischemia referred for PCI might benefit from clopidogrel load

approximately 6-15 hours prior to PCI. However, it was emphasized that the basis of the suggestion was a non-significant trend from a subgroup analysis of the CREDO trial and that no explicit comparison was made between a pre-PCI loading dose vs. a loading dose in the catheterization lab (Anderson, J, et al, 2013). The current clopidogrel label does not specify the optimal timing of load in patients with either UA/NSTEMI or STEMI.

Table 35. Comparison of efficacy endpoints from PLATFORM, PCI, and PHOENIX

CHAMPION TRIALS								
	PLATFORM		PCI		PHOENIX			
	Cangrelor	Clopidogrel	Cangrelor	Clopidogrel	Cangrelor (pre PCI)	Clopidogrel (pre PCI)	Cangrelor (post PCI)	Clopidogrel (post PCI)
Primary End Point	187/2961 (6.9%)	213/2664 (8.0%)	292/3993 (7.4%)	277/3924 (7.1%)	90/2105 (4.3%)	113/2090 (5.4%)	81/1931 (4.2%)	105/1947 (5.4%)
Mortality	8/2961 (0.2%)	19/2664 (0.7%)	8/3993 (0.2%)	6/3924 (0.2%)	4/2105 (0.3%)	7/2090 (0.3%)	2/1931 (0.2%)	1/1947 (0.1%)
ST	5/2961 (0.2%)	16/2664 (0.6%)	7/3933 (0.2%)	11/3924 (0.3%)	18/2105 (0.9%)	31/2090 (1.5%)	12/1931 (0.6%)	19/1947 (1.0%)
Acute ST	5/2691 (0.2%)	14/2664 (0.5%)	5/3933 (0.1%)	9/3924 (0.2%)	—	—	—	—
MI	177/2691 (6.6%)	192/2664 (7.2%)	278/3993 (7.1%)	256/3924 (6.5%)	74/2105 (3.5%)	86/2090 (4.1%)	69/1931 (3.6%)	94/1947 (4.8%)
IDR	19/2691 (0.7%)	26/2664 (1.0%)	15/3933 (0.4%)	23/3924 (0.6%)	13/2105 (0.6%)	10/2090 (0.5%)	7/1931 (0.4%)	14/1947 (0.7%)

Source: PLATFORM: Table 5.1.2.1 CSR; PCI: Table 5.1.2.1 CSR; PHOENIX (pre-PCI administration of study drug): Table 9.106.1.1 CSR; PHOENIX (post-PCI administration of study drug): Table 9.107.1.1 CSR.

Primary Efficacy Endpoint: PLATFORM (All-Cause Mortality, MI, IDR); PCI (All-Cause Mortality, MI, IDR); PHOENIX (All-Cause Mortality, UDMI, IDR, and ST). Population: ITT (PLATFORM, PCI); mITT (PHOENIX)

Dosing of clopidogrel

The PHOENIX study permitted either 300mg or 600mg clopidogrel loading dose in the clopidogrel arm during the double-dummy double-blinded infusion period. Following infusion period, subjects in the cangrelor arm received a protocol mandated 600mg clopidogrel loading dose; subjects in the clopidogrel arm received matching placebo. Approximately 26% of the subjects in the clopidogrel arm received the 300mg clopidogrel loading dose.

Reviewer Comment: The PHOENIX trial can be construed as a comparison between cangrelor + clopidogrel (600mg loading dose + 75mg daily maintenance) vs. clopidogrel (300mg or 600mg loading dose + 75mg daily maintenance). Statistical review and evaluation suggested that the imbalance in the clopidogrel loading dose between the arms of PHOENIX yielded the favorable effect of cangrelor compared to clopidogrel. If all subjects in each arm received clopidogrel 600mg loading dose, the treatment effect would not be statistically significant anymore in the PHOENIX trial. The clopidogrel label specifies a loading dose of 300mg followed by 75mg once daily for patients with ACS (CURE trial). A maintenance dose of 75mg is prescribed in the label for STEMI (COMMIT trial), recent MI or recent stroke or established peripheral arterial disease (CAPRIE trial), and prevention of ischemic events in patients with vascular disease or multiple risk factors for atherosclerosis (CHARISMA trial). The optimal loading dose with clopidogrel has not been rigorously established (Anderson, J, et al, 2013). Higher loading doses have been evaluated (600mg to 900mg) but the database for such higher doses is not sufficiently robust to formulate definitive recommendations (Anderson, J, et al., 2013). The CURRENT-OASIS 7 trial randomized 25,086 patients with ACS who were intended for PCI and who were not considered to be at high risk for bleeding. They received either a higher dose clopidogrel (600mg load and 150mg maintenance for 6 days followed by 75mg daily thereafter) vs. a standard dose of clopidogrel (300mg load and 75mg daily). The primary endpoint was the composite of cardiovascular death, myocardial (re)infarction or stroke at 30 days. The overall trial failed, but a PCI subgroup generated a hypothesis suggesting a significant benefit for the higher dose offset by increased major bleeding.

6.1.2 Bridge Indication

“Platelex IV is indicated to maintain P2Y₁₂ inhibition in acute coronary syndromes (ACS) patients or patients with stents who are at increased risk for thrombotic events (such as stent thrombosis) when oral P2Y₁₂ therapy is interrupted due to surgery.”

6.1.2.1 Methods

The Applicant submitted the Phase II BRIDGE trial results (Stage 1 dose-finding, Stage 2 dose confirmation) to support their proposed indication. The trial focused on platelet reactivity as a prognostic indicator for attenuating both the incidence of thrombotic events pre-CABG and incidence of bleeding during CABG.

The Applicant opined that a treatment dilemma currently exists in patients receiving oral platelet P2Y₁₂ inhibitors for coronary artery disease who require CABG. Product labeling and treatment guidelines for all oral P2Y₁₂ inhibitors (clopidogrel, prasugrel, and ticagrelor) include the warning that premature discontinuation of oral P2Y₁₂ platelet inhibitors confers a high risk for thrombotic cardiac events, such as ST, MI, and death. Complicating matters further, product labeling and treatment guidelines also recommend discontinuation of these agents at least five to seven days prior to any surgery to avoid the high risk of surgical bleeding known to be associated with oral P2Y₁₂ inhibitors when taken at the time of surgery.

The Applicant's treatment-dilemma reconciliation strategy was to optimize the timing of P2Y₁₂ discontinuation prior to CABG in order to minimize both thrombotic and bleeding events by utilizing the fast on—fast off PD effect of cangrelor as measured by the Verify Now assay. In the absence of clinical data from the Applicant's BRIDGE trial to support the PD effect, the Applicant's tactical approach was refer to data from published literature to demonstrate the following: validity of the VerifyNow PRU assay, the risk of thrombosis upon premature termination of oral P2Y₁₂ inhibitors, and the risk of bleeding upon continued therapy with oral P2Y₁₂ inhibitors in the peri-CABG period given the current standard of care. The Applicant utilized the Dutch Stent Thrombosis Registry (van Werkum, JW, et al., 2009) of 21,009 patients in order to demonstrate the risk of ST due to discontinuation of clopidogrel after PCI/stent placement. The Applicant also referenced 2 meta-analyses and a literature review to demonstrate the bleeding risk of continued therapy with oral P2Y₁₂ inhibitors during the peri-CABG period.

The review methodology, pursuant to the review strategy described in section 5.2, focused on endpoint validation:

- Evaluating BRIDGE endpoint data and validity of the Verify Now Assay as a prognostic indicator of clinical events.
- Evaluating the risk of ST from the Dutch Registry and Bleeding Risk from the literature review provided by the Applicant which addressed these risks.

6.1.2.2 Demographics

Table 36 displays the subject demographics for the BRIDGE trial. The average age was approximately 64 years, predominately white male with an average weight of 89 kg.

Table 36. BRIDGE Safety Patient Demographics

	Stage I		Stage II	
	Cohort I (N=5)	Cohort II (N=6)	Cangrelor (N=106)	Placebo (N=101)
Age, years				
Mean \pm SD	64.6 \pm 6.1	62.3 \pm 12.0	64.8 \pm 10.4	63.1 \pm 11.1
Median (Q1, Q3)	64.0 (62, 70)	64.5 (52, 70)	65.0 (57, 73)	62.0 (55, 71)
Age \geq 65 years, n/N (%)	2/5 (40.0)	3/6 (50.0)	54/106 (50.9)	42/101 (41.6)
Age \geq 75 years, n/N (%)	0/5 (0.0)	1/6 (16.7)	20/106 (18.9)	16/101 (15.8)
Male, n/N (%)	5/5 (100)	4/6 (66.7)	80/106 (75.5)	74/101 (73.3)
Ethnicity, n/N (%)				
Asian	0/5 (0.0)	0/6 (0.0)	3/106 (2.8)	0/101 (0.0)
Black or African American	0/5 (0.0)	1/6 (16.7)	6/106 (5.7)	5/101 (5.0)
Hispanic or Latino	2/5 (40.0)	1/6 (16.7)	4/106 (3.8)	2/101 (2.0)
White	3/5 (60.0)	4/6 (66.7)	93/106 (87.7)	94/101 (93.1)
Weight, kg				
Mean \pm SD	90.8 \pm 16.9	88.7 \pm 10.4	88.8 \pm 16.2	86.1 \pm 19.0
Median (Q1, Q3)	93.7 (77, 99)	89.6 (86, 98)	88.0 (79, 97)	85.0 (73, 98)

Source: [Section 14.1, Table 2.1.3](#)

SD = standard deviation

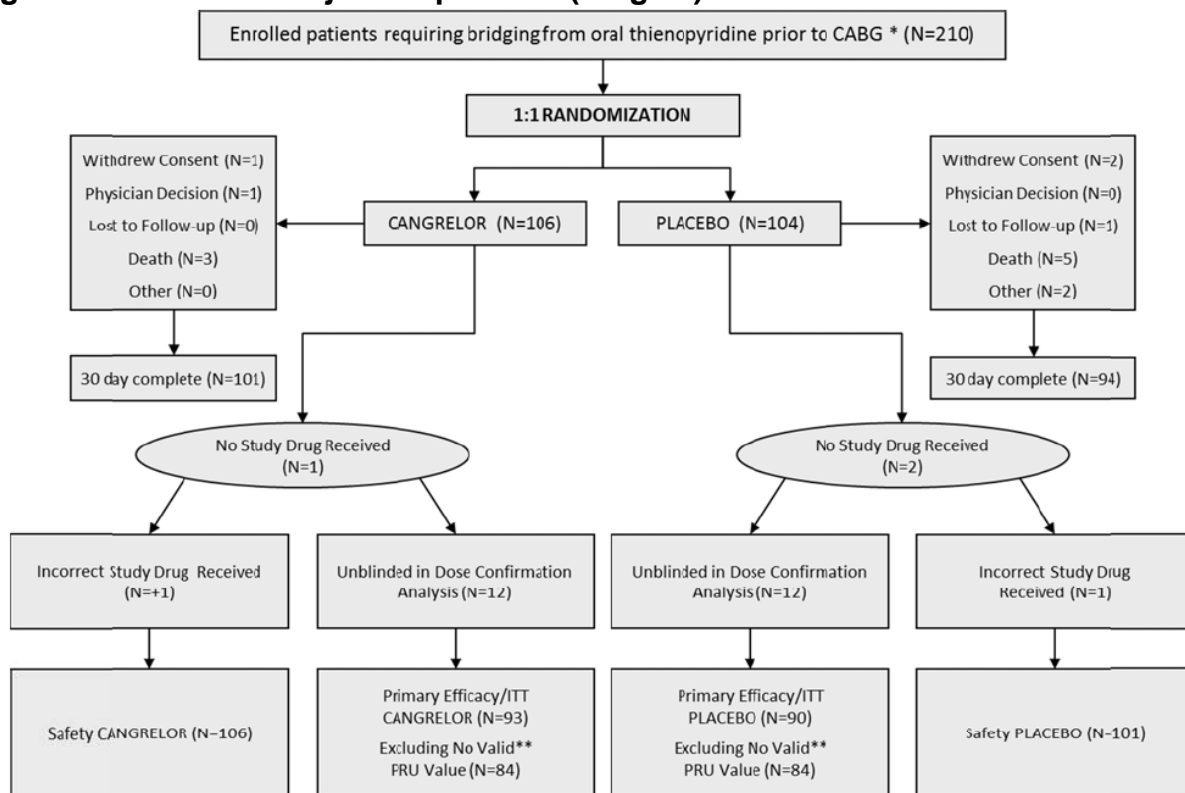
6.1.2.3 Subject Disposition

A total of 11 subjects from 4 US sites participated in Stage I. Of these, 10 subjects had evaluable VerifyNow data for dose assessment; 5 subjects completed the 1st cohort at a dose of 0.5ug/kg/min, and 5 subjects completed the 2nd cohort at a dose of 0.75ug/kg/min. All 11 subjects completed Stage 1 and were considered part of the safety population.

A total of 210 subjects (106 cangrelor, 104 placebo) from 35 global sites (Australia, Czech Republic, Netherlands, UK, US) participated in Stage II. **Figure 14** illustrates the BRIDGE trial Stage II subject disposition. One subject in the cangrelor arm and 2 in the placebo arm did not receive study medication. One subject in the placebo arm was erroneously given active medication. This subject was consequently added to the cangrelor arm. Therefore, a total of 106 subjects in the cangrelor arm and 101 subjects

in the placebo arm were respectively included in the safety population. Of the 106 cangrelor subjects, 1 subject withdrew consent, 1 was withdrawn as per physician discretion, and 3 died. Of the 104 placebo subjects, 2 subjects withdrew consent, 1 was lost to follow-up, 5 died, and 2 were listed as “other”. A total of 101 subjects in the cangrelor arm and 94 subjects in the placebo arm completed the study. The DSMB conducted a pre-specified unblinded review of the initial 24 subjects (12 per group) randomized in Stage II, in order to confirm the dose identified in Stage I. These subjects were excluded from the ITT population and the primary efficacy analysis. Therefore, the “primary efficacy / ITT population” was composed of 93 cangrelor and 90 placebo subjects.

Figure 14. BRIDGE Subject disposition (Stage 2)



* Data on patients screened but not enrolled was not collected

** Samples were not valid if they were taken while the infusion was off, or if they were analyzed outside of the manufacturer specified window

Source: BRIDGE CSR, Section 10.1, Figure 2

6.1.2.4 Analysis of Primary Endpoint(s)

Stage I

Table 37 shows the results from Stage I of the BRIDGE trial. In Cohort 1 (0.5ug/kg/min), platelet inhibition was maintained above 60% in 76.5% (13/17) of subject samples. This result was shy of the primary endpoint of 80% of the subject samples, thereby initiating Cohort II (0.75ug/kg/min). Cangrelor at the dose of 0.75ug/kg/min maintained platelet inhibition above 60% in 94.4% (17/18) of subject samples, thereby meeting the Stage I primary endpoint. A total of 80% (n=4/5) of subjects in Cohort I and 100% (n=6/6) of subjects in Cohort II had all of the cangrelor on-infusion samples < 240 PRU. Based on these results, the dose of 0.75ug/kg/min was selected for advancement to Stage II.

Table 37. BRIDGE Primary Efficacy Result (Stage I)

During Infusion	Statistic	Stage I	
		Cohort I (N=5)	Cohort II (N=6)
Analysis by patient sample			
Primary endpoint: Samples with >60 PPI	n (%)	13 (76.5)	17 (94.4)
Samples <240 PRU	n (%)	16/17 (94.1)	18/18 (100.0)
Analysis by patient			
Patients with all samples <240 PRU	n (%)	4 (80.0)	6 (100.0)

Source: [Section 14.1, Table 5.3.3.1](#)

PPI = percent platelet inhibition; PRU = P2Y₁₂ Reaction Unit(s)

Stage II

The original P2Y₁₂ inhibitor therapy was discontinued for approximately 29 hours in cangrelor arm and 30 hours in the placebo arm prior to randomization (CSR Table 7). Of the 106 subjects in the cangrelor arm, 105 were previously on clopidogrel (n: last dose = 88:75mg; 1:150mg; 4:300mg; 12:600mg) and 1 was previously on prasugrel (n: last dose = 1:10mg). Of the 101 subjects in the placebo arm, 93 were previously on clopidogrel (n: last dose = 65:75mg; 2:150mg; 12:300mg; 13:600mg; 1:900mg) and 8 were previously on prasugrel (n: last dose = 6:10mg; 1:60mg; 1:75mg).

Table 38 shows the stratification data by days to surgery. The number of subjects administered study drug for less than or equal to 3 days prior to surgery, and for greater than 3 days prior to surgery, were equally distributed.

Table 38. BRIDGE Subject Stratification by days to surgery (Stage II)

Stratum	Number (%) of patients		
	Cangrelor	Clopidogrel	Overall
Safety population	N=106	N=101	N=207
≤ 3 days to surgery	55	52	107
> 3 days to surgery	51	49	100
ITT population	N=93	N=90	N=183
≤ 3 days to surgery	49	48	97
> 3 days to surgery	44	42	86

Source: [Section 14.1](#), [Table 5.1.1.3](#) and [Table 5.1.3.3](#)

ITT = Intent to treat.

As determined by investigator at the time of randomization.

The duration of infusion for the cangrelor group was 75.8 ± 34.6 hours (mean) and 67.0 hours (median) with a minimum of 1 hour and a maximum of 162 hours. Similarly, the duration of infusion for the placebo group was 90.4 ± 45.7 hours (mean) and 82.7 hours (median) with a minimum of 2 hours and a maximum of 306 hours (see CSR Table 21).

Table 39 shows the results from Stage II of the BRIDGE trial. The primary efficacy endpoint was achieved with 98.8% of cangrelor treated subjects maintaining target levels of PRU < 240 for all on-infusion timepoints measured over the bridging period compared to 19.0% of placebo subjects (OR 353 [95% CI 45.6, 2728], $p < 0.0001$; ref: page 63 of BRIDGE CSR). The results were unchanged when analyzed using logistic regression adjusted by the stratification variable of expected days to surgery (either ≤ 3 days or > 3 days), (OR 473 [95% CI 56.3, 3974], $p = 0.001$; ref: page 63 of BRIDGE CSR).

Table 39. BRIDGE Primary Efficacy Result (Stage II)

During Infusion Statistic	Stage II			
	Cangrelor (N=93) n/N (%)	Placebo (N=90)	P-value	RR (95% CI)
Patients with all samples PRU <240 ^a	83/84 (98.8)	16/84 (19.0)	<0.0001 CH 0.0000 LR	5.19 (3.34, 8.07) 5.15 (3.32, 8.00)

Source: [Section 14.1](#), [Table 5.1.1.1](#)

^a Primary efficacy analysis

CH = Chi-square test; CI = confidence interval; ITT = intent-to-treat; LR = Logistic regression adjusting for stratification factor, expected CABG ≤ 3 versus > 3 days; OR = odds ratio; PRU = P2Y₁₂ Reaction Unit(s).

The efficacy results remained significant when sensitivity analyses were conducted for the following patient populations (see CSR Table 20, source Table 99.5.1):

- All ITT patients with missing data counted as non-response.
- All randomized subjects (including the 12 subjects in each arm that were unblinded for the dose-confirmation analysis and consequently excluded from the primary efficacy analysis) for whom valid PRU data was available.
- All randomized patients with missing data counted as non-response.
- Safety population with missing data counted as non-response.

6.1.2.5 Analysis of Secondary Endpoint(s)

Table 40 shows the secondary efficacy endpoint results, with analyses performed by patient and by patient samples, respectively. All secondary efficacy endpoints were significantly in favor of cangrelor over placebo.

Table 41 provides an analysis of PRU data in the ITT population before, during, and after study drug infusion. The pre-study drug infusion PRU data shows that approximately 62% of the cangrelor subjects and 52% of the placebo subjects had a PRU level < 240. This was interpreted as residual activity of recently discontinued P2Y₁₂ inhibitor. The post-study drug infusion PRU data showed a platelet reactivity rebound effect such that there was no difference between cangrelor (PRU 280) and placebo (PRU 298).

Table 40. BRIDGE Secondary Efficacy Result (Stage II)

Endpoint	Cangrelor (N=93) %(n/N)	Placebo (N=90) %(n/N)	RR (95% CI)	P value
During Study Drug Infusion (Analyses by patient)				
Patients with last sample during infusion with platelet reactivity < 240 PRU	98.8% (83/84)	31.0% (26/84)	3.19 (2.32,4.40)	<0.001
All samples ≤ baseline PRU value	92.1% (70/76)	12.3% (10/81)	7.46 (4.16, 13.4)	< 0.001
During Study Drug Infusion (Analyses by patient sample)				
Samples with platelet reactivity < 240	99.6% (258/259)	33.3% (98/294)	2.99(2.54, 3.51)	<0.001
Total samples that maintained > 60% platelet inhibition (primary efficacy endpoint Stage 1)	83.8% (217/259)	3.7% (11/294)	22.4(12.5, 40.1)	<0.001

Source: CSR Section 14.1, Table 5.1.1.1 and Table 5.3.1.1

Table 41. BRIDGE Analysis of Platelet Reactivity (ITT population)

Endpoint	Statistic	Cangrelor (N=93)	Placebo (N=90)	P value
Prior to Study Drug Infusion (washout period from oral P2Y12 inhibition)				
Patients with platelet reactivity < 240 PRU	% (n/N)	62.4% (53/85)	52.3% (45/86)	0.185
PRU Values	Mean \pm SD	210.9 \pm 94.0	214.1 \pm 85.9	0.817
During Study Drug Infusion				
Patients with platelet reactivity < 240 PRU and throughout entire infusion period (primary endpoint)	% (n/N)	98.8% (83/84)	19.0% (16/84)	<0.001 <0.001
Patients with last sample during infusion with platelet reactivity < 240 PRU	% (n/N)	98.8% (83/84)	31.0% (26/84)	<0.001
PRU values last sample during infusion	Mean \pm SD	68.9 \pm 67.8	263.7 \pm 68.3	<0.001
Following Discontinuation of Study Drug Infusion				
Patients with Platelet Reactivity < 240 PRU	% (n/N)	26.9% (21/78)	20.0% (15/75)	0.313
PRU Values	Mean \pm SD	279.7 \pm 106.5	297.8 \pm 67.3	0.212

Source: CSR Section 14.1, Table 5.1.1.1 and Table 5.2.1.1

Bleeding was listed as a secondary efficacy endpoint pursuant to the program hypothesis of reducing bleeding during CABG as well as reducing thrombotic events

during the bridging period prior to CABG. There was no difference between cangrelor and placebo for CABG related bleeding events (CSR section 14.3, Tables 4.2.3; 6.1.3.1; 6.1.3.2; and 6.4.3). Regarding non-CABG bleeding during the 5-day bridging period, there were numerical increases in mild (8 vs. 5) and moderate (10 vs. 4) GUSTO bleeding in the cangrelor subjects vs. the placebo subjects, respectively. There was also a numerical increase in Major AQUIITY bleed (12 cangrelor vs. 5 placebo subjects) (source: CSR section 14.3, Table 6.2.3). The Applicant claimed that these numerical differences were based on 3 cangrelor subjects (201018001; 201018003; and 201018007). As will be elucidated in the safety section, the Applicant had attributed bleeding events in these 3 subjects to other interventional procedures and therefore they were not spontaneous. It is not clear what the PRU levels were during these adverse events.

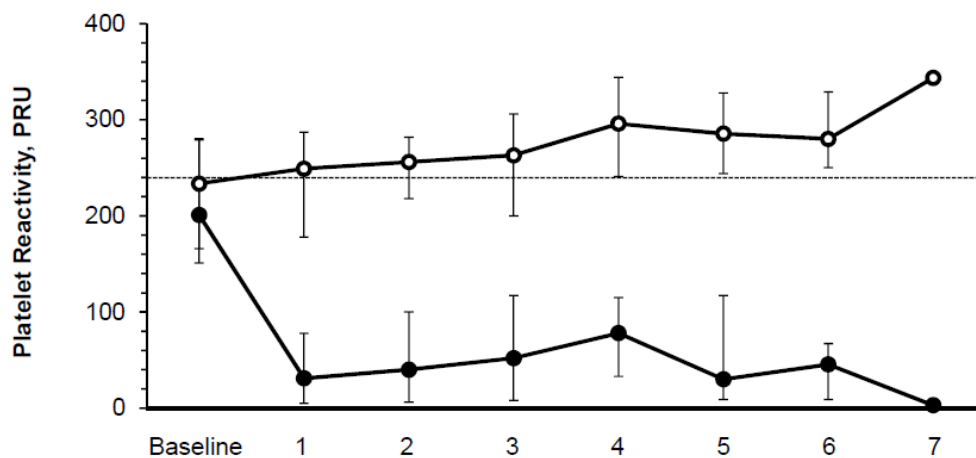
6.1.2.6 Other Endpoints

PRU-Time Dependency

Figure 15 shows the PRU time-course in subjects randomized to cangrelor (closed circles) vs. placebo (open circles) during the infusion period. The data showed a consistent decrease of PRU for the infusion period in the cangrelor arm compared to placebo. The boundary condition of 240 PRU has been opined by the Applicant as the value below which thrombotic events were attenuated (see section 6.1.2.8 in this review).

Figure 16 shows the PRU time-course in subjects randomized to cangrelor (closed circles) vs. placebo (open circles) following discontinuation of study drug. The figure showed that when cangrelor was discontinued, PRU rebounded to a level consistent with placebo. The duration of time for this rebound, although not specified in the Applicant's figure, was reported in the CSR to be a median of 4.2 hours from the last sample taken during the infusion to the pre-CABG sample. The median time from the termination of the infusion until the start of CABG was 3.1 hours (see CSR 11.2.2.1.3).

Figure 15. BRIDGE PRU time-course during infusion period



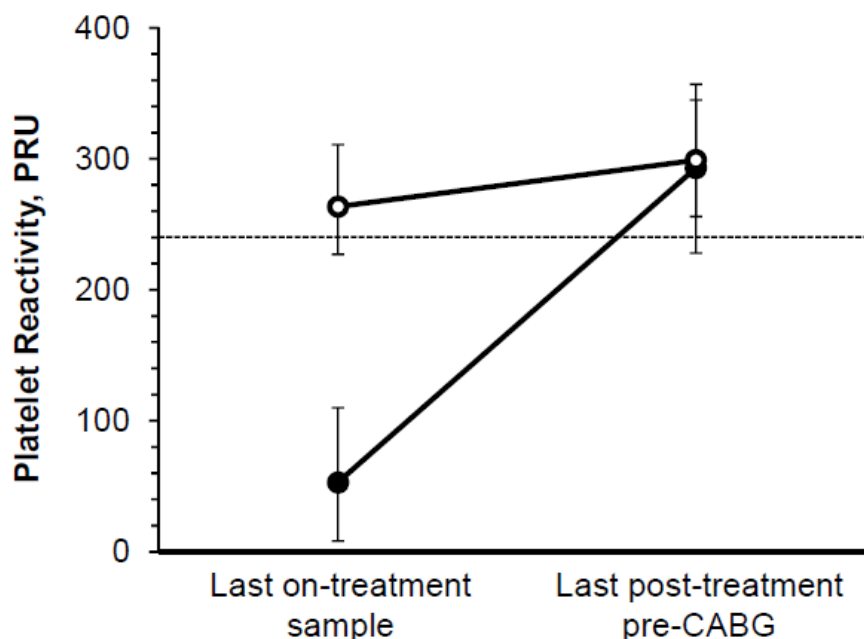
No. of patients with valid sample in the ITT population

Placebo/clopidogrel	86	76	73	57	34	24	14	2
Cangrelor+clopidogrel	85	80	70	55	33	7	6	1

Source: [Section 14.1, Table 5.2.1.1](#)

Open circle: placebo; closed circle: cangrelor

Figure 16. BRIDGE PRU time-course post-study drug infusion



No. of patients with valid sample in the ITT population

Placebo/clopidogrel	84	75
Cangrelor+clopidogrel	84	78

Source: [Section 14.1, Table 5.2.1.1](#)

Open circle: placebo; closed circle: cangrelor

6.1.2.7 Subpopulations

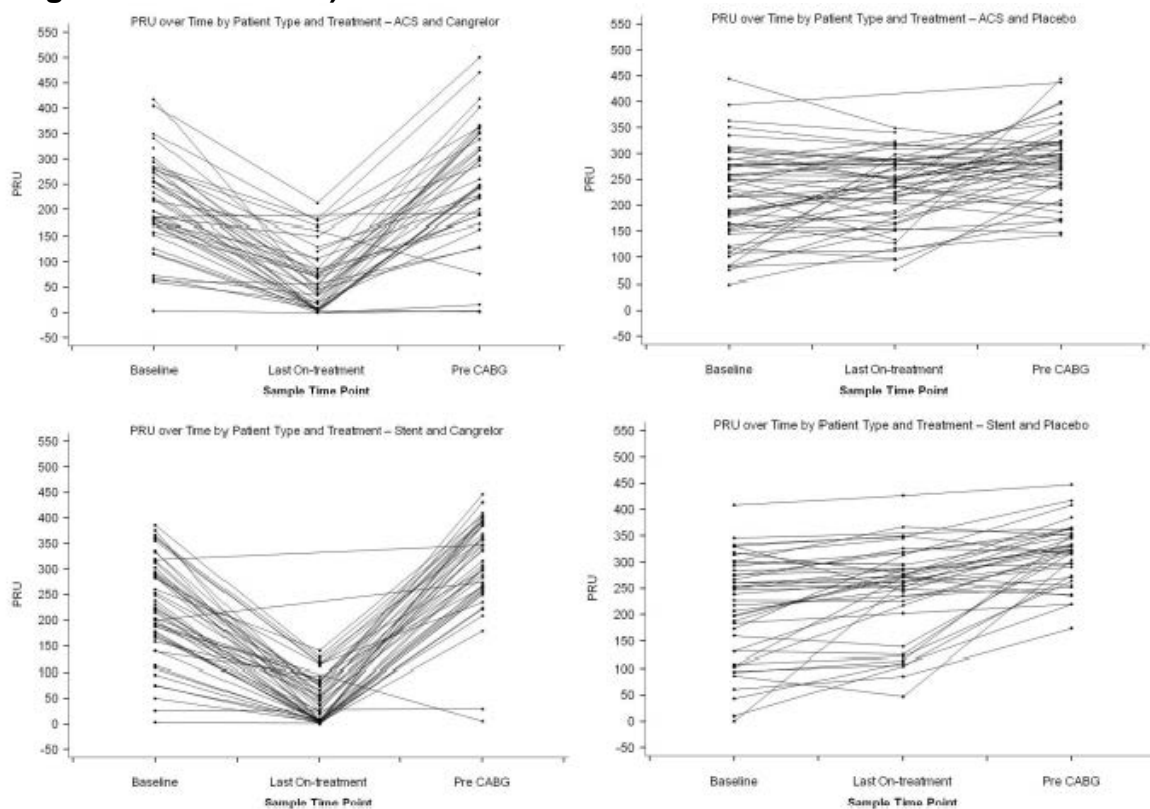
ACS and Stent

Two subpopulations in the BRIDGE trial were those presenting with ACS referred for CABG and those with a history of stent deployment where planned CABG was not based on ACS. **Figure 17** shows PRU over time by subject type for individual subjects (ACS: cangrelor vs. placebo –top half of figure; Stent: cangrelor vs. placebo –lower half of figure). Variability in the baseline PRU levels was attributed to an attenuating effect of recently discontinued oral P2Y₁₂ inhibition. The baseline levels of PRU were not different between subjects treated with cangrelor vs. placebo ($p=0.916$) or subjects bridging to surgery with a stent or with ACS ($p=0.532$) (see CSR 11.2.2.1.3.2, page 68).

The characteristic V-shaped profiles for the individual subjects in the cangrelor treated group (both ACS and PCI/stent) showed decreased PRU below 240 during cangrelor infusion and rebound of PRU to baseline levels upon discontinuation of cangrelor. On-

treatment PRU was significantly lower in the cangrelor group (median PRU 59) vs. the placebo group (median PRU 264), $p < 0.001$ (see CSR 11.2.2.1.3.2, page 68).

Figure 17. PRU values over time by subject type (ACS vs. stent) and treatment (cangrelor vs. Placebo)



Upper left: ACS and cangrelor. Upper right: ACS and placebo. Lower left: stent and cangrelor. Lower right: stent and placebo.

Source: [Section 14.2](#), [Figure 99.1.1.1](#), [Figure 99.1.2.1](#), [Figure 99.1.3.1](#) and [Figure 99.1.4.1](#)

Note: Some on-treatment samples are missing.

Variations in Subject Characteristics

The subjects were stratified by expected time to CABG (3 days or less vs. greater than 3 days) in order to avoid potential bias. The Applicant performed an analysis adjusting for variations in subject characteristics (i.e. subjects with all samples PRU < 240; Baseline PRU < 240 vs. ≥ 240 ; ACS vs. stent; cardiac markers greater than vs. less than or equal to upper limit of normal; duration of infusion < 48 hours vs. ≥ 48 hours or < 72 hours, 72-96 hours, > 96 hours) and confirmed that the primary efficacy results did not change (see CSR Table 19).

6.1.2.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The dose-selection strategy pursuant to the BRIDGE indication was based on the Accumetrics VerifyNow Assay which was developed to provide a rapid and easy method to measure an individual's response to antiplatelet agents. This assay measures the amount of ADP-mediated platelet aggregation as an increase in light transmittance in whole blood. Light transmittance increases due to binding of activated platelets onto fibrinogen-coated beads. This assay is specific to the platelet P2Y₁₂ receptor and is expressed as PRU (P2Y₁₂ Reaction Unit). A higher PRU reflects greater ADP-mediated platelet reactivity.

Bonello, L, et al. (2010) studied the relationship of PRU during clopidogrel treatment to both peri-procedural and long-term ischemic risk, resulting in the conclusion that there was continued controversy regarding the optimal method to quantify PRU and identify a threshold value for clinical correlation. Based on reviewing a series of studies linking high on-treatment ADP-mediated platelet reactivity with clinical outcome, it was suggested that the level of on-treatment platelet reactivity might be a superior predictor of risk compared with the difference between baseline and post-treatment platelet reactivity. This was because platelet reactivity to ADP was variable prior to clopidogrel treatment in patients on aspirin therapy. In using the VerifyNow assay, a cut-off value of 240 PRU was identified where values above this cutoff appeared to be prognostic for subsequent thrombotic events (i.e. cardiovascular death and ST, or cardiovascular death and nonfatal MI and ST). However, the authors stated that there was limited data showing that alteration of therapy as a response to PRU measurement improved clinical outcome. Furthermore, the observed cut-off PRU value had a poor positive predictive value for thrombotic ischemic events despite a high negative predictive value. Finally, the authors have opined that it is unknown whether on-treatment platelet reactivity cut points associated with peri-procedural events are the same as those associated with long-term risk.

Breet, N, et al. (2010) evaluated the capability of multiple platelet function tests to predict clinical outcome. The authors designed a prospective, observational, single-center cohort study of 1069 consecutive patients who were administered clopidogrel and underwent elective coronary stent implantation between December 2005 and December 2007. The primary efficacy endpoint was the 1-year composite of all-cause death, nonfatal acute MI, ST, and ischemic stroke. Each platelet function test (i.e. light transmittance aggregometry at 5umol/L ADP, light transmittance aggregometry at 20umol/L ADP, Verify Now, Plateletworks, IMPACT-R, Dade PFA collagen/ADP, and Innovance PFA P2Y) was evaluated for predicting the occurrence of the primary efficacy endpoint as a function of cut-off values for high on-treatment platelet reactivity established by ROC curve analysis for each respective function test. The light transmittance aggregometry at 5umol/L ADP, light transmittance aggregometry at 20umol/L ADP, Verify Now, and Plateletworks showed an association between the

occurrence of the primary endpoint and the ROC-based platelet reactivity cutoff values for these respective function tests, as shown in [Table 42](#). The IMPACT-R, Dade PFA collagen/ADP, and Innovance PFA P2Y function tests were reportedly unable to discriminate between patients with and without the primary end point. For the VerifyNow assay, the ROC analysis resulted in a cutoff value of 236 PRU. There were 646 patients with PRU below 236, and 406 patients with PRU greater than or equal to 236. The primary endpoint occurred more frequently in patients with high on-treatment platelet reactivity (i.e. above the cutoff): 13.3% vs. 5.7%; OR 2.53 (95% CI 1.63, 3.91), $p < 0.001$. Similar results were achieved with the other function tests shown in [Table 42](#). The authors opined that the predictive accuracy of these tests was modest for those tests showing associations between platelet reactivity and clinical outcome. However, none of them provided accurate prognostic information to identify low-risk patients at higher risk of bleeding following stent implantation.

Table 42. Clinical Outcome Based on Different Platelet Tests (Breet, N, et al., 2010)

Table 3. Clinical Outcome Based on Testing With Light Transmittance Aggregometry, VerifyNow P2Y12, and Plateletworks

Platelet Function Test	On-Treatment Platelet Reactivity, No. (%)		OR (95% CI)	P Value
	Normal	High		
Light transmittance aggregometry, 5 μ mol/L ADP ^a	<42.9% Aggregation (n = 604)	\geq 42.9% Aggregation (n = 445)		
Death combined ^a	36 (6.0)	52 (11.7)	2.09 (1.34-3.25)	<.001
Death	6 (1.0)	11 (2.5)	2.53 (0.93-6.88)	.06
MI	24 (4.0)	37 (8.3)	2.19 (1.29-3.72)	.003
Stent thrombosis	6 (1.0)	7 (1.6)	1.59 (0.53-4.77)	.40
Stroke	7 (1.2)	6 (1.3)	1.17 (0.39-3.49)	.78
Target vessel revascularization	18 (3.0)	7 (1.6)	0.52 (0.22-1.26)	.14
Nontarget vessel revascularization	21 (3.5)	8 (1.8)	0.51 (0.22-1.16)	.10
Rehospitalization	16 (2.6)	11 (2.5)	0.93 (0.43-2.03)	.87
Light transmittance aggregometry, 20 μ mol/L ADP	<64.5% Aggregation (n = 659)	\geq 64.5% Aggregation (n = 392)		
Death combined ^a	41 (6.2)	47 (12.0)	2.05 (1.32-3.19)	.001
Death	11 (1.7)	6 (1.5)	0.92 (0.34-2.50)	.86
MI	24 (3.6)	37 (9.4)	2.76 (1.62-4.68)	.0001
Stent thrombosis	4 (0.6)	9 (2.3)	3.85 (1.18-12.58)	.017
Stroke	8 (1.2)	5 (1.3)	1.05 (0.34-3.24)	.93
Target vessel revascularization	21 (3.2)	4 (1.0)	0.31 (0.11-0.92)	.03
Nontarget vessel revascularization	23 (3.5)	6 (1.5)	0.43 (0.17-1.07)	.06
Rehospitalization	21 (3.2)	6 (1.5)	0.47 (0.19-1.18)	.10
VerifyNow P2Y12	<236 ^b (n = 646)	\geq 236 ^b (n = 406)		
Death combined ^a	37 (5.7)	54 (13.3)	2.53 (1.63-3.91)	<.001
Death	9 (1.4)	9 (2.2)	1.60 (0.63-4.08)	.32
MI	23 (3.6)	40 (9.9)	2.96 (1.74-5.02)	<.001
Stent thrombosis	5 (0.8)	8 (2.0)	2.58 (0.84-7.93)	.09
Stroke	6 (0.9)	7 (1.7)	1.87 (0.62-5.61)	.26
Target vessel revascularization	16 (2.5)	9 (2.2)	0.89 (0.39-2.04)	.79
Nontarget vessel revascularization	20 (3.1)	9 (2.2)	0.71 (0.32-1.57)	.40
Rehospitalization	18 (2.8)	8 (2.0)	0.70 (0.30-1.63)	.41
Plateletworks	<80.5 Aggregation (n = 344)	\geq 80.5 Aggregation (n = 262)		
Death combined ^a	21 (6.1)	33 (12.6)	2.22 (1.25-3.93)	.005
Death	9 (2.6)	4 (1.5)	0.58 (0.18-1.89)	.36
MI	10 (2.9)	25 (9.5)	3.52 (1.66-7.47)	<.001
Stent thrombosis	3 (0.9)	6 (2.3)	2.66 (0.66-10.75)	.15
Stroke	3 (0.9)	4 (1.5)	1.76 (0.39-7.94)	.45
Target vessel revascularization	12 (3.5)	5 (1.9)	0.54 (0.19-1.55)	.24
Nontarget vessel revascularization	11 (3.2)	7 (2.7)	0.83 (0.32-2.17)	.71
Rehospitalization	10 (2.9)	7 (2.7)	0.92 (0.34-2.44)	.86

Abbreviations: ADP, adenosine diphosphate; CI, confidence interval; MI, myocardial infarction; OR, odds ratio.
^aIncludes all-cause death, as well as nonfatal MI, stent thrombosis, and stroke.
^bUnits are P2Y12 reaction units.

Source: Breet, N, et al., 2010, JAMA, 303(8):754-762

Marcucci, R, et al. (2009), in a prospective study, used the VerifyNow assay to determine Residual Platelet Reactivity (RPR) to ADP during clopidogrel therapy and whether or not this predicted adverse clinical events in 683 ACS patients undergoing PCI with either BMS or DES. The primary endpoint was the composite of cardiovascular

death, nonfatal MI, and TVR at 12 months. There were 51 ischemic events (24 cardiovascular deaths [3.5%], 27 non-fatal MIs [3.9%]), and 40 TVRs [5.8%]. ROC analysis identified a PRU of ≥ 240 (defined as high RPR) as a significant and independent predictor of 12 month cardiovascular death (HR 2.55, 95% CI [1.08, 6.07], $p = 0.034$) and nonfatal MI (HR 3.36, 95% CI [1.49, 7.58], $p = 0.004$). There was no association found between a high RPR and TVR.

In the ADAPT-DES prospective registry study involving 10,000 patients (Stone, GW, et al., 2013), platelet reactivity and clinical outcomes after coronary artery implantation of drug-eluting stents were evaluated. The results showed that high on-treatment platelet reactivity (HTPR) (PRU > 208 with clopidogrel as the treatment agent) was strongly related to ARC-ST and MI, inversely related to bleeding, and not related to mortality. However, the authors emphasized that the sensitivity, specificity, and diagnostic accuracy of HTPR with clopidogrel for subsequent ST were poor-to-fair.

Price, M, et al. (2011) described the results of the GRAVITAS (i.e. **G**auging **R**esponsiveness with **A** VerifyNow assay-Impact on **T**hrombosis **A**nd **S**afety) RCT. This trial was designed to evaluate the effect of a high-dose clopidogrel regimen compared to a standard dose of clopidogrel in patients with a high on-treatment VerifyNow measured baseline PRU 12-24 hours after PCI with DES deployment. High on-treatment platelet reactivity was defined as PRU ≥ 230 . A total of 2214 patients were enrolled ($n = 1109$ to the high dose clopidogrel regimen, median PRU 282; $n = 1105$ to the standard dose of clopidogrel, median PRU 283). The high dose clopidogrel was 600mg load + 150mg QD, and the standard dose clopidogrel was no load + 75mg QD. The primary efficacy endpoint was the 6 month incidence of cardiovascular death, nonfatal MI, and ST. The key safety endpoint was moderate or severe GUSTO bleeding. A key PD endpoint was the rate of persistently high on-treatment reactivity at 30 days. The study was powered with an assumed primary efficacy endpoint event rate of 5% in patients with high on-treatment PRU treated with the standard clopidogrel dose, where 1100 patients in each group would provide 80% power to detect a 50% relative risk reduction in the rate of the primary efficacy endpoint. The primary efficacy endpoint occurred in 25 of 1109 (2.3%) patients receiving high dose clopidogrel, and in 25/1105 (2.3%) patients receiving the standard dose clopidogrel. Moderate or severe GUSTO bleeding was not increased with the high dose clopidogrel. Compared to the standard dose clopidogrel, the high dose clopidogrel provided a 22% (95% CI 18%--26%) absolute reduction in the rate of high on-treatment reactivity at 30 days (62%, 95% CI 59%--65%, vs. 40%, 95% CI 37%--43%; $p < 0.001$). The decreased PRU for the high dose clopidogrel vs. the standard dose clopidogrel was not reflected in corresponding differences in clinical events, including bleeding events between the arms of the study. The study might have been underpowered due to the lower than expected event rate in the standard clopidogrel dose arm. This study did not impute missing data and patient lost to follow-up were censored at the date of last contact (only 2 patients in the high dose clopidogrel arm).

Gurbel, P, et al. (2009) wrote an editorial on the GRAVITAS trial where several questions were posed to address the discrepancy between PRU results and clinical outcome. One of the suggestions was that PRU is a biomarker which does not modify the level of risk. The sentiment expressed in this editorial appeared to be consistent with those expressed by Bonello, L, et al. (2010) where it was stated that there was limited data showing that alteration of therapy as a response to PRU measurement improved clinical outcome.

TRIGGER-PCI (Trenk, D, et al., 2012) was a randomized double-blind active comparator control trial designed to investigate the efficacy, safety, and antiplatelet effect of prasugrel compared to clopidogrel in patients who present with stable CAD and HTPR (PRU > 208) after elective PCI with DES. The primary efficacy endpoint was the incidence of CV-death or MI at 6 months. The primary safety endpoint was non-CABG related TIMI Major Bleed. Sample size calculations were based on the following assumptions: 1) an incidence of the primary efficacy endpoint of 4.7% for the clopidogrel-treated population; 2) patients with PRU>208 represented the upper tertile of the entire population with respect to on-clopidogrel platelet reactivity; and 3) the incidence of the primary efficacy endpoint in patients on clopidogrel with PRU>208 was increased 2-fold as compared with patients whose PRU \leq 208. Based on these assumptions, it was anticipated that 1,075 subjects would need to be randomized to each group: α , β not mentioned. In 212 subjects randomized to prasugrel, PRU decreased from 245 (median 225, interquartile range 273) at baseline to 80 (median 42, interquartile range 124). In 211 subjects randomized to clopidogrel, PRU decreased from 249 (median 225, interquartile range 277) to 241 (median 194, interquartile range 275) ($p < 0.001$ vs. prasugrel). The primary efficacy endpoint occurred in nobody on prasugrel vs. 1 subject in clopidogrel. TIMI Major bleed occurred in 3 subjects (1.4%) on prasugrel vs. 1 (0.5%) on clopidogrel. The relationship between PRU and clinical outcome was not demonstrated in TRIGGER-PCI.

ARCTIC (Collet, J-P, et al., 2012) was a randomized open label study comparing bedside platelet function monitoring with treatment adjustment in subjects who had a poor response to antiplatelet therapy, vs. a conventional strategy (no monitoring and no treatment adjustment). Subjects who were enrolled presented with stable CAD or NSTEMI/ACS undergoing DES placement. The primary efficacy endpoint was the incidence of death, MI, ST, stroke, or urgent revascularization at 1 year. The authors hypothesized that the annual event rate would be 15% among subjects with a poor response to antiplatelet therapy (PRU ≥ 235 with thienopyridine; PRU ≥ 550 on aspirin, or 15% less IPA) and 6% among those with a good response. The authors expected that 33% of the subjects would have a poor response. Assuming an annual risk of 9% in the control group (66% of the subjects at an event rate of 6% and 33% of the subjects at an event rate of 15%) for the primary endpoint, and expecting a 33% reduction in relative risk in the monitoring group (two-sided α 5% and β of 20%), it was estimated that 2500 subjects would be required. In the monitored group, high platelet reactivity in

subjects taking clopidogrel (34.5% of the subjects) or aspirin (7.6% of the subjects) led to the administration of an additional bolus of clopidogrel, prasugrel, or aspirin along with GPI during the PCI. If HTPR observed 14-30 days post-PCI, the subjects were switched to prasugrel or to an increased maintenance dose of clopidogrel. The primary efficacy endpoint occurred in 34.6% in the monitored group compared to 31.1% in the conventional group. The study showed that PRU monitoring and subsequent dose adjustment was ineffectual.

The Applicant has argued that these negative trials (i.e. GRAVITAS, TRIGGER-PCI, ARCTIC) were underpowered, focused on low-risk, and demonstrated that individualization strategies are not effective. The Applicant has further argued that an individualization strategy was not the focus of their BRIDGE hypothesis, but rather ensuring the minimization of peri-CABG thrombotic and bleeding risks through management of PRU with cangrelor based on the association of PRU and clinical events. In the opinion of this reviewer, the powering of the failed trials was based on their reasonable apriori statistical assumptions. The end-result was a paucity of data which has created a validation requirement to justify the Bridge indication. Furthermore, the management of PRU during cangrelor treatment in the peri-CABG setting, even in using an “on-off” approach, was analogous to an individualization strategy as it attempted to use PRU to affect a clinical outcome. Although the BRIDGE hypothesis is meritorious, the level of evidence required to support an indication has not been met by the data provided in the Applicant’s NDA.

The salient features of the published data suggested that HTPR is associated with MACE but the observed caveats as expressed by the authors were:

- Limited data showing that alteration of therapy in response to PRU measurement improves clinical outcome.
- Observed cut-off PRU values have a poor predictive value for thrombotic ischemic events.
- No evidence that HTPR cut points with risk for long term risks are the same as those for peri-procedural events.
- No correlation between PRU and clinical outcome.
- Sensitivity, specificity, and diagnostic accuracy for subsequent ST were poor-to-fair.

The data at this point of clinical investigation regarding PRU and clinical outcome is suggestive but inconclusive. In addition to the opinion that PRU may be a biomarker which does not alter the level of risk (Gurbel, P, et al., 2009), it was also opined that platelet function testing “continues to hold promise as a tool to tailor therapy, but the verdict is out on whether this will prove clinically useful or lead to meaningful treatment strategies” (Reed, G, and Cannon, C, 2011).

6.1.2.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

There is no data on persistence of efficacy and /or tolerance effects.

6.1.2.10 Additional Efficacy Issues/Analyses

The Dutch registry identified several predictors of ST in patients having undergone PCI with either a BMS or DES. As shown in [Figure 18](#), the strongest predictors of ST in descending order were discontinuation of clopidogrel, followed by stent under-sizing, malignancy, CAD proximal of culprit lesion, TIMI flow < 3 post-PCI, dissection, bifurcation stenting, LVEF < 30%, PAD, CAD distal to culprit lesion, lack of aspirin, any DES, and diabetes mellitus. [Figure 19](#) shows the independent risk factors for ST as a function of patient presentation (SA in the [Figure 19-A](#), and ACS in [Figure 19-B](#)). [Figure 20](#) shows the independent risk factors for ST as a function of time from PCI: early (≤ 30 days, Fig 18-A) and late (> 30 days, Fig 18-B). Notwithstanding some variations, the data showed a similar set of independent risk factors for patient presentation and time of ST from PCI, respectively (i.e. stent under-sizing, CAD > 50% proximal to the culprit lesion, post PCI TIMI flow < 3). The authors of the Registry emphasized that the time-varying “cessation of clopidogrel” was not included in these multivariate models.

[Table 43](#) shows the number of patients with ST distributed over time from index PCI observed in the Dutch Stent Thrombosis Registry. The table also shows the number of patients who were not on clopidogrel for each type of time-dependent ST (i.e. acute, subacute, late, very late). The median time off clopidogrel for each type of time-dependent ST was also delineated. Of the 437 patients with ST selected for this analysis (436 in the publication analysis), 140 patients had acute ST, 179 patients had subacute ST, 58 patients had a late ST, and 59 patients had a very late ST. Therefore, 319 patients (approx. 73%) had a ST within 30 days from the index PCI. Of these, 39 (approx. 12%) were off clopidogrel at the time of ST. Of the total of 437 selected patients with an ST, approximately 31% were not on clopidogrel (presumably not on any other P2Y12 inhibitor). Of the 58 patients with late thrombosis (> 30 days—1 year from index PCI), 39 (approx. 67%) were not on clopidogrel for a median of 13 days (interquartile range 7-61 days).

[Table 44](#) shows the influence of clopidogrel on ST as extracted from the Dutch Stent Thrombosis Registry publication. Hazard Ratios are shown for two variables: “lack of clopidogrel therapy at time of ST”, and “cessation of clopidogrel within 14 days before ST”, as a function of three temporal groups representing time of ST from index PCI: < 30 days, 30 days—6 months, > 6 months. The former variable was observed to be a significant predictor of ST for all three temporal groups. The latter variable was introduced by the authors based on their hypothesis that it would reveal the temporal relationship between the discontinuation of clopidogrel and ST in the setting where clopidogrel irreversibly inhibits human platelets throughout their lifespan (10-12 days).

This time-varying covariate was observed to be a significant predictor of ST for the temporal groups of < 30 days (HR: 36.9, 95% CI: 7.9 to 173.3) and 30 days—6months (HR: 21, 95% CI: 2.2 to 198.3), but not for > 6 months from the index PCI. In the latter temporal group, the authors concluded that the number of events were too low to reliably estimate the impact of this time-varying covariate on the event of ST in that timeframe. The authors noted that a significantly higher percentage of patients with ST did not use aspirin at the time of the PCI compared to their matched controls (13.1% vs. 4.5%, $p < 0.0001$). The predominant reason for no aspirin therapy was Coumadin use and aspirin allergy. Multivariate logistic regression analysis identified the absence of aspirin as a strong predictor of ST (HR 1.91, 95% CI 1.01 to 3.88, $p = 0.0052$).

In the Bridge study, 50% of the subjects (53/106) in the clopidogrel arm and 45.5% of the subjects (46/101) in the placebo had a stent deployment. Of these, 67.9% (36/53) of subjects in the cangrelor arm and 56.5% (26/46) in the placebo arm had received a stent > 6 months from planned CABG. The majority of stented subjects in the BRIDGE trial have therefore been placed within the timeframe where there has been no data from the Dutch Stent Thrombosis Registry to demonstrate risk of ST consequent to clopidogrel discontinuation. Therefore, there appears to be risk-stratification mismatch between the BRIDGE population and the ST Registry based on the original authors' time-varying covariate analysis.

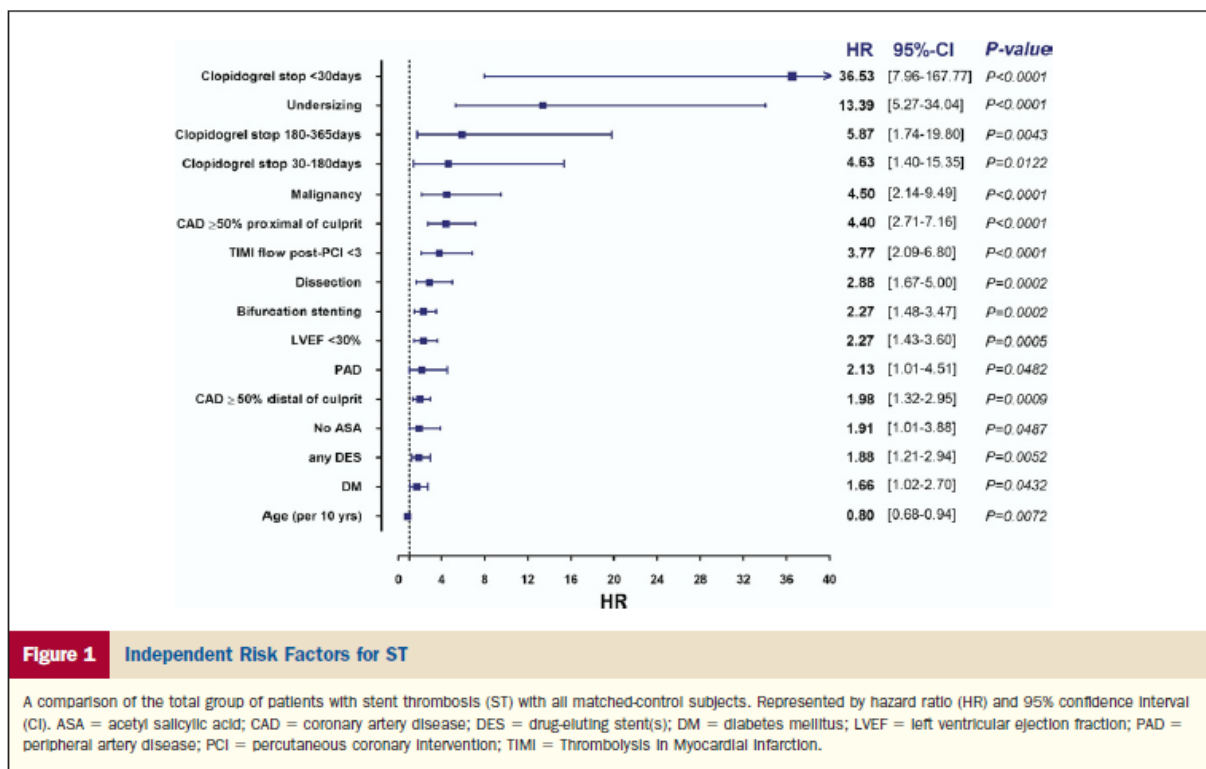
The Applicant reported to have been provided with the original stent thrombosis registry database from which they performed additional analyses not shown in the original publication. This led the Applicant to conclude that the cessation of clopidogrel led to a ST within 7 days independent of the duration of time from the index PCI (see abbreviated CSR of the stent thrombosis registry, section 11.6.5, Figure 11). This contradicts the assessment from the original publication that the number of events beyond the 6-month time frame after stent implantation was too small to reliably assess the impact of "cessation of clopidogrel within 14 days before ST" on the occurrence of ST in this subcategory of patients. The Applicant's analysis appeared to have involved grouping the data into three temporal categories: ≤ 30 days from index PCI; ≤ 180 days from index PCI, and ≤ 365 days from index PCI. Since the majority of patients with ST sustained the ST within 30 days from index PCI (73%), incorporation of these patients into the ≤ 365 day temporal group probably skewed the results toward resembling the data in the ≤ 30 day temporal group. In order to perform an independent analysis, the Applicant was requested to provide the start-stop dates of clopidogrel as well as date of PCI and date of ST from the registry database they were provided. The clopidogrel dates were not available and the Applicant is currently requesting such data at the time of this writing.

In order to confirm the results from the Dutch Stent Registry with another study, the Paris 1-Year (Mehran, R, TCT2012) study was evaluated. This was a multicenter, multinational, observational study designed to determine if discontinuation of dual antiplatelet therapy (DAPT- P2Y₁₂ inhibitor and aspirin) after PCI, secondary to bleeding

or other events (i.e. non-cardiac surgery), led to subsequent ischemic events. The primary efficacy endpoint was MACE (death, TLR, spontaneous MI, and definite/probable ST). The study enrolled 5,033 subjects at 15 centers in 5 countries (France, Germany, Greece, Italy, and the USA). The association between DAPT cessation and non-adherence (defined as interruption-due to need for surgery with DAPT reinstitution within 14 days, or disruption-due to bleeding, including lowering dose) were entered as time-varying covariates. Additional covariates were generated to further assess the impact of DAPT cessation at different time points (0-7 days, 8-30 days and > 30 days). The results showed that DAPT cessation within 1 year was associated with an increase in MACE, strongest in the first 0-7 days from PCI and attenuated at 8-30 days from PCI. Beyond 30 days, the HR subtended unity ($p=0.34$). Increased risk was attributable only to non-adherent subjects, whereas adherent subjects (defined as any subject remaining on DAPT at 1 year or those stopping DAPT due to physician-guided recommendations) did not have an increase in MACE.

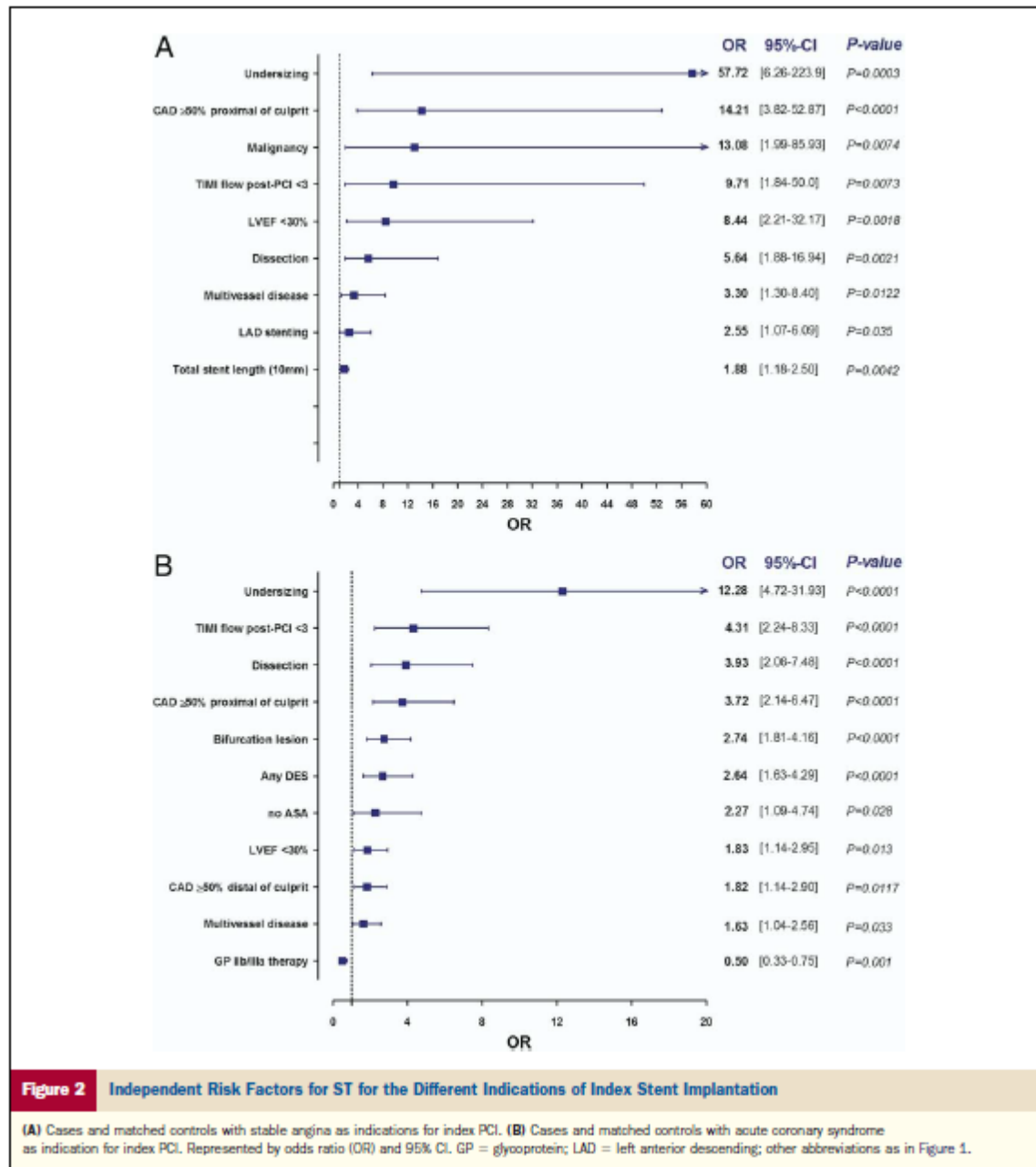
Both the Stent Thrombosis Registry and the PARIS-1Year study were in alignment regarding loss of association between cessation of antiplatelet therapy and MACE beyond 30 days from index PCI (Paris-1 Year) or between cessation clopidogrel therapy and ST within 14 days of cessation 6 months from index PCI. The preponderance of the published data do not support a BRIDGE indication with the population studied in the BRIDGE trial pending validation of the Applicant's analysis of the stent thrombosis registry dataset.

Figure 18. Predictors of Stent Thrombosis derived from Dutch Stent Registry



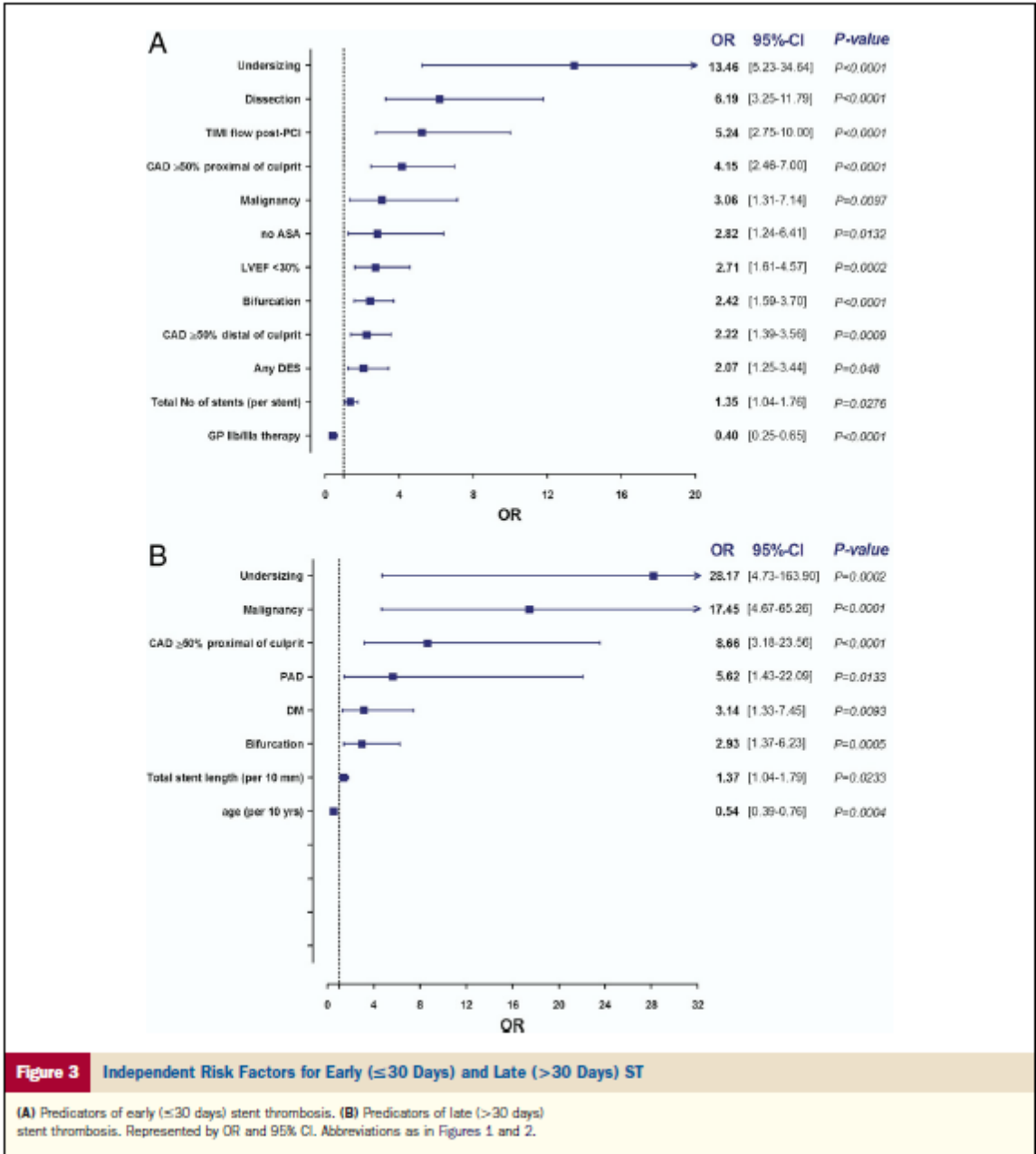
Source: van Werkum, J, et al., 2009, Predictors of Coronary Stent Thrombosis: Dutch Stent Thrombosis Registry, JACC, 53(16):944-954

Figure 19. Independent Risk Factors for ST: A) SA; B) ACS



Source: van Werkum, J, et al., 2009, Predictors of Coronary Stent Thrombosis: Dutch Stent Thrombosis Registry, JACC, 53(16):944-954

Figure 20. Independent Risk Factors for ST: A) Early (≤ 30 days); B) Late (>30 days)



Source: van Werkum, J, et al., 2009, Predictors of Coronary Stent Thrombosis: Dutch Stent Thrombosis Registry, JACC, 53(16):944-954

Table 43: Dutch Stent Thrombosis Registry-distribution of ST over time from index PCI

N (%) of total ST	Type of ST (time from index PCI)	N(%) not on clopidogrel at time of ST	Median Days off clopidogrel at time of ST (interquartile range)
140 (32.1%)	Acute (< 24 h)	9 (6.4%)	Clopidogrel not initiated
179 (41.1%)	Sub-acute (24h-30d)	30 (16.8%)	5 (3-7)
58 (13.3%)	Late (>30d-1 year)	39 (67.2%)	13 (7-61)
59 (13.5%)	Very Late (> 1 year)	58 (94.9%)	200 (23-981)
436 total (100%)	Any	134 (30.7%)	-----

Source: van Werkum, J et al, 2009, Predictors of Coronary Stent Thrombosis, Dutch Stent Thrombosis Registry, JACC, 53:1399-1409). N (%) =number and percent

Table 44: Dutch Stent Thrombosis Registry-influence of clopidogrel on ST

Time from index PCI→	Hazard Ratio, 95% Confidence Interval		
	<30 days	30 days→6 months	>6 months
Lack of clopidogrel therapy at time of ST	36.5, 8.0—167.8	4.6, 1.4—15.3	5.9, 1.7—19.8
Cessation of clopidogrel within 14 days before ST	36.9, 7.9—173.3	21, 2.2—198.3	# events too small to reliably estimate impact of time-varying covariate on ST

Source: van Werkum, J et al, 2009, Predictors of Coronary Stent Thrombosis, Dutch Stent Thrombosis Registry, JACC, 53:1399-1409).

In support of the argument that there is an increased risk of bleeding and mortality after surgery when oral P2Y₁₂ receptor inhibitor therapy is continued during the operative period, the Applicant referred to two meta-analyses (Biancari, F, et al., 2012; Nijjer, S, et al., 2011) and a systematic literature review (Au, A, et al., 2012).

Biancari, F, et al. (2012) performed a meta-analysis of studies evaluating the use of clopidogrel before CABG, taken from the Cochrane Handbook for Systematic Reviews. This yielded 3 prospective randomized trials (i.e. CLARITY, CREDO, and CAPRIE) and 17 observational studies. A meta-analysis of post-hoc studies from the 3 prospective

randomized trials showed a non-significant reduced risk of the 30-day post-operative composite endpoint of death, MI, or stroke in the clopidogrel group vs. control (RR 0.77, 95% CI [0.58, 1.04]). Data from the CREDO and CLARITY trials showed a reduction in the risk of death (RR 0.81, 95% CI [0.20, 3.37]) and MI (RR 0.58, 95% CI [0.25, 1.33]), and an increase in the risk of TIMI Major Bleed (RR 1.48, 95% CI [0.72, 3.04]) for clopidogrel vs. control. In contrast, meta-analysis of the observational studies showed that pre-operative exposure to clopidogrel, compared to control, was associated with an increased risk of death (RR 1.30, 95% CI [1.02, 1.67]), re-operation for bleeding (RR 1.88, 95% CI [1.37, 2.58]), blood loss (mean difference 157.8 ml, 95% CI [61.9, 253.6]), and need for packed red blood cells (RR 1.23, 95% CI [1.10, 1.37]). However, consistent with CREDO and CLARITY, the meta-analysis of observational studies showed a significantly reduced risk of post-operative MI among patients taking clopidogrel (RR 0.63, 95% CI [0.48, 0.82]). Based on the preponderance of the data from the Biancari study, there was a conflict between the meta-analysis of data from randomized trials, which supported the benefit of pre-operative clopidogrel in the post-operative setting, and the meta-analysis of data from observation studies, which detracted from the benefit of pre-operative clopidogrel in the post-operative setting. Both meta-analyses pointed to an increased risk of post-operative bleeding and a decreased risk of post-operative MI. The increased risk of bleeding resulted in an empirical net blood volume loss of 158 ml. The risk-benefit profile of continued clopidogrel therapy based on the Biancari review showing conflicting data did not support the Applicant's unequivocal position that maintaining clopidogrel therapy during surgery was overwhelmingly harmful necessitating a new treatment paradigm.

Nijjer, S, et al. (2011) performed a meta-analysis of 22,584 patients from 34 studies evaluating the risk of CABG in ACS patients while continuing clopidogrel during the 5-7 days prior to CABG. The authors have opined that the studies were "small, non-randomized, retrospective limited subgroup analyses from RCTs". Furthermore, the bleeding and transfusion data were "heterogeneous and with potential for treatment and ascertainment bias". The authors reported that only 4 of the 34 reviewed studies were RCTs that met the criteria for freedom from bias. The remainder of the studies scored poorly on the bias analysis. Although mortality was increased in those patients with a recent exposure to clopidogrel compared to those who were not recently exposed (OR 1.6, 95% CI [1.30, 1.96], $p < 0.00001$), it was influenced by ACS status and urgency for surgery when reviewing studies whose ACS patient population exceeded 50% of the total population. Ironically, in studies which recruited only ACS patients, there was no significant difference in mortality (OR 1.44, 95% CI [0.97, 2.1], $p = 0.07$), in postoperative MI (OR 0.57, 95% CI [0.31, 1.07], $p = 0.08$), and in stroke (OR 1.23, 95% CI [0.66, 2.29], $p = 0.52$). Combined MACE (i.e. stroke, MI, death) were not different between the recent-exposure to clopidogrel group vs. the not-recent-exposure to clopidogrel group (OR 1.10, 95% CI [0.87, 1.41], $p = 0.43$). Although re-operation rates were elevated in the recent-exposure to clopidogrel group, such rates were reduced over time and not different from the not-recent-exposure to clopidogrel group in ACS patients (OR 1.5, 95% CI [0.88, 2.54], $p = 0.13$). The authors have concluded that

“many patients have undergone CABG safely with recent clopidogrel exposure and this practice can continue in expert hands in ACS patients who need to continue clopidogrel”.

Au, A, et al. (2012) systematically reviewed 37 studies involving clopidogrel (31 cardiac and 6 non cardiac where 3 were RCTs and 34 were observational studies) in order to address the hypothesis that pre-operative thienopyridine administration influences postoperative outcome up to 30 days post-surgery. The authors reported that exposure to clopidogrel in the 5 days preceding surgery (compared to no exposure) was not associated with a reduction in postoperative MI (23 studies, 12,872 patients, 3.4% vs. 3.0%, OR 0.98, 95% CI [0.72, 1.34]). However, exposure to clopidogrel vs. no exposure in the 5 days preceding surgery was associated with increased risks of stroke (16 studies, 10,265 patients, 1.9% vs. 1.4%, OR 1.54, 95% CI [1.08, 2.20]), reoperation for bleeding (32 studies, 19,423 patients, 4.3% vs. 1.8%, OR 2.62, 95% CI [1.96, 3.49]), and all-cause mortality (28 studies, 22,990 patients, 3.7% vs. 2.6%, OR 1.38, 95% CI [1.13, 1.69]). The authors concluded that the data supported withholding thienopyridine therapy 5 days before cardiac surgery. There was insufficient evidence to make a definitive recommendation for elective non-cardiac surgery although the direction and magnitude of the associations were similar.

The preponderance of the evidence from published literature was based on 1) a registry with author-recognized liabilities, and 2) meta-analyses which included post-hoc data from retrospective subgroup analyses of randomized trials and from small underpowered non-randomized observational studies. The authors of these meta-analyses recognized the liabilities of these analyzes. The summarizing conclusions based on the published data were:

- Cessation of clopidogrel within the first 6 months following stent deployment, especially in the absence of aspirin, significantly raised the risk of ST within 14 days of clopidogrel termination. However, there was insufficient data, based on the authors' comments, to draw this conclusion beyond 6 months.
- The effect of pre-CABG maintenance of clopidogrel treatment on post-operative complications was not clear. However, there was a consistent trend in reduction of post-op MI and an increase in post-op bleeding.
- The current practice of withholding clopidogrel for 5 days prior to CABG was supported by systematic review of published data.
- Recent clopidogrel exposure prior to CABG in ACS patients was safe and can continue.

The Applicant's position that a treatment dilemma exists in patients requiring surgery (i.e. thrombotic events if P2Y₁₂ inhibitors are discontinued; and bleeding events with increased morbidity and mortality if P2Y₁₂ inhibitors are continued) was not unequivocally supported by the preponderance of the evidence.

Given that the PHOENIX trial's carefully crafted primary endpoint was met in favor of cangrelor vs. clopidogrel with a dose 5.3-fold that which was studied in Bridge and in a different population, it is reasonable to assume that the PRU data from BRIDGE portends efficacy in the BRIDGE population. However, a clinical evaluation of the benefit/risk in the BRIDGE setting was attenuated by the conflicting published data on the relationship between PD and outcome, data paucity in the CABG population where a stent was placed greater than 6 months from the planned CABG, conflicting data on the risk of maintaining P2Y₁₂ inhibitor treatment during the peri-CABG period, and lack of clinical data from the Applicant on cangrelor to support their separate BRIDGE indication. It is therefore challenging to recommend a BRIDGE indication based solely on the Applicant's PD data. It is reasonable to describe the BRIDGE trial in section 12.2 of the label in lieu of an indication.

7 Review of Safety

Safety Summary

Cangrelor is a P2Y₁₂ inhibitor that has been studied in active controlled trials primarily at a dosing regimen of 30 ug/kg bolus followed by a continuous infusion of 2 ug/kg/min for ~ 2 hours during PCI. A total of 12,565 subjects received a dose of cangrelor in the CHAMPION trials (n=5529 in CHAMPION PHOENIX). The BRIDGE trial provides the longest duration of data (~72 hours), albeit at ~¼ the usual dose (n=117 subjects treated with cangrelor) in subjects who underwent cardiac surgery.

The demographics of subjects in the Integrated Summary of Safety (ISS) were balanced between cangrelor and control. In the cangrelor arm the mean age was 63 years, 75% were male, and 86% were White. (See also [Figure 22-24](#))

The safety review focused on the PHOENIX trial. In the PHOENIX trial the primary safety endpoint (not adjudicated) was the incidence of non-CABG GUSTO severe bleed at 48 hours after randomization. The number of subjects with GUSTO severe bleed was small, but numerically greater in cangrelor treated subjects (10, 0.2%) compared to clopidogrel treated subjects (6, 0.1%). The difference was not significant [RR, 95% CI: 1.64 (0.60, 4.52)].

The reviewer and the Applicant classified bleeds (by CABG and non-CABG related) as GUSTO, TIMI, ACUITY, and BARC. In PHOENIX the incidence of total non-CABG related bleed was ~42% greater in cangrelor treated subjects (857/5529, 15.5%) compared to clopidogrel treated subjects (601/5527, 10.9%), [RR 1.42 (1.29, 1.56)]. There were very few CABG related bleeds (4, cangrelor and 3, clopidogrel). The incidence of non-CABG GUSTO severe, GUSTO moderate, and TIMI major bleeds was low, and there was not a significant difference between treatment arms. Generally, the risk of bleeding was significantly greater on cangrelor for the "lesser" bleeds, i.e.,

GUSTO mild, ACUITY major (which was largely classified as such because of hematomas). However, these bleeds are unlikely to have detrimental clinical consequences/sequelae.

In attempts to find subjects with clinically bad bleeds, the reviewer categorized a “bad bleed” as any of the following: ICH, transfused, cardiac tamponade, reoperation for bleeding, surgical intervention, retroperitoneal, requiring or extending hospitalization. In PHOENIX there were 61 (1.1%) bad bleeds in the cangrelor arm and 41 (0.7%) in the clopidogrel arm. The risk of bad bleed was nearly significant [RR, 95% CI, 1.46 (0.99, 2.17)].

According to the death CRF, there were no fatal bleeds in PHOENIX. However, there were four subjects who had a bleed and died within 48 hours of drug initiation. All four subjects received cangrelor.

From the BRIDGE trial, the incidence of excessive CABG related bleeding was balanced between cangrelor (11.8%) and placebo (10.4%), suggesting that cangrelor can be safely used in the CABG setting.

The incidence of transfusion was another safety endpoint in PHOENIX. More subjects treated with cangrelor (25) than clopidogrel (17) received a transfusion, but the difference was not significant.

A total of 88 (1.6%) subjects treated with cangrelor and 66 (1.2%) subjects treated with clopidogrel had nonfatal SAEs in PHOENIX. These were generally balanced (by %) between arms because the number of subjects with events was low.

Adverse events of interest included dyspnea, renal function effects, and hypersensitivity. Dyspnea was a common adverse event that occurred at greater frequency than control (1.2% in cangrelor treated subjects vs. 0.3% in clopidogrel treated subjects in PHOENIX). Dyspnea was also a common reason for cangrelor discontinuation in the CHAMPION trials. The overall incidence of dyspnea in the ISS was low, 1.3% in cangrelor treated subjects compared to 0.4% of control subjects. There was not a clear safety signal with respect to acute renal failure or rise in serum creatinine in the ISS, despite evidence of renal toxicity from pre-clinical studies. CHAMPION-PCI had a greater numerical increase in renal adverse events as renal function declined in the cangrelor arm compared to clopidogrel, but CHAMPION-PLATFORM did not. Hypersensitivity was balanced between cangrelor (0.7%) and control (0.6%) in the ISS, however SAEs were greater in cangrelor treated subjects compared to control (7 vs. 2).

In sum, the most important safety finding is the risk of bleeding. The incidence of a “severe” bleed was low (< 1%) in both treatment arms. Although bleeds were generally numerically higher in the cangrelor arm compared to clopidogrel, the difference was

only significant for the “lesser” severity bleeds (e.g., GUSTO mild). These types of bleeds are less likely to have sequelae/clinical consequences. The PHOENIX data and the BRIDGE data suggest that cangrelor can be safely used in the PCI and CABG setting.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The reviewer focused on the safety data in PHOENIX since the single trial was substantive to support safety. Any discussions that are not of the PHOENIX trial are explicitly stated. The ISS (includes CHAMPION PCI, CHAMPION PLATFORM, and BRIDGE among the trials) was used for analyses of AEs, SAEs and laboratory findings. See [Table 2 and Table 3](#) in section 5.1 for a description of the 16 trials found in the Integrated Summary of Safety (ISS).

In PHOENIX the last patient completed the trial on 14 November 2012. The database was initially locked on 04 January 2013. Shortly afterwards it was noted that some subjects did not receive an anticoagulant prior to or during the PCI procedure. The Applicant thought that this was due to confusion in collecting these data on the eCRF. The database was unlocked on 01 February 2013 to confirm whether any procedural anticoagulant was administered to subjects in whom no data were entered in the eCRF and to edit the data if necessary. A total of 553 subjects from 84 sites were affected. In addition, a date error was fixed for an MI adjudicated result for one subject. Site investigators reviewed chart information and returned the affected eCRF page. The database was re-locked on 18 February 2013.

7.1.2 Categorization of Adverse Events and Bleeding

in [Section 5.3.4.6 Safety Endpoints and Definitions](#) defines the various bleed classifications reported in the Applicant’s CSR for all three CHAMPION trials. Bleeding was not an adjudicated endpoint in PHOENIX. In PHOENIX, the Applicant classified bleeding based on the checked fields on the bleed eCRF.

Reviewer comment: The bleed CRF was generally well designed to collect the components of the various bleeding classifications. However, it was difficult to determine how uniformly investigators completed subjective fields. Some subjective items such as “hemodynamic compromise” were not checked for what might have been a bleed causing hemodynamic compromise. The reviewer did not reclassify subjective fields.

The reviewer used the bleed CRF (including text fields in the CRF) as well as the serious adverse event CRF⁸, narratives and ISS laboratory dataset to identify and classify subjects that bled. For the reviewer's analysis, within a major classification of bleeding, the sub-classifications were mutually exclusive. **Table 45** highlights differences between the bleed definitions and how the Applicant and reviewer classified bleeds.

Table 45. Differences between bleed definitions/what was used for classification

Term	What was used for classification
Clinically overt or overt bleeding	The reviewer defined this as any sign of bleeding (including bleeding seen on imaging). This differs from the Applicant's definition which attempted to assign a severity (see Table 4). This likely affected the counts for TIMI, ACUITY, and BARC.
Drop in hemoglobin or hematocrit	The reviewer noted that this field was sometimes incorrectly marked or not marked on the eCRF, so the reviewer used the ISS lab dataset to obtain the adjusted Hg data for all definitions (TIMI, ACUITY, and BARC) that included a drop in hemoglobin. The Applicant used the field as marked in the eCRF.
BARC	Part of the definition includes a Hg drop of < 5 g/dL and ≥ 5 g/dL. The reviewer and the Applicant used ≤ 5 g/dL and > 5 g/dL.
Intervention	If the investigator took action to stop the bleed, then the reviewer marked it as an intervention. This might have contributed to differences between the reviewer's and Applicant's BARC3b and ACUITY major.
GUSTO mild	The reviewer classified all bleeds that were not GUSTO severe or moderate as mild. The Applicant required that at least one of the following on the CRF also be marked: requiring intervention... leading to hospitalization... prompting evaluation... access site bleeding...

Adverse events for any pooled analyses were coded using MedDRA version 13.1.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The Applicant pooled the data into six different sets: all studies, patient studies, controlled studies, placebo-controlled studies, active controlled studies, and CHAMPION trials. From a safety perspective, this approach was reasonable. In general, analyzing all three CHAMPION trials together is sensible since they all used the same dosing scheme in the setting of subjects that required PCI.

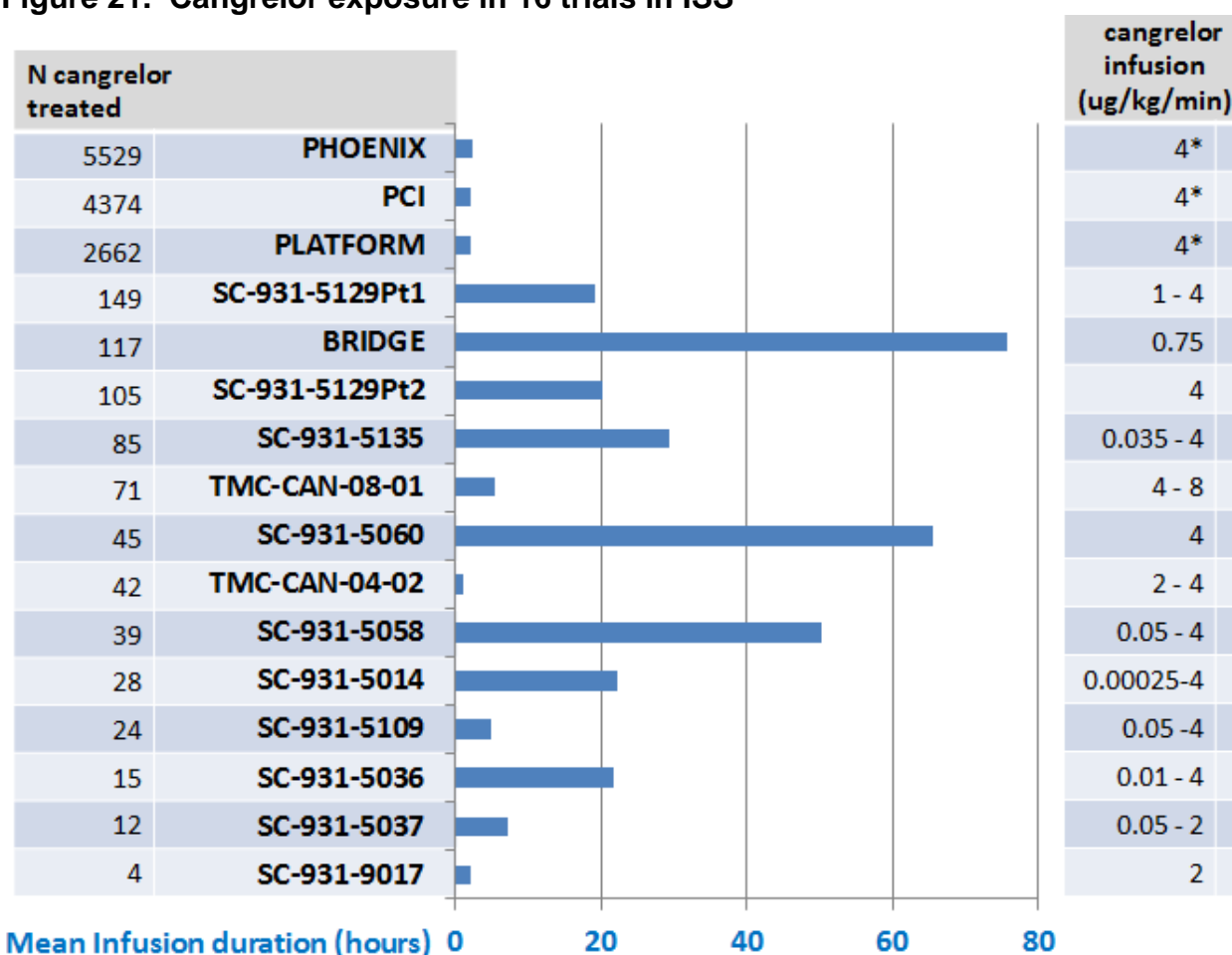
⁸ Bleeding was supposed to be captured on the bleed CRF, however the reviewer found a subject treated with cangrelor who had cardiac tamponade (reported as an SAE) and died. The event was not recorded on a bleed CRF.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The majority of the exposure data are found in the CHAMPION trials ([Figure 21](#)). In all three CHAMPION trials, subjects randomized to cangrelor received a 30 ug/kg/min IV bolus followed by a continuous infusion of 4 ug/kg/min. The mean infusion duration in each CHAMPION trial was 2.2 hours.⁹

Figure 21. Cangrelor exposure in 16 trials in ISS



*infusion preceded by bolus

Infusion duration excludes temporary interruptions. Reviewer's analysis \exposure\infdose. Dataset iss\isd

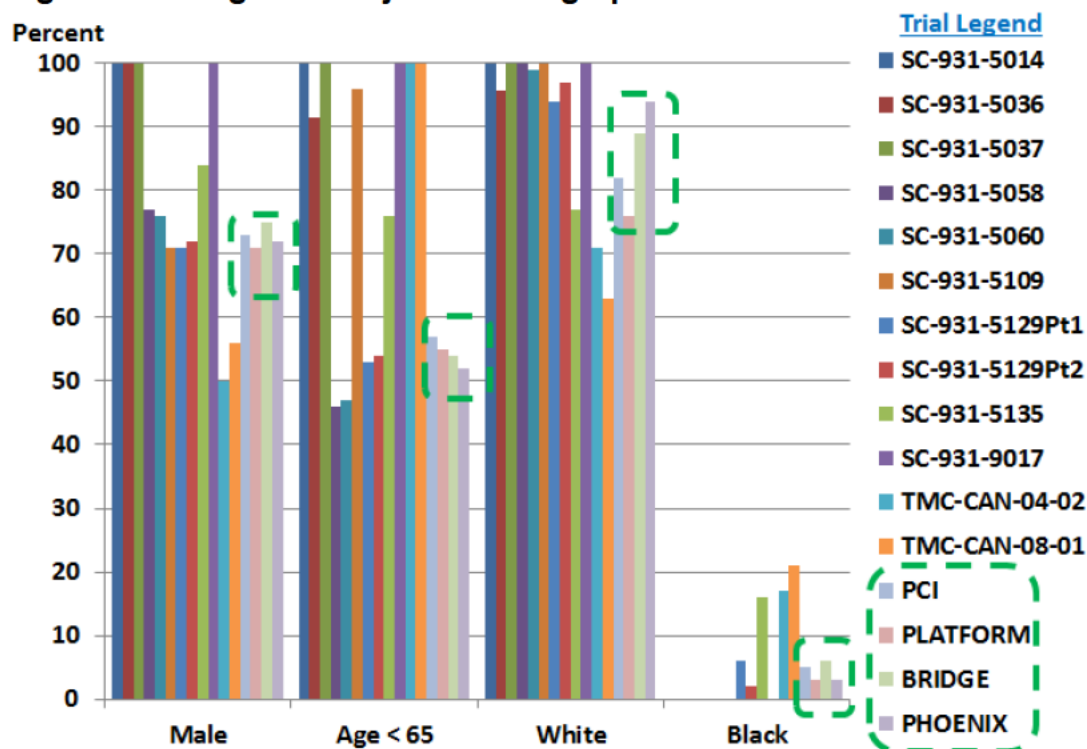
The demographics were balanced between cangrelor and active control or placebo.

[Figure 22](#) shows the demographics for subjects treated with cangrelor in the ISS.

There were a low percentage of treated Black subjects.

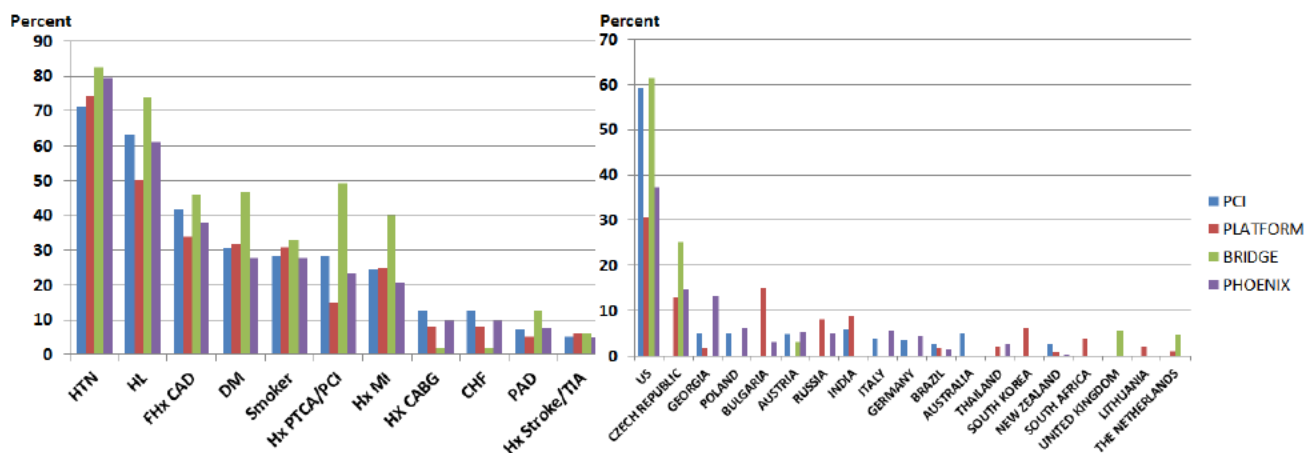
⁹ Infusion time excludes interruptions. Reviewer's analysis: exposure\study exp. Dataset: ISS\isd

Figure 22. Cangrelor subjects' demographics in trials in ISS



Reviewer's analysis: \disp\disp_dem. Dataset iss\disp

Figure 23 Medical history of treated subjects **Figure 24. Country of treated subjects**



Reviewer's analysis: \disp\disp_dem. Dataset iss\disp

Patient demographics were well balanced between arms in the CHAMPION trials also. The mean age was 63 years, 72% of subjects were male, 86% were White, 8% were Asian, and 3% were Black. See also [Table 46](#).

Table 46. CHAMPION trials: Age and patient type

	CHAMPION (N=25,107)	
	Cangrelor N=12565	Clopidogrel N=12542
Treated	(%)	(%)
Age (years)	15.6	10.9
< 55	23.5	24.0
55 to < 65	30.8	30.8
65 to < 75	28.7	28.3
≥ 75	17.0	16.9
Derived patient type		
STEMI	11.7	12.3
NSTEMI [†]	88.3	87.7

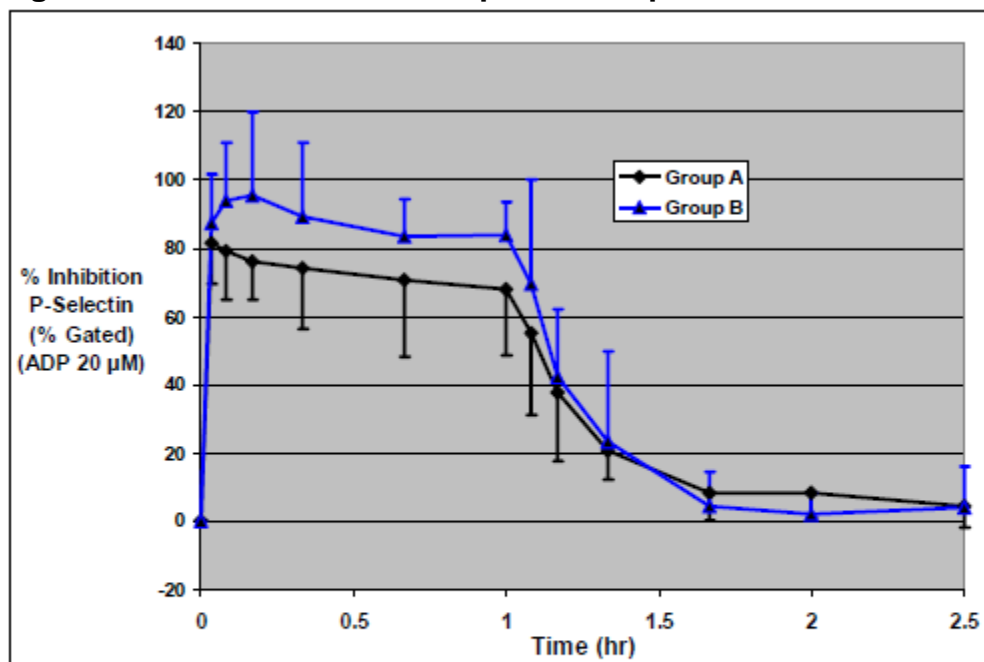
† CAD patients with SA, UA, or NSTEMI
Source: SCS, Table 5.

7.2.2 Explorations for Dose Response

See [Figure 21](#) for dose and duration information. The Applicant evaluated various dosing regimens (infusion alone, bolus followed by an infusion). The Clinical Pharmacology Reviewers concluded that after the start of cangrelor infusion, complete platelet inhibition is achieved in about ~30 minutes. To eliminate this delay the Applicant explored a bolus followed by infusion regimen. The reviewers estimate that a bolus of only ~4.4 fold higher than the target infusion rate of 4 ug/kg/min is needed to achieve platelet inhibition. Thus the 30 ug/kg bolus dose is more than necessary. However, the dose should equilibrate quickly, given its effective half-life of 3-6 minutes.

The Applicant compared 15 mg/kg bolus followed by 2 ug/kg/min to 30 mg/kg bolus followed by 4 ug/kg/min and found that greater inhibition was maintained with the higher continuous infusion ([Figure 25](#)). Thus, a 30 ug/kg bolus followed by 4 ug/kg/min was selected as the dose to carry forward into Phase 3.

Figure 25. Percent inhibition of platelet response



ADP = adenosine diphosphate

Group A: Cangrelor 15 µg/kg IV bolus + 2 µg/kg/min x 1 hour

Group B: Cangrelor 30 µg/kg IV bolus + 4 µg/kg/min x 1 hour

Data presented are mean ± standard deviation

Source: Section 14.3.2, Figure 3

Source: TMC-CAN-04-02, CSR Figure 6

7.2.3 Special Animal and/or In Vitro Testing

According to the finalized Pharmacology/toxicology review the nonclinical testing was adequate to assess the safety of cangrelor.

7.2.4 Routine Clinical Testing

Assessments for safety and adverse events in PHOENIX were limited to 48 hours after the start of the infusion. The mean duration of infusion was 2.2 hours. Based on pharmacokinetics, this was a reasonable duration to collect information. PHOENIX only collected hematocrit, hemoglobin, platelets. Serum creatinine, liver, WBC laboratory data are in CHAMPION PCI, PLATFORM, and BRIDGE.

7.2.5 Metabolic, Clearance, and Interaction Workup

In vitro studies indicate that cangrelor and its metabolite have minimal potential to inhibit or induce CYP enzymes at therapeutic concentrations. The PK of cangrelor and its

metabolite did not alter significantly when co-administered with a combination of aspirin, heparin, and glyceryl trinitrate. See also [4.4.3 Pharmacokinetics](#).

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The Applicant's assessment for adverse events in PHOENIX was generally adequate. See [Section 7.2.4](#). If the investigator was notified of an SAE occurring after 48 hours from randomization and the investigator suspected it to be causally related to study drug, then the event was to be recorded. At the 30 day follow-up contact, only efficacy endpoints were assessed (MI, ischemic symptoms, angiographies, revascularization and death). Non-clinical data showed a reversible effect on renal function, yet PHOENIX did not report serum creatinine values. However, these data were available for CHAMPION PCI, PLATFORM, and BRIDGE (See Section 7.4.2. Laboratory Findings).

7.3 Major Safety Results

7.3.1 Deaths

Since death was an efficacy endpoint, refer to Section 6, review of efficacy for more information.

Based on the death CRF, there were no fatal bleeds in PHOENIX. This information was not collected on the bleed CRF. However, there were four subjects who had a bleed and died within 48 hours of drug initiation. All four subjects received cangrelor.

Subject 401029051 (cangrelor, stable angina) had cardiac tamponade (reported as an SAE, not in the bleed CRF) and died ~ 1 hour after the start of PCI.¹⁰

Subject 407005141 (cangrelor, STEMI) had cardiac tamponade and died ~1 hour after the start of PCI.

Subject 401012052 (cangrelor, STEMI) had PCI without complications, but was noted to have a GI bleed (coffee ground emesis) at some time after the PCI. She had a cardiac arrest and died ~ 23 hours after the last dose of study drug.

Subject 466001077 (cangrelor, STEMI) had PCI without complications. She had a GI bleed (gross hematuria) ~ 2.5 hours after the start of study drug. Approximately

¹⁰ Subject 401029051 was not counted in the Applicant's report of subjects with bleed since no bleed CRF was filled out for him. The reviewer counted this subject as a nonCABG GUSTO severe bleed, TIMI major and BARC 3b. Only baseline Hg/Hct were available for him.

~26 hours after the last dose of study drug she experienced a cardiac arrest, subsequent acute renal failure and died shortly thereafter.

Two more subjects identified through the reviewer's search of text fields in the bleed CRF and SAE CRF had bad bleeds and died after 48 hours.

Subject 407005033 (cangrelor, STEMI) experienced cardiogenic shock 15 minutes after the end of the infusion. She had a retroperitoneal bleed and died 4 days after the start of study drug.

Subject 401009010 (clopidogrel, stable angina) had a GUSTO severe bleed (hemodynamic compromise) ~ 2 hours after the start of PCI. He died approximately 7 weeks after surgery, however his cause of death was adjudicated as cardiovascular and a peri-procedural PCI MI was noted in a comment field.

Table 47 shows that deaths overall were balanced between arms in PHOENIX. So while there were numerically more deaths in subjects that bled on cangrelor, the numbers are too small to make definitive conclusions regarding the risk of death from bleeds caused by cangrelor.

Table 47. Deaths within 48 hours, by preferred terms (PHOENIX safety population)

Preferred Term	Number (%) of patients	
	Cangrelor (N=5529)	Clopidogrel (N=5527)
Any deaths within 48 hours	18 (0.3)	20 (0.4)
Cardiogenic shock	4 (0.1)	2 (0.0)
Acute myocardial infarction	3 (0.1)	2 (0.0)
Thrombosis in device	3 (0.1)	3 (0.1)
Myocardial infarction	2 (0.0)	0 (0.0)
Cardiac arrest	1 (0.0)	2 (0.0)
Cardiac failure	1 (0.0)	1 (0.0)
Coronary artery dissection	1 (0.0)	0 (0.0)
Renal failure acute	1 (0.0)	0 (0.0)
Aortic dissection	1 (0.0)	0 (0.0)
Aspiration	1 (0.0)	0 (0.0)
Cardiac failure congestive	0 (0.0)	1 (0.0)
Coronary artery disease	0 (0.0)	1 (0.0)
Coronary artery occlusion	0 (0.0)	2 (0.0)
Myocardial rupture	0 (0.0)	3 (0.1)
Pulmonary oedema	0 (0.0)	1 (0.0)
Ventricular asystole	0 (0.0)	1 (0.0)
Ventricular fibrillation	0 (0.0)	1 (0.0)

Source: [Section 14.1, Table 8.9.4.1.](#)

PHOENIX CSR, Table 48

In the total pooled ISS dataset fatal bleeding was also balanced between arms. Although the numbers are small, there were numerically more bleed related deaths in the nervous system disorder SOC in the cangrelor arm compared to control (4 vs. 1).

Table 48. Summary of fatal bleeding related deaths by dosing start, ISS

System Organ Class/Preferred Term	Bleeding-Related Deaths within 30 Days from Dosing Start		Bleeding-Related Deaths after 30 Days from Dosing Start	
	Cangrelor (N=13301) n (%)	Control (N=12861) n (%)	Cangrelor (N=13301) n (%)	Control (N=12861) n (%)
Patients died	8 (0.1)	9 (0.1)	5 (0.0)	6 (0.0)
Cardiac disorders	3 (0.0)	4 (0.0)	2 (0.0)	0 (0.0)
Cardiac tamponade	1 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Myocardial rupture	1 (0.0)	4 (0.0)	1 (0.0)	0 (0.0)
Ventricle rupture	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	1 (0.0)	2 (0.0)	1 (0.0)	1 (0.0)
Gastrointestinal haemorrhage	0 (0.0)	2 (0.0)	1 (0.0)	1 (0.0)
Retroperitoneal haemorrhage	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Injury, poisoning and procedural complications	0 (0.0)	0 (0.0)	1 (0.0)	1 (0.0)
Subdural haematoma	0 (0.0)	0 (0.0)	1 (0.0)	1 (0.0)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)
Tumour haemorrhage	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)
Nervous system disorders	4 (0.0)	1 (0.0)	1 (0.0)	3 (0.0)
Cerebral haemorrhage	1 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Haemorrhage intracranial	2 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Haemorrhagic stroke	1 (0.0)	1 (0.0)	0 (0.0)	2 (0.0)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Pulmonary alveolar haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Vascular disorders	0 (0.0)	11 (0.0)	0 (0.0)	0 (0.0)
Shock haemorrhagic	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)

Source: Section 2.7.4.8.2, Table 11.6.23.4.1 and Table 11.6.23.4.2.

Note: Zero percentages associated with non-zero patient numbers are due to rounding.

AE = adverse event; SOC = system organ class.

Applicant's SCS, Table 34

7.3.2 Nonfatal Serious Adverse Events

There were a total of 88 (1.6%) subjects treated with cangrelor and 66 (1.2%) subjects treated with clopidogrel with nonfatal SAEs. [Table 49](#) shows the SOC for these subjects and lists the Preferred Terms where the relative risk was greater than 5. In general the number of subjects with events is too low to make any decisive conclusions that there are greater SAEs with cangrelor than clopidogrel. However it should be noted that there were anaphylactic reaction and anaphylactic shock reported in three subjects

treated with cangrelor (none in clopidogrel). Two subjects on clopidogrel had “hypersensitivity” SAEs.

Table 49. Nonfatal SAE occurring in more cangrelor subjects than clopidogrel

SOC Preferred Term	Cangrelor		Clopidogrel	
	N=5529	(%)	N=5527	(%)
Cardiac disorders	44	(0.8)	36	(0.7)
Cardiogenic shock	12	(0.2)	6	(0.1)
Coronary artery dissection	9	(0.2)	6	(0.1)
Interventricular septum rupture	2	(0.0)	0	(0.0)
Respiratory, thoracic, mediastinal disorders	11	(0.2)	2	(0.0)
Respiratory failure	2	(0.0)	0	(0.0)
Pulmonary embolism	2	(0.0)	0	(0.0)
Vascular disorders	9	(0.2)	5	(0.1)
Renal and urinary disorders	6	(0.1)	5	(0.1)
General disorders and administration site	4	(0.1)	2	(0.0)
Immune system disorders	3	(0.0)	2	(0.0)
Anaphylactic reaction	2	(0.0)	0	(0.0)
Infections and manifestations	3	(0.0)	2	(0.0)

Shown are subjects with nonfatal SAE SOC's occurring with greater number in the cangrelor arm compared to clopidogrel. Note that SOC terms do not include fatal SAEs, but the PT might. Reviewer's analysis saelsae create. Dataset SDTMAE.

Reviewer's comment: Analyses including subjects whose SAE result in death produces similar numbers to the SAE tables in the Applicant's PHOENIX report. The general conclusions are the same.

7.3.3 Dropouts and/or Discontinuations

Table 10 shows the subject disposition in PHOENIX. Only one subject (cangrelor) is reported to have discontinued the study because of an AE. [Error! Reference source not found.](#) shows subjects who were reported to have discontinued treatment because of an AE. Although the numbers are greater in the cangrelor arm, the numbers are too small to show a difference between cangrelor and clopidogrel for any SOC. Of note are the 4 subjects with dyspnea that discontinued cangrelor.

Table 50. Subjects that discontinued treatment because of an AE: PHOENIX

SOC	Cangrelor		Clopidogrel	
	N=5529	(%)	N=5527	(%)
Subjects that discontinued treatment	31	(0.6)	21	(0.4)
Cardiac disorders	18	(0.3)	15	(0.3)
Respiratory and thoracic disorders (PT: Dyspnea)	4	(0.1)	0	(0.0)
Gastrointestinal disorders	3	(0.1)	0	(0.0)
Nervous system disorders	2	(0.0)	1	(0.0)
Eye disorders	1	(0.0)	0	(0.0)
Psychiatric disorders	1	(0.0)	0	(0.0)
Skin and subcutaneous tissue disorders	1	(0.0)	0	(0.0)
General disorders and administration site conditions	1	(0.0)	1	(0.0)
Immune system disorders	2	(0.0)	2	(0.0)
Vascular disorders	3	(0.1)	5	(0.1)

Reviewer's analysis ae\aedc. Dataset analysis\ae

The AEs leading to discontinuation in the CHAMPION studies is similar to PHOENIX. **Table 51.** Dyspnea was a common reason for cangrelor discontinuation.

Table 51. AEs leading to discontinuation in CHAMPION trials

Preferred Term (≥ 2 events)	Cangrelor (N=13301) n (%)	Control (N=12861) n (%)
Coronary artery perforation	14 (0.1)	7 (0.1)
Coronary artery dissection	12 (0.1)	9 (0.1)
Dyspnoea	10 (0.1)	1 (0.0)
Hypotension	8 (0.1)	8 (0.1)

Source: SCS, Table 41. Only frequency of ≥ 0.1% shown

7.3.4 Significant Adverse Events/Adverse Events of Special Interest

7.3.4.1 Dyspnea

In the summary of clinical safety, the Applicant reports that the overall incidence of dyspnea was low, but consistent with cangrelor pharmacology the incidence was greater in the cangrelor arm (179/13301, 1.3%) compared to control (54/12861, 0.4%). Most reports were of just “dyspnea”; dyspnea exertional was reported in 8 subjects on cangrelor and 2 subjects on control. The majority of cases were nonserious (98%); only 3 cases were severe and none led to death. The median time of onset was 2

hours. Of subjects that discontinued cangrelor, 10/179 did so because of dyspnea in the ISS.

7.3.4.2 Renal function effects

Following the adverse renal and urinary findings in rat and dog pharmacology/toxicology studies, the Applicant increased monitoring for renal/urinary effects in Study SC-931-5060 (cangrelor dose 4 ug/kg/min or placebo for 72 hours in 94 subjects), but found no effect on renal function, urinary parameters, blood urea, serum creatinine levels, urine dipstick, urine cytology and SDS-PAGE.

The Applicant's Acute renal failure SMQ of the ISS showed a low frequency and similar pattern of AE between cangrelor and control, however there were numerically higher events in the cangrelor arm compared to control ([Table 56](#)).

Table 52. Summary of renal AEs of interest by SOC and PT in ISS

SMQ or System Organ Class	Preferred Term	Cangrelor (N=13301) n (%)	Control (N=12861) n (%)
Renal Function Effect (SMQ)		93 (0.7)	64 (0.5)
Investigations	Blood creatinine increased	30 (0.2)	14 (0.1)
	Urine output decreased	5 (0.0)	5 (0.0)
	Blood urea increased	4 (0.0)	2 (0.0)
	Protein urine present	2 (0.0)	1 (0.0)
	Glomerular filtration rate decreased	1 (0.0)	0 (0.0)
Renal and urinary disorders	Renal failure acute	19 (0.1)	16 (0.1)
	Proteinuria	12 (0.1)	9 (0.1)
	Renal failure	15 (0.1)	7 (0.1)
	Nephropathy toxic	4 (0.0)	5 (0.0)
	Renal impairment	2 (0.0)	4 (0.0)
	Oliguria	3 (0.0)	3 (0.0)
	Renal tubular necrosis	0 (0.0)	1 (0.0)
	Anuria	1 (0.0)	0 (0.0)
	Azotaemia	2 (0.0)	0 (0.0)

Source: 2.7.4.8.2, [Table 11.6.24.4.1](#).

Note: Zero percentages associated with non-zero patient numbers are due to rounding.

AE = adverse event; SOC = system organ class; SMQ = standardized MedDRA query.

Source: Applicant's SCS, Table 25, PT=preferred term

The Applicant also examined adverse events by baseline glomerular filtration rate (GFR) in CHAMPION PCI ([Table 53](#)) and CHAMPION-PLATFORM ([Table 54](#)). CHAMPION-PCI had a greater numerical increase in renal adverse events as renal function declined in the cangrelor arm compared to clopidogrel, but CHAMPION-PLATFORM did not.

Table 53. Adverse events of SMQ by baseline renal function in CHAMPION PCI

Preferred term	Baseline Glomerular Filtration Rate							
	Severe (<30 mL/min/1.73 m ²)		Moderate (30 - <60 mL/min/1.73 m ²)		Mild (60 - 90 mL/min/1.73 m ²)		Normal (≥ 90 mL/min/1.73 m ²)	
	Cangrelor N=165 n (%)	Clopidogrel N=162 n (%)	Cangrelor N=1332 n (%)	Clopidogrel N=1302 n (%)	Cangrelor N=1823 n (%)	Clopidogrel N=1800 n (%)	Cangrelor N=902 n (%)	Clopidogrel N=956 n (%)
Patients with at least 1 SMQ event	8 (4.8)	3 (1.9)	19 (1.4)	10 (0.8)	5 (0.3)	9 (0.5)	1 (0.1)	0 (0.0)
Oliguria			1 (0.1)	0 (0.0)				
Blood creatinine increased	3 (1.8)	1 (0.6)	8 (0.6)	3 (0.2)	2 (0.1)	2 (0.1)	1 (0.1)	0 (0.0)
Renal failure	0 (0.0)	1 (0.6)	3 (0.2)	0 (0.0)	3 (0.2)	1 (0.1)		
Renal failure acute	5 (3.0)	1 (0.6)	7 (0.5)	5 (0.4)	0 (0.0)	2 (0.2)		
Renal impairment			0 (0.0)	2 (0.2)	0 (0.0)	1 (0.1)		
Renal tubular necrosis					0 (0.0)	1 (0.1)		
Protein urine present					0 (0.0)	1 (0.1)		
Urine output decreased					0 (0.0)	1 (0.1)		

Sources: [Section 2.7.4.8.2](#), [Table 16.6.24.4.10](#), [Table 16.6.24.4.11](#), [Table 16.6.24.4.12](#) and [Table 16.6.24.4.13](#).

Source: Applicant's SCS, Table 28

Table 54. Adverse events of SMQ by baseline renal function in CHAMPION PLATFORM

Preferred terms	Baseline Glomerular Filtration Rate					
	Severe (<30 mL/min/1.73 m ²)		Moderate (30 - <60 mL/min/1.73 m ²)		Mild (60 - 90 mL/min/1.73 m ²)	
	Cangrelor N=116 n (%)	Clopidogrel N=120 n (%)	Cangrelor N=865 n (%)	Clopidogrel N=857 n (%)	Cangrelor N=986 n (%)	Clopidogrel N=990 n (%)
Patients with at least 1 SMQ event	2 (1.7)	2 (1.7)	6 (0.7)	4 (0.5)	0 (0.0)	2 (0.2)
Blood creatinine increased	1 (0.9)	1 (0.8)	1 (0.1)	0 (0.0)	0 (0.0)	2 (0.2)
Proteinuria			0 (0.0)	1 (0.1)		
Renal failure	1 (0.9)	1 (0.8)	2 (0.2)	1 (0.1)		
Renal failure acute			1 (0.1)	1 (0.1)		
Renal impairment			0 (0.0)	1 (0.1)		
Nephropathy toxic			2 (0.2)	1 (0.1)		
Urine output decreased					0 (0.0)	1 (0.1)

Sources: [Section 2.7.4.8.2](#), [Table 16.6.24.4.14](#), [Table 16.6.24.4.15](#), [Table 16.6.24.4.16](#).

AE = adverse event; SMQ = standardized MedDRA query.

Source: Applicant's SCS, Table 29

Serum creatinine in placebo or active controlled trials was reported in CHAMPION PCI, CHAMPION PLATFORM, and BRIDGE. [Table 55](#) shows that the subjects with potentially clinically significant changes in serum creatinine were balanced.

Table 55. Subjects with potentially clinically significant serum creatinine†

	Cangrelor, n/N (%)	Clopidogrel, n/N (%)
TMC-CAN-05-02 PCI	78/4063 (1.9)	73/4073 (1.8)
TMC-CAN-05-03 PLATFORM	65/2500 (2.6)	61/2464 (2.5)
TMC-CAN-08-02 BRIDGE	2/107 (1.9)	1/91 (1.1)

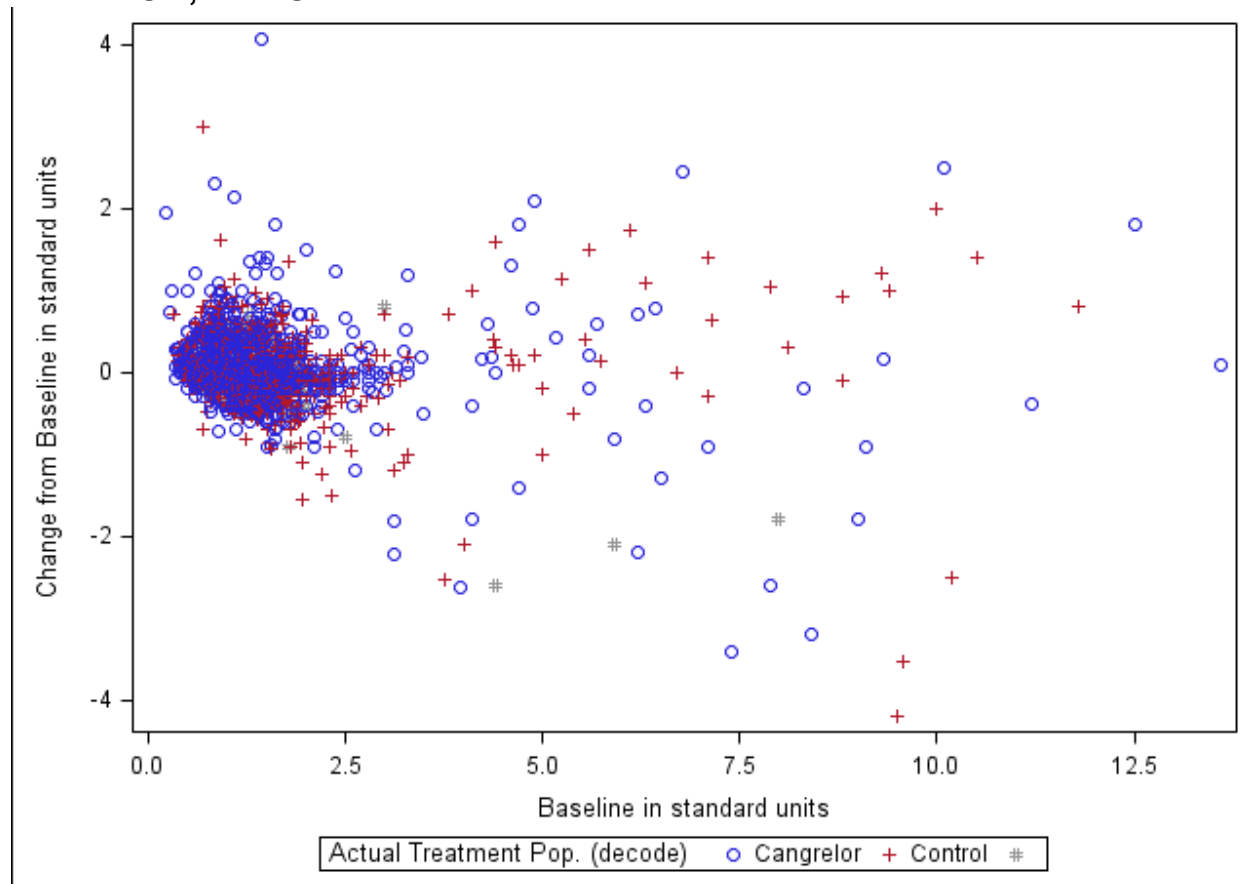
† on treatment values ≥ 2 mg/dL

N is the number of subjects with Scr measured at baseline and on treatment

Reviewers' analysis: lab\scr. Dataset ISS\lab (lbpcsaf lbstres)

Figure 26 of baseline serum creatinine versus change from baseline does not show a clear pattern of risk.

Figure 26. Baseline serum creatinine versus change in serum creatinine in PCI, PLATFROM, BRIDGE



Reviewer's analysis: lab\scr. Dataset iss\lab (lbchgblo)

The Applicant concludes, and the reviewer agrees, that there are no clear safety issues related to renal function. There were small increases in acute renal adverse events that may be worth noting.

7.3.4.3 Hypersensitivity

The Applicant did a modified SMQ search of Angioedema and Anaphylactic reactions and identified 93 (0.7%) subjects on cangrelor with hypersensitivity and 75 (0.6%) on control. The most common events were rash, pruritus, urticarial, and wheezing (all nonserious). The majority of the events were mild or moderate in intensity and non-serious. None were fatal. There were 7 subjects with SAEs treated with cangrelor compared to 2 treated with control. These subjects also received multiple drugs, including contrast agents. Although uncommon, hypersensitivity should also be described.

Table 56. AEs of hypersensitivity in ISS

Preferred Term	Cangrelor (N=13301) n (%)	Control (N=12861) n (%)
Patients with at least one AE of Hypersensitivity	93 (0.7)	75 (0.6)
Rash ^a	34 (0.3)	33 (0.3)
Pruritus ^b	15 (0.1)	14 (0.1)
Urticaria	13 (0.1)	9 (0.1)
Wheezing	12 (0.1)	5 (0.0)
Bronchospasm	5 (0.0)	2 (0.0)
Hypersensitivity	4 (0.0)	6 (0.0)
Throat tightness	4 (0.0)	3 (0.0)
Anaphylactic reaction	2 (0.0)	1 (0.0)
Angioedema	2 (0.0)	0 (0.0)
Tongue oedema	1 (0.0)	0 (0.0)
Drug hypersensitivity	1 (0.0)	2 (0.0)
Anaphylactic shock	1 (0.0)	0 (0.0)
Laryngeal oedema	1 (0.0)	1 (0.0)
Pharyngeal oedema	1 (0.0)	0 (0.0)
Stridor	1 (0.0)	0 (0.0)
Swelling face	1 (0.0)	0 (0.0)
Shock	1 (0.0)	1 (0.0)

Source: Section 2.7.4.8.2, Table 11.6.24.4.2.

^a Includes the terms rash, rash erythematous, rash generalized, rash pruritic.

^b Includes the terms pruritus and pruritus generalized.

Note: Zero percentages associated with non-zero patient numbers are due to rounding.

Applicant's SCS. Table 23

7.3.5 Submission Specific Primary Safety Concerns: Bleeding

The primary safety endpoint in PHOENIX was the incidence of GUSTO severe bleeding at 48 hours. The incidence of blood product transfusion up to 48 hours, categorized according to relationship with CABG surgery was another key safety endpoint.

Reviewer comment: As stated in [Section 5.3.4.6 Safety Endpoints and Definitions](#) the final protocol and SAP did not distinguish between CABG and non-CABG bleeding for the primary safety endpoint. Nevertheless, the Applicant's bleeding results in the main CSR is primarily of non-CABG bleeding. This is not to say that this is unreasonable, it just was not clearly stated in the protocol or SAP. Because of the small number of CABG related bleeds in PHOENIX, the reviewer also presents most of the bleeding data by non-CABG related bleeding.

Overall bleeding was 42% greater in cangrelor treated subjects compared to clopidogrel treated subjects ([Table 57](#)). Most bleeds were non-CABG related.

Table 57. Total subjects with bleed in PHOENIX

	Cangrelor		Clopidogrel		Cangrelor vs. Clopidogrel		Cangrelor vs. Clopidogrel	
	N=5529	(%)	N=5527	(%)	RR	(95% CI)	OR	(95% CI)
Any Bleed	863	(15.61)	605	(11.0)	1.42	(1.29, 1.56)	1.50	(1.34, 1.68)
Any Bleed at 48 hours	860	(15.55)	604	(10.9)	1.42	(1.29, 1.56)	1.49	(1.34, 1.67)
Non CABG bleeds	857	(15.5)	601	(10.9)	1.42	(1.29, 1.56)	1.50	(1.34, 1.67)
CABG bleed	4 [†]	(0.1)	3	(0.1)	1.34	(0.30, 5.99)	1.34	(0.30, 6.00)

Reviewer's analysis: bleedsummarybleed total. (PTSTATUS and GENDER factors in logistic regression)

Datasets: r_bl.c_rev created with raw\bld, iss lab.

[†]Subject 401079027 had both a nonCABG and a CABG bleed within 48 hours

Reviewer comment: Although bleed at any time is reported in the [Table 57](#), AEs (including bleeding) were only required to be collected up to 48 hours after randomization (or after study drug start if study drug administration delayed). The reviewer reports an additional subject (ID 401029051, cangrelor) with a bleed that the Applicant did not report. This subject was found because of how the reviewer identified bleeds (as discussed in [Section 7.1.2 Categorization of Adverse Events and Bleeding](#)). The Applicant reports 856 vs. 601 on cangrelor and clopidogrel, respectively.

CABG

The number of subjects with CABG in PHOENIX was low (see [Table 58](#)), but interestingly the numbers between treatment arms was imbalanced. The only urgent CABGs were in treated subjects. Of these one out of seven subjects in the cangrelor arm had a bleed associated with CABG, whereas three out of five subjects treated with clopidogrel had bleeding associated with CABG.

Table 58. CABG and bleeding in PHOENIX

	Cangrelor	Clopidogrel
Randomized population	45	29
CABG as index procedure	19	9
CABG within 48 hours from randomization	29	15
Bleeding not associated with CABG	5	0
Bleeding associated with CABG	6	3
CABG from > 48 hours to < 30 days	16	14
Bleeding not associated with CABG	1	3
Bleeding associated with CABG	0	0
Treated population	31	25
CABG within 48 hours from treatment start	20	11
Bleeding associated with CABG	4	3
Bleeding not associated with CABG	4	0
Urgent CABG	7	5
Bleeding associated with CABG	1	3
CABG from > 48 hours to < 30 days	11	14
Bleeding not associated with CABG	1	3
Bleeding not associated with CABG	5	3

Reviewer's analysis: cabg\cabg. Datasets raw\idr, cabg

The primary safety endpoint in the BRIDGE trial was excessive CABG related bleeding; there were 12/102 (11.8%) in the cangrelor arm and 10/96 (10.4%) in the placebo arm. In total, the data suggest that cangrelor can be used safely in the CABG setting.

Bleed Classifications and Primary Safety Endpoint, Non-CABG Bleeding

More subjects treated with cangrelor than clopidogrel had a GUSTO severe bleed (primary safety endpoint), but the numbers were low (0.2% on cangrelor) and the difference was not significant ([Table 59](#)).¹¹ [Table 59](#) shows the reviewer's and Applicant's (denoted by an asterisk *) number of subjects with bleeds of various classifications. Reasons for differences between the reviewer and the Applicant's counts were described in [Section 7.1.2 Categorization of Adverse Events and Bleeding](#). In addition, the reviewer's analysis shown in the table used a logistic regression model adjusting for baseline status¹² and gender. Analyses conducted without baseline status and gender as factors show minor differences in the estimates.

¹¹ There were no CABG related GUSTO severe bleeds.

¹² Baseline status (variable PTSTATUS) was adjudicated by the CEC as "normal" or "abnormal" based on troponin level, ischemic symptoms and ECG changes. This factor was in the model because the Applicant used it for their primary efficacy analysis and this model was used for the reviewer's risk benefit analysis.

In general, the bleeds that showed significant differences between treatment arms were bleeds that are generally unlikely to have extensive clinical consequences (GUSTO mild, TIMI minor). There was a ~67% higher risk of ACUITY major bleed in cangrelor treated subjects compared to clopidogrel. A large number of subjects in this category were because of hematoma ≥ 5 cm.

In attempts to identify a bad bleed, the reviewer classified subjects with any of the following into a “Bad” category: ICH, transfused, cardiac tamponade, reoperation for bleeding, surgical intervention, retroperitoneal, requiring or extending hospitalization. With this classification, the risk was ~46% higher on cangrelor and it approached significance.

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Table 59. Non CABG Bleeding Classification Risk at 48 hours in PHOENIX

	Cangrelor		Clopidogrel		Cangrelor vs. Clopidogrel		Cangrelor vs. Clopidogrel	
	N=5529	(%)	N=5527	(%)	RR	(95% CI)	OR	(95% CI)
Non CABG bleeds	857 [†]	(15.5)	601	(10.9)	1.42	(1.29, 1.56)	1.50	(1.34, 1.67)
GUSTO severe or moderate	32	(0.6)	20	(0.4)	1.57	(0.90, 2.74)	1.57	(0.90, 2.75)
GUSTO severe	10	(0.2)	6	(0.1)	1.64	(0.60, 4.52)	1.64	(0.60, 4.53)
GUSTO severe*	9	(0.2)	6	(0.1)	1.50	(0.53, 4.21)	1.50	(0.53, 4.22)
GUSTO moderate	22	(0.4)	14	(0.6)	1.54	(0.79, 3.00)	1.54	(0.79, 3.01)
GUSTO moderate*	22	(0.4)	13	(0.2)	1.69	(0.85, 3.35)	1.69	(0.85, 3.37)
GUSTO mild	825	(14.9)	581	(10.5)	1.41	(1.28, 1.56)	1.49	(1.33, 1.67)
GUSTO mild*	150	(2.7)	88	(1.6)	1.70	(1.31, 2.21)	1.72	(1.32, 2.25)
TIMI Major or Minor	38	(0.7)	12	(0.2)	3.14	(1.64, 6.00)	3.15	(1.65, 6.04)
TIMI Major	9	(0.2)	3	(0.1)	3.00	(0.81, 11.09)	3.01	(0.81, 11.11)
TIMI Major*	5	(0.1)	5	(0.1)	1.00	(0.29, 3.45)	1.00	(0.29, 3.45)
TIMI Minor	29	(0.5)	9	(0.2)	3.18	(1.51, 6.71)	3.19	(1.51, 6.75)
TIMI Minor*	9	(0.2)	3	(0.1)	3.00	(0.81, 11.07)	3.00	(0.81, 11.10)
Acuity Major	242	(4.4)	143	(2.6)	1.67	(1.36, 2.05)	1.71	(1.39, 2.11)
Barc2	111	(2.0)	66	(1.2)	1.67	(1.23, 2.26)	1.68	(1.24, 2.29)
Barc3a	41	(0.7)	14	(0.3)	2.88	(1.57, 5.27)	2.90	(1.58, 5.32)
Barc3b	15	(0.3)	7	(0.1)	2.11	(0.86, 5.16)	2.11	(0.86, 5.18)
Barc3c	3	(0.1)	1	(0.0)	2.98	(0.31, 28.63)	2.98	(0.31, 28.68)
Bad [‡]	61	(1.1)	41	(0.7)	1.46	(0.99, 2.17)	1.47	(0.99, 2.19)

* Applicant's classification and analysis

[†] Reviewer identified an extra bleed (CSUBJECT 401029051) based on SAE report (no BLD CRF page so subject was excluded from Applicant's report). Classified as GUSTO severe, TIMI major and BARC 3b.

[‡] Bad defined as any of the following: ICH, transfused, cardiac tamponade, reoperation for bleeding, surgical intervention, retroperitoneal, requiring or extending hospitalization

Reviewer's analysis with factors patient status, gender. Reviewer code: bleed\primary safety ptstatus gender final. Datasets: raw\blld, iss\fdla_bld, iss lab.

Table 60. Bleeding type at 48 hours (non-CABG)

	n (%) of patients	
	Cangrelor (N=5529)	Clopidogrel (N=5527)
PCI-related bleeding	737 (13.3)	502 (9.1)
Hematoma	461 (8.3)	312 (5.6)
Oozing at puncture site	236 (4.3)	158 (2.9)
Ecchymosis	200 (3.6)	118 (2.1)
Transfusion	25 (0.5)	16 (0.3)
Gastrointestinal bleeding	16 (0.3)	9 (0.2)
Epistaxis	15 (0.3)	15 (0.3)
Gross hematuria	11 (0.2)	6 (0.1)
Access site bleeding requiring radiologic or surgical intervention	10 (0.2)	7 (0.1)
Genitourinary bleeding	10 (0.2)	5 (0.1)
Bleeding leading to hemodynamic compromise	7 (0.1)	5 (0.1)
Retroperitoneal	7 (0.1)	3 (0.1)
Cardiac tamponade	7 (0.1)	1 (0.0)
Hematemesis	4 (0.1)	3 (0.1)
Intracranial hemorrhage	3 (0.1)	1 (0.0)
Thrombocytopenia	2 (0.0)	5 (0.1)
Pulmonary bleeding	2 (0.0)	1 (0.0)
Hemorrhoidal bleeding	1 (0.0)	0 (0.0)
Reoperation for bleeding	0 (0.0)	1 (0.0)
Chest tube output ≥2 liters within a 24 hour period	0 (0.0)	0 (0.0)
Intraocular bleeding	0 (0.0)	0 (0.0)

Source: Section 14.1, Table 6.2.4.1.

NOTE: Not all categories from source table are represented, including some with frequencies >0.1% and Other. For more detail on the Other category from source Table 6.2.4.1, see Appendix 16.2, Listing 6.3.4.4.

Source: PHOENIX CSR, Table 38. Table based on eCRF fields checked by investigator.

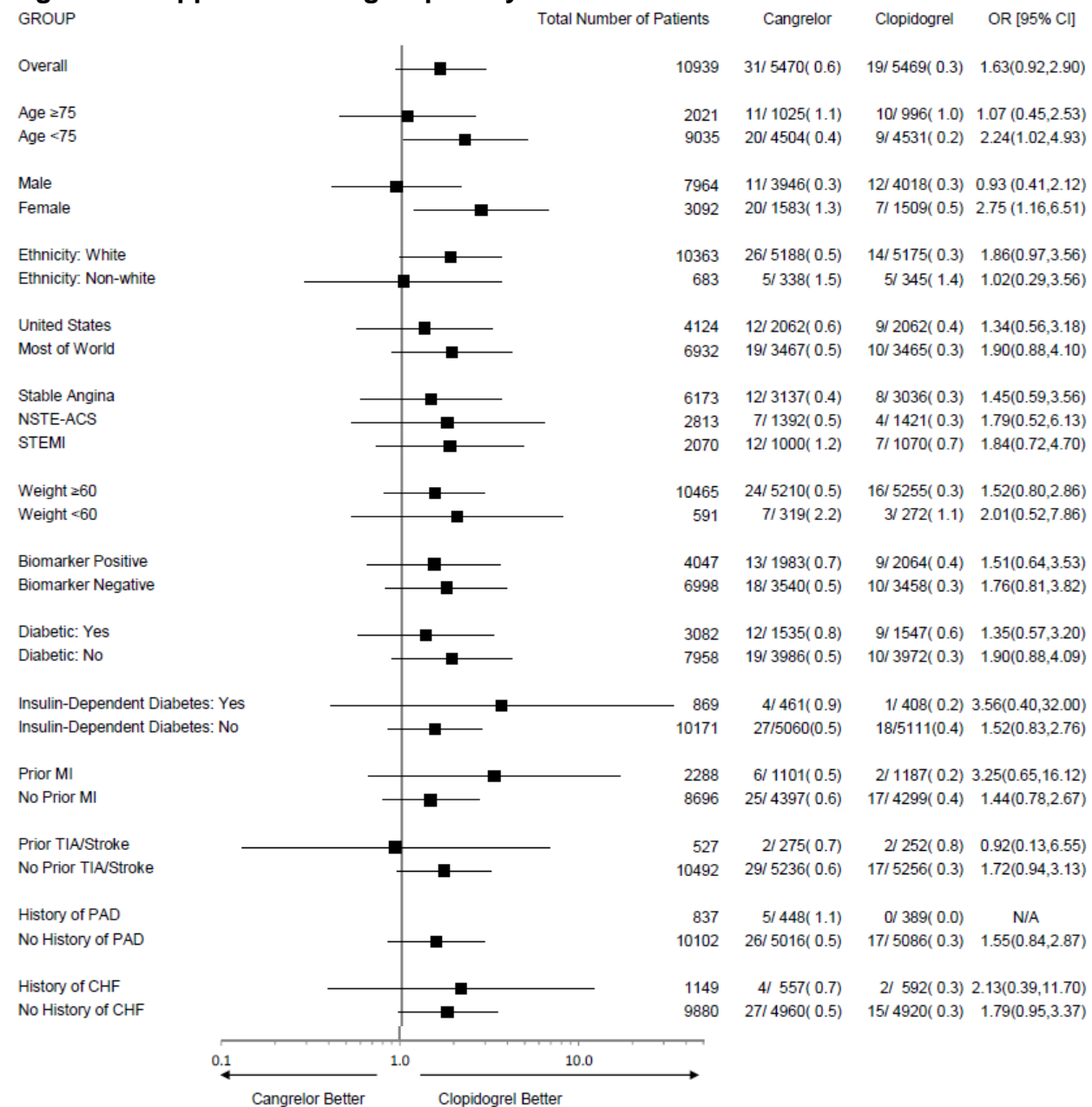
Transfusion

There were more subjects treated with cangrelor that received transfusions, but the difference was not significant (25 vs. 17, respectively).

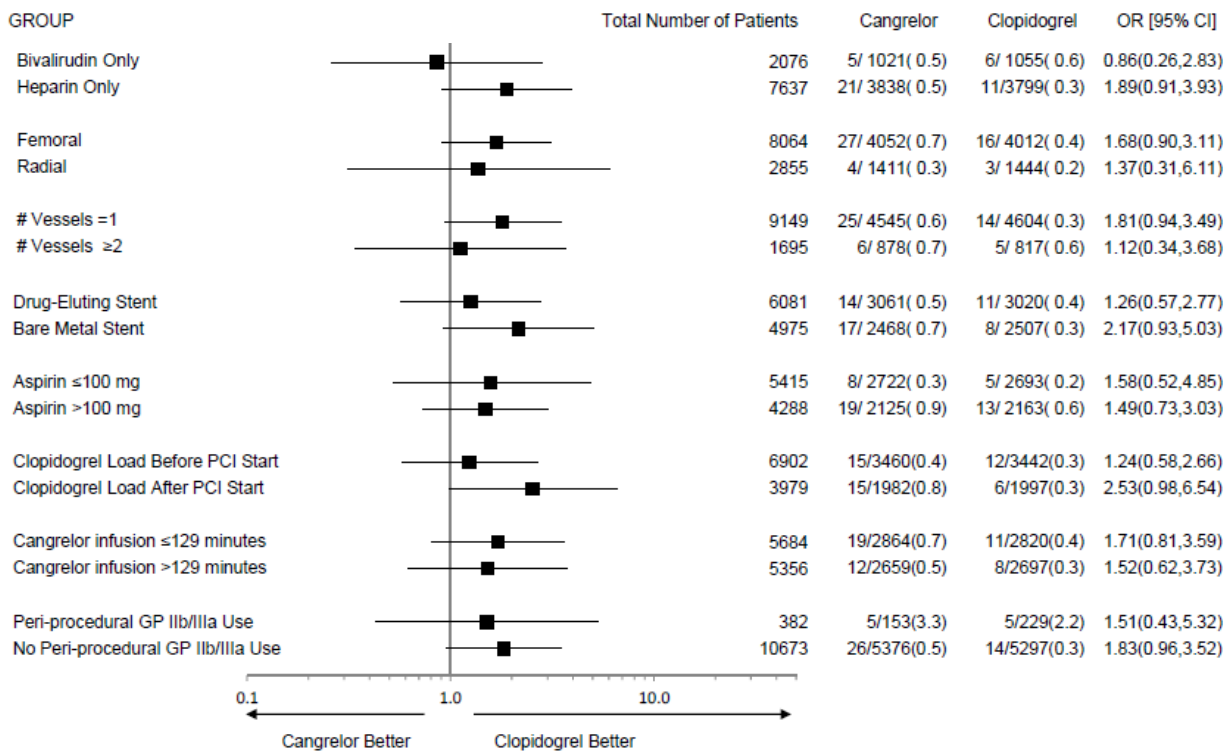
Subgroups

The Applicant combined GUSTO moderate and severe bleeds to do exploratory subgroup analyses. They did not find a difference in GUSTO moderate/severe bleeds for any subgroup.

Figure 27. Applicant's subgroup analysis of GUSTO moderate/severe bleed



(continued)



Source: PHOENIX CSR, Figure 11

Concomitant medications

Post procedural concomitant medications were balanced between treatment arms.

Table 61. Post procedural concomitant medications (ITT population)

Parameter Category	n/N (%)	
	Cangrelor (N=5581)	Clopidogrel (N=5564)
After index procedure		
Clopidogrel (per protocol) ^a	5423/5581 (97.2)	5416/5564 (97.3)
Aspirin	4408/5576 (79.1)	4403/5557 (79.2)
Prasugrel (10 mg)	17/5581 (0.3)	20/5564 (0.4)
Prasugrel (60 mg)	11/5581 (0.2)	7/5564 (0.1)
Ticagrelor (90 mg)	1/5581 (0.0)	2/5564 (0.0)
Ticagrelor (180 mg)	1/5581 (0.0)	0/5564 (0.0)
At hospital discharge		
Aspirin	5525/5576 (99.1)	5498/5557 (98.9)
Clopidogrel	5332/5581 (95.5)	5323/5564 (95.7)
Prasugrel	88/5581 (1.5)	88/5564 (1.6)
Ticagrelor	24/5581 (0.4)	23/5564 (0.4)

Source: Section 14.1, Table 3.5.2.1 and Table 3.6.2.1.

^a For post-procedural clopidogrel, administration per protocol was 75 mg for 48 hours after index PCI.

ITT = intent-to-treat.

PHOENIX CSR, Table 14

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Approximately 20% of subjects in each arm had an AE. The most commonly reported AEs (≥ 2% of subjects in each arm) were balanced between treatment arms (Table 62). There was a higher incidence of dyspnea in subjects treated with cangrelor (1.2%) then clopidogrel (0.3%). Most dyspnea events were mild (n=46) in severity; 18 were moderate, 1 was severe (likely an allergic reaction to cangrelor).

Table 62. AEs reported by ≥ 1% of subjects

Preferred Term	Number (%) of patients	
	Cangrelor (N=5529)	Clopidogrel (N=5527)
Patients with at least one AE	1125 (20.3)	1064 (19.3)
Back pain	147 (2.7)	155 (2.8)
Nausea	117 (2.1)	107 (1.9)
Vessel puncture site pain	114 (2.1)	102 (1.8)
Hypertension	112 (2.0)	93 (1.7)
Headache	101 (1.8)	110 (2.0)
Vomiting	70 (1.3)	53 (1.0)
Dyspnea	65 (1.2)	18 (0.3)
Hypotension	63 (1.1)	48 (0.9)
Chest pain	55 (1.0)	94 (1.7)

Source: PHOENIX CSR, Table 43

The number of subjects with TEAEs was balanced between treatment arms. More subjects on cangrelor had dyspnea. More subjects on clopidogrel had nausea.

Table 63. Treatment emergent AE

Preferred Term	Number (%) of patients	
	Cangrelor (N=5529)	Clopidogrel (N=5527)
Patients with any AE related to study drug	64 (1.2)	61 (1.1)
Dyspnea	13 (0.2)	1 (0.0)
Vomiting	12 (0.2)	12 (0.2)
Nausea	8 (0.1)	18 (0.3)
Headache	6 (0.1)	3 (0.1)
Hypotension	5 (0.1)	1 (0.0)
Vessel puncture site pain	4 (0.1)	2 (0.0)
Rash	2 (0.0)	4 (0.1)
Dyspepsia	1 (0.0)	3 (0.1)
Pruritus	1 (0.0)	3 (0.1)
Hypersensitivity	0 (0.0)	3 (0.1)

Source: PHOENIX CSR, Table 46

7.4.2 Laboratory Findings

The only reported labs were ALT, AST, alkaline phosphatase, total bilirubin, creatinine, GFR, hematocrit, hemoglobin, platelets, and WBCs. Hemoglobin and hematocrit were analyzed as part of the bleeding analysis. See section [7.3.4.2 Renal function effects](#) for analysis of serum creatinine.

Liver ([Table 64](#)), platelets, and WBCs values ([Table 65](#)) were balanced between arms in the CHAMPION trials. Thrombocytopenia was reported in 2 subjects on cangrelor and 6 subjects on clopidogrel.¹³

Table 64. Post baseline changes >1x upper limit of normal in CHAMPION and placebo controlled studies

Post baseline changes >1xULN	CHAMPION Program		Placebo controlled	
	Cangrelor n/N (%)	Clopidogrel n/N (%)	Cangrelor n/N (%)	Control n/N (%)
Creatinine (mg/dL) >1xULN	307/5346 (5.7)	257/5374 (4.8)	11/273 (4.0)	6/174 (3.4)
ALT (U/L) >1xULN	325/4909 (6.6)	336/4916 (6.8)	21/232 (9.1)	17/143 (11.9)
AST (U/L) >1xULN	725/4153 (17.5)	725/4134 (17.5)	34/203 (16.7)	12/128 (9.4)
Total bilirubin (mg/dL) >1xULN	392/5191 (7.6)	365/5154 (7.1)	6/273 (2.2)	3/169 (1.8)
Alkaline phosphatase (U/L) >1xULN	71/5162 (1.4)	64/5072 (1.3)	2/272 (0.7)	0/180 (0.0)

Source: Section 2.7.4.8.2, Table 16.6.7.4.1 and Table 14.6.7.4.1.

ULN = upper limit of normal.

Source: SCS, Table 54

¹³ PHOENIX, CSR, Table 6.2.4.1

Table 65. Potentially clinical significant tests, platelets and WBC in CHAMPION and placebo-controlled studies

Hematology Parameters	CHAMPION		Placebo Controlled	
	Cangrelor (N=12565) n/N (%)	Clopidogrel (N=12542) n/N (%)	Cangrelor (N=354) n/N (%)	Control (N=218) n/N (%)
Platelets ≥ 700 k/ μ L	3/11914 (0.0)	1/11889 (0.0)	0/340 (0.0)	0/213 (0.0)
Platelets ≤ 75 k/ μ L	18/11914 (0.1)	18/11889 (0.2)	11/340 (3.2)	8/213 (2.8)
WBC ^a ≥ 16 k/ μ L	113/6268 (1.8)	106/6290 (1.7)	37/342 (10.8)	29/211 (13.7)
WBC ^a ≤ 2.8 k/ μ L	4/6268 (0.1)	1/6290 (0.0)	0/342 (0.0)	0/211 (0.0)

Source: Section 2.7.4.8.2, Table 16.6.6.4.1 and Table 14.6.6.4.1.

^a WBC was not provided in the TMC-CAN-10-01 CHAMPION PHOENIX study.

Note: Zero percentages associated with non-zero patient numbers are due to rounding.

LLN = lower limit of normal.

Source: SCS, Table 52

7.4.3 Vital Signs

Vital signs were not collected in PHOENIX. CHAMPION PCI and PLATFORM collected vital signs. No significant differences in blood pressure or heart rate were observed.

7.4.4 Electrocardiograms (ECGs)

In the dedicated thorough QT study TMC CAN 08-01 the QT IRT group and the Applicant concluded that cangrelor does not affect cardiac repolarization at a dose of 60 ug/kg bolus followed by 8 ug/kg/min for 3 hours.

7.4.5 Special Safety Studies/Clinical Trials

None.

7.4.6 Immunogenicity

N/A

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Only one dose was explored in the pivotal trials.

7.5.2 Time Dependency for Adverse Events

Cangrelor is given as a short infusion (median time 2.2 hours). Time dependency for AEs was not examined.

7.5.3 Drug-Demographic Interactions

Gender had a significant effect on bleeding when added as a factor in the regression.

7.5.4 Drug-Disease Interactions

A study in subjects with renal impairment showed that impairment of renal function did not significantly alter cangrelor PK. Hepatic impairment is not expected to affect cangrelor because cangrelor is biotransformed by nucleotidases in systemic circulation.

7.5.5 Drug-Drug Interactions

Pharmacokinetic interactions are unlikely for reasons already discussed in the Clinical Pharmacology Section.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

N/A.

7.6.2 Human Reproduction and Pregnancy Data

There are no controlled studies in women. See [Section 4.3 Preclinical Pharmacology/Toxicology](#).

7.6.3 Pediatrics and Assessment of Effects on Growth

N/A.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

In the CHAMPION trials 24 subjects (12 at US sites) received cangrelor infusions between 5.5 – 13.8 ug/kg/min.¹⁴ The majority of the dosing errors were because the weight recorded in pounds was used as the dosing weight, thus subjects received more than twice the correct dose. Another common reason for the dosing errors was because of incorrect solution preparation.

¹⁴ Reviewer's analysis: ae\ae od check. Datasets: iss\isd, iss\fda_bld

Most of these subjects did not have reports of bleeding related AEs; only one subject had a bleeding report (in CHAMPION PCI, GUSTO mild).¹⁵ There was also no correlation with other AEs.

Six subjects had other AEs of interest noted (hyperbilirubinemia, dyspnea, back pain, visual impairment, dysphagia, and acute renal failure). All were moderate or less in intensity and did not result the infusion being stopped. Subject 401021001 had a reduction in hemoglobin and platelets and a note of dysphagia occurring after 48 hours (not reported as an AE since it occurred after 48 hours, thus investigators were not required to report). No other information was provided on this subject. Subject 449001032 had an AE of acute renal failure of mild intensity reported on the same day as drug start. No time of onset was recorded, but the investigator assessed the event as unrelated to study drug and did not change the dose based on this AE.

In studies that measured pre and post infusion platelet aggregation there was no evidence of increased (rebound) platelet reactivity following cessation of cangrelor infusion at doses up to 4 ug/kg/min.

7.7 Additional Submissions / Safety Issues

None.

8 Postmarket Experience

N/A

9 Appendices

9.1 Risk benefit tables

Table 66. Non-CABG bleed / benefit

Endpoint	Cangrelor	Clopidogrel	Cangrelor vs. Clopidogrel	
	N=5529	N=5527	RR	95% CI
Non-CABG Bleed (NCB)	857	601	1.42	(1.29, 1.56)
NCB +D	871	621	1.40	(1.27, 1.54)
NCB+D+ST	905	677	1.33	(1.21, 1.46)
NCB+D+MI	1037	841	1.23	(1.13, 1.33)
NCB+D+MI+ST	1059	877	1.20	(1.11, 1.31)
NCB+PEP	1065	885	1.20	(1.11, 1.30)

¹⁵ TMC-CAN-05-02-043007-001

D= all cause death; ST=stent thrombosis=ARC-ST+IPST; MI= all adjudicated MI (type 1, 2, 3, 4a, 4b, 5); PEP=primary efficacy endpoint=composite of D, ST, MI, IDR;
IDR=Ischemic Driven Revascularization

Table 67. GUSTO severe/moderate bleed / benefit

Endpoint	Cangrelor	Clopidogrel	Cangrelor vs. Clopidogrel	
	N=5529	N=5527	RR	95% CI
GUSTO (severe or moderate)(G)	32	20	1.57	(0.90, 2.74)
G +D	48	40	1.18	(0.78, 1.79)
G+D+ST	88	109	0.80	(0.61, 1.05)
G+D+MI	248	293	0.84	(0.71, 0.99)
G+D+MI+ST	276	333	0.83	(0.71, 0.96)
G+PEP	285	343	0.83	(0.71, 0.96)

D= all cause death; ST=stent thrombosis=ARC-ST+IPST; MI= all adjudicated MI (type 1, 2, 3, 4a, 4b, 5); PEP=primary efficacy endpoint=composite of D, ST, MI, IDR;
IDR=Ischemic Driven Revascularization

Table 68. TIMI major/minor bleed / benefit

Endpoint	Cangrelor	Clopidogrel	Cangrelor vs. Clopidogrel	
	N=5529	N=5527	RR	95% CI
TIMI (major or minor)(T)	38	12	3.14	(1.64, 6.00)
T +D	55	32	1.70	(1.10, 2.62)
T+D+ST	96	100	0.95	(0.72, 1.26)
T+D+MI	255	284	0.89	(0.76, 1.05)
T+D+MI+ST	284	324	0.87	(0.75, 1.02)
T+PEP	293	334	0.87	(0.75, 1.02)

D= all cause death; ST=stent thrombosis=ARC-ST+IPST; MI= all adjudicated MI (type 1, 2, 3, 4a, 4b, 5); PEP=primary efficacy endpoint=composite of D, ST, MI, IDR;
IDR=Ischemic Driven Revascularization

Table 69. ACUITY major bleed / benefit

Endpoint	Cangrelor	Clopidogrel	Cangrelor vs. Clopidogrel	
	N=5529	N=5527	RR	95% CI
ACUITY Major (A)	242	143	1.67	(1.36, 2.05)
A +D	260	163	1.57	(1.30, 1.91)
A+D+ST	297	227	1.29	(1.09, 1.53)
A+D+MI	449	406	1.10	(0.97, 1.25)
A+D+MI+ST	474	445	1.06	(0.94, 1.20)

A+PEP	483	455	1.06	(0.93, 1.19)
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D= all cause death; ST=stent thrombosis=ARC-ST+IPST; MI= all adjudicated MI (type 1, 2, 3, 4a, 4b, 5); PEP=primary efficacy endpoint=composite of D, ST, MI, IDR; IDR=Ischemic Driven Revascularization

Table 70. Bad bleed / benefit

Endpoint	Cangrelor	Clopidogrel	Cangrelor vs. Clopidogrel	
	N=5529	N=5527	RR	95% CI
Bad Bleed (BB)	61	41	1.46	(0.99, 2.17)
BB +D	76	61	1.22	(0.88, 1.71)
BB+D+ST	116	127	0.90	(0.70, 1.16)
BB+D+MI	273	309	0.88	(0.75, 1.03)
BB+D+MI+ST	301	349	0.86	(0.74, 1.00)
BB+PEP	310	359	0.86	(0.74, 1.00)

D= all cause death; ST=stent thrombosis=ARC-ST+IPST; MI= all adjudicated MI (type 1, 2, 3, 4a, 4b, 5); PEP=primary efficacy endpoint=composite of D, ST, MI, IDR; IDR=Ischemic Driven Revascularization; Bad Bleed=any of the following: intracranial hemorrhage, blood transfusion, cardiac tamponade, reoperation for bleeding, any surgical intervention, retroperitoneal bleed, or bleeding events requiring hospitalization or extension of hospitalization

9.2 Universal Definition of Myocardial Infarction

As per Thygesen et al. (2007), the criteria for diagnosing acute myocardial infarction and the clinical classifications of different types of myocardial infarction based on UDMI are delineated herewith.

Definition of myocardial infarction

Criteria for acute myocardial infarction

The term myocardial infarction should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischaemia. Under these conditions any one of the following criteria meets the diagnosis for myocardial infarction:

- Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischaemia with at least one of the following:
 - Symptoms of ischaemia;
 - ECG changes indicative of new ischaemia [new ST-T changes or new left bundle branch block (LBBB)];
 - Development of pathological Q waves in the ECG;
 - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
- Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischaemia, and accompanied by presumably new ST elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.
- For percutaneous coronary interventions (PCI) in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers greater than 3×99 th percentile URL have been designated as defining PCI-related myocardial infarction. A subtype related to a documented stent thrombosis is recognized.
- For coronary artery bypass grafting (CABG) in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers greater than 5×99 th percentile URL plus either new pathological Q waves or new LBBB, or angiographically documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium have been designated as defining CABG-related myocardial infarction.
- Pathological findings of an acute myocardial infarction.

Criteria for prior myocardial infarction

Any one of the following criteria meets the diagnosis for prior myocardial infarction:

- Development of new pathological Q waves with or without symptoms.
- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischaemic cause.
- Pathological findings of a healed or healing myocardial infarction.

Table 1 Clinical classification of different types of myocardial infarction

Type 1

Spontaneous myocardial infarction related to ischaemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection

Type 2

Myocardial infarction secondary to ischaemia due to either increased oxygen demand or decreased supply, e.g. coronary artery spasm, coronary embolism, anaemia, arrhythmias, hypertension, or hypotension

Type 3

Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischaemia, accompanied by presumably new ST elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood

Type 4a

Myocardial infarction associated with PCI

Type 4b

Myocardial infarction associated with stent thrombosis as documented by angiography or at autopsy

Type 5

Myocardial infarction associated with CABG

Endpoint Definition	Baseline MI status	Angiographic evidence ² ; ECG ³ ; ischemic symptoms ⁴	CKMB ¹ mass (core lab)
MI	Baseline normal NSTEMI-ACS	<i>Not required to qualify MI</i>	elevation $\geq 3 \times$ ULN
	Baseline normal SA/elective	<i>Not required to qualify MI</i>	elevation $\geq 3 \times$ ULN
Reinfarction	Baseline decreasing & returns to normal and no intervening event from elevated sample to PCI	<i>Not required to qualify MI</i>	elevation $\geq 3 \times$ ULN
	Baseline decreasing & remains abnormal and no intervening event from elevated sample to PCI	(1 of 3): Angiographic complication Or Ischemic Symptoms Or New ECG changes	AND: Re-elevation of CKMB $\geq 3 \times$ ULN & $\geq 50\%$ from the NADIR (lowest previous sample prior to the peak)
	Baseline abnormal increasing	(2 of 2): Angiographic complication AND new ECG changes ⁵	AND: Re-elevation of CKMB $\geq 3 \times$ ULN & $\geq 50\%$ from the NADIR (lowest previous sample prior to the peak)
	Baseline unknown	(2 of 2): Angiographic complication AND new ECG changes ⁵	AND: Elevation of CKMB $\geq 3 \times$ ULN
Not adjudicated	STEMI patients	Patient too early in presentation to assess post PCI events	Patient too early in presentation to assess post PCI cardiac markers

¹CKMB collection post PCI: 6 hourly collection through 24 hours (minimum of 3 samples required). Core lab values take priority; hospital labs may be used if core lab not available (CKMB priority but troponin may be used)

²Angiographic evidence of complication (assessed by the angiographic core laboratory):

- New onset of vessel closure or compromise defined as TIMI 0/1 flow after baseline TIMI 2/3 flow (also termed acute closure or no reflow) or
 - TIMI 2 flow after baseline TIMI 3 flow (also termed slow reflow) or
 - Sustained distal embolization; or
 - Sustained side-branch closure of a vessel ≥ 2 mm in diameter or
- Intra-Procedural Thrombotic Event (IPTE): new or worsening thrombus formation at anytime during the procedure. The occurrence of IPTE can be a stent related or not stent related complication phenomena or intra procedural stent thrombosis (IPST) new or worsening thrombus related to the stent or abrupt closure due to thrombosis. Abrupt closure due to non-thrombotic causes, including major dissections, perforation, or other etiologies, will not be considered IPST. If a non-thrombotic cause of abrupt stent closure can not be definitively determined, the cause will be considered IPST. IPST may present as either acute thrombotic stent closure after a stent was implanted in a patient with a patent vessel beforehand, or new thrombus formation within or adjacent to a stent in a vessel in which thrombus either was not present or had diminished or resolved before the stent was implanted.

³ECG changes: ST segment elevation/ depression > 0.1 mV (>1 mm) in at least 2 contiguous leads; new LBBB; new Q wave (greater than 0.03 seconds). ECG collection post PCI: within 1 hour after PCI; pre-discharge

9.3 Stent Thrombosis

ST was defined according to ARC (Cutlip, D, et al., 2007) taking into account acute (\leq 24 hours post-procedure) and subacute stent thrombosis (>24 hours and ≤ 30 days), and discriminating Definite from Probable ST. All occurrences of ST were adjudicated by the CEC. ST timing and ST ARC definitions are respectively described in this appendix.

IPST (Brener, S, et al., 2013) was defined as a new or increasing thrombus (compared with baseline) within or adjacent to a deployed stent occurring during the index procedure, whether occlusive or non-occlusive. IPST was also deemed present when the baseline level thrombus was decreasing or resolved after balloon angioplasty or thrombus aspiration but then increased any time after stent implantation (including stent post-dilation). IPST was a secondary endpoint identified in a protocol amendment.

TABLE 6. Stent Thrombosis: Timing

Acute stent thrombosis*	0 to 24 hours after stent implantation
Subacute stent thrombosis*	>24 hours to 30 days after stent implantation
Late stent thrombosis†	>30 days to 1 year after stent implantation
Very late stent thrombosis†	>1 year after stent implantation

Stent thrombosis should be reported as a cumulative value over time and at the various individual time points specified above. Time 0 is defined as the time point after the guiding catheter has been removed and the patient has left the catheter laboratory.

*Acute or subacute can also be replaced by the term early stent thrombosis. Early stent thrombosis (0 to 30 days) will be used in the remainder of this document.

†Includes primary as well as secondary late stent thrombosis; secondary late stent thrombosis is a stent thrombosis after a target lesion revascularization.

TABLE 7. Definite,* Probable, and Possible Stent Thrombosis

Definite stent thrombosis

Angiographic confirmation of stent thrombosis†

The presence of a thrombus‡ that originates in the stent or in the segment 5 mm proximal or distal to the stent and presence of at least 1 of the following criteria within a 48-hour time window:

Acute onset of ischemic symptoms at rest

New ischemic ECG changes that suggest acute ischemia

Typical rise and fall in cardiac biomarkers (refer to definition of spontaneous MI)

Nonocclusive thrombus

Intracoronary thrombus is defined as a (spheric, ovoid, or irregular) noncalcified filling defect or lucency surrounded by contrast material (on 3 sides or within a coronary stenosis) seen in multiple projections, or persistence of contrast material within the lumen, or a visible embolization of intraluminal material downstream.

Occlusive thrombus

TIMI 0 or TIMI 1 intrastent or proximal to a stent up to the most adjacent proximal side branch or main branch (if originates from the side branch).

Pathological confirmation of stent thrombosis

Evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy.

Probable stent thrombosis

Clinical definition of probable stent thrombosis is considered to have occurred after intracoronary stenting in the following cases:

Any unexplained death within the first 30 days§

Irrespective of the time after the index procedure, any MI that is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause

Possible stent thrombosis

Clinical definition of possible stent thrombosis is considered to have occurred with any unexplained death from 30 days after intracoronary stenting until end of trial follow-up.

*Definite stent thrombosis is considered to have occurred by either angiographic or pathological confirmation.

†The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered a confirmed stent thrombosis (silent occlusion).

‡Intracoronary thrombus.³⁶

§For studies with ST-elevation MI population, one may consider the exclusion of unexplained death within 30 days as evidence of probable stent thrombosis.

9.4 Ischemic Driven Revascularization

IDR was defined as any refractory ischemia-driven repeat PCI or CABG surgery involving any native coronary or pre-existing bypass graft vessel. In the absence of pain, new ST-segment changes indicative of ischemia, acute pulmonary edema, ventricular arrhythmias, or hemodynamic instability presumed to be ischemic in origin, constituted sufficient evidence of ischemia. The episode of ischemia leading to repeat PCI or CABG must have occurred following completion of the index procedure.

9.5 Literature Review/References

- Anderson, J, et al., 2013, 2012 ACCF/AHA Focused Update Incorporated into the ACCF/AHA 2007 Guidelines for the Management of Patients with Unstable Angina / Non-ST-Elevation Myocardial Infarction, JACC, 61 (23):e180-e347
- Anderson, J, et al., 2011, 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery, JACC, 58 (24): e123-e210
- Antman EM, Morrow DA, McCabe CH et al. Enoxaparin versus unfractionated heparin as antithrombin therapy in patients receiving fibrinolysis for ST-elevation myocardial infarction. Design and rationale for the Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment-Thrombolysis In Myocardial Infarction study 25 (ExTRACT-TIMI 25). Am Heart J. 2005;149(2):217-226.
- Au, AG, et al., 2012, Preoperative Thienopyridine Use and Outcomes after Surgery: A Systematic Review, Am J Med, 125: 87-99
- Biancari, F, et al., 2012, Benefits and risks of using clopidogrel before coronary artery bypass surgery: Systematic review and meta-analysis of randomized trials and observational studies, J Thorac Cardiovasc Surg, 143:665-675
- Bhatt, DL, et al. 2013, Effect of platelet inhibition with cangrelor during PCI on ischemic events, the New Eng J Med, 2013;368:1303-1313.
- Bonello, L, et al., 2010, Consensus and Future Directions on the Definition of High On-Treatment Platelet Reactivity to Adenosine Diphosphate, JACC, 56 (12): 919-933
- Breet, N, et al., 2010, Comparison of Platelet Function Tests in Predicting Clinical Outcome in Patients Undergoing Coronary Stent Implantation, JAMA, 303 (8):754-762
- Brener, S, et al., 2013, Intra-Procedural Stent Thrombosis, JACC: Cardiovascular Interventions, 6(1):36-43
- Byrt, T, 1996, how good is that agreement? (Letter to editor), Epidemiology, 7:561
- Collet, J-P, et al., 2012, Bedside monitoring to adjust antiplatelet therapy for coronary stenting (ARCTIC), NEJM, 367: 2100-2109

- Cutlip, D, et al., 2007, Clinical Endpoints in Coronary Stent Trials, *Circulation*, 115:2344-2351
- Dafni, U, 2011, Landmark Analysis at the 25-Year Landmark Point, *Cardiovasc Qual Outcomes*, 4:363-371
- Genereux, P, et al., 2011, SYNTAX score reproducibility and variability between interventional cardiologists, core laboratory technicians, and quantitative coronary measurements, *Circ Cardiovasc Interv*, 4:553-561
- Gurbel, P, et al., 2009, Randomized Double-Blind Assessment of the ONSET and OFFSET of the Antiplatelet Effects of Ticagrelor Versus Clopidogrel in Patients with Stable Coronary Artery Disease: the ONSET/OFFSET Study, *Circulation*, 120:2577-2585
- The GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Eng J Med*. 1993;329:673-682.
- Gurbel, P, et al., 2011, An initial Experiment with Personalized Antiplatelet Therapy: the GRAVITAS Trial editorial, *JAMA*, 305 (11):1136-1137
- Hillis, L, D, et al., 2011, 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery, *JACC*, 58 (24): e123-e210
- Landis, JR, et al., 1977, The Measurement of Observer Agreement for Categorical Data, *Biometrics*, 33:159-174
- Leonardi, S, et al., 2013, A novel approach to systematically implement the universal definition of myocardial infarction: insights from the CHAMPION PLATFORM trial, 0:1-6,doi:10.1136/heartjnl-2012-303103
- Levine, G, et al., 2011, 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention, *JACC*, 58 (24): e44-e122
- Marcucci, R, et al., 2009, Cardiovascular Death and Nonfatal Myocardial Infarction in Acute Coronary Syndrome Patients Receiving Coronary Stenting are Predicted by Residual Platelet Reactivity to ADP by a Point-of-Care Assay, *Circ*, 119:237-242
- Mehran R, Rao SV, Bhatt DL et al. Standardized bleeding definitions for cardiovascular clinical trials, A consensus report from the Bleeding Academic Research Consortium. *Circulation*. 2011;123:2736-2747.
- Mehran, R, 2012, PARIS 1-Year: Impact of DAPT cessation and non-adherence of adverse events following PCI, Featured Clinical Research II, TCT2012
- Nijjer, S, et al., 2011, Safety of Clopidogrel being continued until the time of coronary artery bypass grafting in patients with acute coronary syndrome: a meta-analysis of 34 studies, *Circ*, 116:2544-2552
- O’Gara, P, et al., 2013, 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction: Executive Summary: A Report of the American College of Cardiology Foundation / American Heart Association Task Force on Practice Guidelines, *Circulation*, 127: 00-00

- Price, M, et al., 2011, Standard- vs. High-Dose Clopidogrel Based on Platelet Function Testing after Percutaneous Coronary Intervention; The GRAVITAS Randomized Trial, JAMA, 305 (11): 1097-1105
- Reed, G, and Cannon, C, 2011, Personalized therapy following drug-eluting stenting using platelet function testing and C-reactive protein, editorial comment, JACC, 58 (25): 2640-2641
- Stone GW, Bertrand M, Colombo A et al. Acute Catheterization and Urgent Intervention Triage strategY (ACUITY) trial: study design and rationale. Am Heart J. 2004;148:764–775.
- Stone, GW, et al., 2013, Platelet reactivity and clinical outcomes after coronary artery implantation of drug-eluting stents (ADAPT-DES): a prospective multicenter registry study, Lancet, 382: 614-623
- Thygesen, K, et al., 2007, Universal Definition of Myocardial Infarction, Circulation, 116:2634-2653
- Trenk, D, et al, 2012, A randomized trial of prasugrel versus clopidogrel in patients with high platelet reactivity on clopidogrel after elective percutaneous coronary intervention with implantation of drug-eluting stents (TRIGGER-PCI), JACC, 59 (24):2159-2164
- Welsh, R, et al., 2012, A Randomized, Double-Blind, Active-Controlled Phase 2 trial to Evaluate a Novel Selective and Reversible Intravenous and Oral P2Y₁₂ Inhibitor Elinogrel Versus Clopidogrel in Patients Undergoing Nonurgent Percutaneous Coronary Intervention: The INNOVATE-PCI Trial, Circ Cardiovasc Interv., 5:00-00
- White, H, et al., 2012, Reduced immediate ischemic events with cangrelor in PCI: a pooled analysis of the CHAMPION trials using the universal definition of myocardial infarction, Am Heart J, 163:182-190.e4
- Van Werkum, JW, et al., 2009, Predictors of Coronary Stent Thrombosis: the Dutch Stent Thrombosis Registry, JACC, 53:1399-1409

9.6 Labeling Recommendations

Deferred until further discussions.

9.7 Advisory Committee Meeting

An AC meeting is scheduled on February 12, 2014.

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/s/

BACH N BEASLEY

01/14/2014

FORTUNATO F SENATORE

01/14/2014

THOMAS A MARCINIAK

01/14/2014

Please see also my review dated January 10, 2014, regarding the ethicalness of the cangrelor development program and my review dated January 13, 2014, regarding the risk-benefit of cangrelor.



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA Serial Number: NDA 204-958 (SN 0000)

Drug Name: Cangrelor

Indication(s): Reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with coronary artery disease undergoing percutaneous coronary intervention (PCI)

Applicant: The Medicines Company

Date(s): Date of Document: April 30, 2013
PDUFA due date: April 30, 2014

Review Priority: Standard

Biometrics Division: Biometrics I, HFD-710

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Concurring Reviewers: James Hung, Ph.D.

Medical Division: Division of Cardiovascular and Renal Products, HFD-110

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Safety Reviewer: Nhi Beasley, PharmD

Project Manager: Alison Blaus

Keywords: clopidogrel loading dose, logistic regression, sample size re-estimation

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1. EXECUTIVE SUMMARY

The sponsor submitted this NDA to seek approval of cangrelor for the following indications:

- reduce thrombotic cardiovascular events (including stent thrombosis [ST]) in patients with coronary artery disease undergoing PCI
- maintain P2Y₁₂ inhibition in acute coronary syndrome (ACS) patients 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

The NDA submission included three CHAMPION trials (CHAMPION PCI, CHAMPION PLATFORM and CHAMPION PHOENIX). All three trials were randomized, double-blind and double-dummy studies. All three trials were designed to test whether IV P2Y₁₂ inhibition with cangrelor at the time of PCI followed by transition to oral clopidogrel is superior to oral clopidogrel at reducing thrombotic events during and immediately after PCI.

CHAMPION PCI and CHAMPION PLATFORM were terminated early due to a low chance of meeting the primary objective. The reductions in the incidence of stent thrombosis in both CHAMPION PLATFORM and CHAMPION PCI led to the hypothesis methodological failure in measurement of peri-procedural MI and prompted more restrictive criteria for defining a PCI MI in patients with abnormal biomarkers at baseline in CHAMPION PHOENIX.

The sponsor proposed an interim analysis at 70% information time with potential sample size re-estimation in CHAMPION PHOENIX. The early stopping efficacy boundary was crossed at the 70% interim analysis, which implied that the trial can be terminated for efficacy. The DSMB decided to continue the trial as planned. No sample size increase occurred.

CHAMPION PHOENIX demonstrated a statistically significant reduction in the CEC-adjudicated primary efficacy endpoint of death/MI/IDR/stent thrombosis at 48 hours in cangrelor arm when compared with clopidogrel treatment arm. However, there was an imbalance on the actual loading dose between two treatment groups in the study. Almost all cangrelor patients had 600 mg clopidogrel loading dose but over 25% clopidogrel patients received 300 mg loading dose. 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.

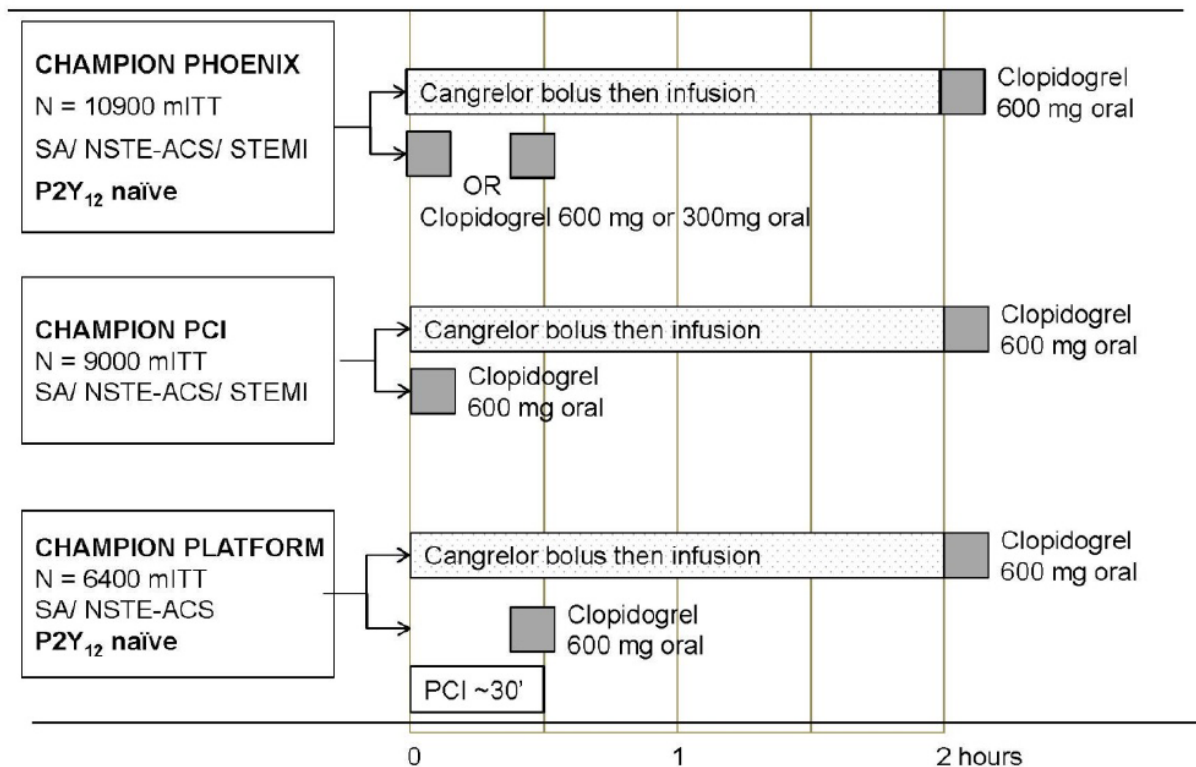
2. INTRODUCTION

2.1 Overview

The three CHAMPION trials (CHAMPION PHOENIX, CHAMPION PCI and CHAMPION PLATFORM) were very similar in design. They were all designed to test the hypothesis that profound, rapid and reversible P2Y₁₂ platelet inhibition with IV cangrelor reduces thrombotic events and improves clinical outcomes compared with oral P2Y₁₂ inhibition in the acute setting of PCI, while maintaining an acceptable safety profile with no additional risk of bleeding.

Figure 1 and Table 1 summarized and compared all three CHAMPION study designs.

Figure 1. Comparisons on CHAMPION studies



[Source: Sponsor's Summary of Clinical Efficacy Figure 1]

Table 1. List of all studies included in analysis

Study	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population
CHAMPION PHOENIX	Phase 3	Treatment duration was 2 hours or until the end of the index procedure, whichever was longer. Treating physician may decide to continue IV infusion for a total of 4 hours	Endpoint data were collected at the 48-hour and 30-day follow-up	5581 patients in the cangrelor group and 5564 patients in the clopidogrel arm	Patients with SA, NSTEMI-ACS (including patients with unstable angina or NSTEMI) and STEMI
CHAMPION PLATFORM	Phase 3	The IV infusion treatment was at least 2 hours or until the end of PCI (whichever was longer)	Endpoint data were collected at the 48-hour and 30-day follow-up, mortality data were also collected at 1-year follow up	2695 and 2669 patients were randomized to cangrelor and clopidogrel, respectively. Trial was stopped early.	Patients who required PCI and either NSTEMI or UA. Until May 8, 2007, patients with SA were also eligible
CHAMPION PCI	Phase 3	The IV infusion treatment was at least 2 hours or until the end of PCI (whichever was longer)	Endpoint data were collected at the 48-hour and 30-day follow-up, mortality data were also collected at 1-year follow up	4435 and 4447 patients were randomized to cangrelor and clopidogrel, respectively. Trial was stopped early.	patients requiring PCI with or without stent implantation

CHAMPION PHOENIX met its primary objective and was the major study in this NDA. CHAMPION PCI and CHAMPION PLATFORM were terminated early following the 70% interim analysis in PLATFORM, due to a low likelihood of reaching the primary efficacy endpoint per pre-specified stopping rules.

This review focused on CHAMPION PHOENIX and also briefly touched on the other two studies, CHAMPION PCI and CHAMPION PLATFORM, both of which failed to meet the primary objective.

2.2 Data Sources

The analysis datasets of CHAMPION PHOENIX trial is located at <\\Cdsub1\evsprod\NDA204958\0000\m5\datasets\tmc-can-10-01\analysis\legacy\datasets>.

The raw and SDTM datasets of CHAMPION PHOENIX can be found under directory <\\Cdsub1\evsprod\NDA204958\0000\m5\datasets\tmc-can-10-01\tabulations>.

The sponsor also submitted CHAMPION PLATFORM and CHAMPION PCI datasets with this NDA application in <\\Cdsub1\evsprod\NDA204958\0000\m5\datasets\tmc-can-05-03\analysis\legacy\datasets> and <\\Cdsub1\evsprod\NDA204958\0000\m5\datasets\tmc-can-05-02\analysis\legacy\datasets>.

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The reviewer was able to reproduce the results of the primary analysis and secondary analyses. The applicant submitted the tabulation datasets used to derive the primary analysis dataset and the reviewer was able to trace how the primary endpoint was derived in CHAMPION PHOENIX.

3.2 Evaluation of Efficacy

3.2.1 CHAMPION PHOENIX

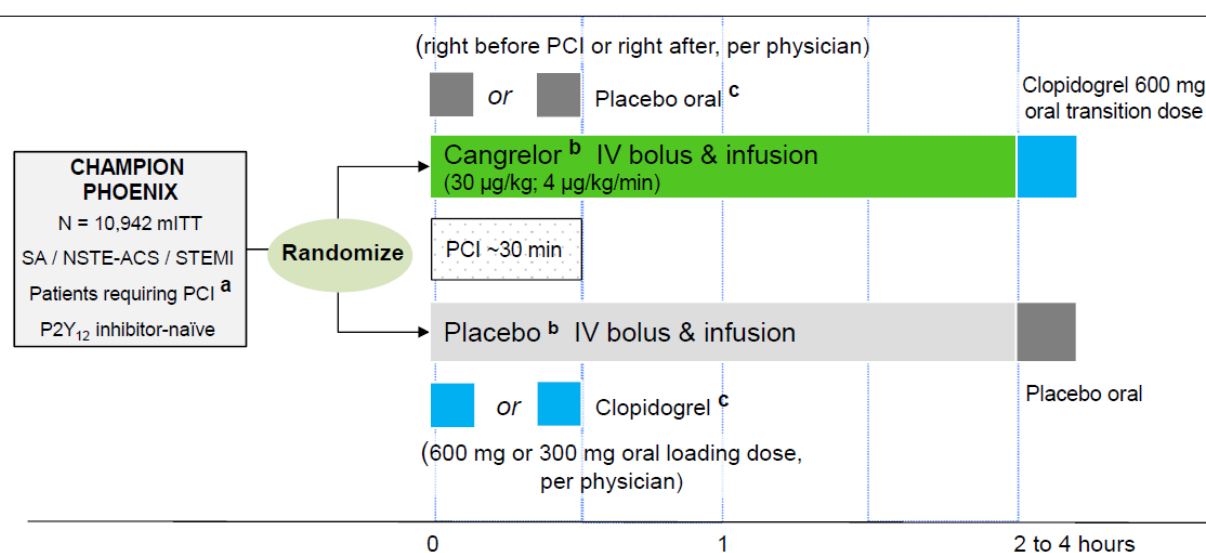
3.2.1.1 Study Design and Endpoints

The CHAMPION PHOENIX trial was a randomized, double-blind, parallel-group, superiority study of cangrelor efficacy compared with clopidogrel standard of care. The study population consisted of patients ≥ 18 years of age with coronary atherosclerosis who required PCI and had not recently received a P2Y₁₂ inhibitor. Enrolled patients had stable angina (SA), non-ST-segment elevation acute coronary syndrome (NSTEMI), or ST-segment elevation myocardial infarction (STEMI). Initial diagnostic angiography was required to confirm atherosclerotic disease indicating the need for PCI and suitable coronary anatomy, except for STEMI patients. It

was expected that the majority of the study population would have diagnostic coronary angiography conducted immediately prior to PCI. But patients with stable angina had a window of 90 days and NSTEMI-ACS patients had a window of 72 hours for initial angiography.

This study consisted of a screening period, a randomization period, the PCI procedural period, and a follow-up period through 48 hours and 30 days. Patients were randomized in a 1:1 ratio to receive either cangrelor infusion or matching placebo infusion, initiated after angiography but prior to the index PCI. Patients in the cangrelor treatment arm received cangrelor IV bolus (30 µg/kg) and a 2- to 4-hour infusion (4 µg/kg/min) followed by a dose of oral clopidogrel 600 mg administered immediately after cangrelor infusion was discontinued. Patients in the comparator treatment arm received clopidogrel oral loading dose 600 mg or 300 mg determined by the investigator and matching placebo IV bolus/infusion. Treatments were blinded using double-dummy techniques. The patients were randomized with stratification by study site, planned clopidogrel loading dose (600 mg or 300 mg) and patient baseline status (normal or abnormal as defined by a combination of biomarkers and symptoms).

Figure 2 Study Design of CHAMPION PHOENIX



- a Randomization occurred once suitability for PCI was confirmed either by angiography or STEMI diagnosis. Double-blind study medication was administered as soon as possible following randomization.
- b Study drug Infusion (cangrelor or matching placebo) was continued for 2 to 4 hours at the discretion of the treating physician. Immediately after infusion end, patients received a transition oral dose of clopidogrel or matching placebo and were transitioned to maintenance clopidogrel therapy.
- c Clopidogrel oral loading dose (or matching placebo) was administered as soon as possible after randomization, as directed by the investigator. At the time of patient randomization, a clopidogrel loading dose of 600 mg or 300 mg was specified by the investigator.

[Source: Sponsor's clinical study report Figure 1]

The primary efficacy endpoint was the composite incidence of all-cause mortality, MI, IDR, and

ST in the 48 hours after randomization. The primary endpoint were adjudicated by a blinded and independent CEC. The key secondary endpoint was the incidence of ST at 48 hours post randomization. Other secondary endpoints include

1. the incidence of composite of all-cause mortality and ST at 48 hours post randomization
2. the incidence of all-cause mortality at 48 hours post randomization
3. the incidence of IDR at 48 hours post randomization
4. the incidence of MI at 48 hours post randomization

In the original protocol dated June 25, 2010 and protocol amendment dated September 28, 2010, the key secondary endpoint was the same as in the SAP. The secondary endpoints specified in the protocols were different from the SAP. The protocols stated that no multiple comparison adjustment will be applied to the secondary endpoint analyses. The SAP, on the other hand, ordered the secondary endpoints and tested them sequentially. Note that there is only one version of SAP and the issue date was October 25, 2012, which is less than a month apart from the completion date of the last patient in the trial (November 14, 2012).

The primary endpoint, other ischemic endpoints, and all-cause mortality were also assessed at 30 days, to examine the consistency of any observed study results in 48-hour study findings.

3.2.1.2 Patient Disposition, Demographic and Baseline Characteristics

A total of 11,145 patients were enrolled into the trial. 5581 patients were assigned to cangrelor arm and 5564 were assigned to clopidogrel arm. 109 patients in the cangrelor arm and 94 patients in the clopidogrel arm did not receive study drug or did not undergo the index PCI procedure and were excluded from the mITT population. The mITT population thus consisted of 5472 patients in the cangrelor arm and 5470 patients in the clopidogrel arm.

Table 2 Patient Disposition

Category	Stat	Cangrelor	Clopidogrel	Overall
Number of subject randomized	N	5581	5564	11145
ITT Population	n/N (%)	5581 / 5581 (100.0)	5564 / 5564 (100.0)	11145 / 11145 (100.0)
mITT Population	n/N (%)	5472 / 5581 (98.0)	5470 / 5564 (98.3)	10942 / 11145 (98.2)
Number of subject completing study	n/N (%)	5498 / 5581 (98.5)	5482 / 5564 (98.5)	10980 / 11145 (98.5)
Number of subject discontinued from study	n/N (%)	83 / 5581 (1.5)	82 / 5564 (1.5)	165 / 11145 (1.5)
Death	n/N (%)	64 / 5581 (1.1)	57 / 5564 (1.0)	121 / 11145 (1.1)
AE	n/N (%)	1 / 5581 (0.0)	0 / 5564 (0.0)	1 / 11145 (0.0)
Withdrew Consent	n/N (%)	5 / 5581 (0.1)	7 / 5564 (0.1)	12 / 11145 (0.1)
Physician Decision	n/N (%)	1 / 5581 (0.0)	4 / 5564 (0.1)	5 / 11145 (0.0)
Lost to Follow-up	n/N (%)	10 / 5581 (0.2)	12 / 5564 (0.2)	22 / 11145 (0.2)
Other	n/N (%)	2 / 5581 (0.0)	2 / 5564 (0.0)	4 / 11145 (0.0)

[Source: Sponsor's Clinical Study Report Section 14.1 Table 1.0, verified by the reviewer]

A total of 660 out of 11,145 patients had major protocol deviations. The most commonly reported major deviation was incorrect administration of IV study drug.

Table 3 Protocol Deviation (ITT population)

Deviation	Cangrelor (N=5581) N (%)	Clopidogrel (N=5564) N (%)
Any major deviation	341 (6.1)	319 (5.7)
Deviation from any inclusion/exclusion criteria	132 (2.4)	111 (2.0)
Did not receive assigned study drug kit	3 (0.1)	2 (0.0)
Did not undergo index PCI procedure	91 (1.6)	83 (1.5)
Did not receive any study drug	52 (0.9)	37 (0.7)
Incorrect administration of IV study drug	238 (4.3)	212 (3.8)
Did not receive bolus dose	54 (1.0)	41 (0.7)
Did not receive infusion	54 (1.0)	44 (0.8)
Infusion rate (<3.2 or >4.8 µg/kg/min)	76 (1.4)	64 (1.2)
Infusion duration too short (<2 hours)	221 (4.0)	197 (3.5)
Bolus dose (<24 or >36 µg/kg)	68 (1.2)	59 (1.1)
Incorrect administration of oral study drug	141 (2.5)	136 (2.4)
Did not receive pink capsules	92 (1.6)	73 (1.3)
Did not receive blue capsules	136 (2.4)	131 (2.4)
Amount of pink capsules (<2 or >4)	1 (0.0)	3 (0.1)
Amount of blue capsules (not=4)	3 (0.1)	2 (0.0)
Study drug not taken within 48 hours post-randomization	57 (1.0)	42 (0.8)
Received blue capsules prior to end of infusion	22 (0.4)	19 (0.3)
Not a 48-hour completer	8 (0.1)	3 (0.1)

[Source: Table 7 in the updated sponsor's clinical study report submitted on 7/26/2013, verified by the reviewer]

Approximately 56% patients had stable angina, 25% were NSTEMI-ACS, and 19% were STEMI. Overall, the mean age was 64 years; 48% of patients were ≥65 years old. Majority of ITT patients were male (72%). 94% were white.

Table 4 Patient Demographic

		Cangrelor	Clopidogrel	Overall
Age	N	5581	5564	11145
	Mean (SD)	64.0 (11.0)	63.8 (11.0)	63.9 (11.0)
	<65, n (%)	2892 (51.8)	2902 (52.2)	5794 (52.0)
	>=65, n (%)	2689 (48.2)	2662 (47.8)	5351 (48.0)
Gender	Male, n (%)	3982 (71.3)	4042 (72.6)	8024 (72.0)
Race	N	5578	5557	11135
	White, n (%)	5231 (93.8)	5206 (93.7)	10437 (93.7)
	Asian, n (%)	173 (3.1)	177 (3.2)	350 (3.1)
	Black, n (%)	156 (2.8)	152 (2.7)	308 (2.8)
	other, n (%)	18 (0.3)	22 (0.4)	40 (0.4)
Patient types	N	5581	5564	11145
	SA	3158 (56.6)	3059 (55.0)	6217 (55.8)
	NSTE-ACS	1401 (25.1)	1424 (25.6)	2825 (25.3)
	STEMI	1022 (18.3)	1081 (19.4)	2103 (18.9)
Region	N	5581	5564	11145
	US	2099 (37.6)	2089 (37.5)	4188 (37.6)

The distribution of the intended clopidogrel loading dose among various types of patients was shown in **Table 5**. The intended loading dose was balanced between treatment groups (**Table 6**).

Table 5. Administration of 600 mg or 300 mg Clopidogrel by Patient Type

	n/N (%); N=10,942	
	Clopidogrel 600 mg	Clopidogrel 300 mg
All patients	8136 (74.4%)	2806 (25.6%)
Stable angina	4854 (44.4%)	1286 (11.8%)
Unstable angina	434 (4.0%)	187 (1.7%)
NSTEMI	1591 (14.5%)	598 (5.5%)
STEMI	1257(11.5%)	735 (6.7%)

[Source: Sponsor's clinical study report Table 16, verified by the reviewer]

Table 6 Intended Loading Dose by Treatment Group

	Clopidogrel arm	Cangrelor arm	Total
300 mg CPD loading dose	1401	1405	2806
600 mg CPD loading dose	4069	4067	8136
Total	5470	5472	

The PHOENIX trial was conducted using double-dummy techniques, with placebo IV infusion and placebo oral capsules administered to maintain the double blind. While the clopidogrel patients received a loading dose of either 600 mg or 300 mg as specified by the investigator immediately after the randomization, the cangrelor patients received oral placebo capsules to match the clopidogrel 600 mg or 300 mg loading dose. The cangrelor patients, on the other hand, received an oral transition dose of clopidogrel 600 mg immediately after discontinuation of study drug infusion. Therefore, the actual clopidogrel loading dose received by clopidogrel patients can be either 300 mg or 600 mg but the actual loading dose received by all cangrelor patients were 600 mg.

Table 7 showed the distribution of the actual loading dose by treatment group. Only 5 patients in cangrelor group received 300 mg or less of clopidogrel loading dose.

Table 7 Actual Loading Dose by Treatment Group

	0	300mg	600mg	750mg	900mg	<=300mg	>=600mg	Total*
Cangrelor	2	3	5410	0	0	5	5410	5415
clopidogrel	0	1403	4034	1	2	1403	4037	5440

* 87 patients did not have information on actual loading dose

3.2.1.3 Statistical Methodologies

A logistic regression model adjusted for baseline patient status (“normal” vs. “abnormal”) was used to analyze the primary endpoint. According to the SAP, if more than 15% of the patient population was observed to receive 300 mg clopidogrel loading dose at the time of randomization, the primary analysis would also be adjusted by planned clopidogrel loading dose.

Sequential testing was used to test secondary endpoints in the order listed below to control the overall type I error.

1. The incidence of ST at 48 hours post randomization (the key secondary endpoint)
2. the incidence of composite of all-cause mortality and ST at 48 hours post randomization
3. the incidence of all-cause mortality at 48 hours post randomization
4. the incidence of IDR at 48 hours post randomization
5. the incidence of MI at 48 hours post randomization

The key secondary endpoint was analyzed using the same statistical model as the primary endpoint.

The composite event rate was assumed to be 5.1% in the clopidogrel arm and 3.9% in the cangrelor arm (24.5% reduction in odds ratio) based on results from the CHAMPION PCI and PLATFORM studies. Approximately 5,450 patients in each arm (approximately 10,900 in total) would provide a power of 85% to detect this difference at the two-sided overall Type I error of 0.05.

The sponsor proposed an interim analysis for the purpose of efficacy and sample size re-estimation. The interim analysis would be conducted after approximately 70% of enrolled study patients had undergone 48-hour follow-up and CEC adjudication of 48-hour events. In both the original protocol dated June 15, 2010 and protocol amendment dated September 28, 2010, the sponsor proposed to re-estimate sample size using CHW method. Then the sponsor changed the sample size re-estimation algorithm to Gao's method in the interim statistical analysis plan dated April 18, 2011. The final statistical analysis plan was submitted in October 2012. The interim analysis plan was also discussed in the DSMB meeting on May 16, 2011. According to the DSMB meeting minutes, at the 70% interim analysis, "the trial will only be stopped if there is overwhelming efficacy or safety concerns. If the conditional power $\geq 80\%$, the trial will continue as planned. If not, the sample size will be re-estimated and if the power $\geq 80\%$ and the re-estimated sample size $\leq 45,000$ then will increase sample size up to 45,000 and continue enrolling. If the re-estimated sample size is $> 45,000$ to achieve 80% power, then the trial will continue with the originally planned sample size of 10,900 patients." This appears to be consistent with the proposal in the interim statistical analysis plan.

The test statistics used for interim analysis was

$$Z = \log \left(\frac{\hat{p}_1(1 - \hat{p}_2)}{\hat{p}_2(1 - \hat{p}_1)} \right) \left[\frac{1}{n_1 \hat{p}_1(1 - \hat{p}_1)} + \frac{1}{n_2 \hat{p}_2(1 - \hat{p}_2)} \right]^{-1/2}$$

where \hat{p}_1, \hat{p}_2 are the composite incidences for cangrelor arm and control arm, respectively. n_1, n_2 are the sample size in cangrelor arm and control arm respectively.

Group sequential test was performed using the Gamma family alpha spending function (with Gamma = -5). The trial could be stopped for efficacy if the efficacy boundary was crossed ($Z < -2.546$, nominal alpha 0.0109). The stopping boundary is shown in the table below.

Percent of enrollment	Critical value	Nominal alpha	Cumulative alpha
0.7	-2.546	0.0109	0.0109
1.0	-1.984	0.0473	0.05

Conditional power was calculated as follows if the efficacy boundary was not crossed,

$$\phi \left(\frac{\hat{\theta}(t_k - t_{k-1}) - [c_k \sqrt{t_k} - z_{k-1} \sqrt{t_{k-1}}]}{\sqrt{t_k - t_{k-1}}} \right)$$

Where $\hat{\theta}$ is the observed drift parameter at interim analysis, t is the scaled information at interim analysis ($t_{k-1} = t_1$).

If the above calculated conditional power was greater than 80%, the trial would continue as planned with no modification of sample size.

If the above conditional power was less than 80%, the sample size would need to be increased with a cap of 45,000 total patients to achieve a conditional power of at least 80% assuming the observed trend continues. The new sample size would be calculated as $n_{new} \approx \frac{\tau_k}{t_k} n_{planned}$,

$$\text{where } \tau_k = \frac{1}{\theta^2} \left(\frac{1}{\sqrt{t_k - t_{k-1}}} (c_k \sqrt{t_k} - z_{k-1} \sqrt{t_{k-1}}) + Z_\beta \right)^2 + t_{k-1}$$

Type I error would be adjusted for the planned 70% efficacy interim analysis. The nominal alpha at final analysis would be set at 0.047 for primary analysis according to the Gamma family spending function with gamma=-5 if no sample size modification was implemented after the 70% interim analysis. If a sample size increase was implemented, the adjusted final critical value would be:

$$c'_k = \frac{1}{\sqrt{\tau_k}} \left(\frac{\sqrt{\tau_k - t_{k-1}}}{\sqrt{t_k - t_{k-1}}} (c_k \sqrt{t_k} - \sqrt{t_{k-1}} Z(t_{k-1})) + \sqrt{t_{k-1}} Z(t_{k-1}) \right)$$

The planned 70% interim analysis and review took place on June 27, 2012. After review of the interim efficacy and safety data and conditional power analysis, the DSMB recommended to continue the PHOENIX study as planned. No sample size increase was implemented and the final nominal alpha stayed at 0.047.

The primary analysis population was mITT population, which was defined as all patients randomized into the trial and received at least one dose of study drug and underwent the index PCI procedure.

3.2.1.4 Results and Conclusions

The primary efficacy endpoint was the composite incidence of all-cause mortality, MI, IDR, and ST in the 48 hours after randomization. In mITT patient population, 8136 (74.4%) patients were assigned by investigators at the time of randomization to receive a 600 mg loading dose of clopidogrel or matching placebo, and 2806 (25.6%) were assigned to a 300 mg loading dose of clopidogrel or matching placebo. Since more than 15% of the patient population received a 300 mg clopidogrel loading dose, the primary analysis used a logistic regression model adjusted for planned clopidogrel loading dose and baseline patient status (normal vs abnormal as defined by a combination of biomarkers and symptoms).

Table 8 Primary Efficacy Analysis Results

	n (%) of patients		OR and 95% CI	P value
	Cangrelor (N=5472)	Clopidogrel (N=5470)		
Death/MI/IDR/ST (adjusted analysis)	257/5470 (4.7)	322/5469 (5.9)	0.78 (0.66, 0.93)	0.005 LR
Death/MI/IDR/ST (non-adjusted analysis)	257/5470 (4.7)	322/5469 (5.9)	0.79 (0.67, 0.93)	0.006

[Source: Sponsor's clinical study report Table 18, verified by the reviewer]

The primary endpoint results appeared to be driven by stent thrombosis and MI. One major component that contributed to the stent thrombosis events was Intra Procedural Stent Thrombosis (IPST). Removal of IPST from the primary composite endpoint did not change the conclusion. The odds ratio was 0.80 with 95% confidence interval (0.67, 0.95) after removal of IPST. The results remained significant. Table 9 also showed individual components of the primary endpoint.

Table 9 Individual Components of the Primary Efficacy Endpoint

	n (%) of patients		RR and 95% CI	OR and 95% CI	P-value
	Cangrelor (N=5472)	Clopidogrel (N=5470)			
N	5470	5469			
Primary endpoint					
Death/MI/IDR/ST	257 (4.7)	322 (5.9)	0.80 (0.68, 0.94)	0.79 (0.67, 0.93)	0.006
Key secondary endpoint					
Stent thrombosis	46 (0.8)	74 (1.4)	0.62 (0.43, 0.90)	0.62 (0.43, 0.90)	0.010
Death	18 (0.3)	18 (0.3)	1.00 (0.52, 1.92)	1.00 (0.52, 1.92)	>0.999
CV Death	18 (0.3)	18 (0.3)	1.00 (0.52, 1.92)	1.00 (0.52, 1.92)	>0.999
MI	207 (3.8)	255 (4.7)	0.81 (0.68, 0.97)	0.80 (0.67, 0.97)	0.022
Q-wave MI	11 (0.2)	18 (0.3)	0.61 (0.29, 1.29)	0.61 (0.29, 1.29)	0.193
IDR	28 (0.5)	38 (0.7)	0.74 (0.45, 1.20)	0.74 (0.45, 1.20)	0.217

[Source: Sponsor's clinical study report Table 21, verified by the reviewer]

The results of composite endpoint of all-cause mortality, MI, IDR, and ST at 30 days after randomization were consistent with the primary endpoint result. The estimate on odds ratio was 0.85 with 95% CI (0.73, 0.99).

The key secondary efficacy analysis on stent thrombosis at 48 hours after randomization (Table 10) was consistent with primary efficacy results. The odds ratio on the incidence of CEC-adjudicated stent thrombosis was 0.62 with 95% CI (0.43, 0.90) in cangrelor patients compared with clopidogrel patients. The result was statistically significant with p-value of 0.01.

Table 10 Key Secondary Endpoint 48-hour Stent Thrombosis

	n (%) of patients		RR and 95% CI	OR and 95% CI	P-value
	Cangrelor (N=5472)	Clopidogrel (N=5470)			
N	5470	5469			
Stent thrombosis	46 (0.8)	74 (1.4)	0.62 (0.43, 0.90)	0.62 (0.43, 0.90)	0.010
IPST	35 (0.6)	54 (1.0)	0.65 (0.42, 0.99)	0.65 (0.42, 0.99)	0.043
Definite ST	12 (0.2)	22 (0.4)	0.55 (0.27, 1.10)	0.54 (0.27, 1.10)	0.086
Probable ST	0	0	N/A	N/A	N/A
Possible ST	0	0	N/A	N/A	N/A
Acute ST	11 (0.2)	21 (0.4)	0.52 (0.25, 1.09)	0.52 (0.25, 1.09)	0.077

[Source: Sponsor's clinical study report Table 20, verified by the reviewer]

Table 11 summarized the results of other secondary endpoints in the order listed in SAP. The composite endpoint of all-cause mortality and ST at 48 hours post randomization was statistically significant (p-value=0.02). The all-cause mortality had an odds ratio of 1 and a p-value > 0.99 so the sequential testing of secondary endpoints should be stopped here.

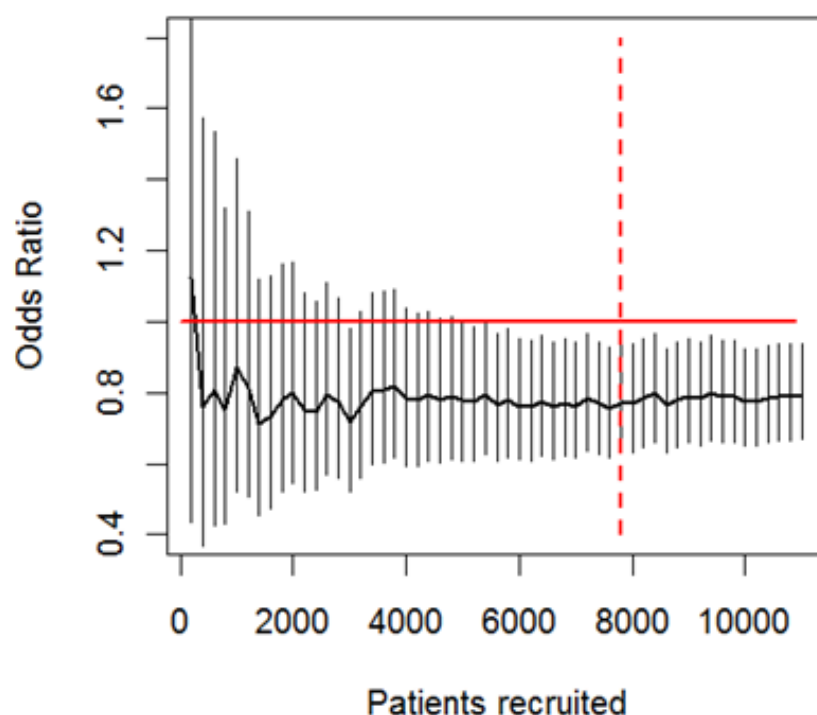
Table 11. Analyses on Secondary Endpoints

Endpoint	Cangrelor (N=5470)	Clopidogrel (N=5469)	RR and 95% CI	OR and 95% CI	p-value
Death/ST	59 (1.1)	87 (1.6)	0.68 (0.49, 0.93)	0.67 (0.49, 0.93)	0.02
Death	18 (0.3)	18 (0.3)	1.0 (0.52, 1.92)	1.0 (0.52, 1.92)	>0.99
MI	207 (3.8)	255 (4.7)	0.81 (0.68, 0.97)	0.80 (0.67, 0.97)	
IDR	28 (0.5)	38 (0.7)	0.74 (0.45, 1.2)	0.74 (0.45, 1.2)	

According to the DSMB June 21 open session meeting minutes, interim analysis “was performed on 7753 ITT and 7614 mITT patients”. This was based on participants enrolled through May 11, 2012. “The 70% interim analysis was performed using the 48 hour best available primary composite from the June 22, 2012 download.” The DSMB had another closed session for the PHOENIX trial on June 27, 2012, in which the 70% interim analysis results were discussed. According to the meeting minutes, there is “a statistically significant reduction in the 48 hour best available primary composite when comparing treatment B with Treatment A (6.1 % (A) vs 4.6%(B))”. The early stopping efficacy boundary was crossed, which implied that the trial may be terminated for efficacy. The DSMB decided to continue the trial as planned.

The reviewer performed independent interim analysis by analyzing only patients enrolled before the cut-off date. There were a total of 7753 ITT subjects and 7615 mITT subjects (3809 in clopidogrel arm and 3806 in cangrelor arm) enrolled by May 11, 2012. There were 179 adjudicated primary events (4.7%) within 48 hours in cangrelor group and 232 events in clopidogrel group (6.1%). The numbers are slightly different from what the meeting minutes reported. This likely was due to the dataset used for interim analysis by then is the “best available” while the adjudication process was still ongoing. The test statistics at the interim look was -2.67, which exceeded the efficacy boundary of -2.546. The conditional power was 88% if the trial went on to the end as planned. The statistical evidence supported the early stopping for efficacy. The DSMB decided to continue the trial as planned and the details on the deliberation for whether or not to continue the trial were in the DSMB meeting minutes. **Figure 3** showed the change on odds ratio along the time. As the vertical dotted line marks the approximate timing for 70% interim analysis, the overall change on odds ratio appears to be robust.

Figure 3 Odds Ratio Estimate Along Time in PHOENIX Study



Note: horizontal red line marks odds ratio of 1. Vertical dotted red line marks the time that 70% interim analysis was done.

Since there was an imbalance on the actual clopidogrel loading dose between the two treatment groups, the reviewer examined the 48 hour composite event rate by the actual clopidogrel loading dose (**Table 12**). The clopidogrel patients with 300 mg loading dose appeared to have higher event rate than the ones with 600 mg loading dose. This was also true for the composite event of Death/MI/IDR/ST at 30 days. The event rates at 30 days were 7.9% and 6.5% for clopidogrel patients with 300 mg loading dose and with 600 mg loading dose, respectively. The composite event rate at 30 days was 5.8% in cangrelor group.

Table 12 Primary Endpoint Event Rate by Actual Clopidogrel Loading Dose

Actual clopidogrel loading dose	Clopidogrel		cangrelor	
	Events	N	Events	N
<=300mg	95 (6.8%)	1403	0	5
>=600mg	218 (5.4%)	4036	244 (4.5%)	5408

The primary analysis pre-specified by the sponsor had the intended loading dose in the logistic regression model. If the intended loading dose 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 higher event rate in patients taking 300 mg clopidogrel loading dose (Table 13). The analyses in Table 13 excluded 87 patients without actual loading dose information. Similar analyses were also performed by imputing the missing loading dose by either intended loading dose or 600 mg. The conclusion remained the same. Nevertheless, the comparisons between cangrelor group and clopidogrel subgroups in Table 13 were not randomized comparisons and the results needed to be interpreted with caution.

Table 13 Comparison of Cangrelor to Clopidogrel with Different Loading Dose

	OR	95% CI	nominal p-value
cangrelor vs clopidogrel with 300 mg loading dose	0.58	(0.46, 0.75)	<0.001
cangrelor vs clopidogrel with 600 mg loading dose	0.84	(0.70, 1.02)	0.07

In summary, CHAMPION PHOENIX demonstrated a statistically significant reduction in the CEC-adjudicated primary efficacy endpoint of death/MI/IDR/stent thrombosis at 48 hours in cangrelor arm when compared with clopidogrel treatment arm. However, there was an imbalance on the actual loading dose between the two treatment groups. The clopidogrel patients with 300 mg loading dose had the highest primary event rate and appeared to drive the study results.

3.2.2 CHAMPION PLATFORM

CHAMPION PLATFORM was a phase III clinical trial in patients who were known to require PCI (with or without stent implantation). Enrolled patients had either non-ST segment elevation myocardial infarction (NSTEMI) or unstable angina (UA). Patients with stable angina (SA) were also eligible until May 8, 2007. The major difference from CHAMPION PCI was that CHAMPION PLATFORM treated patients with clopidogrel at the end of PCI procedure while CHAMPION PCI treated patients at the start of the PCI procedure.

The initial proposed sample size was 4400 and the sample size was increased to 6400 in the protocol submitted to FDA on May 21, 2007. According to the sponsor, the increase was based on the decrease in the overall event rate assumption. The study was also designed to allow for the possibility of re-estimation of sample size based on the interim data following the 70% interim analysis. The study was eventually terminated early for futility based upon Interim Analysis Review Committee (IARC) review of the 70% data from this study.

The primary efficacy endpoint for this study was the incidence of the composite of all-cause mortality, MI, and IDR at 48 hours after randomization. Table 14 showed the primary efficacy result in CHAMPION PLATFORM. The treatment effect was leaning to the right direction but was not statistically significant. Table 15 showed the primary efficacy result in CHAMPION PLATFORM.

Table 14 Primary Efficacy Result in CHAMPION PLATFORM

Population	n/N (%) of patients		Treatment Comparison		
	Cangrelor	Clopidogrel	Odds Ratio	95% CI	P-value
mITT	185/2654 (7.0)	210/2641 (8.0)	0.87	0.71, 1.07	0.1746
ITT	187/2691 (6.9)	213/2664 (8.0)	0.86	0.70, 1.05	0.1456

[Source: Table 13 in sponsor's CHAMPION PLATFORM clinical study report, verified by the reviewer]

Table 15 Secondary Efficacy Result in CHAMPION PLATFORM

Variable	Number (%) of patients		Treatment Comparison		
	Cangrelor (N=2656)	Clopidogrel (N=2645)	Odds Ratio	95% CI	P value
N	2654	2641			
All-cause mortality or MI	180 (6.8)	204 (7.7)	0.87	0.71, 1.07	0.1866
All-cause mortality	6 (0.2)	18 (0.7)	0.33	0.13, 0.83	0.0189
MI	177 (6.7)	191 (7.2)	0.92	0.74, 1.13	0.4207
IDR	19 (0.7)	24 (0.9)	0.79	0.43, 1.44	0.4354
Stent thrombosis	5 (0.2)	16 (0.6)	0.31	0.11, 0.85	0.0223
Stroke	7 (0.3)	5 (0.2)	1.39	0.44, 4.40	0.5708

[Source: Table 14 in sponsor's CHAMPION PLATFORM clinical study report, verified by the reviewer]

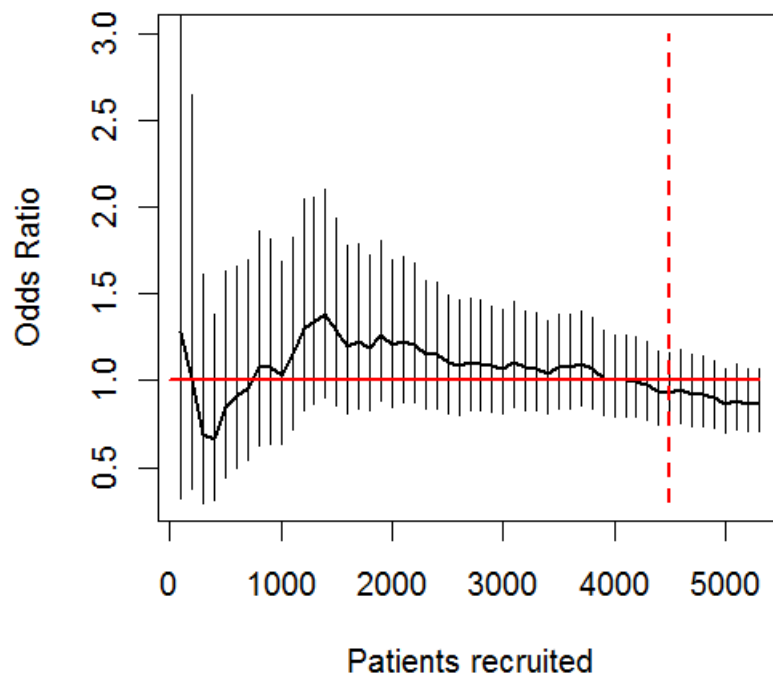
The first patient enrolled in CHAMPION PLATFORM on Oct 3, 2006. 50% interim analysis was based on data received by October 30, 2008. IARC had a closed session meeting to discuss 70% interim analysis results on May 1, 2009. The 70% interim analysis was based on 2260 patients in cangrelor and 2256 patients in clopidogrel (total N=4516). According to the meeting

minutes, the conditional power with a maximum sample size of 6400 was 0.6% under the current trend and only increased to 2.1% when sample size increased to 15,000. If future enrollment was to be restricted to a subpopulation, the results were also similar. The conditional power is 0.5% assuming the same treatment effect as currently observed in the subpopulation. And the conditional power only increased to 2.1% when the sample size increased to 15,000 and future enrollment was to be restricted to the subpopulation only. Based on this analysis, the IARC recommended the sponsor terminate the trial due to futility. The results reported in the IARC meeting minutes were verified by the reviewer. The meeting minutes also reported the trend in mortality (6 in cangrelor arm and 14 in clopidogrel arm in PLATFORM).

The company subsequently announced its plan to stop the trial on May 13, 2009 following the recommendation of IARC. The final total number of subjects enrolled in the trial was 5364. Last patient completed 1-year follow up in the study on December 12, 2010.

Figure 4 showed the change on odds ratio along the time.

Figure 4 Odds Ratio Estimate Along Time in PLATFORM



Note: horizontal red line marks odds ratio of 1. Vertical dotted red line marks the time that 70% interim analysis was conducted.

3.2.3 CHAMPION PCI

CHAMPION PCI was a randomized, double-blind, double-dummy, active controlled, parallel group clinical study in patients requiring PCI with or without stent implantation.

The primary endpoint was the composite of all-cause mortality, MI, and IDR at 48 hours after randomization and it did not win. According to the sponsor, no statistically significant differences between treatment groups were found for the secondary efficacy endpoints.

Table 16 Primary Efficacy Result in CHAMPION PCI

Population	n/N (%) of patients		Treatment Comparison		
	Cangrelor	Clopidogrel	Odds Ratio	95% CI	P-value
mITT SA/UA/NSTEMI patients	290/3889 (7.5)	276/3865 (7.1)	1.05	0.88, 1.24	0.5929
All mITT patients (including STEMI)	308/4335 (7.1)	293/4312 (6.8)	1.05	0.89, 1.24	0.5709

[Source: Sponsor's clinical study report Table 13, verified by the reviewer]

Table 17 Secondary Efficacy Result in CHAMPION PCI

Population Variable	n/N (%) of patients		Treatment Comparison		
	Cangrelor	Clopidogrel	Odds Ratio	95% CI	P value
N	4335	4312			
All-cause mortality or MI	300 (6.9)	273 (6.3)	1.10	0.93, 1.30	0.2709
All-cause mortality	9 (0.2)	9 (0.2)	0.99	0.39, 2.51	0.9910
MI	292 (6.7)	264 (6.1)	1.11	0.93, 1.32	0.2451
IDR	19 (0.4)	30 (0.7)	0.63	0.35, 1.12	0.1140
Stent thrombosis	11 (0.3)	15 (0.3)	0.73	0.33, 1.59	0.4261
Stroke	6 (0.1)	7 (0.2)	0.85	0.29, 2.54	0.7742

[Source: Sponsor's clinical study report Table 14, verified by the reviewer]

The Interim Analysis Review Committee (IARC) had 70% interim analysis meeting on September 22, 2008 and recommended termination of the study due to futility. Detailed discussions can be found in the IARC meeting minutes. Nevertheless, the sponsor decided to continue to enroll in CHAMPION PCI despite the IARC recommendations since no safety issues had been noted. The study, however, was still terminated early when CHAMPION PLATFORM 70% interim analysis results came out.

According to the sponsor, the reductions in the incidence of stent thrombosis in both CHAMPION PLATFORM and CHAMPION PCI led to the hypothesis methodological failure in measurement of peri-procedural MI and prompted more restrictive criteria for defining a PCI MI in patients with abnormal biomarkers at baseline in CHAMPION PHOENIX.

The sponsor believed that CHAMPION PCI and CHAMPION PLATFORM failed because that the protocol definition of MI was not specific enough to differentiate between evolving pre-procedural biomarker MIs and MI events that developed during PCI, when the study drug could have an effect. The sponsor attributed the success of CHAMPION PHOENIX to applying

contemporary endpoint definitions for MI and stent thrombosis that had not been published at the time of CHAMPION PCI and CHAMPION PLATFORM study design. Compared to the earlier CHAMPION trials, the CHAMPION PHOENIX trial was designed to avoid confounding peri-procedural MIs with evolving pre-procedural MIs in patients with elevated biomarkers.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

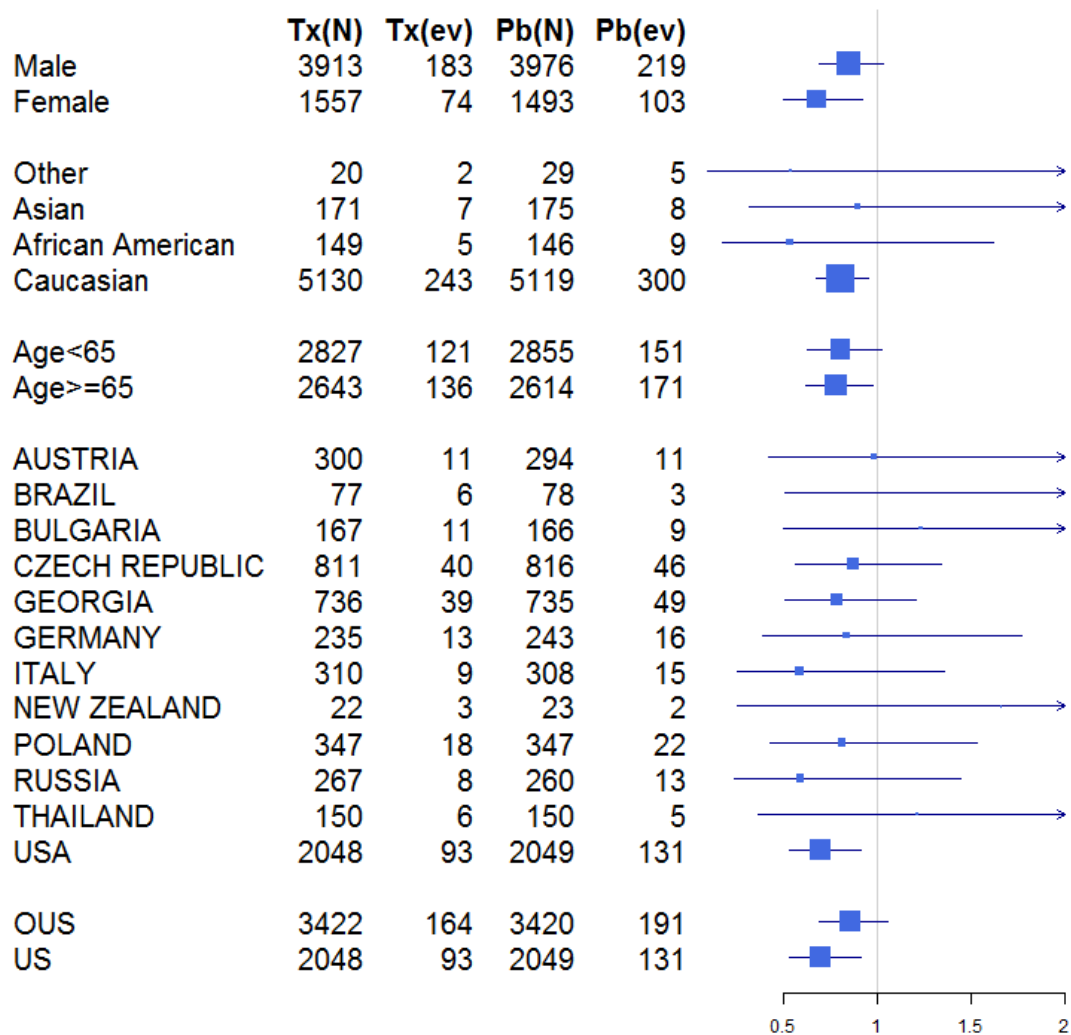
4.1 Gender, Race, Age, and Geographic Region

Subgroup analyses were performed in CHAMPION PHOENIX study to examine the consistency of study results among various subgroups. Table 18 and Figure 5 summarized the composite incidence of all-cause mortality, MI, IDR, and ST in the 48 hours after randomization by subgroups.

Table 18 Subgroup Analysis Results in PHOENIX

Subgroups	Value	Cangrelor			Clopidogrel			Odds Ratio	95% CI
		N	Event	Event rate	N	Event	Event rate		
Gender	Male	3913	183	0.05	3976	219	0.06	0.84	(0.69, 1.03)
	Female	1557	74	0.05	1493	103	0.07	0.67	(0.5, 0.92)
Race	Other	20	2	0.1	29	5	0.17	0.53	(0.09, 3.07)
	Asian	171	7	0.04	175	8	0.05	0.89	(0.32, 2.51)
	African American	149	5	0.03	146	9	0.06	0.53	(0.17, 1.62)
	Caucasian	5130	243	0.05	5119	300	0.06	0.8	(0.67, 0.95)
Age	Age<65	2827	121	0.04	2855	151	0.05	0.8	(0.63, 1.02)
	Age≥65	2643	136	0.05	2614	171	0.07	0.78	(0.61, 0.98)
US	Non US	3422	164	0.05	3420	191	0.06	0.85	(0.69, 1.05)
	USA	2048	93	0.05	2049	131	0.06	0.7	(0.53, 0.92)

Figure 5 Forest Plot on Subgroups in PHOENIX



5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The NDA submission included three CHAMPION trials (CHAMPION PCI, CHAMPION PLATFORM and CHAMPION PHOENIX). All three trials were randomized, double-blind and double-dummy studies.

The sponsor proposed an interim analysis at 70% information time with potential sample size re-estimation in CHAMPION PHOENIX. The early stopping efficacy boundary was crossed at the 70% interim analysis, which implied that the trial can be terminated for efficacy. The DSMB decided to continue the trial as planned. No sample size increase occurred.

CHAMPION PHOENIX demonstrated a statistically significant reduction in the CEC-adjudicated primary efficacy endpoint of death/MI/IDR/stent thrombosis at 48 hours in cangrelor arm when compared with clopidogrel treatment arm. However, there was an imbalance on the actual loading dose between two treatment groups. Almost all cangrelor patients had 600 mg clopidogrel loading dose but over 25% clopidogrel patients received 300 mg loading dose. 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 taking 300 mg clopidogrel loading dose.

CHAMPION PCI and CHAMPION PLATFORM were terminated early due to a low chance of meeting the primary objective. The two trials had a similar adaptation rule with possible sample size re-estimation and enrichment at 70% interim analysis. Both trials met the futility criteria at the interim analysis and the DSMB recommended termination of the trials.

5.2 Conclusions and Recommendations

CHAMPION PHOENIX demonstrated a statistically significant reduction in the CEC-adjudicated primary efficacy endpoint of death/MI/IDR/stent thrombosis at 48 hours in cangrelor arm when compared with clopidogrel treatment arm. However, there was an imbalance on the actual loading dose between the two treatment groups. The clopidogrel patients with 300 mg loading dose appeared to have a higher event rate than the ones with 600 mg loading dose. 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.

APPENDIX

Abbreviations of Medical Terms Used in this Review

IDR	ischemia-driven revascularization
IPST	Intraprocedural stent thrombosis
NSTE-ACS	non-ST segment elevation acute coronary syndrome
NSTEMI	non-ST segment elevation myocardial infarction
PCI	percutaneous coronary intervention
SA	stable angina
ST	stent thrombosis
STEMI	ST-segment elevation myocardial infarction

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/s/

JIALU ZHANG
01/11/2014

HSIEN MING J HUNG
01/13/2014

CLINICAL PHARMACOLOGY REVIEW

NDA Number:	204958
Submission Dates:	04/30/2013
Submission Type:	Original NDA (NME, Standard Review)
Brand Name:	To be finalized
Generic Name:	Cangrelor for injection
Drug Class:	P2Y ₁₂ antagonist
Dosage Form/Route:	Lyophilized powder for injection/intravenous (IV)
Proposed Indications & Dose:	<p>(1) For reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with coronary artery disease undergoing percutaneous coronary intervention (PCI)</p> <p>Proposed dose: 30 µg/kg IV bolus + 4 µg/kg/min IV infusion for at least 2 hours or duration of procedure whichever is longer</p> <p>(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 due to surgery</p> <p>Proposed dose: 0.75 µg/kg/min IV infusion as soon as possible after discontinuation of oral P2Y₁₂ inhibitors until 1 hour prior to surgery</p>
Applicant:	The Medicines Company
OCP Division:	DCP1
OND Division:	Division of Cardiovascular and Renal Products (DCRP)
Reviewers:	Sreedharan Sabarinath, PhD Jeffry Florian, PhD
Team Leaders:	Yaning Wang, PhD Rajanikanth Madabushi, PhD

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1. EXECUTIVE SUMMARY

The Medicines Company has submitted an original New Drug Application (NDA 204958) for cangrelor for injection. The applicant is seeking approval for two proposed indications: (1) for 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 due to surgery.

Cangrelor is an intravenous (IV), reversible P2Y₁₂ antagonist that inhibits adenosine diphosphate (ADP)-induced activation and aggregation of platelets. Cangrelor is a substituted nucleotide and undergoes rapid de-phosphorylation by nucleotidases in the circulation. The effective elimination half-life of cangrelor is about 3-6 minutes and its clearance is independent of the hepatic function.

The clinical development program supporting this NDA included one pivotal efficacy study called CHAMPION-PHOENIX in the PCI setting. There were two other similar Phase III studies (CHAMPION-PCI and CHAMPION-PLATFORM) that were considered as supportive and were used to assess the safety of cangrelor in patients. All these studies used a 30 µg/kg bolus IV dose followed immediately by 4 µg/kg/min continuous IV infusion for at least 2 hours or for the duration of the index procedure, whichever was longer. The CHAMPION-PHOENIX was a double-blind, randomized, controlled study in patients with coronary artery disease (stable angina, ACS and patients with stents) who require P₂Y₁₂ inhibition for PCI (N~10939, 1:1 randomization to cangrelor or clopidogrel). Clopidogrel was the comparator for this study. The primary efficacy endpoint was a composite of death/myocardial infarction (MI)/ischemia driven re-vascularization (IDR)/stent thrombosis (ST) at 48 hours post randomization. The applicant reported a 21 % relative risk reduction with cangrelor compared to treatment with clopidogrel (Odds Ratio: 0.79, 95 % CI 0.66-0.93, p=0.005).

A double-blind, randomized, placebo controlled, PK/PD study (BRIDGE) in patients undergoing cardiac surgery (N~183 for stage II, 1:1 randomization to cangrelor or placebo) formed the basis for seeking approval for the second indication. The BRIDGE study tested cangrelor for bridging patients with ACS or patients with stents at increased risk of thrombotic events due to discontinuation of an oral platelet P2Y₁₂ inhibitor prior to surgery. Platelet reactivity units (PRU) were measured during the treatment period (about 5 days) and the primary efficacy analysis was the percentage of patients with all samples during the infusion achieving PRU < 240, as determined by *VerifyNow*TM P2Y₁₂ test. More than 98 % of patients treated with

cangrelor maintained target platelet reactivity levels (PRU < 240) at all times during the infusion (0.75 µg/kg/min for about 5 days) period compared to about 19 % of placebo treated patients. The threshold platelet reactivity (PRU < 240) used in BRIDGE efficacy analysis is not based on any established pharmacodynamics (PD)-outcome relationships. However, it is not unreasonable to expect that inhibition of platelet reactivity is important for the reduction of thrombotic cardiovascular events. From this perspective the efficacy could be expected to be maintained when platelet reactivity is reduced. Further, upon stopping the IV infusion of cangrelor at least 1 hour before the surgery, the platelet reactivity levels are comparable to that of the control arm (i.e., 5-7 days after stopping oral P2Y₁₂ treatment). The results from the PHOENIX trial, even though in a different population with a different dosing regimen for shorter duration, provide some assurance of bridging between antiplatelet activity and efficacy. Cangrelor can therefore be considered as a viable option to provide antiplatelet effect for up to 1 hour prior to surgery compared to the current standard of care, which requires cessation of the treatment with oral P2Y₁₂ inhibitors for at least 5-7 days before surgery.

The IV formulation used in the Phase III program was similar to the to-be-marketed formulation and therefore no pivotal BE study was required.

1.1 Recommendations

The Office of Clinical Pharmacology (OCP) has reviewed the clinical pharmacology information submitted to the NDA 204958 (cangrelor for injection). The NDA can be approved from a clinical pharmacology perspective.

1.2 Post Marketing Requirements/Commitments

None.

2. SUMMARY OF OCP FINDINGS

2.1 Background

Cangrelor is a platelet P2Y₁₂ antagonist and other approved drugs in this class include ticlopidine, clopidogrel, prasugrel and ticagrelor. Cangrelor reversibly blocks P2Y₁₂ receptors and inhibits ADP induced platelet activation and aggregation. The applicant (The Medicines Company) is seeking approval for cangrelor for injection for two indications: 1) for reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with coronary artery disease undergoing PCI, and 2) to maintain P2Y₁₂ inhibition in patients with 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.

2.2 Current Submission

The current NDA is supported by a single pivotal efficacy study CHAMPION-PHOENIX. There are two other Phase III studies, CHAMPION-PCI and CHAMPION-PLATFORM, which are considered supportive and were used for safety assessments. The clinical pharmacology program for cangrelor comprised of about 16 clinical studies. These studies describe ADME of cangrelor in healthy subjects, PK/PD in healthy subjects and in patients, a renal impairment study, a thorough QT study, PD studies testing transition strategies for cangrelor with clopidogrel and ticagrelor, and characterization of drug-drug interaction with concurrent administration of aspirin, heparin and glyceryl trinitrate.

2.3 Pharmacokinetics

- The pharmacokinetics of cangrelor is linear over the range of 0.025 - 4 µg/kg/min infusion.
- Cangrelor is metabolized rapidly in the systemic circulation by nucleotidases and is considered independent of hepatic function.
- The major circulating metabolite AR-C69712 is several thousand fold less active at human platelet P2Y₁₂ receptors. All other metabolites detected are reported to be pharmacologically inactive.
- Upon continuous infusion, steady-state is reached in ~ 30 minutes. Based on this, the average effective elimination half-life of cangrelor is about 3-6 minutes. Upon stopping of the infusion, cangrelor displays a biphasic decline, with a longer terminal elimination half-life of 14-26 hours at higher doses.

- The plasma protein binding of cangrelor is ~ 98 %
- About 58 % and 35 % of the radiolabeled dose is excreted in urine and feces, respectively

2.4 Exposure-Response relationships

There was no pharmacokinetic (PK) data collected in the Phase III studies and the pharmacodynamics (PD) sampling (to assess platelet inhibition) was limited to about 104 patients from the supportive study CHAMPION-PCI and did not include any subjects from the pivotal efficacy study CHAMPION-PHOENIX. Therefore, any potential relationships between cangrelor exposure and its PD with safety or efficacy outcome measures could not be evaluated.

2.5 Intrinsic factors

2.5.1 Body weight, Sex, Age and Race

A population PK analysis indicated that body weight is the only significant covariate for cangrelor exposure. This impact of body weight is already accounted for in the weight-based cangrelor infusion regimen.

2.5.2 Renal Impairment

A dedicated study comparing healthy subjects with normal renal function (creatinine clearance CrCL > 90 mL/min) and patients with renal impairment (CrCL 20-70 mL/min) studied two maximum infusion rates (2 µg/kg/min and 4 µg/kg/min) for cangrelor in an unbalanced design. Direct comparison of exposures between healthy subjects and renally impaired subjects within dose groups was difficult in this study because of the lesser number of subjects in the reference groups (N ~ 3 for the higher infusion rate group). However, the effective elimination half-life and PK/PD for platelet inhibition of cangrelor were not significantly altered in renally impaired subjects. Further, comparison of the PK in patients with renal impairment in this study with pooled healthy controls from the cangrelor development program showed that impairment of renal function did not significantly alter the pharmacokinetics of cangrelor. The Phase III studies for cangrelor included patients with impaired renal function (CHAMPION-PLATFORM: N ~ 623 and CHAMPION-PCI: N ~ 688 patients with CrCL < 60 mL/min) and no significant changes in the safety/efficacy profile of cangrelor was evident in these patients. Therefore, no dose adjustments are proposed for cangrelor in patients with renal impairment.

2.5.3 Hepatic Impairment

Since the biotransformation of cangrelor is believed to be mediated through nucleotidases in systemic circulation, which is considered independent of hepatic function, there was no dedicated hepatic impairment study included in the clinical development program.

2.5.4 Pediatrics

The PK of cangrelor is not studied in pediatrics.

2.6 Drug-Drug Interactions

In vitro studies indicated that cangrelor and its metabolite AR-C69712 have minimal potential to inhibit or induce CYP enzymes at therapeutic concentrations. The PK of cangrelor and AR-C69712 did not alter significantly when co-administered with a combination of aspirin, heparin and glyceryl trinitrate. The inhibition in ADP induced platelet aggregation by cangrelor was comparable between both treatment groups in this study. But there were prolongation in bleeding times and higher incidence of adverse events like purpura and headaches when cangrelor was co-administered with a combination of aspirin, heparin and glyceryl trinitrate.

Clinical studies also evaluated the transition strategies while switching from and to oral P2Y₁₂ drugs like clopidogrel and ticagrelor with cangrelor. There is attenuation in clopidogrel pharmacological effects on platelets when co-administered with cangrelor. This could probably be because of the competition between cangrelor and the active metabolite of clopidogrel (which has very short plasma half-life) for P2Y₁₂ receptors. However, administering clopidogrel after stopping cangrelor infusion did not alter the anti-platelet effects usually seen with clopidogrel. This is because of the short effective half-life (3-6 minutes) of cangrelor. However, the pharmacological effect of ticagrelor ($t_{1/2}$ ~ 7 hours for ticagrelor and ~ 9 hours for the active metabolite) was not significantly altered when co-administered with cangrelor.

2.7 Biopharmaceutics

The pivotal efficacy study CHAMPION-PHOENIX and the Phase II Study BRIDGE used the same IV formulation (cangrelor diluted in sterile normal saline) as the proposed marketing image formulation.

3. QUESTION BASED REVIEW

3.1 General Attributes

Cangrelor is a reversible P2Y₁₂ antagonist that blocks ADP induced platelet activation and aggregation. The chemical structure of cangrelor is similar to that of adenosine triphosphate, ATP (Figure 1). Other approved drugs in this class include ticlopidine, clopidogrel, prasugrel (all are thienopyridine pro-drugs and are irreversible blockers of platelet P2Y₁₂ receptors) and ticagrelor (a reversible blocker).

3.1.1 Drug Substance

Cangrelor for injection is a sterile white to off-white lyophilized powder for IV infusion. The chemical name of cangrelor is tetra sodium salt of N6-[2-(methylthio)ethyl]-2-[(3,3,3-trifluoropropyl)-5'-adenylic acid, monohydride with (dichloromethylene)bisphosphonic acid. It has a molecular formula of C₁₇H₂₁N₅Cl₂F₃Na₄O₁₂P₃S₂ and a molecular weight of 864.3 g/mol (See Figure 1B).

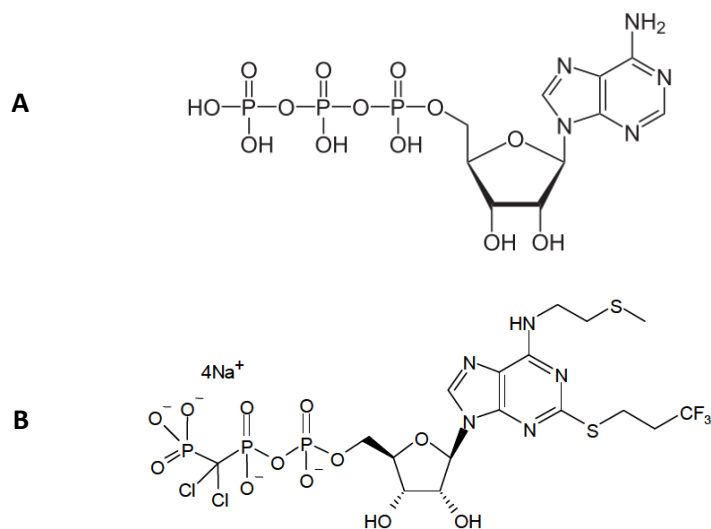


Figure 1 The chemical structures of (A) adenosine triphosphate, ATP and (B) cangrelor

3.1.2 What are the proposed mechanism of action and therapeutic indication?

Cangrelor reversibly blocks the P2Y₁₂ platelet receptors and prevents ADP-induced platelet activation and aggregation. ADP plays a key role in the genesis of physiological platelet-rich hemostatic plugs and of pathological arterial thrombi. The transduction of the ADP signal involves its interaction with 2 platelet receptors, the G_q-coupled P2Y₁ receptor and the G_i-

coupled P2Y₁₂ receptor. Concomitant activation of both the G_q and G_i pathways by ADP is necessary to elicit normal platelet aggregation (Figure 2).

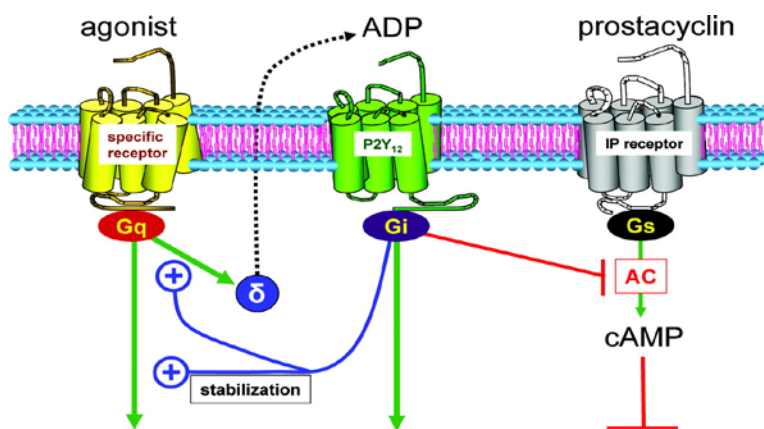


Figure 2 Role of P2Y₁₂ receptors in platelet aggregation¹. Green arrows indicate activation; red line, inhibition; blue line, amplification; and dotted black line, secretion. Ref. Cattaneo M *et al.* Circulation. 2010, 121:171-179

The applicant is seeking approval for cangrelor for the following two indications:

- **PCI:** For the reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with coronary artery disease undergoing percutaneous coronary intervention (PCI), and
- **BRIDGE:** 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

¹ ADP, by interacting with P2Y₁₂, a 7-transmembrane receptor that is coupled to the inhibitory G protein G_i, induces platelet aggregation and amplifies the aggregation response that is induced by other agonists or by ADP itself, interacting with its other platelet receptor, P2Y₁. In addition, P2Y₁₂ stabilizes the platelet aggregates and amplifies the secretion of platelet dense granules stimulated by secretion-inducing agonists (which are coupled to G_q). Although P2Y₁₂ is coupled to inhibition of adenylyl cyclase (AC) through G_i, this function does not appear to be directly related to P2Y₁₂-mediated platelet activation. However, it could have important implications *in vivo*, where platelets are exposed to the inhibitory prostaglandin PGI₂ (prostacyclin), which inhibits platelet aggregation by increasing platelet cAMP through activation of AC mediated by G_s; inhibition of AC by P2Y₁₂ counteracts the inhibitory effect of prostacyclin, thereby favoring the formation of platelet aggregates *in vivo*.

3.1.3 What are the current treatments available for the proposed indication?

Several oral P2Y₁₂ antiplatelet drugs, such as ticlopidine, clopidogrel, prasugrel, and ticagrelor are available that can reduce thrombotic risks by inhibiting platelet activation and aggregation. The ACCF/AHA/SCAI practice guidelines² for PCI recommends the use a loading dose of a P2Y₁₂ inhibitor in patients undergoing PCI with stenting (options include clopidogrel 600 mg or prasugrel 60 mg or ticagrelor 180 mg) before the procedure (within 24 hours) and then continue on maintenance oral antiplatelet therapy after the procedure.

Most of the currently approved oral antiplatelet drugs have an onset of pharmacological action of few hours and an offset of up to few days. Patients receiving oral antiplatelet drugs who require elective surgery are currently advised to stop taking their antiplatelet drugs for 5-7 days so as to minimize the risk for bleeding during surgery. Such discontinuation may result in an elevated risk for thrombosis. The applicant is seeking an indication where cangrelor provides continued platelet inhibition while oral P2Y₁₂ antiplatelet drugs are stopped, prior to an elective surgery. The offset in pharmacological activity for cangrelor is approximately < 2 hours and the treatment can continue up to few hours prior to surgery without increasing the risk for bleeding during surgery. There are no drugs approved specifically for this proposed indication, even though bridging anticoagulant therapy (*e.g.* heparins) is available for some instances.

3.1.4 What are the proposed dosages and route of administration?

Cangrelor is available as lyophilized powder for IV infusion. Each 10 mL vial containing 50 mg of cangrelor (free acid) is reconstituted with sterile water for injection and further diluted with normal saline (0.9 % NaCl) or 5 % dextrose for intravenous infusion.

The proposed dose for the PCI indication is a bolus IV dose of 30 µg/kg prior to the procedure followed immediately by a continuous IV infusion of 4 µg/kg/min for 2 hours or for the duration of the PCI procedure, whichever is longer.

For the bridge indication a continuous IV infusion of cangrelor at a rate of 0.75 µg/kg/min after stopping oral P2Y₁₂ inhibitors and continuing the infusion until one hour prior to administration of anesthesia for surgery is proposed. The bridging period could be up to 7 days.

² 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. Journal of the American College of Cardiology, 2011, 58: e44-122

3.2 General Clinical Pharmacology

3.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The primary evidence for efficacy in support of the PCI indication is from CHAMPION-PHOENIX Phase III study (TMC-CAN-10-01) in patients with stable angina (SA), non-ST-segment elevation ACS (NSTEMI) and ST-segment elevation myocardial infarction (STEMI). A single placebo-controlled Phase II study called BRIDGE (TMC-CAN-08-02) in patients with ACS or with stents awaiting cardiac surgery supports the bridge indication. The clinical pharmacology program included PK studies in healthy subjects (SC-931-5014, SC-931-5036, SC-931-9064, TMC-CAN-04-02) as well as in patients with UA or myocardial infarction (SC-931-5058, SC-931-5060, SC-931-5135), mass balance and excretion studies (SC-931-9017 and SC-100199), a DDI study with concurrent administration of a combination of aspirin, heparin and glyceryl trinitrate (SC-931-5037), a PK study in patients with impaired renal function (SC-931-5109) and studies assessing transition strategies while switching from or to cangrelor for oral P2Y₁₂ drugs like clopidogrel and ticagrelor (MDCO-CAN-12-03, TMC-CAN-04-02, TMC-CAN-08-02). The design features of the Phase III studies are described in section 3.2.3.

3.2.2 Were correct moieties identified and properly measured to access clinical pharmacology?

The applicant measured cangrelor (AR-C69931) and its major circulating metabolite AR-C69712, a nucleoside formed by de-phosphorylation in human plasma using validated analytical methods. This metabolite is reported to be several thousand (~ 70,000) fold less potent than cangrelor at human P2Y₁₂ receptors. Some clinical pharmacology studies (*e.g.* SC-931-5014, SC-931-5036 and SC-931-5109) monitored additional pharmacologically inactive metabolites AR-C90439, AR-C90441 and AR-C71301.

3.2.3 What are the key features of the Phase III trials of cangrelor?

The applicant conducted three Phase III studies (CHAMPION-PCI, PLATFORM and PHOENIX) in patients with ACS/coronary artery disease (CAD) undergoing PCI (Figure 3). All these studies used a single dose level of 30 µg/kg/min IV bolus followed by 4 µg/kg/min infusion for cangrelor and had clopidogrel (300 or 600 mg) as comparator.

CHAMPION-PHOENIX was the pivotal efficacy study and used more restrictive criteria to define per-procedural myocardial infarction (MI) in patients for whom baseline MI could not be excluded compared to other two studies, in addition to other subtle design differences. CHAMPION-PHOENIX was a prospective, randomized (1:1), double-blind, double-dummy, comparator controlled (clopidogrel 300 or 600 mg), parallel-group, superiority study in

approximately 11145 patients. The primary efficacy endpoint was a composite of death/MI/IDR/ST assessed at 48 hours after randomization. The components of primary efficacy endpoint were also assessed at 30 days. The safety endpoints included various bleeding assessments, such as GUSTO bleeding. There was no PK/PD assessments included in this study. Details of the dose selection are provided in Section 3.2.4.

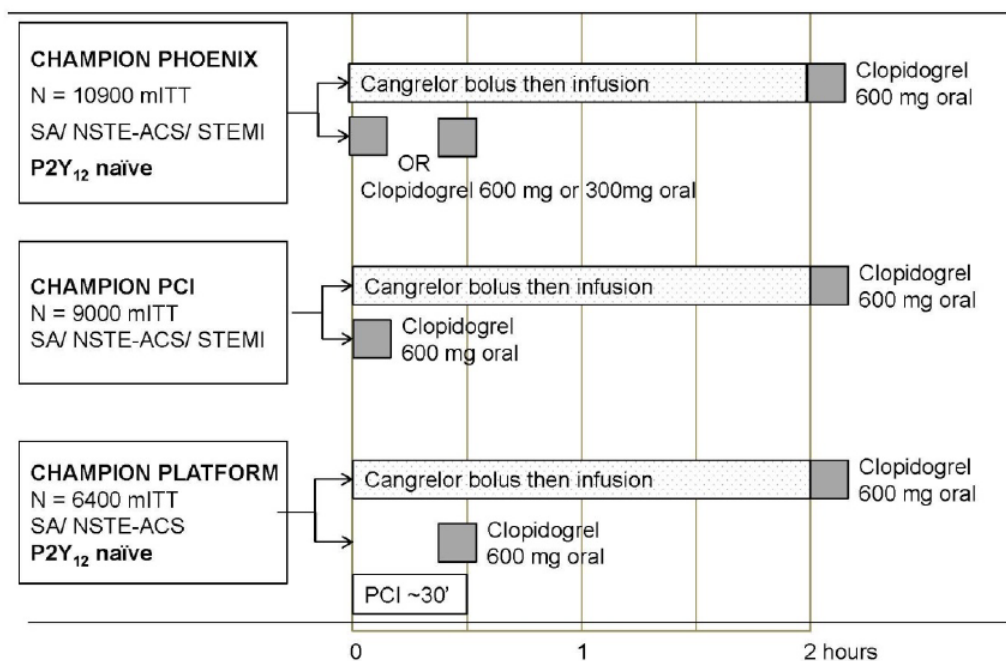


Figure 3. CHAMPION study designs. The shaded square box represents the approximate timing of clopidogrel dose post randomization. CHAMPION-PLATFORM did not include STEMI patients and the clopidogrel dose (600 mg) was administered immediately post-PCI procedure in the comparator arm in this study. The average duration of the PCI procedure is ~ 30 minutes. CHAMPION-PCI study included both P2Y₁₂ naïve and experienced patients. SA - Stable Angina, NSTE-ACS – non-ST segment elevation acute coronary syndrome, STEMI – ST-segment elevation myocardial infarction, PCI – percutaneous coronary intervention, mITT – modified intent-to-treat.

3.2.4 How was the Phase III doses selected?

3.2.4.1 For PCI indication

The cangrelor dose selection was based on results from early phase PK/PD studies. Results from studies in healthy subjects (SC-931-5014 and SC-931-5036) demonstrated the dose-response (platelet inhibition) of cangrelor and provided justification for using an IV bolus dose to achieve steady state cangrelor concentrations (hence, targeted platelet inhibition) faster on

treatment. A Study in patients with unstable angina or non-Q-wave MI (SC-931-5058) provided additional support for 2 and 4 µg/kg/min intravenous infusion rates in a PCI population based on a target of 90 % platelet inhibition in > 80 % of patients. Finally, the study TMC-CAN-04-02 in healthy subjects evaluated a dosing regimen with combined IV bolus and maintenance infusion. This study was used for supporting the use of 30 µg/kg IV bolus dose followed by a 4 µg/kg/min IV infusion based on platelet inhibition assessments.

3.2.4.1.1 Dose-response in healthy volunteers and justification for bolus dosing

The dose-ranging studies conducted in healthy volunteers (SC-931-5014 and SC-931-5036) demonstrated the relationship between inhibition of platelet aggregation and cangrelor infusion rate, with near complete inhibition at infusion rates at or exceeding 1 µg/kg/min (Figure 4). In addition, as steady state exposures of cangrelor are achieved after ~ 30 minutes, there is a period (~ 30 minutes) between the start of the infusion and steady-state where the percentage of platelet inhibition is increasing to near maximum. To eliminate this initial 30-minute period required to achieve complete inhibition, the applicant used a bolus dose that is 7.5-fold higher than the proposed target infusion rate.

The bolus dose necessary to achieve similar exposures to a target infusion rate is calculated as³: $\text{bolus dose} = \text{Target Infusion}/\text{CL} \times V$. The Target Infusion rate here is 4 µg/kg/min (See Section 3.2.4.1.2 for details). Based on the clearance (46.1 L/hr) and central volume of distribution (3.4 L) estimates from the population PK model, a bolus dose, which is about 4.4-fold higher than the target infusion rate would be necessary for cangrelor. The bolus dose selected by the applicant will exceed the dose necessary to achieve platelet inhibition expected at steady state for the accompanying target infusion, but will quickly equilibrate given the rapid effective half-life of 3-6 minutes for cangrelor.

³ Under the assumption of a One-Compartment PK model

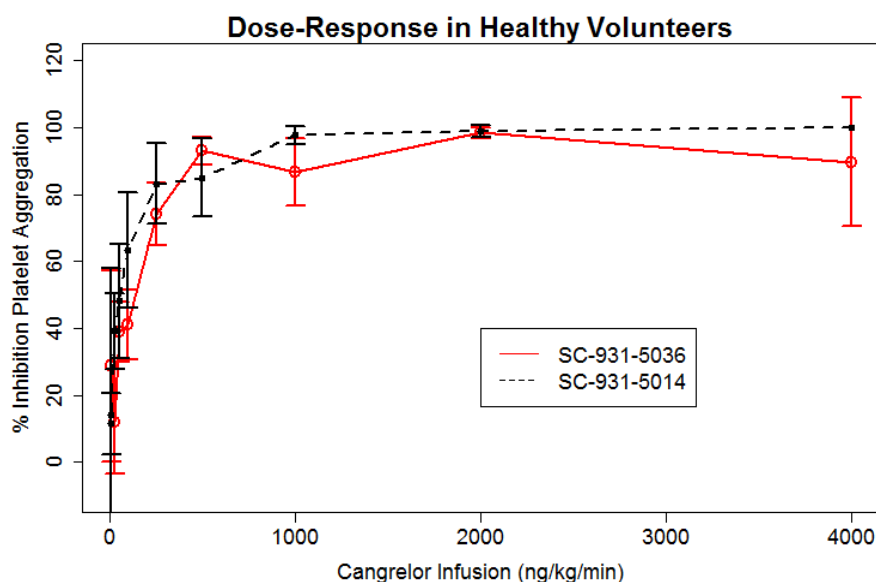


Figure 4. Percent inhibition of platelet aggregation to 3 μ M ADP as measured by whole blood impedance assay (WBIA) versus cangrelor infusion rate in healthy male/female volunteers.

3.2.4.1.2 Dose-response in patients and justification for target infusion rate

Study SC-931-5058 evaluated cangrelor at three separate stepped, dose titration schemes followed by a plateau infusion in patients with UA or non-Q-wave MI. For the purpose of this analysis, we will focus on the observed percentage of platelet inhibition 30-minutes following each dose step (0.05, 0.2, 0.5, 1, 2, or 4 μ g/kg/min) across the three dose escalation schemes (Parts I & II: 0.05, 0.2, 0.5 and 2 μ g/kg/min, Part III: 0.2, 1, 2, 4 μ g/kg/min) and treatment duration. Similar to the observations in healthy volunteers, cangrelor doses of 1 μ g/kg/min or higher were associated with a mean percentage inhibition of ADP-induced platelet aggregation approaching 100 % (Figure 5). However, a categorical analysis of individual patient platelet inhibition demonstrates that while the mean percentage of platelet inhibition may have been similar at cangrelor doses of 1 μ g/kg/min or higher, cangrelor doses of 2 or 4 μ g/kg/min were associated with a greater percentage of patients achieving complete (~100 %) inhibition of ADP-induced platelet aggregation (Table 1). This observation supports that while average maximum inhibition may be achieved at lower infusion rates, higher cangrelor doses may be necessary to achieve maximum inhibition in the overall population. The applicant used this observation as a justification for carrying forward a high infusion rate (4 μ g/kg/min) to the Phase III studies in the PCI setting.

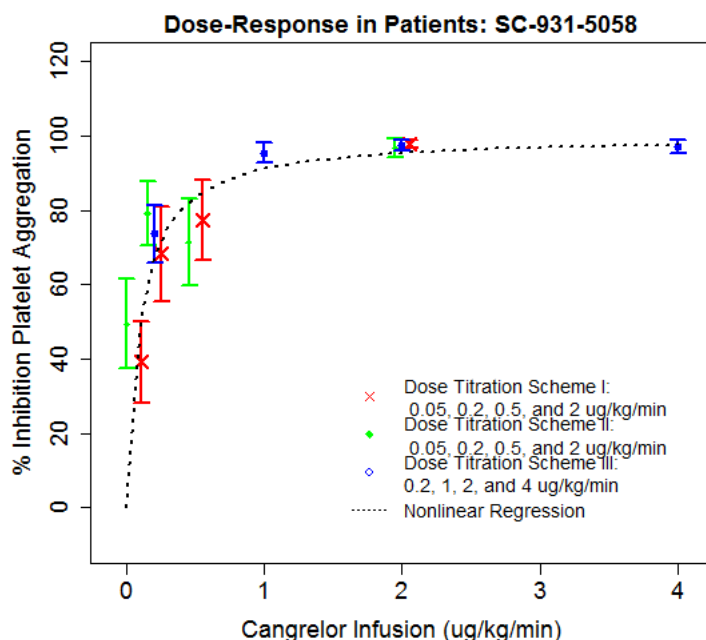


Figure 5. Percent inhibition of platelet aggregation to 3 μ M ADP as measured by whole blood impedance assay (WBIA) versus cangrelor infusion rate in patients with unstable angina or non-Q-wave myocardial infarction. Parts I, II and III represent different dose escalation schemes. Values are mean and standard error.

Table 1 Percentage of patients in study SC-931-5058 exhibiting different levels of platelet inhibition with 3 μ M ADP as measured by WBIA for various cangrelor infusions (0.05 – 4 μ g/kg/min).

Cangrelor IV (μ g/kg/min)	N	Number (%) of Patients Exhibiting Different Levels of Platelet Inhibition			
		≤ 60 %	> 60 to 80 %	> 80 to < 100 %	100 %
0.05	24	17 (71 %)	3 (13 %)	4 (17 %)	0
0.2	34	10 (29 %)	9 (26 %)	10 (29 %)	5 (15 %)
0.5	21	6 (29 %)	5 (24 %)	5 (24 %)	5 (24 %)
1	14	0	1 (7 %)	8 (57 %)	5 (36 %)
2	38	0	0	13 (34 %)	25 (66 %)
4	14	0	0	2 (14 %)	12 (86 %)

3.2.4.1.3 Combined IV bolus and maintenance infusion regimen

A combined bolus and infusion maintenance dose was evaluated in study TMC-CAN-04-02. This study was conducted in healthy volunteers and compared platelet inhibition using cangrelor administered as either: 15 μ g/kg IV bolus followed by 2 μ g/kg/min infusion or 30 μ g/kg IV bolus

followed by 4 µg/kg/min infusion. The duration of the cangrelor infusion was 1-hour, and ADP-induced platelet inhibition was assessed using a variety of PD measurements including whole blood impedance aggregation (WBIA) and flow cytometry for platelet activation in response to ADP. Based on WBIA complete inhibition of platelet activation was achieved following bolus administration for both doses and maintained throughout the cangrelor infusion period.

Based on a 5 µM ADP-induced P-Selectin expression assessed by flow cytometry, maximum inhibition was achieved in both treatment arms after the bolus, but it was only maintained during the infusion in the high infusion rate arm while it declined to 85 % by the end of the infusion in the low infusion rate arm. Further separation between the tested regimens was observed at 20 µM ADP-induced P-Selectin expression (Figure 6) with greater maximum inhibition in the high dose arm following the bolus administration and maintained throughout the infusion. Median percent inhibition was about 96 % in the high dose arm and about 87 % in the low dose arm, respectively.

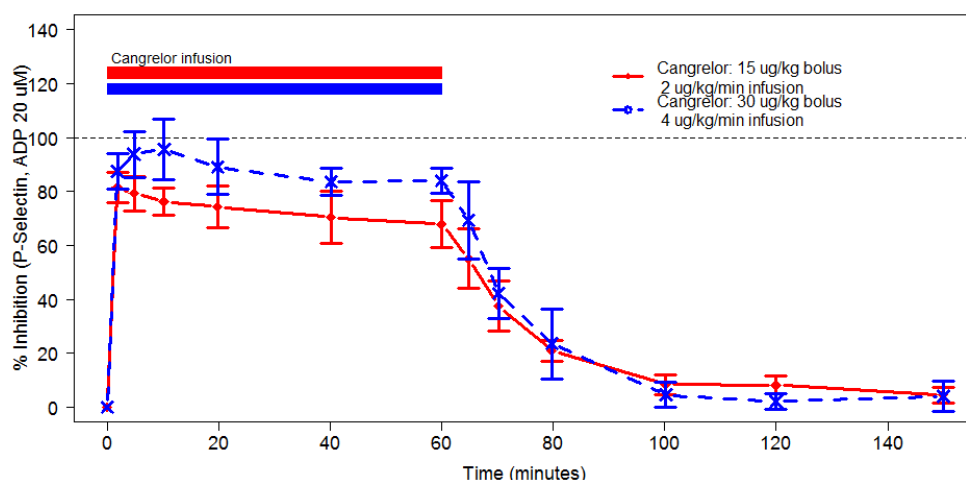


Figure 6. Percent inhibition of platelet response to 20 µM ADP as measured by flow cytometry for the low dose (15 µg/kg IV bolus followed by 2 µg/kg/min infusion) and high dose (30 µg/kg IV bolus followed by 4 µg/kg/min infusion) regimens

3.2.4.2 For BRIDGE indication

The Phase II study TMC-CAN-08-02 (BRIDGE, Stage I) provided supporting evidence for the proposed bridging dose for transitioning patients from oral P2Y₁₂ inhibitor therapy to cangrelor while awaiting coronary artery bypass graft (CABG) surgery. Dose-escalating cohorts (n=5) of 0.5, 0.75, 1.0, and 1.5 µg/kg/min IV infusions were planned until > 60 % platelet inhibition (as assessed by *VerifyNow*TM P2Y₁₂ assay) was achieved in 80 % of the daily samples. A cangrelor dose of 0.5 µg/kg/min maintained platelet inhibition > 60 % in about 77 % (13/17) of patient

samples. The second dose cohort at 0.75 $\mu\text{g}/\text{kg}/\text{min}$ maintained platelet inhibition $> 60\%$ in 94 % (17/18) of daily samples and was chosen for testing in Stage II of BRIDGE study. A cumulative distribution plot (Figure 7) of the observations for 0.5 and 0.75 $\mu\text{g}/\text{kg}/\text{min}$ infusions supports the conclusion that the higher dose cangrelor arm achieved a greater percentage of samples with platelet inhibition $> 60\%$. Both doses achieved a similar percentage of samples with platelet inhibition $> 80\%$. The conclusion regarding the inadequacy of 0.5 $\mu\text{g}/\text{kg}/\text{min}$ is based on one additional sample falling below the pre-specified platelet inhibition criteria.

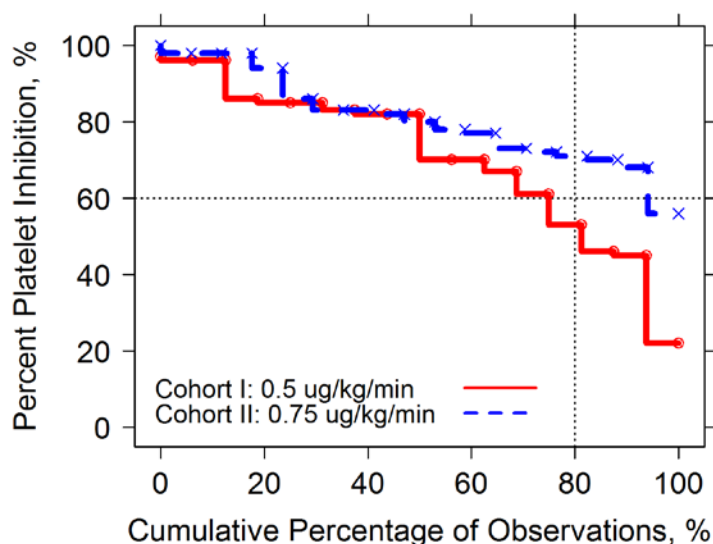


Figure 7. Cumulative frequency of samples with platelet inhibition $> 60\%$ as reported by *VerifyNow*TM P2Y₁₂ test for cangrelor infusion rates of 0.5 and 0.75 $\mu\text{g}/\text{kg}/\text{min}$ in Stage I of BRIDGE study.

Stage II of BRIDGE study was a randomized, double-blind, placebo-controlled trial comparing cangrelor 0.75 $\mu\text{g}/\text{kg}/\text{min}$ and placebo infusions in patients transitioning from oral P2Y₁₂ therapy while awaiting CABG surgery. The PRU value profiles for the two treatment arms from the start of treatment (left) and prior to/following surgery (right) are shown below in Figure 8. In patients randomized to placebo, PRU values increased from baseline reflective of waning effect from their previous oral P2Y₁₂ therapy. In contrast, PRU values remained suppressed in the cangrelor treatment arm while on cangrelor infusion. The primary efficacy endpoint for this stage was a comparison of percentage of patients with PRU < 240 as determined by *VerifyNow*TM P2Y₁₂ assay between placebo and cangrelor treatment groups. This endpoint was achieved with 99 % of cangrelor patients (83/84) with all PRU samples < 240 compared to 19 % (16/84) in the placebo arm.

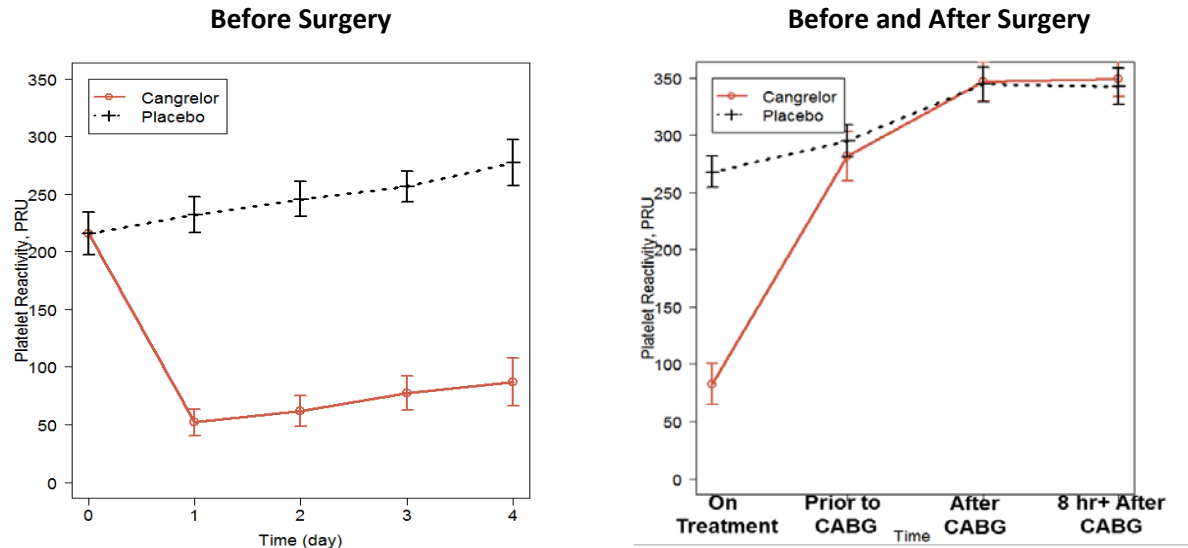


Figure 8. Platelet reactivity measured as *VerifyNow*TM P2Y₁₂ PRU versus time from Study TMC-CAN-08-02 for cangrelor (red solid line) and placebo (black dotted line) treatment arms. PRU values from baseline up until the time of CABG surgery are shown on the left pane. PRU values from the last on-treatment assessment, prior to, and following CABG surgery are shown on the right.

Physicians were instructed to discontinue cangrelor treatment 1 to 6 hours prior to surgery to permit recovery of platelet activity prior to surgery. The median time between the end of the cangrelor infusion and the start of surgery was about 3 hours with an interquartile range of about 2-4 hours. Using this approach, the PRU values were similar between cangrelor and placebo treatment arms prior to initiation of surgery (280 versus 298; p-value=0.21). The CABG-related bleeding events were similar between cangrelor (10/102; 10 %) and placebo (10/96; 10 %) treatment arms, though the sample size was not sufficient enough to determine whether there was a difference in CABG-related bleeding events between treatment arms. There were slightly higher non-CABG bleeding events in the cangrelor arm. For GUSTO (severe/life-threatening), TIMI (major), and AUCITY (major) bleeds, there were 2 % (2/102), 0 % (102), and 17 % (12/102) events in the cangrelor arm compared to 1 % (1/96), 0 % (0/96), and 5 % (5/96) events in the placebo arm.

In summary, the proposed dose of 0.75 µg/kg/min IV infusion resulted in significantly greater platelet inhibition based on PRU as assessed by *VerifyNow*TM than placebo while transitioning patients awaiting CABG surgery from oral P2Y₁₂ therapy. The study also demonstrated that

discontinuation of 0.75 µg/kg/min cangrelor infusion at a median of 3 hours (interquartile range: 2 to 4 hours) prior to CABG surgery resulted in similar PRU values between the cangrelor and placebo arms just prior to surgery. The selected dose of cangrelor achieved platelet inhibition similar to or greater than that achieved with clopidogrel at steady state as the Day-1 PRU values were significantly lower than baseline. The benefit of achieving PRU values lower than that achieved with the regular maintenance dose of oral P2Y₁₂ drugs is not known.

3.2.5 What are the characteristics of the exposure or dose-response relationships for efficacy or safety?

The three Phase III studies (CHAMPION-PCI, PLATFORM, and PHOENIX) included only one dose level (30 µg/kg IV bolus followed by 4 µg/kg/min IV infusion) so a dose-response analysis could not be conducted.

There was no PK data collected from these studies and the PD sampling (to assess platelet inhibition) was limited to about 104 patients from the supportive CHAMPION-PCI and CHAMPION-PLATFORM studies and did not include any subjects from the pivotal efficacy study CHAMPION-PHOENIX. Therefore, any potential relationships between cangrelor exposure or its PD with safety and efficacy outcome measures could not be evaluated.

3.2.6 Does cangrelor prolog QT or QTc interval?

A double-blind, placebo and positive (moxifloxacin 400 mg) controlled, cross-over study assessed the effect of cangrelor at therapeutic (30 µg/kg IV bolus plus 4 µg/kg/min infusion for 3 hours) and supra-therapeutic dose (60 µg/kg IV bolus plus 8 µg/kg/min infusion for 3 hours) levels on QT/QTc interval in healthy volunteers (Study TMC-CAN-08-01). The applicant concluded that cangrelor does not affect cardiac repolarization and the QT-IRT review concurred with this conclusion (Ref. QT-IRT Review, DARRTS dated 11/17/2011).

3.3 *Pharmacokinetics of Drug and Metabolite(s)*

Cangrelor undergoes rapid de-phosphorylation in systemic circulation and forms its primary circulating metabolite AR-C69712. This metabolite is reported to be 70, 000 times less potent than cangrelor at P2Y₁₂ human platelet receptors.

3.3.1 What are the single and multiple dose PK parameters?

Ascending dose PK/PD studies with 4-step IV infusions up to 4 µg/kg/min were performed in healthy male and female subjects (SC-931-5014 and SC-931-5036). The total treatment duration was about 24 hours. The maximum plasma concentrations (C_{max}), AUC and steady state plasma concentrations (C_{ss}) were dose-linear up to the maximum tested infusion rate of 4 µg/kg/min. At the end of infusion, cangrelor concentrations declined in a bi-phasic manner, with an

effective initial half-life of about 3.5 to 6 minutes and a longer terminal elimination half-life up to 14 to 26 hours at the highest dose level. The PK of the primary metabolite AR-C69712 was also linear with dose and showed a $t_{1/2}$ of about 2-3 hours. The molar ratio of AR-C69712 to cangrelor at steady state was approximately 0.8-0.9.

3.3.2 How does the PK of the drug and metabolite(s) in healthy volunteers compare to that in patients?

The PK of cangrelor is comparable in healthy volunteers and in patients included in the clinical development program.

3.3.3 Based on the PK parameters, what is the degree of linearity or non-linearity in dose-concentration relationship?

The maximum plasma concentrations (C_{max}), AUC and steady state plasma concentrations (C_{ss}) were dose-linear up to the maximum tested infusion rate of 4 $\mu\text{g/kg/min}$ in healthy subjects for cangrelor (Figure 9) and its primary circulating metabolite AR-C69712.

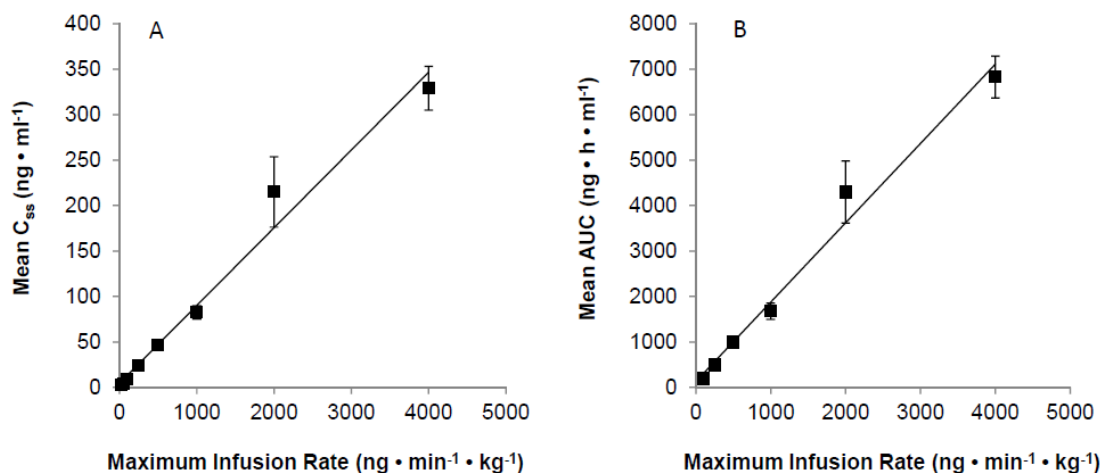


Figure 9. Dose-linearity plots for steady state plasma concentrations (A) and AUC (B) for cangrelor in healthy volunteers. Ref. Study Report SC-931-5014

3.3.4 What is the inter- and intra-subject variability of PK parameters, and what are the major causes of variability?

The inter-individual variability (% CV) for PK parameters in healthy volunteers ranged from 19-32 % for cangrelor (Study TMC-CAN-04-02). Based on the population PK analysis the between subject variability on clearance (CL) and volume of distribution (V_d) were about 19 and 23 % respectively. Since cangrelor is administered as a one-time single dose regimen the within subject variability was not estimated.

3.3.5 What intrinsic factors (age, sex, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

3.3.5.1 Body weight, Sex, Age and Race

Of the demographic and laboratory covariates evaluated, only body weight was identified as having a significant effect on cangrelor pharmacokinetics. The body weight effect was included as an allometric scaling coefficient on all compartmental parameters (coefficient of 0.75 for central compartment clearance [CL] and intra-compartment transit rate [Q]; coefficient of 1.0 for central [V1] and peripheral [V2] volume of distribution). This impact of body weight was already accounted for in the weight-based cangrelor infusion regimen. Over a weight range of 50 to 100 kg and the proposed dosing regimens for the proposed BRIDGE and PCI indications, the range of expected exposures (AUC and steady state plasma concentration) is predicted to be 9 % lower for a patient weighing 50 kg relative to a reference patient with 70 kg body weight, and approximately 9 % higher for a patient weighing 100 kg relative to the same reference patient.

Neither sex nor age was identified as having a significant effect on cangrelor pharmacokinetics. There were insufficient numbers of Asian and African-American subjects in the pharmacokinetic dataset to assess race differences on the pharmacokinetics of cangrelor.

3.3.5.2 Renal Impairment

The current NDA includes a renal impairment study (SC-931-5109) in normal healthy subjects (creatinine clearance > 90 mL/min, N=8) and in subjects with impaired renal function (creatinine clearance of 20-70 mL/min, N=16). Three-step, ascending IV infusions of cangrelor were used in this study, with Part I using a maximum infusion rate of 2 µg/kg/min and Part II using 4 µg/kg/min maximum infusion rate, respectively. The distribution of subjects was not balanced across treatments, with lesser number of subjects (N ~ 3-4) in the reference treatment groups. The plasma concentration profiles of cangrelor and its derived PK parameters were comparable in healthy volunteers and renally impaired subjects in Part I (maximum dose 2 µg/kg/min) of the study. The observed C_{max} and AUC for cangrelor showed an increase of 11 % and 9 % respectively in renally impaired patients relative to healthy subjects in Part I. But the C_{max} and AUC for cangrelor showed an increase of 54 % and 117 %, respectively in renal impairment relative to healthy subjects in the Part II where a maximum infusion rate of 4 µg/kg/min was tested. The steady state plasma concentrations (C_{ss}) were 5 % and 44 % higher in renally impaired subjects for cangrelor infusion rates of 2 µg/kg/min and 4 µg/kg/min,

respectively. Two healthy subjects (16 and 18) had to be excluded from analysis in Part II, making the comparisons less informative. Besides, the cangrelor exposure in healthy volunteers in the Part II of the renal impairment study was lower than that from previous observations in healthy volunteers who received 4 µg/kg/min infusion rate (Table 2). If a cross-study comparison was used, the increase in cangrelor C_{ss} in renal impairment relative to healthy subjects would be ~ 16 % in contrast to the 44 % increase seen in the dedicated renal impairment study. The PK/PD of cangrelor was also comparable between healthy subjects and subjects with renal impairment in the renal impairment study. Cangrelor treatment was generally well tolerated, but one subject experienced a syncopal attack and was not included in the analysis (subject 16). Another subject (subject 2) had deterioration in renal function and required dialysis. This was considered as progression in the underlying renal disease.

Table 2 Comparison of cangrelor steady-state exposures in healthy subjects and in subjects with renal impairment. Data pooled from three Phase I studies and the renal impairment study.

Infusion Rate (µg/kg/min)	Study	N	Steady State Plasma Concentration (ng/mL)		
			GM (% CV)	Median	Ratio (RIS/HS)
2	Healthy Subjects –Other Studies*	14	222 (22)	241	0.93
	Healthy Subjects –Renal Imp Study**	4	198 (24)	214	1.05
	RIS – Renal Imp Study	8	207 (20)	203	-
4	Healthy Subjects –Other Studies*	18	399 (26)	409	1.16
	Healthy Subjects –Renal Imp Study**	3	322 (10)	321	1.44
	RIS – Renal Imp Study	7	464 (19)	461	-

*Other - Combined Studies SC-931-5014, SC-931-5036, TMC-CAN-04-02

** Renal Impairment Study SC-931-5109

RIS-Renally Impaired Subjects, HS-Healthy Subjects with Normal Renal Function

GM-Geometric Mean, N-Number of Subjects

The Phase III studies for cangrelor included patients with impaired renal function (CHAMPION-PLATFORM: N ~ 623 and CHAMPION-PCI: N ~ 688 patients with CrCL < 60 mL/min) and used the same dosing regimen as CHAMPION-PHOENIX. There was no significant difference in the safety and efficacy profiles of cangrelor in these patients compared to the overall study results. Altogether, the available data supports that no dose adjustments are necessary for cangrelor in renally impaired subjects.

3.3.5.3 Hepatic Impairment

Since the biotransformation of cangrelor is believed to be mediated through nucleotidases in systemic circulation which is considered independent of hepatic function there was no dedicated hepatic impairment study included in the clinical development program.

3.3.6 What are the characteristics of drug absorption (transporters and pH impact)?

The impact of transporters on the PK of cangrelor and vice versa was not studied. Cangrelor is administered by intravenous route for shorter duration (~ 2 hours for PCI indication) as a single use regimen and the expectation for any potential impact in this setting is considered to be low.

3.3.7 What are the characteristics of drug distribution, including plasma protein binding?

In vitro plasma protein binding determined by equilibrium dialysis method (SC-10009) was about 97 - 98 % for cangrelor and 88 - 89 % for its metabolite AR-C69712, respectively. Another *in vitro* study (SC-103039) showed that cangrelor predominantly binds to albumin and reported > 98 % plasma protein binding. The RBC partitioning was up to 5 % for cangrelor and that for AR-C69712 was about 28-34 %.

3.3.8 What are the characteristics of drug metabolism?

Cangrelor is a substituted nucleotide (See Figure 1) and is believed to be inactivated rapidly in the circulation by de-phosphorylation mediated through nucleotidases to a nucleoside metabolite, AR-C69712. This major circulating metabolite is reported to be several thousand fold less potent (~70,000 X) than cangrelor at human P2Y₁₂ receptors. After the initial de-phosphorylation, various other sulfoxide metabolites are formed and are considered pharmacologically inactive. The primary enzyme systems responsible for this biotransformation are not yet identified. The proposed metabolic pathway for cangrelor in humans is shown in Figure 10 below.

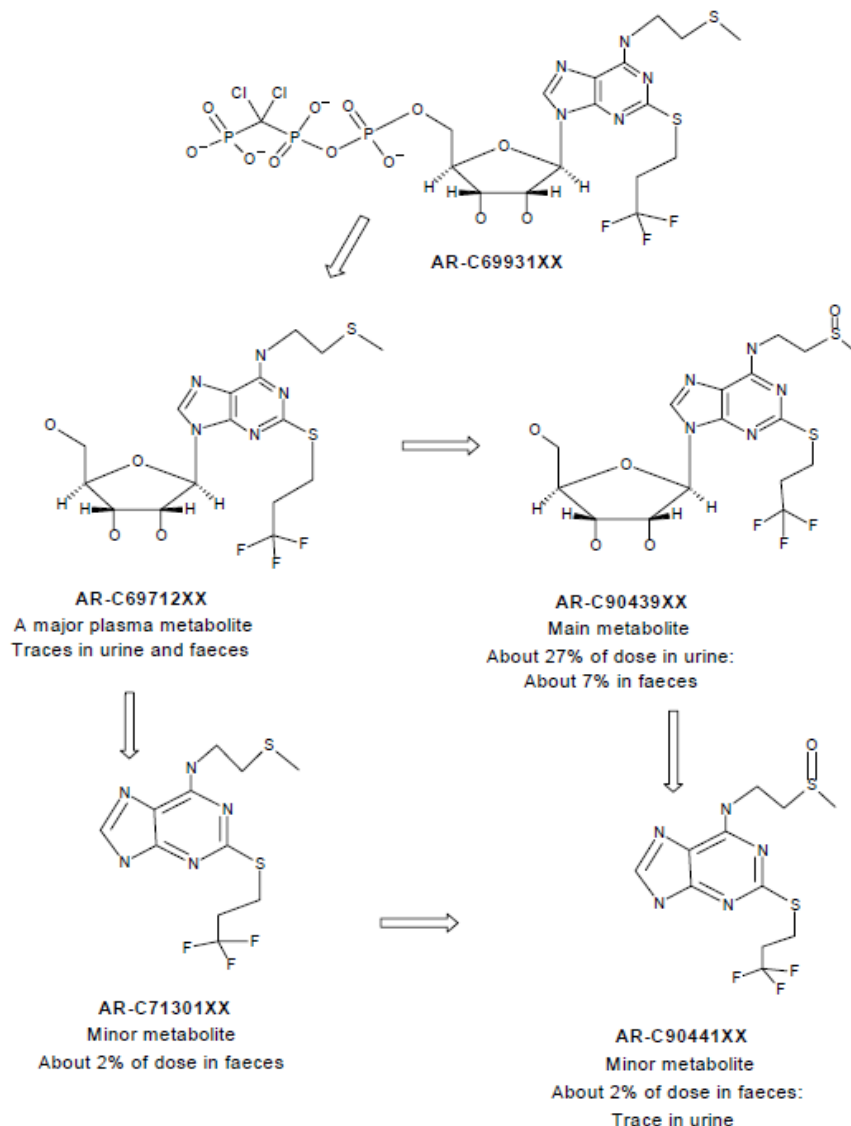


Figure 10. Proposed metabolic pathway for cangrelor in humans

Source: Figure 10, Study Report SC-100199, Page 44

3.3.9 Does the mass balance study suggest renal or hepatic as the major route of elimination for cangrelor?

In the mass balance study (SC-931-9017/SC-100199) with [^3H]-cangrelor 2 $\mu\text{g/kg/min}$ infusion for 2 hours in healthy subjects, the mean cumulative recovery of radioactivity was about 93 %, with approximately 58 % and 35 % found in urine and feces, respectively (Table 3). Approximately 50 % of the radioactivity was recovered within the first 24 hours. The chromatographic method used did not differentiate between cangrelor (AR-69931) and one of its metabolite AR-C90439 in this study and so the presence or absence of cangrelor (AR-

C69931) in urine or feces cannot be confirmed. About 10 % and 19 % of the recovered radioactivity was not fully characterized. The Table describes the relative contributions of the moieties identified in urine and feces.

Table 3 Percentage of radioactive dose recovered from urine and feces and relative contribution of various moieties

Identified Moiety/Matrix	Urine	Feces
Cangrelor (AR-C69931)	*	*
AR-C69712	0.6	0.4
AR-C90439	27.3	6.6
AR-C71301	-	2.0
AR-C90441	0.7	1.8
Oxidized AR-C90441 or AR-C69712 derivative	5.1	5.0
Glucuronide-AR-C69712	10.4	-
Sulphone and Glucuronide of AR-C69712	4.4	-
Unidentified ⁺	~ 9.5	~ 19.3
% of Dose Recovered	~ 58.0	~ 35.1

From Study SC-100199, N=4, [³H]-Cangrelor 2 µg/kg/min IV infusion for 2 hours

*Presence/absence not confirmed in this study; - not detected; ⁺ difference between recovered and identified radioactivity

3.3.10 What is the drug-drug interaction (DDI) potential for cangrelor?

3.3.10.1 *In Vitro* Studies

The *in vitro* evaluation of DDI potential focused on CYP inhibition and CYP induction by cangrelor and its primary circulating metabolite AR-C69712. The biotransformation of cangrelor to AR-C69712 is proposed to be mediated by nucleotidases in systemic circulation and is believed to be independent of hepatic function. Induction potential for CYP1A2, 2C9 and 3A4 by were tested in primary cultured human hepatocytes. Cangrelor and AR-C69712 were found to have the potential to induce CYP2C9 and 3A4 at 100 µM concentration level (Studies 300736967 and 300739180) but was significantly lower than that seen with rifampin, the positive control used.

The potential for cangrelor, AR-C69712 and AR-C90439 to inhibit CYP1A2, 2A6, 2C9, 2C19, 2D6, 2E1 and 3A4 were assessed with human liver microsomes (SC-102858). It was reported that cangrelor and its metabolites have no potential to inhibit CYP1A2, 2A6, 2C9, 2D6, 2E1 and 3A4 systems, with observed IC₅₀ values of > 100 µM. However, AR-C69712 and AR-C90439 showed a potential to inhibit CYP2C19 at very high concentrations (IC₅₀ of 58-59 µM). Based on the

observed therapeutic concentrations of cangrelor and its metabolites no significant clinical DDIs are anticipated at the proposed dose.

3.3.10.2 *In Vivo* Studies

A double-blind, placebo-controlled, two-way cross-over study (AC-931-5037) investigated the combined effects of aspirin, heparin and glyceryl trinitrate pre-treatment with stepped IV infusions of cangrelor (six steps from 50 ng/kg/min to 2 µg/kg/min, with a total infusion duration of 4 hours and 15 minutes) in healthy male subjects. The PK of cangrelor and AR-C69712 did not alter significantly when co-administered with aspirin, heparin and glyceryl trinitrate (given together). The inhibition in ADP induced platelet aggregation by cangrelor was comparable between both treatment groups. But there were prolongation in bleeding times and higher incidence of adverse events like purpura and headaches when cangrelor was co-administered with a combination of aspirin, heparin and glyceryl trinitrate. No major adverse events were reported from this study.

3.3.11 What is the transition strategy while switching from cangrelor to oral P2Y₁₂ inhibitors like clopidogrel, prasugrel or ticagrelor?

3.3.11.1 Transition to clopidogrel

Study TMC-CAN-04-02 in healthy subjects included clopidogrel with or without cangrelor administration, offset by different times (See Figures 11-13 below). Platelet inhibition was measured using whole blood impedance aggregation (WBIA), P-Selectin expression measured with flow-cytometry and light transmittance aggregometry (LTA). The antiplatelet effects of clopidogrel was attenuated when administered at the start of cangrelor infusion (about 35 % inhibition of platelets after cangrelor infusion was stopped) while full effect (about 78 % platelet inhibition) was seen when clopidogrel was administered after the cangrelor infusion, compared to clopidogrel administered alone in the control, group (about 82 % platelet inhibition).

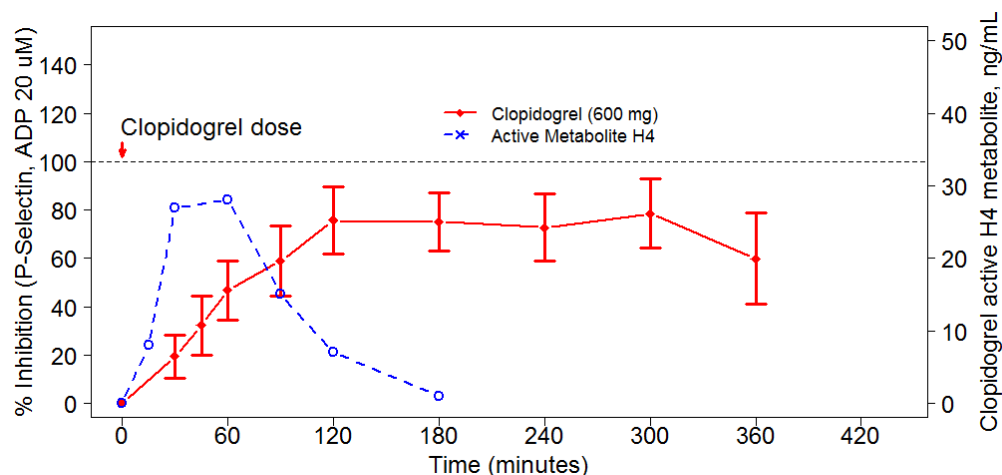


Figure 11. Average platelet inhibition-time course for a single 600 mg dose of clopidogrel administered at time 0 minutes. Percentage inhibition in P-Selectin expression to 20 μ M ADP measured by Flow Cytometry was used. A representative plasma profile of the active metabolite H4 following administration of 600 mg clopidogrel in CYP2C19 extensive metabolizers (extracted from Study PKD11147; NDA 20839) is shown as a blue dotted line and repeated in Figures 12 and 13.

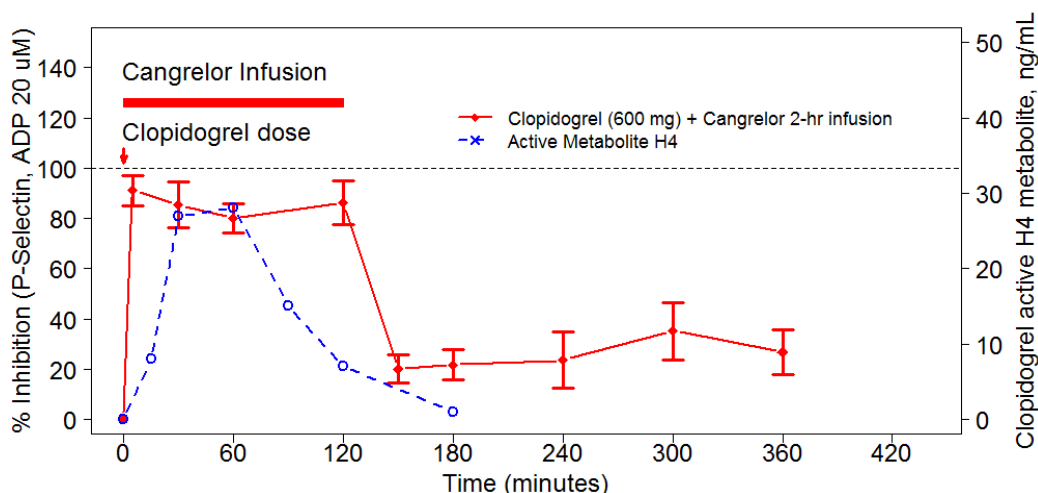


Figure 12 The antiplatelet effect of clopidogrel was attenuated when co-administered with cangrelor. Both clopidogrel 600 mg and cangrelor (30 μ g/kg bolus + 2 hour of 4 μ g/kg/min infusion) were administered at time 0 minutes. The red horizontal bar indicates cangrelor infusion duration. Clopidogrel's active metabolite H4 reaches its peak plasma levels during the cangrelor infusion when the platelet P2Y₁₂ receptors are still occupied by cangrelor. When cangrelor infusion was stopped at 120 minutes, most of H4 metabolite was already cleared from systemic circulation.

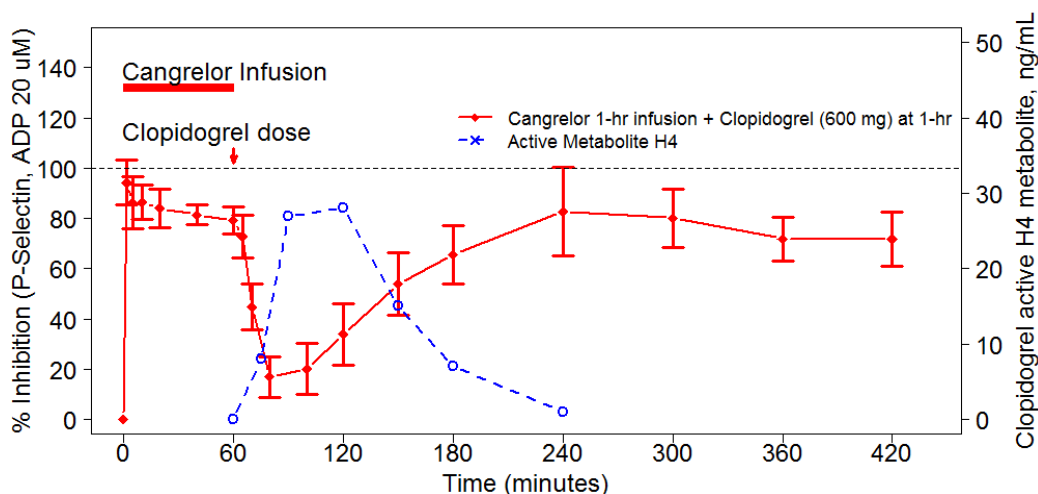


Figure 13 Administering the clopidogrel dose after stopping cangrelor infusion did not alter the expected PD effect from clopidogrel. The horizontal red bar indicates cangrelor infusion duration. Cangrelor 30 $\mu\text{g}/\text{kg}$ bolus + 1 hour of 4 $\mu\text{g}/\text{kg}/\text{min}$ infusion followed by clopidogrel 600 mg administered at time 60 minutes (shown by red arrow) were used in the study. Clopidogrel's active metabolite H4 reaches its peak plasma levels after the cangrelor infusion was stopped and therefore can bind with the available platelet P2Y_{12} receptors and exert its expected PD effects.

It is hypothesized that the attenuation of clopidogrel's PD effect when co-administered with cangrelor is because of the competition between clopidogrel's active metabolite H4 and cangrelor for the platelet P2Y_{12} ADP-receptors. The active metabolite of clopidogrel has short plasma half-life (cleared from plasma in about 3 hours after oral clopidogrel dose) and can irreversibly bind to P2Y_{12} receptors on the platelets if they are available. If this overlaps with cangrelor administration, both cangrelor and the active metabolite H4 will compete for the same receptors. This scenario is depicted in Figure 12 where cangrelor and clopidogrel are both administered at time zero minutes. The cangrelor infusion duration overlaps with the t_{max} of clopidogrel's active metabolite, which is reached 30-60 minutes after oral administration of clopidogrel, decreasing the ability of clopidogrel's active metabolite to irreversibly bind to P2Y_{12} receptors. This translates to a decreased platelet inhibition compared to clopidogrel administered after stopping the cangrelor (with faster offset in PD effects) infusion (Figure 13). Such a phenomenon mediated by competitive inhibition at the same target site is observed when reversible agents are co-administered with irreversibly acting agents e.g., aspirin +

ibuprofen interaction through competitive inhibition of the acetylation site of cyclooxygenase in the platelet⁴.

Other irreversible oral P2Y₁₂ inhibitors, such as prasugrel, may also show some attenuation in platelet inhibition if co-administered with cangrelor. However, the active metabolite of prasugrel has an elimination half-life of about 7 hours (range 2-15 hours) and the attenuation in platelet inhibition may be lesser than with clopidogrel upon co-administration.

These results suggest that administration of clopidogrel at the end of cangrelor infusion overcomes the loss of clopidogrel effect when compared to clopidogrel administration at the start of infusion. However, there still exists a temporary dip in the antiplatelet activity at the end of cangrelor infusion. In fact, applicant's transition strategy has only managed to shift the delay in the time to reach the maximum inhibition achieved with clopidogrel loading dose. Alternatively, a potential transition strategy that can be envisioned is to split the loading dose of clopidogrel and span the timing of administration to 'before' and 'after' stopping of cangrelor infusion. It should be noted that even with this strategy, the possibility of an overlap in PK and thus a potential for attenuation of the PD effects of the first dose of clopidogrel exists. However, this may result in lesser attenuation of the antiplatelet activity during transition and shorter time to reach the maximum platelet inhibition.

3.3.11.2 Transition to ticagrelor

The transition from cangrelor to ticagrelor was evaluated in study MDCO-CAN-12-03 in 12 patients with stable coronary artery disease who were taking aspirin 81 mg daily. Patients were administered cangrelor (30 µg/kg bolus followed by 4 µg/kg/min for 2 hours) and a 180 mg dose of ticagrelor 30 or 75 minutes after the start of cangrelor infusion (see Figure 14 below).

⁴ FDA Information for Healthcare Professionals: Concomitant Use of Ibuprofen and Aspirin
<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm125222.htm>

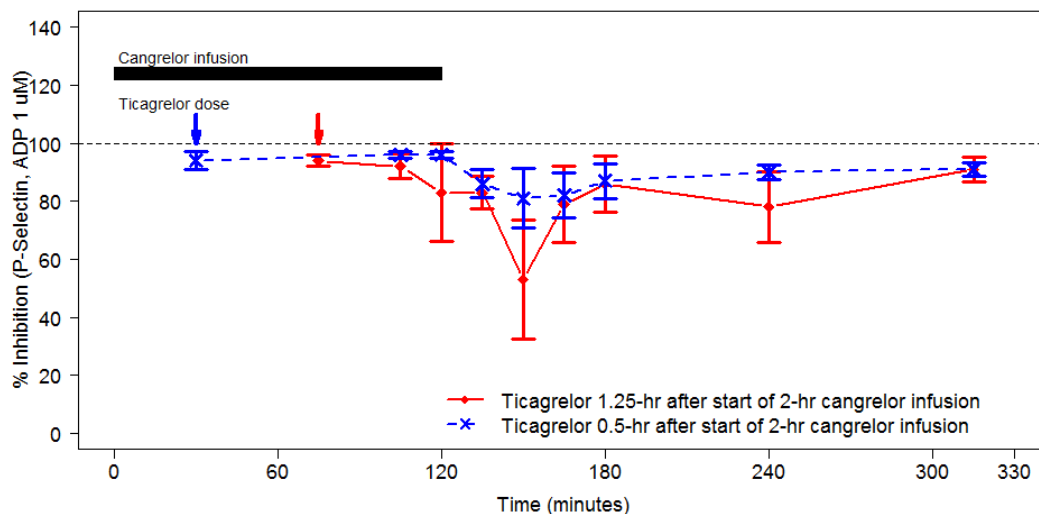


Figure 14. Transition from IV cangrelor to oral ticagrelor – Percentage inhibition in P-selectin expression to 1 μ M ADP measured by Flow Cytometry for IV cangrelor (30 μ g/kg bolus + 2 hours of 4 μ g/kg/min infusion) and a 180 mg oral dose of ticagrelor administered at 0.5 hours (blue dashed line with cross symbols) or at 1.25 hours (red solid line with diamond symbols) after the start of the infusion. The arrows indicate ticagrelor dose administration and the solid black bar indicate cangrelor infusion duration from time 0 minute to 120 minutes.

The inhibitory effect of cangrelor and ticagrelor was preserved when both products were co-administered and that patients can be transitioned to ticagrelor from cangrelor during infusion. Following discontinuation of the infusion, there was a decrease in platelet inhibition for about 30 minutes in treatment arms scenarios ranging from 96 % and 83 % inhibition at the end of the cangrelor infusion to 81% and 53 % inhibition. However, earlier administration of ticagrelor resulted in more consistent maintenance of antiplatelet activity after stopping of the cangrelor infusion for these two scenarios. This observation is in agreement with reported ticagrelor PK/PD that showed its maximum plasma concentrations at \sim 1.5 hours and elimination half-life of \sim 7 hours for ticagrelor (and \sim 9 hours for active metabolite) as well as peak platelet inhibition at approximately 1.5 to 2 hours after administration.

3.3.12 What is the transition strategy for switching from oral P2Y₁₂ inhibitors to IV cangrelor?

The transition from oral P2Y₁₂ inhibitors like clopidogrel or prasugrel to cangrelor was evaluated in study TMC-CAN-08-02 (BRIDGE) in patients awaiting CABG surgery. Shown in Figure 15 below are baseline and on-treatment *VerifyNow*TM PRU assessments for subjects who were on oral P2Y₁₂ therapy and either stopped treatment or stopped treatment and switched to cangrelor.

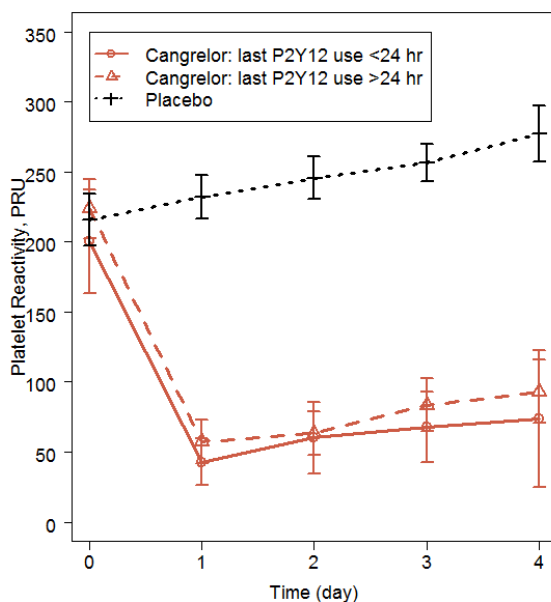


Figure 15. Platelet reactivity unit (PRU) values versus time for patients transitioning from oral P2Y₁₂ inhibitors to placebo (black, dotted line) or cangrelor whose last P2Y₁₂ use was within 24 hours (red, circles with solid line) or more than 24 hours (red, triangles with broken line) prior to baseline

The majority of patients in all treatment arms were transitioning from clopidogrel use (~ 99 % in placebo and ~ 92 % in cangrelor groups) while the remaining patients were transitioning from prasugrel. Most patients were on 75 mg clopidogrel (~ 84 % in placebo and ~ 70 % in cangrelor groups). The cangrelor patients were further divided into patients whose last oral P2Y₁₂ inhibitor dose was within 24 hours versus more than 24 hours. This division was chosen as patients whose last dose was within 24 hours represents a direct transition from clopidogrel to cangrelor. The PRU profiles for the cangrelor treatment arms overlap whether patients had received their last oral P2Y₁₂ inhibitor dose within 24 hours or more than 24 hours prior to initiation of cangrelor treatment. This observation supports that patients on an oral P2Y₁₂ inhibitor can be transitioned to cangrelor therapy without any significant changes in observed pharmacological effect.

3.4 Biopharmaceutics

3.4.1 What are the characteristics of the bioanalytical method(s) used in the clinical pharmacology studies?

The PK analyses focused on plasma concentrations of cangrelor and its primary circulating metabolite AR-C69712. The Phase I program used solid phase extraction (SPE)/column

switching high performance liquid chromatographic (HPLC) method (SC-100236), while the Phase II program used a semi-automated SPE/SPE/HPLC method (SC-101725) or its variants (FL05-TMC-TR005R1) with ultra-violet absorbance detection at 281 nm. In addition, there were additional LC-MS/MS methods for the estimation of cangrelor (BPM-1044-R1) and AR-C69712 (BTM-1075-R0) from human plasma (Table 4). All the assay methods were validated for use in the clinical studies.

Table 4 Reported bioanalytical assay linearity, accuracy and precision

Analytes/Parameters	Cangrelor*	AR-C69712**
LLOQ	5.0 ng/mL	0.5 ng/mL
Range	5.0-1000 ng/mL	0.5-500 ng/mL
QC Precision (inter-day % CV)	2.1-3.1	2.2-6.8
QC Accuracy (% range)	101.7-106.6	104.2-106.1

LC-MS/MS Methods: *BTM-1044-R1, **BTM-1075-R0

The analytes were stable for 3 freeze-thaw cycles and for up to a day at room temperature. The reported recovery of the analytes from human plasma was consistent and adequate. The reported accuracy and precision of the assays were within the acceptable limits ($\leq 20\%$ at LOQ and $\leq 15\%$ at all other QC levels) and the validation parameters are acceptable.

3.4.2 How is the final marketing image formulation bridged to the Phase III formulation?

The pivotal efficacy study CHAMPION-PHOENIX used the same IV formulation (cangrelor diluted in sterile normal saline) as the proposed marketing image formulation. Cangrelor for injection is provided in 10 mL vials, each containing 50 mg cangrelor as tetra-sodium salt and should be reconstituted with 5 mL sterile water for injection and further diluted with normal saline or 5% dextrose injection, before use.

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/s/

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CLINICAL REVIEW

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: January 10, 2014

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

NDA: 204-958
Drug: cangrelor

Indication: For the reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with coronary artery disease undergoing percutaneous coronary intervention (PCI)

Subject: Ethicalness of the cangrelor development program

Summary and Recommendation

Cangrelor is an intravenously (IV) administered P2Y₁₂ platelet inhibitor studied in three large clinical outcomes trial in patients undergoing percutaneous coronary intervention (PCI). The ethicalness of all three trials is questionable because all three protocols specified delaying the use of clopidogrel to varying degrees. One of the two earlier trials, PLATFORM, delayed clopidogrel use until after the PCI; PLATFORM showed dramatically higher rates of stent thrombosis and of death in the clopidogrel arm. The last trial, PHOENIX, was unethical because it delayed use of clopidogrel until after coronary angiography or later and because it prohibited routine use of prasugrel, ticagrelor, and glycoprotein IIb/IIIa inhibitors (GPIs). The PHOENIX informed consent documents (ICDs) failed to inform patients regarding the advantages of earlier use of clopidogrel and the use of prasugrel, ticagrelor, and GPIs. The patients in PHOENIX were not informed about “appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject” as required by 21 CFR §50.25.

21 CFR §314.125 states that “(b) FDA may refuse to approve an application for any of the following reasons” including:

“(16) Any clinical investigation involving human subjects described in the application, subject to the institutional review board regulations in part 58 of this chapter or informed consent regulations in part 50 of this chapter, was not conducted in compliance with those regulations such that the rights or safety of human subjects were not adequately protected.”

Hence we have the authority to refuse approval of this NDA based on ethical grounds alone. However, while such a nonapproval addresses well the ethical issues, it possibly creates a different problem: If PHOENIX did show that cangrelor is a fast-acting and reversible platelet inhibitor with acceptable benefit-risk, then cangrelor would prove a useful addition to the available treatments for managing patients undergoing PCI in the US. We do want to make effective treatments available as rapidly as possible.

Besides the ethical issues the delayed use of clopidogrel has a second implication: Because clopidogrel was used badly in all of the CHAMPION trials, they can not demonstrate that a cangrelor regimen¹ is superior to—or even noninferior to—clopidogrel used appropriately. There are other defects in the trials and problems with the results that I detail in a parallel review on the benefit-risk of cangrelor. (Marciniak 2014) Because the downsides of being inferior are not mere inconvenience but irreversible harm and death, the sponsor needs to document prior to approval the benefit-risk of a cangrelor regimen compared to the approved regimens with superiority claims over clopidogrel.

I recommend not approving cangrelor until another trial succeeds in correcting the flaws that I have documented in this review and in my parallel review on the benefit-risk of cangrelor.

Background

Cangrelor is a new platelet inhibitor studied for use with PCI for the treatment of stable angina or acute coronary syndromes (ACS, or myocardial infarction (MI) and unstable angina (UA)). Cangrelor is a platelet P2Y₁₂ receptor inhibitor like clopidogrel, the first approved P2Y₁₂ inhibitor. Cangrelor, unlike orally-administered clopidogrel, is administered intravenously and is a reversible rather than an irreversible inhibitor. Cangrelor has a quick onset and offset and short half-life compared to clopidogrel and other approved P2Y₁₂ inhibitors, potentially making it very useful in situations in which these qualities are desirable, such as recent onset ACS.

The PHOENIX trial was a randomized, double-blind, active-controlled trial comparing a bolus and infusion of cangrelor to a loading dose of 300 or 600 mg of clopidogrel. (Bhatt, Stone et al. 2013) The trial was conducted from September 30, 2010, to October 3, 2012, in 11,145 patients who were undergoing either urgent or elective PCI, i.e., in both stable angina and ACS patients, and who did not receive pretreatment with platelet inhibitors (except aspirin). The trial was an international trial conducted in the US, Europe (including Austria, Germany, and the Czech Republic), Brazil, New Zealand, and Thailand. The primary endpoint was the composite of death, MI, ischemia-driven revascularization, or stent thrombosis at 48 hours. The rate of this endpoint was significantly lower in the cangrelor arm than in the clopidogrel arm (4.7% vs. 5.9%; odds ratio, 0.78; 95% confidence interval 0.66 to 0.93; P = 0.005).

¹ In this review for brevity I refer to the “cangrelor” regimen or arm and the “clopidogrel” regimen or arm. The more complete references are the “cangrelor infusion followed by clopidogrel” regimen or arm and the “clopidogrel alone” regimen or arm.

More details on the trial can be found in the NEJM publication (Bhatt, Stone et al. 2013). NEJM also posted additional trial documentation including the protocol, the financial disclosures (not discussed here), and supplementary material including lists of investigators and sites. The investigators also published a rationale for the design. (Leonardi, Mahaffey et al. 2012)

I assert that the protocol has three serious flaws: (1) Administration of clopidogrel was delayed until after angiography or after PCI. (2) The use of prasugrel and ticagrelor, other approved P2Y₁₂ inhibitors with superior efficacy to clopidogrel, was not allowed. (3) The use of GPIs, another class of platelet inhibitors having approved IV formulations, was prohibited except as bailout therapy. These three flaws should have been addressed differently in the protocol and in the ICDs. The editorial accompanying the PHOENIX NEJM publication mentions the first two flaws. (Lange and Hillis 2013). Furthermore, if all three of these approved alternative or supplemental therapies were not discussed in the informed consent document (ICD), then the trial was unethical. Because these flaws are the primary focuses of this review, I discuss them in detail below.

PHOENIX was not the first clinical outcomes trial of cangrelor. Two similar trials preceded it: CHAMPION PCI and CHAMPION PLATFORM. (Bhatt, Lincoff et al. 2009; Harrington, Stone et al. 2009) Both were conducted in patients undergoing PCI, both used clopidogrel with a 600 mg loading dose, and both had a primary endpoint of death, MI, or ischemia-driven revascularization at 48 hours. The major difference was that in CHAMPION PCI clopidogrel was given prior to the PCI (but after angiography except early use was allowed in STEMI) while in PLATFORM clopidogrel administration was delayed until after the PCI. CHAMPION PCI included ST segment elevation MI (STEMI) patients while PLATFORM excluded them; both included 5-15% stable angina. At second planned interim analyses (at 70% enrollment) the sponsor terminated both trials early allegedly because the estimated conditional power to demonstrate superiority was low, i.e., for futility. I summarize relevant published results in Table 1.

Table 1: Cangrelor CHAMPION Trials Results at 48 Hours

		PCI	PLATFORM
N		8877	5301
clopidogrel within 5 days		34%	0%
study clopidogrel timing		immediately prior to PCI	after PCI
primary endpoint	cangrelor	7.5%	7.0%
	clopidogrel	7.1%	8.0%
efficacy OR*		1.05 NS†	0.87 NS†
deaths	cangrelor	0.2%	0.2%
	clopidogrel	0.1%	0.7%
death OR*		1.59 NS†	0.33 (p=0.02)
stent thrombosis	cangrelor	0.2%	0.2%
	clopidogrel	0.3%	0.6%
stent thrombosis OR*		0.63 NS†	0.31 (p=0.02)
bleeding ORs*		1.2-1.4	1.3-1.6

* OR = odds ratio cangrelor:clopidogrel; †NS = not significant

For all three CV endpoints the rate that is substantially higher than those in the other three arms is the one in the clopidogrel arm of PLATFORM. In that latter arm clopidogrel use was delayed. For the PCI trial in which clopidogrel was given earlier—although still not optimally—the point estimates for the primary endpoint and death actually favor clopidogrel. For cangrelor the claim is that “When a bolus of cangrelor is administered, the antiplatelet effect is immediate.” (Bhatt, Stone et al. 2013) For clopidogrel the label states that “Dose-dependent inhibition of platelet aggregation can be seen 2 hours after single oral doses of Plavix.” (sanofi-aventis and Bristol-Meyers-Squib 2010) Hence we would expect that the differing effects in CHAMPION PCI compared to PLATFORM are related to the delayed use of clopidogrel in PLATFORM. The CHAMPION trials confirmed that delaying clopidogrel use is bad. These results should have been presented explicitly to the sites and their IRBs.

Because clopidogrel use was delayed longer in PLATFORM than it was in PHOENIX, we should also question whether PLATFORM was unethical. Furthermore, its termination would appear to be justified on the basis of safety—deaths and stent thromboses with delayed clopidogrel use—rather than futility. I discuss more details regarding the conduct of PLATFORM below after presenting the evidence regarding the timing of clopidogrel.

Timing of Clopidogrel

I have presented above the evidence from the CHAMPION trials that delaying clopidogrel use is bad. Just as the comparison of the CHAMPION trials is not a randomized comparison, the overall evidence regarding the effects of different timings of clopidogrel administration has the same limitation: Despite the fact that clopidogrel was approved initially in 1997, there has never been an adequately powered clinical outcomes trial addressing timing of clopidogrel administration. Hence we depend upon the interpretation of small trials and non-randomized data, e.g., comparing CHAMPION PCI to PLATFORM or comparing outcomes of subgroups of patients with different, non-randomized clopidogrel timings in clinical trials designed for other purposes. The necessity of interpreting non-randomized data has led to differences between the US and Europe in the interpretation of the importance of clopidogrel timing, as I present next.

European Guidelines for Revascularization and MI

The Europeans appear to consider valid the non-randomized timing comparisons in the clopidogrel trials, such as CREDO, that suggest that earlier use of clopidogrel is better. (Steinhubl, Berger et al. 2006) The 2007 European Society of Cardiology (ESC) guidelines for non-STEMI (NSTEMI) ACS discuss delaying clopidogrel and recommend against it:

“Pre-treatment of unselected patients with clopidogrel before angiography results in better outcome of PCI. The approach of postponing clopidogrel administration until coronary anatomy is known in patients submitted to very early invasive angiography is not based on evidence. The potential advantage of this approach is to avoid

increased bleeding risk in patients requiring immediate surgery. However, this situation is rare, and frequently surgery can be deferred for a few days. Therefore, postponing clopidogrel to after angiography cannot be recommended, because the highest rates of events are observed in the early phase of NSTEMI-ACS.” (Bassand, Hamm et al. 2007)

The ESC/European Association for Cardio-Thoracic Surgery (EACTS) 2010 Guidelines on myocardial revascularization (the European guidelines in effect during the PHOENIX trial) had the following recommendation regarding timing of clopidogrel:

“Since the vast majority of PCI procedures eventually conclude with stent implantation, every patient scheduled for PCI should be considered for pre-treatment with clopidogrel, regardless of whether stent implantation is intended or not. To ensure full antiplatelet activity, clopidogrel should be initiated at least 6 h prior to the procedure with a loading dose of 300 mg, ideally administered the day before a planned PCI.” (Wijns, Kolh et al. 2010)

The 2008 and 2012 ESC guidelines for STEMI recommend immediate treatment with clopidogrel:

“Based on these data, clopidogrel should be given as soon as possible to all patients with STEMI undergoing PCI.” (Van de Werf, Bax et al. 2008; Steg, James et al. 2012)

The 2011 ESC guidelines for NSTEMI ACS recommend immediate treatment with a P2Y₁₂ inhibitor:

“A P2Y₁₂ inhibitor should be added to aspirin as soon as possible and maintained over 12 months, unless there are contraindications such as excessive risk of bleeding.

“Ticagrelor (180-mg loading dose, 90 mg twice daily) is recommended for all patients at moderate-to-high risk of ischaemic events (e.g. elevated troponins), regardless of initial treatment strategy and including those pre-treated with clopidogrel (which should be discontinued when ticagrelor is commenced).

“Prasugrel (60-mg loading dose, 10-mg daily dose) is recommended for P2Y₁₂-inhibitor-naïve patients (especially diabetics) in whom coronary anatomy is known and who are proceeding to PCI unless there is a high risk of life-threatening bleeding or other contraindications.

“Clopidogrel (300-mg loading dose, 75-mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel.” (Hamm, Bassand et al. 2011)

Note that the 2011 ESC guidelines recommend ticagrelor or prasugrel first rather than clopidogrel.

The PHOENIX investigators should have been familiar with these ESC guidelines. In fact, some of the PHOENIX investigators chaired some of the ESC guideline committees and others co-authored the guidelines. In a non-exhaustive search I identified the following PHOENIX investigators who participated in the ESC guidelines:

- Christian Hamm (Germany, a member of the PHOENIX Executive Committee) was the co-chair for the 2007 ESC ASC guidelines and the chairperson for the 2011 ESC ACS guidelines.
- Magnus Ohman (US, a Duke member of the Data and Safety Monitoring Committee) and Freek Verheugt (the Netherlands, a member of the Data and Safety Monitoring Committee) were co-authors or document reviewers of both the 2007 and 2011 ESC ACS guidelines.
- Kurt Huber (Austria National Coordinator) and Petr Widimsky (Czech Republic National Coordinator) were co-authors of the 2011 ESC ACS and the 2010 ESC revascularization guidelines. Kurt Huber was a document reviewer and Petr Widimsky was a member of the Executive Committee for the 2007 ESC ACS guideline.
- Frans Van de Werf (Belgium, a member of the Data and Safety Monitoring Committee) was the chairperson for the 2008 ESC STEMI guideline. Kurt Huber, Frank Verheugt, and Gabriel Steg (France, a PHOENIX Executive Committee member) were co-authors and Petr Widimsky was a member of the committee.
- Kenneth Mahaffey (US, a Duke member of the PHOENIX Executive Committee) was a co-author of the 2012 ESC STEMI guideline as were Kurt Huber, Gabriel Steg, and Petr Widimsky.

Note that some of the investigators who are co-authors of ESC guidelines are from countries, e.g., the US, Austria, Germany, and the Czech Republic, in which PHOENIX was conducted.

While local standards of practice could differ, in Europe all of the published guidelines from 2007 to the present recommend against delaying clopidogrel administration. Regardless, many of the investigators, including US ones, appear to have endorsed the concept that delaying clopidogrel use is bad. The investigators should have explicitly described in the ICD the negative impact of delaying clopidogrel. They should have informed the sponsor that all IRBs should be explicitly informed regarding this issue.

US Guidelines for PCI and MI

Several US medical professional organizations have issued guidelines for PCI and MI in two different series: (1) The American College of Chest Physicians (ACCP) has issued a series of anti-thrombotic guidelines, two of which in 2008 addressed antithrombotic therapy for non-ST-segment elevation ACS and for STEMI. (2) The American College of Cardiology (ACC) and the American Heart Association (AHA) have issued joint

guidelines on many cardiology topics, including PCI and MI. The Society for Cardiovascular Angiography and Interventions also participated in the ACC/AHA PCI guidelines. I reference these joint guidelines as the “ACC” guidelines.

The 2008 ACCP ACS guideline recommended “upstream”, i.e., early, clopidogrel administration:

“For NSTEMI 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 NSTEMI ACS patients who are at least moderate risk for an ischemic event and for whom an early conservative or a delayed invasive strategy of management is to be used, we recommend “upstream” treatment with clopidogrel (300 mg oral bolus, followed by 75 mg/d) [Grade 1A]. For NSTEMI ACS patients who undergo PCI, we recommend treatment with both clopidogrel and an IV GP IIb/IIIa inhibitor (Grade 1A). We recommend a loading dose of 600 mg of clopidogrel given at least 2 h prior to planned PCI followed by 75 mg/d (Grade 1B).” (Harrington, Becker et al. 2008)

The 2008 ACCP STEMI guideline recommended immediate clopidogrel for STEMI patients:

“However, given the very small chance that a patient would require emergent coronary artery bypass surgery coupled with the apparent benefit of clopidogrel administered 2 to 8 days prior to (nonprimary) PCI in patients with recent STEMI, clopidogrel could be administered immediately after the diagnosis of STEMI has been made and need not await visualization of the coronary anatomy in a patient about to undergo primary PCI.” (Goodman, Menon et al. 2008)

Robert Harrington, the Duke co-Principal Investigator for PHOENIX, was the first author of the ACCP UA/NSTEMI guideline and the anchor author of the STEMI guideline. Gabriel Steg, a member of the PHOENIX Executive Committee, was a co-author of both and Magnus Ohman, a Duke member of the Data and Safety Monitoring Committee, was a co-author of the ACCP STEMI guideline. I could not find any updates to these guidelines.

The ACC guidelines have evolved from a position recommending early clopidogrel use in the guidelines prior to 2007 (similar to the ESC recommendations) to one recommending either early use or “when PCI is performed”, with some ambiguity regarding the necessity of early use or what “when PCI is performed” means. The 2005 ACC PCI guidelines had the following recommendation:

“A loading dose of clopidogrel should be administered before PCI is performed. (Level of Evidence: A) An oral loading dose of 300 mg, administered at least 6 hours before the procedure, has the best established evidence of efficacy. (Level of Evidence: B)” (Smith, Feldman et al. 2006)

The 2007 ACC UA/NSTEMI guidelines were similar:

“For UA/NSTEMI patients in whom an initial invasive strategy is selected, antiplatelet therapy in addition to aspirin should be initiated before diagnostic angiography (upstream) with either clopidogrel (loading dose followed by daily maintenance dose) or an intravenous GP IIb/IIIa inhibitor. (Level of Evidence: A)” (Anderson, Adams et al. 2007)

The 2007 ACC PCI update changed the PCI recommendation to the following:

“A loading dose of clopidogrel, generally 600mg, should be administered before or when PCI is performed. (Level of Evidence: C) Inpatients undergoing PCI within 12 to 24 hours of receiving fibrinolytic therapy, a clopidogrel oral loading dose of 300 mg may be considered. (Level of Evidence: C)” (King, Smith et al. 2008)

However, the discussion of timing of clopidogrel in this guideline does not appear to justify this vague recommendation:

“There is agreement that the loading dose should be administered before PCI. What is unclear is the precise time when the loading dose must be given to achieve a desirable therapeutic effect. Evidence from the CREDO (Clopidogrel for the Reduction of Events During Observation) trial suggests that with a 300-mg dose, 6 hours is the minimum time. With the 600-mg dose, 2 hours may be sufficient, although maximal platelet inhibition may not be achieved until 3 to 4 hours.”

The 2011 ACC UA/NSTEMI update changed its recommendation to the following:

“Patients with definite UA/NSTEMI at medium or high risk and in whom an initial invasive strategy is selected should receive dual-antiplatelet therapy on presentation. (Level of Evidence: A) ASA should be initiated on presentation. (Level of Evidence: A) The choice of a second antiplatelet therapy to be added to ASA on presentation includes 1 of the following:

“Before PCI:

- Clopidogrel (Level of Evidence: B); or
- An IV GP IIb/IIIa inhibitor. (Level of Evidence: A) IV eptifibatide or tirofiban are the preferred GP IIb/IIIa inhibitors.

“At the time of PCI:

- Clopidogrel if not started before PCI (Level of Evidence: A); or
- Prasugrel (Level of Evidence: B); or
- An IV GP IIb/IIIa inhibitor. (Level of Evidence: A)” (Wright, Anderson et al. 2011)

In general STEMI is viewed as a condition in which rapid action is indicated, i.e., primary PCI as rapidly as possible is indicated because “time is myocardium.” The 2009 ACC update for STEMI, however, has the following complicated recommendations:

“A loading dose of thienopyridine is recommended for STEMI patients for whom PCI is planned. Regimens should be 1 of the following:

a. At least 300 to 600 mg of clopidogrel should be given as early as possible before or at the time of primary or nonprimary PCI. (Level of Evidence: C)

b. Prasugrel 60 mg should be given as soon as possible for primary PCI. (Level of Evidence: B)

c. For STEMI patients undergoing nonprimary PCI, the following regimens are recommended:

(i) If the patient has received fibrinolytic therapy and has been given clopidogrel, clopidogrel should be continued as the thienopyridine of choice (Level of Evidence: C);

(ii) If the patient has received fibrinolytic therapy without a thienopyridine, a loading dose of 300 to 600 mg of clopidogrel should be given as the thienopyridine of choice (Level of Evidence: C);

(iii) If the patient did not receive fibrinolytic therapy, either a loading dose of 300 to 600 mg of clopidogrel should be given or, once the coronary anatomy is known and PCI is planned, a loading dose of 60 mg of prasugrel should be given promptly and no later than 1 hour after the PCI. (Level of Evidence: B)” (Kushner, Hand et al. 2009)

The PHOENIX investigators were typically not co-authors of the ACC guidelines. However, other physicians from their institutions were. For example, Duke physicians co-authored the 2007 and 2011 UA/NSTEMI updates as well as the 2009 STEMI/PCI update.

These guidelines suggest that early clopidogrel use is better. The ACCP guidelines are consistent with the ESC guidelines in stating that clopidogrel use should not be delayed while the later ACC guidelines are somewhat ambiguous regarding this issue. However, even if one believes that there is equipoise between early vs. delayed clopidogrel use in general, the results of CHAMPION PCI and PLATFORM tip the balance towards early clopidogrel use being preferable in cangrelor trials.

Other Investigator or Site Publications

In addition to guidelines some investigators published articles expressing their opinions about clopidogrel timing (or prasugrel use). Publications by investigators are not the only relevant publications. Publications by other staff at the sites should reveal the local practices at the sites. I found the following examples of such investigator or site publications:

- Robert Harrington, the Duke PHOENIX co-Principal Investigator, co-authored a review of new antiplatelet agents published in 2009. (Sellers, Tricoci et al. 2009) He wrote that “The benefits of clopidogrel for patients with acute coronary

syndromes and patients undergoing percutaneous coronary intervention (PCI) have been established by large, well done randomized clinical trials” but “The need for liver metabolism to convert clopidogrel from the prodrug to the active form delays the onset of the antiplatelet effect, which may not be optimal for the treatment of acute coronary thrombosis or in the setting of coronary intervention.” This publication suggests that delaying clopidogrel is bad.

- Depak Bhatt, the other PHOENIX co-Principal Investigator who is affiliated with the VA Boston Healthcare System (one of the PHOENIX sites), co-authored a review “Antiplatelet Agents in Acute Coronary Syndromes” published in March 2010. (Sakhuja, Yeh et al. 2010) He wrote that “While clopidogrel pretreatment 2-24 hours before PCI has been shown to be beneficial, practitioners are often hesitant to initiate clopidogrel in NSTEMI-ACS before defining the anatomy given concerns over coronary artery bypass grafting (CABG)-related bleeding if patients require surgical revascularization” and “Earlier initiation of clopidogrel must be reconciled with delays in surgical revascularization. It is contraindicated (class III) to use clopidogrel around the time of CABG. Preliminary data suggest that a 600-mg load at the time of angiography may be sufficient, which may alter initiation of clopidogrel in NSTEMI-ACS.” This review implies that, in 2010, the standard of practice was clopidogrel pretreatment 2-24 hours before PCI.
- Depak Bhatt also authored a perspective on “Prasugrel in Clinical Practice” published in NEJM on September 3, 2009. (Bhatt 2009) He wrote that “Prasugrel represents an advance in antiplatelet therapy for acute coronary syndromes. TRITON–TIMI 38 supports its use in patients with such syndromes when there is a very high probability of PCI, such as in myocardial infarction with ST-segment elevation or after coronary angiography in patients with non–ST-segment elevation myocardial infarction.” (After angiography in NSTEMI patients was the way TRITON was conducted because prasugrel, like cangrelor, has a more rapid onset than clopidogrel.²) This publication supports allowing prasugrel use in PHOENIX.
- Eric Topol, a cardiologist and Senior Consultant, Scripps Clinic, Division of Cardiovascular Diseases (the Scripps Green Hospital was a PHOENIX site), co-authored a meta-analysis of three trials of clopidogrel pretreatment published in 2008. He wrote that “We have previously shown that pretreatment with clopidogrel before PCI significantly reduces cardiovascular death and ischemic complications after PCI” and concluded that “Clopidogrel pretreatment before PCI is beneficial and safe regardless of whether a GPI is used at the time of PCI.” This publication strongly supports early use of clopidogrel.
- John Kim and other Duke staff performed an observational study regarding clopidogrel use and bypass surgery published in 2008. (Kim, Newby et al. 2008) They concluded “Clopidogrel administration ≤ 5 days before CABG was not

² The prasugrel TRITON trial is another trial whose ethicalness is questionable because of forced delayed use of clopidogrel.

significantly associated with reoperation for bleeding or a bleeding composite and only weakly with red cell transfusion after surgery. The impact of withholding clopidogrel acutely in those for whom clopidogrel has proven benefits and the impact of delaying CABG to prevent bleeding among patients treated with clopidogrel should be viewed in the context of other stronger determinants of bleeding.” This publication supports early clopidogrel use.

- John Alexander of Duke authored a review of antiplatelet therapy published in 2009. (Alexander 2009) He quoted the guidelines that “For patients in whom an early invasive strategy is planned, therapy with either clopidogrel or a glycoprotein IIb/IIIa inhibitor should be started upstream (before diagnostic angiography) in addition to aspirin (class I, level A).” He described “In my practice, if a patient is high risk and has a low likelihood of early CABG, I use both clopidogrel and a glycoprotein IIb/IIIa inhibitor upstream (prior to going to the catheterization laboratory).” This publication supports early clopidogrel use and use of GPIs.
- Petr Widimsky, the Czech national coordinator, published a study alleging to show that pretreatment with clopidogrel was not beneficial in patients with stable angina undergoing PCI. (Widimsky, Motovska et al. 2008) However, the study was powered (80%) to detect a decrease in absolute incidence of the primary endpoint (death/MI/stroke/re-intervention within 7 days) from 3% to 0.5%, an 83% relative decrease. The observed decrease was 20%, from 1% to 0.8%, so the study was grossly underpowered. The efficacy endpoints numerically but not statistically significantly favored pretreatment but bleeding was higher with pretreatment. The authors state that “Our results cannot be extrapolated to patients with acute coronary syndromes, in whom the benefit from early clopidogrel therapy is unequivocal.” While their results in stable angina are arguable, these Czech investigators believed that early clopidogrel was beneficial in ACS.

The publications by the PHOENIX investigators and by site staff support the early use of clopidogrel.

Ethicalness of CHAMPION PLATFORM

PLATFORM enrolled patients from October 2006 to May 2009. At its start both the European and US guidelines recommended early use of clopidogrel (see the above discussion of the guidelines) so it is questionable why PLATFORM was allowed to proceed delaying clopidogrel use until after the PCI.

On July 6, 2005, the FDA and the sponsor discussed plans for the two CHAMPION trials at the end-of-phase-2 meeting chaired by Dr. Robert Temple. For the proposed placebo-controlled trial (PLATFORM) the sponsor estimated that about 10% of the patients would present with NSTEMI or ACS—STEMI patients were to be excluded. The planned protocol discouraged the use of GPIs, which the FDA advised against. The minutes state that “Once the procedure is stopped patients will all get clopidogrel” but

there is no reported discussion of delaying clopidogrel use in the FDA minutes. The sponsor's minutes state that "The protocol defined use of a clopidogrel loading dose following the procedure was discussed. It was noted that this means the patients will be on different therapies only during the short time of the PCI (1-2 hours)." There is no mention in either version of the minutes that the guidelines recommended administering clopidogrel prior to the start of the procedure.

The CHAMPION Executive Committee (EC) and the DSMB did discuss concerns about the delayed use of clopidogrel. The EC meeting minutes from March 13, 2006, stated the following:

"Site Selection – EC advised careful scrutiny of potential sites to ensure:

- Plavix admin post procedure is true 'standard of practice'; **Action:** provide market data/ local guidelines/ site statistics where feasible. [bolding in original]
- Sites are motivated to enroll correct patients
- Number of developing countries – limit? Increase number of NA sites."

The DSMB discussed the issue of delaying clopidogrel use at its open meeting on March 24, 2007. The minutes state the following:

"It was pointed out that it is the DSMB role to ensure safety of patient. In a country where clopidogrel use pre-procedure is pretty standard there is a concern over the ethics of excluding clopidogrel pre-procedure in the U.S. Dr. Bhatt acknowledged that criticism will be there. There is no FDA indication that clopidogrel is required pre-procedurally. It is not evidence-based medicine, therefore it is not considered unethical. Clopidogrel will be given in PLATFORM two hours after start of cangrelor."

Despite this directive the discussion apparently continued:

"The issue of not allowing pre-procedural clopidogrel continued to arise. It was recommended that TMC survey their PLATFORM sites and determine what is SOC. TMC responded by saying that they had done this during the site selection process. Sites couldn't participate if they couldn't treat patients per protocol. Each site IRB reviewed and approved the protocol."

The sponsor implemented the protocol unchanged with the delayed clopidogrel use. The sponsor amended the protocols on May 8, 2007, to restrict enrollment to patients with ACS and to exclude patients with upstream GPI use. The amended protocols also discouraged concomitant use of GPIs, from "These agents should be administered per the site standard of care" to "The use of these agents should be considered carefully based on the anti-platelet effect already provided by the study drug, i.e. clopidogrel 600 mg or cangrelor." The estimated enrollment in PLATFORM was increased from 4400 to 6400. The reported justification was to increase the estimated event rate to be consistent with

the expected event rate. At this time enrollment in PCI was about 39% and in PLATFORM about 20% of the original estimated enrollment.

The sponsor discussed with the FDA at a meeting on December 7, 2007, a proposal for an adaptive sequential test to occur at the second planned interim analysis. The meeting minutes state that “The statistical design and calculation of sample size for both of these studies assumed that at least 60% of the patients enrolled in these studies will be a higher risk ACS patients, such as Troponin + patients” while, as noted above, at the EOP2 meeting the estimate for NSTEMI/ACS patients in PLATFORM was 10%. The sponsor presented a complex approach for assessing futility for the 70% enrollment interim analyses based on conditional probabilities; the FDA statisticians agreed that the approach preserved alpha. The meeting minutes also state that clopidogrel in PLATFORM was to be delayed until after the PCI but do not report any discussion of this topic. The focus of the discussion was upon the interim analyses.

COMMENT: The meeting minutes summarized above document that some FDA staff were aware of and did not object to the delayed clopidogrel use in PLATFORM (and PCI). This lack of objection seems inappropriate. For the original discussion at the EOP2 meeting the sponsor presented PLATFORM as primarily enrolling non-ACS patients, i.e., ones for whom delayed use of clopidogrel might be acceptable. The FDA staff reviewing the one amendment appear to have missed the implications of restricting enrollment to ACS patients in that amendment.

Besides the guidelines and publications authored by the CHAMPION investigators a CHAMPION newsletter documents that the investigators and sites knew the problems of delaying clopidogrel. The September 2008 CHAMPION CANGRELOR Newsletter had a “Q&A” article featuring a cangrelor investigator. The response for question 1, “Other than we are conducting a research protocol, what is the rationale for not loading subjects with clopidogrel?”, was “Delayed and variable onset of oral PLAVIX – In some situations it isn’t possible to adequately load a patient – minimum of 2 hour delay after 600mg and 15 to 24 hours after 300mg”. (See Attachment 1).

COMMENT: If one can’t load patients in less than 2 hours, why did CHAMPION allow loading at best 30 minutes before PCI and at worst after PCI? The wording of the response for question 1 also implies a mistaken belief that, because they “are conducting a research protocol”, inappropriate care is ethical.

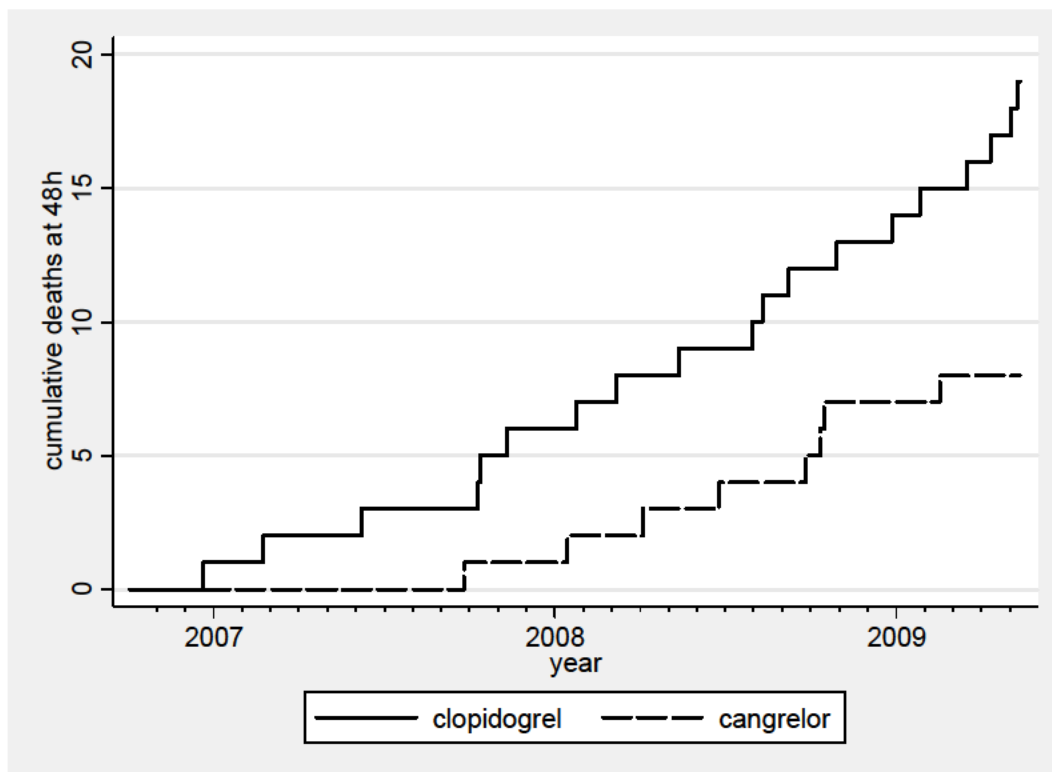
There is an additional ethical issue with PLATFORM: Its NEJM publication states that “After a second interim analysis, trial enrollment was terminated because the review committee decided that the trial was unlikely to show the superiority of cangrelor.” However, the results in Table 1 suggest that PLATFORM should have been terminated for safety in the clopidogrel arm rather than or in addition to futility as the NEJM article reported. Hence I examined the DSMB minutes to determine whether the DSMB had noted any problems during the trial.

The DSMB, at its November 8, 2008, meeting for reviewing the PLATFORM results at 50% enrollment, noted a mortality signal: “The all-cause mortality rates are significantly higher in the placebo arm ($p \approx 0.04$ according to Dr. Hasselblad, using Fishers mid-p formula). . . The significant mortality difference noted at 48 hours was also seen at 30 days, though not statistically significant ($p \approx 0.06$).” However, the DSMB also noted then that “The overall trend in the composite endpoint was still present at 30 days, with the cangrelor arm having a higher event rate than the placebo arm.” The DSMB made the following recommendation to the sponsor:

“The DSMB did note a potential safety signal with respect to mortality differences between the treatments. In order to properly protect the patients enrolling in the PLATFORM study, the DSMB has asked to reconvene after enrollment of 70% of patients to determine if the mortality differences persist.”

The DSMB did not meet again. I analyzed the 48-hour mortality results in PLATFORM by enrollment date to determine whether the mortality trend changed such that the DSMB shouldn’t have met. I show the results of that analysis in Figure 1.

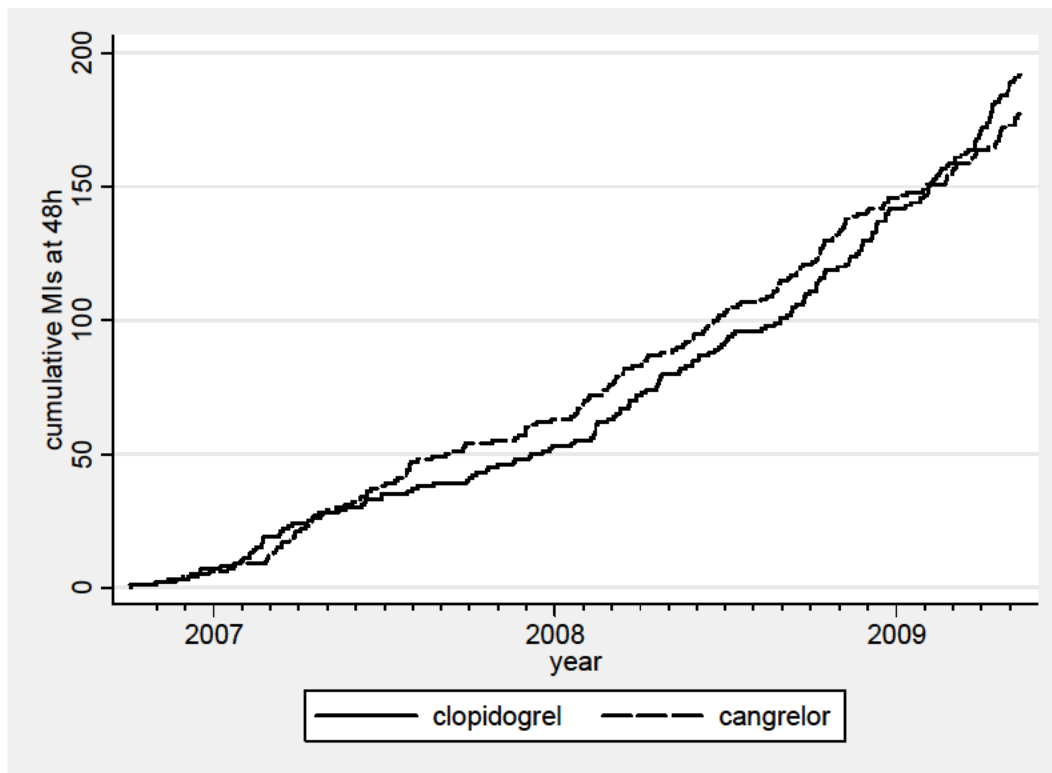
Figure 1: Cumulative Deaths at 48 Hours by Enrollment Date in PLATFORM



From the date of the last DSMB meeting (November 8, 2008) to the date of 70% enrollment (February 19, 2009) the mortality safety signal in PLATFORM strengthened. The DSMB should have reviewed the mortality findings at the time.

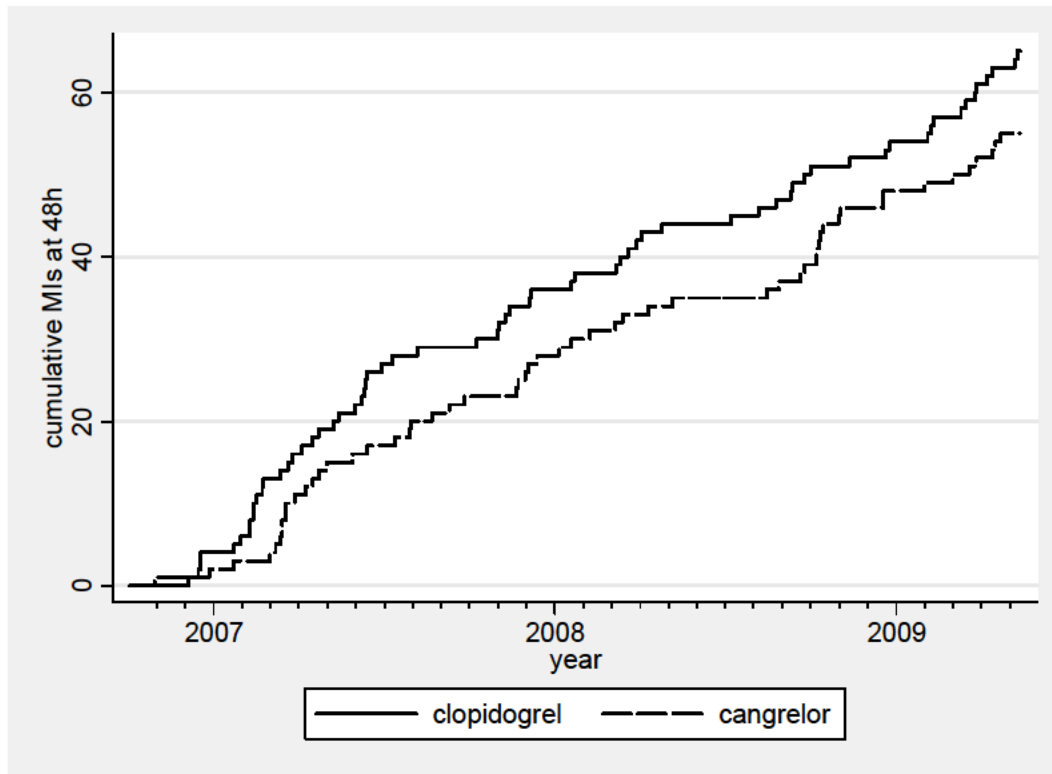
One reason why the DSMB may not have recommended terminating the trial early was that reported myocardial infarction (MI) results numerically favored clopidogrel despite mortality and ischemia-driven revascularization favoring cangrelor. I show the cumulative adjudicated MIs at 48h by enrollment date in Figure 2.

Figure 2: Cumulative Adjudicated MIs at 48 Hours by Enrollment Date in PLATFORM



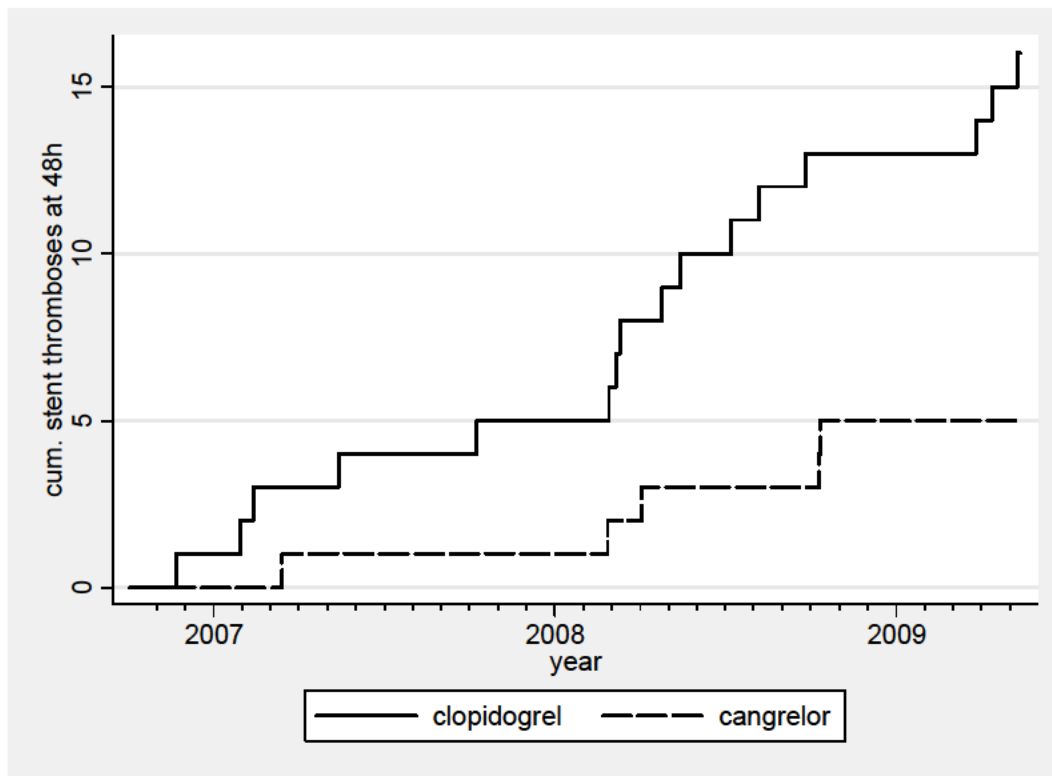
The relatively neutral adjudicated MI results do appear inconsistent with the dramatic difference in deaths. Because Figure 2 portrays adjudication MIs and because I have observed inconsistencies between adjudicated and site-reported MIs, I also analyzed site-reported MIs. The CRFs included a “MI Header” CRF with a single question “Did patient experience an MI?” with the directions for the 48 hours follow-up of “Select YES or NO to indicate if this patient experienced a myocardial infarction since randomization and prior to the 48-hour follow up.” I show the cumulative site-reported MIs at 48h (from the MI Header CRF) by enrollment date in Figure 3.

Figure 3: Cumulative Site-Reported MIs at 48 Hours by Enrollment Date in PLATFORM



The sites reported fewer MIs than were adjudicated, but the site-reported MI results favor cangrelor and hence are consistent with the mortality results. The sponsor and the investigators have claimed that there were problems with the MI definition used for adjudication. The inconsistency of the adjudicated MIs and the consistency of the site-reported MIs with other endpoints would appear to confirm a problem with the adjudicated MIs. Regardless, the DSMB should have been greatly concerned about the mortality results because of another potentially explanatory event: stent thrombosis. I show the cumulative stent thromboses at 48h by enrollment date in Figure 4.

Figure 4: Cumulative Stent Thromboses at 48 Hours by Enrollment Date in PLATFORM



COMMENT: PLATFORM demonstrates the dangers of delaying clopidogrel use. The DSMB should have recommended terminating PLATFORM for safety, and, if they had met again, they likely would have.

PLATFORM was allegedly not terminated for safety. Instead, the CHAMPION Interim Analysis Review Committee (IARC), chaired by Dr. Califf from Duke, met on May 1, 2009, to review the 70% enrollment results for it. (See Attachment 2 for the minutes.) The unusual charge given to the committee by the sponsor was stated as follows:

“Dr. Meanwell [TMC] had written to Dr. Califf encouraging the IARC to play an expanded role in the PLATFORM trial, allowing them more flexibility to review any information they considered of interest, above and beyond the guidelines written in the IARC Charter.”

Per the minutes an IARC statistician member initially noted that mortality results in both PLATFORM (6:14) and PCI (1:3) favored cangrelor but later a DCRI statistician “reported that the current PCI trial mortality favored the clopidogrel arm (8 cangrelor and 5 clopidogrel).” The IARC member reviewed the interim futility analyses and the minutes record that “Based on this analysis, the recommendation prescribed by the protocol is to terminate the trial for futility.”

The further discussion regarding other options included the following statement: “The only reason TMC may wish to stop the trial was if there were data supporting an adverse effect of cangrelor or if patients were being denied a better treatment.” The IARC appears to have ignored the possibility that the data supported an adverse effect of delayed clopidogrel or that patients were being denied a better treatment, i.e., clopidogrel administered earlier.

The minutes record further that “Under the expanded IARC role, the IARC wanted to look at the bleeding data as presented to the DSMB. The DSMB had determined that they did not have any safety concerns after reviewing this information.” The minutes do not relate that the DSMB had safety concerns regarding the mortality data.

The IARC provisionally recommended that the study be terminated due to futility, pending review of some efficacy results by subgroup and a discussion with the DSMB chair regarding bleeding. The sponsor terminated both trials allegedly for futility.

COMMENT: Regardless of whether PLATFORM was terminated for futility or for safety, the sponsor and the CHAMPION principal investigators should have presented explicitly the results regarding mortality and regarding stent thromboses to the IRBs for PHOENIX. The sponsor and principal investigators should have discussed the likelihood that these negative results reflected delayed use of clopidogrel and raised the question of what is the optimal timing for clopidogrel use, i.e., is just prior to PCI adequate?

Availability and Benefit-Risk of Prasugrel

PHOENIX specified clopidogrel as the only comparator and excluded patients administered any P2Y₁₂ antagonist within 7 days prior to randomization. However, prasugrel, like clopidogrel, is an approved thienopyridine antagonist of the platelet P2Y₁₂ receptor. Prasugrel, like clopidogrel, is administered as a prodrug that requires metabolic activation to an active metabolite. The advantage of prasugrel is that its metabolic activation is less susceptible to metabolic inhibition and pharmacogenomic variation than clopidogrel’s activation. Prasugrel is supposed to produce faster, more consistent platelet inhibition than clopidogrel and pharmacodynamic studies and the TRITON outcomes trial support this premise. However, in the marketed dosages prasugrel also leads to more bleeding than clopidogrel so the efficacy benefits of prasugrel must be weighed against the bleeding risks. I present below the different interpretations of the benefit-risk of prasugrel in the US and European labels.

European Approval and Labeling

The European Medicines Agency (EMA) approved prasugrel (Efient—European spelling) on February 25, 2009, for marketing in the European Union. The EMA public assessment report is available at

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000984/WC500021971.pdf

(EMA 2009) The approved indication is the following:

“Effient, co-administered with acetylsalicylic acid (ASA), is indicated for the prevention of atherothrombotic events in patients with acute coronary syndrome (i.e. unstable angina, non-ST segment elevation myocardial infarction [UA/NSTEMI] or ST segment elevation myocardial infarction [STEMI]) undergoing primary or delayed percutaneous coronary intervention (PCI).”

While the indication statement does not mention superiority to clopidogrel, the description of the TRITON study does:

“Effient showed superior efficacy compared to clopidogrel in reducing the primary composite outcome events as well as the pre-specified secondary outcome events, including stent thrombosis (see Table 3). The benefit of prasugrel was apparent within the first 3 days and it persisted to the end of study. The superior efficacy was accompanied by an increase in major bleeding.”

Effient has a warning regarding bleeding risk. The EMA recommendation is that “the use of Effient in patients at increased risk of bleeding should only be considered when the benefits in terms of prevention of ischaemic events are deemed to outweigh the risk of serious bleedings.” The label states that this concern applies especially to the elderly (age ≥ 75); those with a propensity to bleed from recent trauma, surgery, or gastrointestinal bleeding, or active peptic ulcer disease; body weight < 60 kg; or with concomitant administration of drugs that increase bleeding risk. Use in the elderly is not generally recommended but may be undertaken with a careful individual benefit-risk evaluation.

US Approval and Labeling

We approved prasugrel (Effient—US spelling) on July 1, 2009. The approved labeling effective at the start of PHOENIX is available at

http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022307s001lbl.pdf.

(Lilly 2010) The approved indication is the following:

“Effient is a P2Y₁₂ platelet inhibitor indicated for the reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with acute coronary syndrome who are to be managed with PCI as follows:

- Patients with unstable angina or, non-ST-elevation myocardial infarction (NSTEMI).
- Patients with ST-elevation myocardial infarction (STEMI) when managed with either primary or delayed PCI (1.1).”

The indication does not include a stated superiority claim over clopidogrel, although the Indications and Usage section continues “Effient has been shown to reduce the rate of a combined endpoint of cardiovascular death, nonfatal myocardial infarction (MI), or

nonfatal stroke compared to clopidogrel.” The rationale for not stating a superiority claim follows:

“It is generally recommended that antiplatelet therapy be administered promptly in the management of ACS because many cardiovascular events occur within hours of initial presentation. In the clinical trial that established the efficacy of Effient, Effient and the control drug were not administered to UA/NSTEMI patients until coronary anatomy was established. For the small fraction of patients that required urgent CABG after treatment with Effient, the risk of significant bleeding was substantial [see Warnings and Precautions (5.2)]. Because the large majority of patients are managed without CABG, however, treatment can be considered before determining coronary anatomy if need for CABG is considered unlikely. The advantages of earlier treatment with Effient must then be balanced against the increased rate of bleeding in patients who do need to undergo urgent CABG.”

Effient has a boxed warning regarding bleeding risk. As the label states, “In TRITON-TIMI 38, overall rates of TIMI Major or Minor bleeding adverse reactions unrelated to coronary artery bypass graft surgery (CABG) were significantly higher on Effient than on clopidogrel.” For TIMI Major or Minor bleeding the rates were 4.5% for prasugrel vs. 3.4% for clopidogrel, about 24% higher. In the elderly (age ≥ 75) rates of fatal and intracranial bleeding were increased such that prasugrel is not recommended for the elderly except in high-risk patients (diabetes or prior MI.)

COMMENT: Prasugrel demonstrated superior efficacy to clopidogrel but also increased risk of bleeding. Hence prasugrel represents a contemporaneously available alternative treatment that should have provided superior benefit-risk for many patients who had higher cardiac event risks but low or average bleeding risks. Prasugrel should have been allowed as a comparator or, as a minimum, discussed in the protocol, investigator’s brochure, and ICDs.

Availability and Benefit-Risk of Ticagrelor

Ticagrelor is another approved oral P2Y₁₂ antagonist. However, ticagrelor was approved in Europe on December 3, 2010, and in the US on July 20, 2011—both approvals are during the conduct of PHOENIX. Ticagrelor is unlike clopidogrel in that ticagrelor is not a thienopyridine and does not require activation. It, like prasugrel, provides faster, more consistent platelet inhibition than clopidogrel. Furthermore, it is a reversible inhibitor, while clopidogrel and prasugrel are irreversible inhibitors. Reversibility should provide some advantages when the inhibitor needs to be discontinued for active bleeding. Finally, in its pivotal PLATO trial in ACS it allegedly showed a long term mortality benefit, something that both clopidogrel and prasugrel have not shown. Also noteworthy regarding PLATO is that it allowed prior thienopyridine use and specified study drug use immediately after randomization without requiring a delay for angiography. I summarize below the relevant parts of the European and US labels.

European Approval and Labeling

The EMA approved ticagrelor (Brilique) on December 3, 2010, for marketing in the European Union. The EMA product information report is available at

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001241/WC500100494.pdf

(EMA 2010) The approved indication is the following:

“Brilique, co-administered with acetylsalicylic acid (ASA), is indicated for the prevention of atherothrombotic events in adult patients with Acute Coronary Syndromes (unstable angina, non ST elevation Myocardial Infarction [NSTEMI] or ST elevation Myocardial Infarction [STEMI]); including patients managed medically, and those who are managed with percutaneous coronary intervention (PCI) or coronary artery by-pass grafting (CABG).”

The Clinical efficacy and safety section of the label has this statement regarding superiority to clopidogrel:

“On a background of daily ASA, ticagrelor 90 mg twice daily showed superiority to 75 mg daily clopidogrel in preventing the composite endpoint of cardiovascular [CV] death, myocardial infarction [MI], or stroke, with the difference driven by CV death and MI.”

The label text does not discuss the lower all-cause mortality with ticagrelor. Table 3, Outcome Events in PLATO, has a row for all-cause mortality listing 4.3% of patients dying with ticagrelor vs. 5.4% with clopidogrel, $p = 0.0003$, with the footnote “nominal significance value; all others are formally statistically significant by pre-defined hierarchical testing”.

US Approval and Labeling

We approved ticagrelor (Brilinta) on July 20, 2011. The initial approved labeling is available at

http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022433s000lbl.pdf.

(AstraZeneca 2011) The approved indication is the following:

“BRILINTA is a P2Y₁₂ platelet inhibitor indicated to reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS) (unstable angina, non-ST elevation myocardial infarction, or ST elevation myocardial infarction). BRILINTA has been shown to reduce the rate of a combined endpoint of cardiovascular death, myocardial infarction, or stroke compared to clopidogrel. The difference between treatments was driven by CV death and MI with no difference in stroke. In patients treated with PCI, it also reduces the rate of stent thrombosis.”

The Clinical Studies section of the label has the following description of the PLATO results:

“The difference between treatments on the composite resulted from effects on CV death and MI; each was statistically significant when considered as a secondary endpoint and there was no beneficial effect on strokes. For all-cause mortality the benefit was also statistically significant ($p = 0.0003$) with a hazard ratio of 0.78.”

COMMENT: Both the European and US labels describe the superiority of ticagrelor to clopidogrel for the primary endpoint. Both note that CV death and MI contributed to the superiority with no beneficial effects upon stroke. The US label mentions the mortality benefit in text while the European label includes it in a table. Note that, as documented above, the European (ESC) 2011 guidelines recommend ticagrelor or prasugrel over clopidogrel, relegating clopidogrel use “for patients who cannot receive ticagrelor or prasugrel”. Ticagrelor upon approval should have been allowed as an option in PHOENIX.

Glycoprotein IIb/IIIa Inhibitors (GPIs)

Three GPIs are approved in the US and Europe: abciximab (ReoPro), eptifibatide (Integrilin), and tirofiban (Aggrastat). All three are administered IV; oral agents have been tested but abandoned because of safety problems or lack of efficacy. Many of the studies supporting GPI use were conducted prior to the widespread use of clopidogrel for PCI. GPIs have been studied in trials with clopidogrel as well as the newer P2Y₁₂ inhibitors but the optimal use of GPIs and P2Y₁₂ inhibitors is not well defined. In particular the GPI labels do not address well how GPIs and P2Y₁₂ inhibitors should be used. Because of the limitations of the labels and the fact that there are six of them (between the US and Europe), I have not included excerpts of the labels in this review. I summarize the guideline recommendations regarding GPIs below.

European Guidelines for Revascularization and MI

The 2007 ESC guidelines for NSTEMI ACS recommended the following:

“They may be used as first-line treatment in addition to other antithrombotic agents, before invasive evaluation of the patient is undertaken. This so-called ‘upstream’ use of GP IIb/IIIa inhibitors prior to revascularization has been shown in meta-analyses to further reduce the risk of death and MI at 30 days, if GP IIb/IIIa inhibitors are prescribed upstream of and maintained during the PCI procedure.” (Bassand, Hamm et al. 2007)

The recommended use was in addition to oral antiplatelet agents.

The 2011 ESC guidelines for NSTEMI ACS recommend the following:

“The choice of combination of oral antiplatelet agents, a GP IIb/IIIa receptor inhibitor, and anticoagulants should be made in relation to the risk of ischaemic and bleeding events.”

“Among patients who are already treated with DAPT [dual antiplatelet therapy, i.e., aspirin plus a P2Y₁₂ inhibitor], the addition of a GP IIb/IIIa receptor inhibitor for high-risk PCI (elevated troponin, visible thrombus) is recommended if the risk of bleeding is low.”

“In high-risk patients eptifibatide or tirofiban may be considered prior to early angiography in addition to DAPT, if there is ongoing ischaemia and the risk of bleeding is low.” (Hamm, Bassand et al. 2011)

These 2011 guidelines do not recommend routine use before angiography.

The ESC/ EACTS 2010 Guidelines on myocardial revascularization recommended GPI use, along with unfractionated heparin, in NSTEMI ACS with very high-risk of ischemia and in both NSTEMI ACS and STEMI in patients with evidence of high intracoronary thrombus burden. (Wijns, Kolh et al. 2010) For elective PCI it recommended GPI use for bailout only.

The 2008 ESC guideline for STEMI listed all three GPIs as “Anti-platelet cotherapy” for “Primary PCI” in a table of “Reperfusion therapy”. (Van de Werf, Bax et al. 2008) It discussed that abciximab was the GPI most studied, that upstream use did not appear to be beneficial, and that “it remains to be elucidated whether abciximab provides an additional benefit to STEMI patients who receive an optimal clopidogrel treatment prior to PCI.”

The 2012 ESC guideline for STEMI state similarly that “there is no definitive answer regarding the current role of routine use of GP IIb/IIIa inhibitors in primary PCI in the era of potent DAPT, particularly when prasugrel or ticagrelor is used, and the value of starting upstream of the catheterization laboratory is, at best, uncertain.” (Steg, James et al. 2012) It does recommend, however, that “routine use of a GP IIb/IIIa inhibitor as an adjunct to primary PCI performed with unfractionated heparin may be considered in patients without contraindications.”

US Guidelines for PCI and MI

The 2008 ACCP ACS guideline recommended upstream treatment with a GPI and, for patients undergoing PCI, both clopidogrel and a GPI. (Harrington, Becker et al. 2008) See the quote under Timing of Clopidogrel above. The 2008 ACCP STEMI guideline recommended abciximab and a GPI prior to coronary angiography. (Goodman, Menon et al. 2008)

The 2007 ACC UA/NSTEMI guideline stated that “An intravenous platelet GP IIb/IIIa inhibitor is generally recommended in UA/NSTEMI patients undergoing PCI. (Level of Evidence: A)” (Anderson, Adams et al. 2007) The 2007 ACC PCI update was similar and stated that “an intravenous platelet GP IIb/IIIa inhibitor is useful in UA/NSTEMI patients undergoing PCI. (Level of Evidence: A)” and “it is reasonable to give . . . GP IIb/IIIa antagonists, administered at the time of PCI. (Level of Evidence: C)” The 2011

ACC UA/NSTEMI update modified these recommendations to designate eptifibatide or tirofiban as the preferred GPIs before PCI as quoted under Timing of Clopidogrel above.

The 2009 ACC update for STEMI stated the following:

“It is reasonable to start treatment with glycoprotein IIb/IIIa receptor antagonists (abciximab [Level of Evidence: A], tirofiban [Level of Evidence: B] or eptifibatide [Level of Evidence: B] at the time of primary PCI (with or without stenting) in selected patients with STEMI.”

“Early GP IIb/IIIa therapy in patient groups continues to appear reasonable if they are judged clinically to be at high risk of thrombotic events relative to bleeding risk.” (Kushner, Hand et al. 2009)

COMMENT: There is more uncertainty regarding the optimal use of GPIs than there is regarding timing of clopidogrel or the use of prasugrel and ticagrelor. However, I do not see a justification for excluding their use during the trial in patients for whom GPI use is standard of care. The ethical alternative would have been to exclude such patients.

PHOENIX Ethicalness and PHOENIX Documentation

Ethical Options for PHOENIX

Considering the PCI and PLATFORM results, the guidelines (European and US), the investigator and site publications, and the availability and risk/benefit of prasugrel, I believe that there were only the following options for conducting PHOENIX ethically:

- For patients in the cangrelor arm prasugrel or ticagrelor (after approval) should have been allowed after the cangrelor infusion. Because of their rapid onset the transition from cangrelor to prasugrel or ticagrelor should be advantageous compared to the transition to clopidogrel. However, ideally the pharmacodynamics of the transition should be studied and understood. Because the latter is valuable for the post-approval use of cangrelor—we should presume it will be used with prasugrel and ticagrelor as well clopidogrel—I do not see this requirement as disadvantageous or unduly burdensome.
- STEMI patients randomized to the control arm should have been given early (on presentation) clopidogrel or prasugrel or ticagrelor (after approval).
- UA/NSTEMI should have been handled in one of the following ways:
 - Control patients should have been additionally randomized to early (on presentation) clopidogrel or ticagrelor (after approval) vs. delayed prasugrel. If one judges that there is equipoise between early vs. delayed clopidogrel for UA/NSTEMI patients, then an alternative would be randomization to early vs. delayed clopidogrel or prasugrel or ticagrelor. (Allowing delayed ticagrelor can be debated because PLATO did not

specify delaying for angiography.) However, the PLATFORM results argue against allowing any delayed use of clopidogrel. PLATFORM established that delaying clopidogrel until after the PCI is bad but it and CHAMPION PCI are not informative regarding the optimal timing of clopidogrel use. The preponderance of evidence still suggests that clopidogrel should be administered six or more hours prior to PCI.

- Control patients should have been given early clopidogrel (or ticagrelor when approved) or prasugrel after angiography.
- The ICD should have described the potential benefits of early clopidogrel and prasugrel (and ticagrelor when approved) and advised patients that these latter alternatives are not available to trial participants. While full disclosure in the ICD of potentially beneficial but unavailable options seems consistent with the US regulations, I believe that the ethics of this option are still questionable and it would be impractical because of subject recruitment problems.
- Stable angina patients should have been given early clopidogrel. One could argue for randomizing these patients or allowing standard of care. Prasugrel and ticagrelor have not been studied and are not approved for stable angina patients so their specification for stable angina patients is not justified.
- GPIs should have been allowed per standard of care. Alternatively, the protocol should have stated that patients in whom a GPI would ordinarily be used per standard of care should be excluded. GPIs have been used in patients concurrently receiving clopidogrel, prasugrel, and ticagrelor. If the sponsor believes that it is not safe to use cangrelor and a GPI simultaneously, then the alternative of excluding patients in whom a GPI would ordinarily be used per standard of care should have been implemented.

There are trial conduct complications introduced by the necessity of allowing prasugrel and ticagrelor in addition to clopidogrel. The study drug stocking is more complex because prasugrel and its dummy and ticagrelor and its dummy must be stocked in addition to clopidogrel and its dummy. Note that PHOENIX had an additional problem (not discussed in this review) because the clopidogrel study drug was simply overencapsulated clopidogrel tablets, making it trivial to break the blind by opening the capsule.

I summarize the PHOENIX documentation relevant to the above options next.

Cangrelor Investigator's Brochure (IB)

I have included the Cangrelor IB dated May 4, 2010, as Attachment 3. The one problem I identified in the IB is that the descriptions of the CHAMPION studies are misleading. The IB includes the following descriptions of them:

- “The PCI study (TMC-CAN-05-02) planned enrollment of 9,000 patients within the following categories: SA, UA, NSTEMI, or STEMI. Patients received a dose of clopidogrel at the start of the PCI procedure and the study was designed to demonstrate superiority to a 600 mg loading dose of clopidogrel.
- “The Platform study (TMC-CAN-05-03) planned enrollment of 6,400 patients within the following categories: SA, UA, or NSTEMI. In contrast to PCI, STEMI patients were not enrolled in the Platform study. The other key difference was that patients did not receive a dose of clopidogrel at the start of the PCI procedure; instead, clopidogrel was given at the end of the PCI procedure. Therefore, the study was designed to demonstrate superiority to usual care. Exclusion criteria required patients to be clopidogrel-naïve, eg, no clopidogrel within 7days prior to randomization.”

Because clopidogrel should be given at presentation, the PCI study could not demonstrate superiority to clopidogrel used appropriately. Because in PLATFORM clopidogrel was given at the end of PCI, PLATFORM did not compare to usual care.

PHOENIX Protocol

The protocol version in effect for the entire trial included one amendment and was dated September 28, 2010. An FDA protocol advice letter dated September 9, 2010, motivated the amendment. Among other suggestions that letter recommended the following:

“The protocol stipulates a loading dose of clopidogrel (300 to 600 mg) will be administered to subjects randomized to clopidogrel “at the time of PCI”. The onset of action of clopidogrel is not rapid; therefore delaying administration of clopidogrel may result in inadequate platelet inhibition at the time of PCI. Please revise your protocol to allow the investigator to determine the timing of clopidogrel administration.”

The intent was to allow clopidogrel administration on presentation, rather than waiting for angiography. I present below how the sponsor implemented that recommendation.

The protocol synopsis has what appears to be an appropriate (except for lack of prasugrel) description of the reference treatment:

“Reference Therapy, Dose and Mode of Administration: Clopidogrel standard of care: Clopidogrel loading dose administered in patients undergoing PCI as soon as possible following randomization as directed by the investigator. Placebo IV bolus and infusion with dosing to match active treatment.”

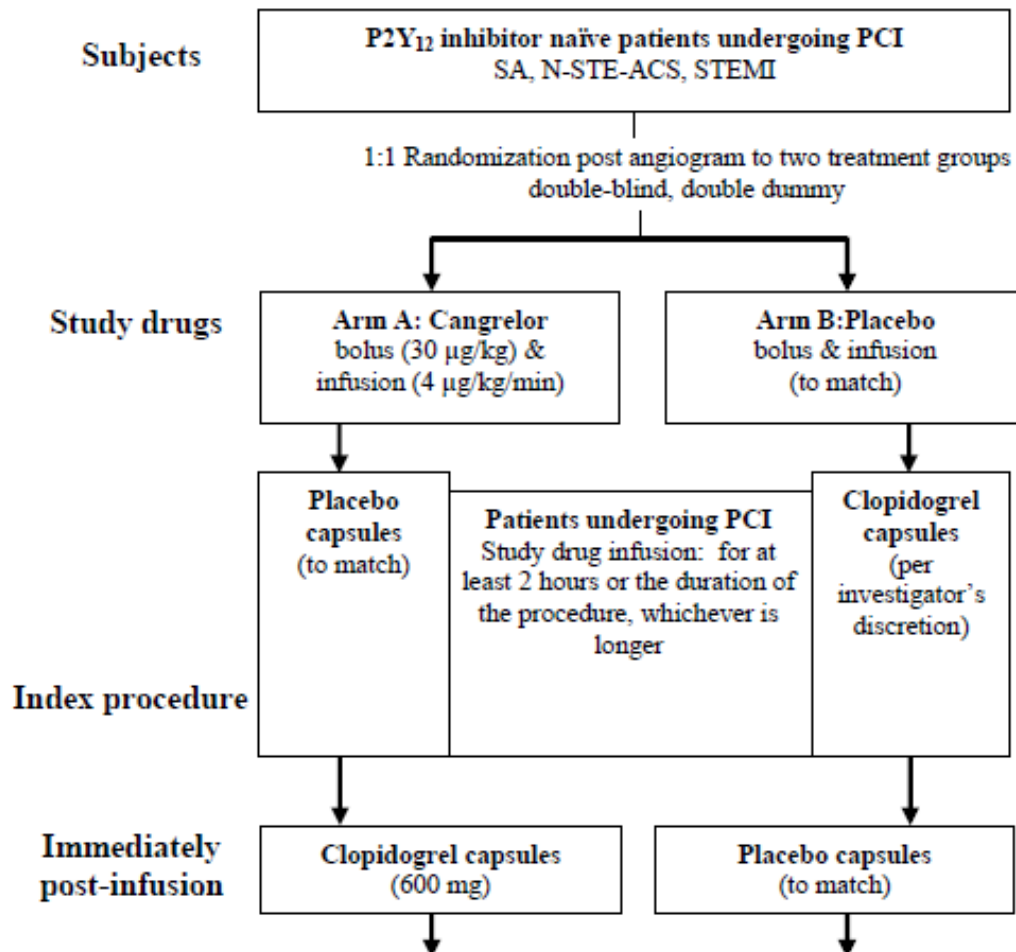
“Clopidogrel standard of care” sounds appropriate but the specifications are immediately hedged by “as directed by the investigator”. Is it “clopidogrel standard of care” or “directed by the investigator”? The full protocol confirms that it is the latter with additional inappropriate wordings.

The “Duration of Treatment” section in the synopsis confirms one problem:

“Duration of Treatment: Initiated immediately prior to the index procedure . . .”

What the synopsis failed to state explicitly is that the protocol specified randomization to be done after angiography. The following excerpt from Figure 2, the Trial Design, shows this specification:

Figure 2: Trial Design



This Trial Design figure, however, has two flaws:

1. The intent of the FDA advice letter—and standard of care—was to allow clopidogrel use at any time after presentation, not only after angiography as the figure portrays.
2. The protocol did not require STEMI patients to undergo angiography prior to randomization as the figure implies. The protocol mentions the lack of this requirement under Inclusion Criterion 2 “Patients undergoing PCI”, “c. STEMI patients (diagnostic angiography not required).” The protocol does elaborate as follows:

“Importantly, the treating physician must have knowledge of the coronary anatomy and suitability for PCI prior to randomization, except for patients diagnosed with STEMI. Due to the compelling nature of STEMI and the high likelihood of a percutaneous intervention, these subjects may be randomized on diagnosis, allowable in the emergency department, provided there is no impediment to primary PCI.”

COMMENT: Regarding the delay in randomization and clopidogrel loading for most patients until after angiography my FDA colleagues appear to have missed that the protocol changes were not responsive to the advice letter. Given that the synopsis starts out by declaring “Clopidogrel standard of care” it should not be surprising that IRBs also missed the inappropriate treatment in the control arm.

Regarding STEMI patients not requiring angiography, the investigators appear to have followed the figure rather than the text recommendation. I document in a parallel review on the benefit-risk of cangrelor that the majority of STEMI patients were randomized after angiography. (Marciniak 2014)

The protocol appears to have been both misleading and ambivalent regarding the timing of clopidogrel. In the Study Rationale section it begins the discussion of the comparator with the following statements:

“The comparator is clopidogrel standard of care. In line with guidelines and common practice, it is expected that the majority of patients will receive 600 mg loading dose given as soon as possible after randomization per investigator’s discretion.”

However, randomization was after angiography (except perhaps in STEMI patients) and the ESC guidelines recommend giving clopidogrel earlier. The discussion of the comparator continues as follows:

“It is recognized that there are clinical settings in which the administration of a 600 mg loading dose pre-PCI is not feasible or desirable. Such clinical settings could include patients who are sedated, those with nausea or vomiting, patients who are intubated, patients in whom gastrointestinal absorption may be questionable; patients in whom the anatomy is unknown and are likely to require surgery, patients at high risk of bleeding or any other circumstance deemed appropriate by the treating physician. In these clinical settings, the administration of 600 mg clopidogrel following PCI is allowed per investigator’s discretion.”

COMMENT: The protocol provides a wide range of excuses for delaying clopidogrel including “patients in whom the anatomy is unknown and are likely to require surgery”. This latter argument justifies delaying clopidogrel until after angiography, not following PCI. Regardless, the expectation that “the majority of patients will receive 600 mg loading dose given as soon as possible after randomization” was not achieved: Only about 39% of patients in the clopidogrel arm received a 600 mg loading dose pre-PCI. About 30% of patients in the clopidogrel arm received the loading dose after completion

of PCI. The control arm did not represent clopidogrel standard of care even by the protocol expectations, much less by the guidelines.

There are other problems with the protocol besides the delay in clopidogrel use:

- Exclusion of prasugrel. An exclusion criteria excluded “1. Receipt of any P2Y₁₂ inhibitor at any time in the 7 days preceding randomization.” The section on Required Medication During Follow-up Period states that “All patients should receive standard of care antiplatelet therapy per ACC/AHA/ESC guidelines. 75 mg of clopidogrel will be used for P2Y₁₂ inhibition during the first 48 hours post PCI.” However, the ACC/AHA guidelines allow the use of prasugrel, including during the first 48 hours and the later ESC guidelines even specify prasugrel (and ticagrelor) as preferable to clopidogrel.
- Exclusion of routine GPIs. The exclusion criteria excluded “2. Eptifibatide and tirofiban usage within 12 hours preceding randomization (most recent dose must have been administered \geq 12 hours prior to randomization)” and “3. Abciximab usage within 7 days preceding randomization”. Excluding patients with prior use of GPIs is acceptable. However, the section on Permitted Concomitant Medications states that “Physicians may administer a GP IIb/IIIa inhibitor during the index PCI as bailout therapy only when new or persistent thrombus formation during PCI, slow or no reflow, side branch compromise, dissection or distal embolization is observed.” Excluding concurrent use of GPIs is acceptable only if the exclusion criteria clearly stated that patients for whom GPIs are considered standard of care were to be excluded.
- Incomplete description of the CHAMPION trials. The protocol describes CHAMPION PCI and CHAMPION PLATFORM briefly as follows:

“Two Phase III multinational, randomized, double-blind, double dummy, active controlled, parallel group studies (CHAMPION PCI and CHAMPION PLATFORM) were designed to enroll approximately 15,400 patients with coronary atherosclerosis who require PCI. The primary objective for both studies was to demonstrate the superior efficacy of cangrelor versus placebo as measured by a composite of all cause mortality, MI, and IDR at 48 hours post randomization.”

Note that this brief description does not mention the difference in timing of clopidogrel between the two studies.

- Incomplete quotes from the guidelines. The protocol quotes the ACC 2009 update on STEMI and PCI, the ESC 2007 NSTEMI guidelines, and the ESC 2008 STEMI guidelines. While the quote from the ACC 2009 STEMI update includes that clopidogrel “should be given as early as possible before or at the time of non-primary PCI”, the quote from the ASC 2008 guideline does not include that “clopidogrel should be given as soon as possible to all patients with STEMI undergoing PCI.” The quote from the 2007 ESC guideline for NSTEMI does

include that “an immediate 300 mg loading dose of clopidogrel is recommended” but does not include the more specific advice that “Pre-treatment of unselected patients with clopidogrel before angiography results in better outcome of PCI.”

- No amendments to allow ticagrelor use after the US and European approvals.

The protocol concludes its section on Study Rationale, immediately following its discussion of guidelines, with “This study is designed to demonstrate that in patients requiring PCI, cangrelor provides superior efficacy to clopidogrel standard of care.” The protocol does not appear to support clopidogrel standard of care nor the contemporaneous standard of care including prasugrel, ticagrelor, and GPI use.

PHOENIX Informed Consent Document (ICD)

One could argue that, if the ICD fully informed patient regarding the possible advantages of early clopidogrel and of prasugrel and GPIs and ticagrelor (when approved), then the trial as conducted was ethical. Hence analyzing the ICD is appropriate.

For a multicenter international trial such as PHOENIX there is not one ICD. The ICDs ultimately used vary by the languages and local practices within the countries in which the sites are located. The institutional review boards (IRBs) or independent ethics committees involved may also edit the ICDs. What the trial sponsor typically provides to the FDA is a model ICD or ICD template. The PHOENIX sponsor provided an ICD template for the US that I have included as Attachment 4.

Note the following about the PHOENIX ICD template:

- The ICD does not mention prasugrel, e.g., from the introductory Background and purpose: “The initial dose of Plavix that you will receive when you have a PCI can be up to two times the approved dose depending on your institution’s standard of care. The purpose of this study is to compare the safety and effectiveness of cangrelor combined with Plavix to the safety and effectiveness of Plavix alone.”
- The ICD specifies giving clopidogrel in the placebo arm at the time of PCI: “Per your institutions’ standard of care, you will receive 2 - 4 150 mg capsules of Plavix at the time of the PCI.” There is no mention that delaying clopidogrel might be bad.
- The ICD does not mention the possible benefits of and exclusion of GPIs.
- The ICD was not updated for ticagrelor after the US approval.

Because the IRBs involved could have modified the template, I requested copies of the actual ICDs used from several sites. I picked two US sites (the VA Boston and Scripps Institute) for which physicians at the sites had published articles describing clopidogrel use and two European countries (Austria and Germany) from which PHOENIX investigators had co-authored the European guidelines. I obtained a copy from Scripps,

which I have included as Attachment 5. I did not obtain a copy from the VA Boston. I did obtain copies of the versions (in the original German) used in Austria and Germany and translated them. I have included parallel versions of the original German and translated English for the ICD from Austria as Attachment 6 and from Germany as Attachment 7.

The Scripps ICD also does not mention prasugrel. It does differ slightly from the sponsor's US ICD template regarding clopidogrel use:

“Prior to the start of the infusion, you will also be required to take 2 to 4 capsules of either Plavix or placebo. The number of pills you receive will depend on your doctor's decision what is best for your procedure.” “These drugs [cangrelor, Plavix] will be given during the procedure.”

The Scripps ICD also does not discuss that delaying clopidogrel might be bad. It includes a California Experimental Subject's Bill of Rights that states one right as the following:

“Learn about the risks and benefits of any other available procedures, drugs or devices that might be helpful to me.”

I also queried Scripps regarding what documentation the sponsor had provided to them for IRB use. I've included their response as Attachment 8. The sponsor provided to Scripps the IB (dated May 4, 2010), the protocol, an ICD, a CKMB manual, and a pharmacy manual.

The Austrian and German ICDs had limitations similar to those of the US ICD template and the Scripps ICD. They do not mention prasugrel, that delaying clopidogrel may be bad, and the possible benefits of and exclusion of GPIs. Given that the copies provided are the final versions, the ICDs were not updated for ticagrelor after the EMA approval.

FDA Interactions

The primary clinical review dated July 29, 2010, of the PHOENIX protocol included as its first comment the following:

“We believe that delayed administration of clopidogrel may not be optimal medical care. The onset of action of clopidogrel is known to be delayed; therefore delaying administration of clopidogrel may not result in adequate platelet inhibition at the time of PCI. Please revise your protocol to leave the timing of a thienopyridine to the investigator's discretion.”

It also commented:

“In addition, compared to clopidogrel, prasugrel has faster onset of action and does not interact with CYP2C19 inhibitors. Therefore, please revise your protocol to leave the choice of a thienopyridine to the investigator's discretion.”

It did not comment on the exclusion of GPIs.

I could not find a letter in DARRTS communicating the comments to the sponsor. However, there is an email from the sponsor dated August 12, 2010, referencing an August 10, 2012, tcon with the following comment:

- We agree that the administration of clopidogrel should be both as early as possible after definitive diagnosis as directed by the investigator, and will amend the protocol in Section 5.1.2 to state the following:

Clopidogrel: to be administered as soon as possible following randomization as directed by the investigator

The protocol was amended with the latter statement. However, because randomization was not done until after angiography, clopidogrel use was delayed in the trial. In fact, the addition of “as directed by the investigator” appears to have increased the delay of clopidogrel use for many patients. As I summarize below, clopidogrel administration was delayed until after the completion of PCI in a substantial fraction of patients rather than after angiography but before the start of PCI.

The email did not address prasugrel use. It also did not address GPI use.

The only other communication in DARRTS regarding these issues is an FDA letter dated September 9, 2010, to the sponsor. I quoted the paragraph in that letter regarding the timing of the loading dose under PHOENIX Protocol above. The letter also included the following regarding prasugrel:

“Please revise your protocol to prohibit concomitant use of clopidogrel with moderate or strong CYP2C19 inhibitors. Alternatively, you could revise the protocol to leave the choice of a platelet P2Y₁₂ inhibitor to investigator discretion. Compared to clopidogrel, prasugrel has faster onset of action and does not interact with CYP2C19 inhibitors.”

The protocol prohibited “CYP2C19 inhibitors (eg. omeprazole)” for the first 48 hours post-randomization.³

None of the FDA documents or sponsor communications discusses informed consent. I did not find further follow-up on these issues beyond the September 9, 2010, letter.

Actual Timings of Clopidogrel Loading

I have documented above that the protocol-specified timings of clopidogrel administration in all three studies were not consistent with the contemporaneous practice guidelines. A good question is how closely did sites adhere to the protocol-specified

³ I disagree that prohibiting CYP2C19 inhibitors was adequate. Prasugrel is a more effective platelet inhibitor that demonstrated superior results to clopidogrel particularly in patients with STEMI. Furthermore, in August 2010 we added a boxed warning to the clopidogrel label regarding diminished effectiveness in poor metabolizers and advising prescribers to consider alternative treatments, e.g., prasugrel. Prohibiting CYP2C19 inhibitors accomplishes nothing regarding pharmacogenomics.

timings. In particular, while the protocols specified that oral study drug be administered after angiography for stable angina and UA/NSTEMI patients, the protocols for the two trials that enrolled STEMI patients (PCI and PHOENIX) allowed earlier administration of oral study drug for the STEMI patients.

I document the actual timing results in a parallel review on the benefit-risk of cangrelor. (Marciniak 2014) I summarize selected timing results below:

- About 78% of STEMI patients in PCI and 71% in PHOENIX received clopidogrel after angiography.
- About 17% of STEMI patients in PCI and 9% in PHOENIX received clopidogrel after the completion of PCI.
- About 22% of the UA/NSTEMI patients and 39% of the stable angina patients in PHOENIX received clopidogrel after the completion of PCI.
- The median times from clopidogrel administration to PCI were 0 minutes in the stable angina subgroup, 2 minutes in the UA/NSTEMI subgroup, and 4 minutes in the STEMI subgroup of PHOENIX.

COMMENT: The sites appeared not to have endorsed the concept that “time is myocardium” in STEMI and frequently delayed clopidogrel loading. They delayed loading until after PCI in substantial fractions of the UA/NSTEMI and stable angina patients despite the frightening PLATFORM results. I doubt that the sponsor adequately presented the PLATFORM results to the sites and their IRBs.

Discussion

While I argue that PHOENIX was unethical and I present below the reasons why I believe so, the counterarguments are that, other than the cangrelor infusion, PHOENIX used “standard of care” and that the control arm received an “established effective intervention” (the latter the terminology of the CIOMIS International Ethical Guidelines for Biomedical Research).

(Council_for_International_Organizations_of_Medical_Sciences 2002) I address these counterarguments below and discuss the reasons why I believe PHOENIX was unethical.

- Regarding timing of clopidogrel, the US guidelines appear to allow delayed use while the European guidelines do not. The investigators’ publications and participations in guideline writing indicate that the principal investigators believed that delaying clopidogrel use increases cardiac events. It seems inappropriate to me that they would support studies forcing delayed use. One could argue that PHOENIX was ethical if the standard of care at all participating sites was delayed clopidogrel use. However, I argue that that would only be acceptable if the following conditions were also satisfied:
 - The IRBs were fully informed about the data supporting early use of clopidogrel.

- The IRBs were fully informed about the evidence from the cangrelor CHAMPION trials that delaying clopidogrel was disadvantageous.
- The IRBs confirmed that delaying clopidogrel was the standard of care at the sites for which they were responsible and that they had considered the evidence from the CHAMPION trials that delaying clopidogrel was bad.
- The patients were fully informed in the ICDs that delaying clopidogrel might be harmful and that other treatments were available, i.e. prasugrel, GPIs, and later ticagrelor, that might be beneficial to them but that were not allowed in the trial.

Because these conditions were not met in PHOENIX, I believe that PHOENIX was unethical.

- The disadvantage of delayed clopidogrel use is not just a matter of inconvenience or a transient adverse effect. The evidence strongly suggests that delaying clopidogrel leads to adverse effects with irreversible consequences, i.e., MI and death. The prohibitions of prasugrel, ticagrelor, and GPIs have the same dire implications. When interventions involve irreversible consequences the ethical standard should not be any “established effective intervention” but the “best current interventions.” If there is uncertainty about the “best current intervention” then it should be the discretion of the IRB—not the sponsor—to confirm the “best current interventions” based on complete information. The latter was not done for PHOENIX.
- While the US ethical conduct regulations do not state explicitly the “best current intervention” requirement, they do require at 21 CFR §50.2 that the subjects receive information about “appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.” The PHOENIX ICDs did not inform patients about the appropriate alternative procedures that the protocol excluded.
- Cangrelor is allegedly a faster onset P2Y₁₂ inhibitor than clopidogrel and its pharmacodynamic data support this assertion of the sponsor. As such, delaying clopidogrel gave cangrelor an artificial advantage over clopidogrel. As such, prohibiting prasugrel, ticagrelor, and GPIs—all of which are faster onset platelet inhibitors than clopidogrel—maintained the artificial advantage of cangrelor over the inappropriately restricted control. However, an artificial advantage means that PHOENIX patients suffered, and the PHOENIX patients’ sufferings included irreversible harm such as MIs and death.

[REDACTED]

References

- Alexander, J. H. (2009). "The current state of antiplatelet therapy in acute coronary syndromes: the data and the real world." *Cleve Clin J Med* **76 Suppl 1**: S16-23.
- Anderson, J. L., C. D. Adams, et al. (2007). "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): developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons: endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine." *Circulation* **116**(7): e148-304.
- AstraZeneca. (2011). "Brilinta prescribing information." from http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022433s000lbl.pdf.
- Bassand, J. P., C. W. Hamm, et al. (2007). "Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes." *Eur Heart J* **28**(13): 1598-660.
- Bhatt, D. L. (2009). "Prasugrel in Clinical Practice." *N Engl J Med* **361**(10): 940-942.
- Bhatt, D. L., A. M. Lincoff, et al. (2009). "Intravenous platelet blockade with cangrelor during PCI." *N Engl J Med* **361**(24): 2330-41.
- Bhatt, D. L., G. W. Stone, et al. (2013). "Effect of Platelet Inhibition with Cangrelor during PCI on Ischemic Events." *New England Journal of Medicine* **368**(14): 1303-1313.
- Council_for_International_Organizations_of_Medical_Sciences (2002). "International ethical guidelines for biomedical research involving human subjects." *Bull Med Ethics*(182): 17-23.
- EMA. (2009). "Efient Product Information." from http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000984/WC500021971.pdf.
- EMA. (2010). "Brilique product information." from http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001241/WC500100494.pdf.
- Goodman, S. G., V. Menon, et al. (2008). "Acute ST-segment elevation myocardial infarction: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition)." *Chest* **133**(6 Suppl): 708S-775S.
- Hamm, C. W., J. P. Bassand, et al. (2011). "ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC)." *Eur Heart J* **32**(23): 2999-3054.
- Harrington, R. A., R. C. Becker, 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* **133**(6 Suppl): 670S-707S.

- Harrington, R. A., G. W. Stone, et al. (2009). "Platelet inhibition with cangrelor in patients undergoing PCI." *N Engl J Med* **361**(24): 2318-29.
- Kim, J. H., L. K. Newby, et al. (2008). "Clopidogrel use and bleeding after coronary artery bypass graft surgery." *Am Heart J* **156**(5): 886-92.
- King, S. B., 3rd, S. C. Smith, Jr., et al. (2008). "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: 2007 Writing Group to Review New Evidence and Update the ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention, Writing on Behalf of the 2005 Writing Committee." *Circulation* **117**(2): 261-95.
- Kushner, F. G., M. Hand, et al. (2009). "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* **120**(22): 2271-306.
- Lange, R. A. and L. D. Hillis (2013). "The Duel between Dual Antiplatelet Therapies." *New England Journal of Medicine* **368**(14): 1356-1357.
- Leonardi, S., K. W. Mahaffey, et al. (2012). "Rationale and design of the Cangrelor versus standard therapy to achieve optimal Management of Platelet Inhibition PHOENIX trial." *American Heart Journal* **163**(5): 768-776.e2.
- Lilly. (2010). "Effient Prescribing Information." from http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022307s001lbl.pdf.
- Marciniak, T. A. (2014). Clinical Review: Benefit-risk of cangrelor, FDA.
- Sakhuja, R., R. W. Yeh, et al. (2010). "Antiplatelet agents in acute coronary syndromes." *Curr Probl Cardiol* **35**(3): 123-70.
- sanofi-aventis and Bristol-Meyers-Squib. (2010). "Plavix Prescribing Information." from http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020839s048lbl.pdf.
- Sellers, M. B., P. Tricoci, et al. (2009). "A new generation of antiplatelet agents." *Curr Opin Cardiol* **24**(4): 307-12.
- Smith, S. C., Jr., T. E. Feldman, et al. (2006). "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 (ACC/AHA/SCAI Writing Committee to Update 2001 Guidelines for Percutaneous Coronary Intervention)." *Circulation* **113**(7): e166-286.
- Steg, P. G., S. K. James, et al. (2012). "ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation." *Eur Heart J* **33**(20): 2569-619.
- Steinhubl, S. R., P. B. Berger, et al. (2006). "Optimal timing for the initiation of pre-treatment with 300 mg clopidogrel before percutaneous coronary intervention." *J Am Coll Cardiol* **47**(5): 939-43.
- Van de Werf, F., J. Bax, et al. (2008). "Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation: the Task Force on the Management of ST-Segment Elevation Acute Myocardial Infarction of the European Society of Cardiology." *Eur Heart J* **29**(23): 2909-45.

- Widimsky, P., Z. Motovska, et al. (2008). "Clopidogrel pre-treatment in stable angina: for all patients >6 h before elective coronary angiography or only for angiographically selected patients a few minutes before PCI? A randomized multicentre trial PRAGUE-8." European Heart Journal **29**(12): 1495-1503.
- Wijns, W., P. Kolh, et al. (2010). "Guidelines on myocardial revascularization." Eur Heart J **31**(20): 2501-55.
- Wright, R. S., J. L. Anderson, et al. (2011). "2011 ACCF/AHA Focused Update of the Guidelines for the Management of Patients With Unstable Angina/ Non-ST-Elevation Myocardial Infarction (Updating the 2007 Guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines." Circulation **123**(18): 2022-60.

Q&A with Dr. Steven Steinhubl

1. Other than the fact that we are conducting a research protocol, what is the rationale for not loading subjects with PLAVIX?

- Delayed and variable onset of oral PLAVIX – In some situations it isn't possible to adequately load a patient – minimum of 2 hour delay after 600mg and 15 to 24 hours after 300mg
- Unpredictable effect – while the clinical implications of variability in response to clopidogrel are not clearly understood a number of small studies suggest that lower levels of inhibition are associated with an increased incidence of thrombotic events. Cangrelor provides immediate and dependable high levels of platelet inhibition.
- Prolonged effect – the major limitation to using an irreversible platelet inhibitor in the treatment of an ACS patient is that a significant minority of ACS patients will require surgical revascularization.
- Activation inhibition only (Both Plavix and cangrelor inhibit activation only.)



2. What are the potential advantages of cangrelor?

- Fast onset to peak: <5 minutes (vs. clopidogrel 2+ hours)
- Fast reversal: <60 minutes (vs. clopidogrel 5 days)
- Optimal inhibition: >95% suppression (vs. clopidogrel ~40-60%)
- Direct effect (vs. clopidogrel indirect effect)
- Mechanism of action: suppresses platelet activation (vs. GPIIb/IIIa inhibitors—suppress platelet aggregation)
- No dose adjustment for renal/hepatic dysfunction
- Linear, weight-based IV dosing; therefore a consistent, predictable high level of inhibition.



**Interim Analysis Review Committee (IARC) Meeting for the
CHAMPION Program: PLATFORM Trial**

**May 1, 2009
Washington, D.C**

Attendees:

IARC Members

Robert Califf, M.D. (Chairman)

Christian Hamm, M.D. (via conference call)

Cyrus Mehta, Ph.D.

Carl Pepine, M.D.

James Ware, Ph.D.

Duke Clinical Research Institute

Steven McNulty, M.S.

The Closed Session commenced at 11:45 a.m. There was no Open Session.

Dr. Califf opened the meeting by stating that he has had several conversations with Dr. Clive Meanwell of The Medicines Company (TMC) concerning the PCI trial. Dr. Califf reiterated that the IARC had followed all of the prescribed processes when reviewing the PCI trial, determining that the futility criteria had been met. No safety issues had been reported by the Data and Safety Monitoring Board (DSMB) concerning the PCI study at that time. TMC decided to continue to enroll in the PCI trial despite the IARC recommendations since no safety issues had been noted. Enrollment in the PCI trial is expected to finish in June 2009.

Dr. Meanwell had written to Dr. Califf encouraging the IARC to play an expanded role in the PLATFORM trial, allowing them more flexibility to review any information they considered of interest, above and beyond the guidelines written in the IARC Charter. Per Dr. Califf, Dr. Meanwell's letter had been sent to all of the IARC members.

Dr. Mehta reported that he had looked at the trend in mortality for both trials and that the combined results favored the cangrelor arm. He noted that PCI had 4 deaths (1 cangrelor and 3 clopidogrel) and PLATFORM 20 (6 cangrelor



and 14 placebo). Based on these data, the p-value when combining the samples together without adjustment is 0.04, favoring cangrelor. When stratifying by study, since they do differ in study drug application, the p value is 0.06.

Before the data were reviewed, Dr. Califf explained the potential clinical importance of cangrelor in real-world care. P₂Y₁₂ inhibition (clopidogrel, prasugrel) has proven to be quite successful, even though it was not clear it would be when the drugs first became available. All oral inhibitors are long-acting but must be discontinued for at least 5-7 days prior to interventions or surgeries. The discontinuation itself and the 5-7 days without effective P₂Y₁₂ inhibition expose patients to increased risk for atherothrombotic adverse events. In the setting of PCI, cangrelor was thought to be an important addition to cover the period from when P₂Y₁₂ drugs were terminated until the start of PCI ("bridging"). Cangrelor is rapid acting and can be loaded quickly via IV to cover the period before the oral drugs can be restarted. Clinicians would welcome this option since it is believed that the patients are at increased risk for adverse events in that interval. It would be much more challenging to prove that cangrelor is superior to the other oral drugs so they could be replaced altogether. The IV nature of cangrelor would be a problem and new trials would need to be developed to explicitly test that hypothesis.

There is the possibility that TMC may be willing to test for non-inferiority versus the current superiority noted in the protocol. In the clinical world, non-inferiority would be demonstrated by showing that the cangrelor effects fall within a narrow confidence interval around the effect of the current treatment. The FDA requires that same criterion but also adds the need for a putative placebo comparison. With the change in FDA leadership, the non-inferiority rules could be more stringent or less so. TMC is not looking for a blockbuster drug. Instead they would like a product that could be used in a specialty market, such as the PCI setting. TMC can either do another trial to satisfy the



putative placebo requirement, needing a lot of sites and patients, or they could argue with the FDA that an adequate placebo controlled trial doesn't exist in the setting of PCI. Clopidogrel made it to the market for another indication, bypassing that requirement. If TMC can declare that cangrelor is not worse than standard of care, it implies that it can be used when other oral treatments are not possible.

There was a concern that the IARC is being asked to make a business decision. Based on the results provided by Dr. Mehta, it was felt that there is an ethical obligation to recommend futility and stop the trial. If any other recommendation is made, there would be a perception that there is something positive in the results that really is not there.

A question was raised about whether TMC would actually stop the trial since they chose to ignore the IARC recommendation concerning the PCI study. The early preference of the IARC members would be to recommend futility but provide secondary recommendations, if any, after that.

Another question was raised concerning the mortality signal mentioned by Dr. Mehta earlier in the meeting. If the mortality signal across both trials persisted if they both completed enrollment, that could be lost if we stopped PLATFORM at this time. This would deny TMC some benefit to their drug. Mr. McNulty reported that the current PCI trial mortality favored the clopidogrel arm (8 cangrelor and 5 clopidogrel) so the issue may be moot.

Dr. Mehta proceeded to review the steps leading to his recommended conclusions. He started by discussing what is called the G_0 population, which consists of the mITT patients. He pointed out that the Z statistic did not cross the efficacy boundary. Using a sample size of 6400 maximum, he had computed the conditional power and announced that it was 0.6% if the true effect size equals the observed effect size based on accumulating data. Even if



the sample size was increased to 15,000, the conditional power would only rise to 2.1%. Since the design specification calls for increasing the sample size only if such an increase could raise the conditional power to 80%, the sample size of the G_0 population should not be increased.

For completeness, Dr. Mehta also presented conditional power results under the assumption that the effect size is 0.73, as specified in the original study design. If the true effect size is that assumed in the original study design, the conditional power is 11.5%. To attain 80% power under this assumption, a sample size of 13,900 would be required. The 95% confidence interval on the odds ratio estimate (0.945) for the observed data is 0.75 to 1.18. Thus, the effect size hypothesized in the protocol, 0.73, is not consistent with the data accumulated thus far. Therefore, even by this criterion, the sample size of the G_0 population should not be increased. The next step is to proceed in analyzing the G_1 population, which is a subset of G_0 containing only diabetic or baseline cardiac marker positive patients.

If the assumption is made that future enrollment will be restricted to the G_1 population, the results are similar to that seen with G_0 . The conditional power is 0.5% under the assumption that the event rates estimated in the G_1 population continue to hold for the duration of the study. If the sample size is increased to 15,000, the conditional power only increases to 1.6%. The method of computing conditional power using event rates specified at the design stage is not applicable here since the case for population enrichment can only be based on the observed data at the interim analysis.

Based on this analysis, the recommendation prescribed by the protocol is to terminate the trial for futility. The next step is to determine, under the broader role of the IARC, if any other recommendation can be made.



Several positions were presented for discussion. The IARC members thoroughly reviewed the two trial schema to determine the differences in study treatment between the trials. It is expected that enrollment in PCI will finish in June and PLATFORM will finish in July or August.

One suggestion would be to terminate both projects, cutting TMC losses, and designing a bridging trial using the currently enrolling sites to provide patients.

Another suggestion was to provide the recommendation of futility, allowing TMC to continue enrollment as they saw fit. The integrity of the trial will be preserved since the IARC did their job. TMC has little incentive to stop enrollment at this time since it is only a few months from completion anyway. The only reason TMC may wish to stop the trial was if there were data supporting an adverse effect of cangrelor or if patients were being denied a better treatment.

The case was made that the IARC has an ethical obligation to recommend termination of the PLATFORM trial. Another aspect to consider is that cangrelor is a newer compound, without long term safety information. Continuing to treat patients with no possibility of benefit puts patients at risk if there are long-term safety issues with cangrelor. Declaring that it is unethical to continue would shift the burden of proof back to the IARC, since TMC will want to see the data supporting that recommendation. Hard data demonstrating a negative effect against cangrelor has not yet been noted during this data review.

A question was raised about potential FDA changes in requirements for non-inferiority trials. If the FDA rules that the putative placebo trial requirement is no longer needed, what effect on the two trials would there be? PLATFORM can't claim non-inferiority since there is a key period of placebo control. If you



are equivalent to no treatment, your active treatment is not needed at all. PCI involves a comparison to clopidogrel, so could meet a less restrictive definition. The results are currently trending in favor of clopidogrel for the 48 hour primary endpoint.

It was noted that if the trial is stopped early, there would be a negative perception of the drug and TMC would not be able to control the message that is publically presented. The IARC decided that the image control issues were not their concern.

Under the expanded IARC role, the IARC wanted to look at the bleeding data as presented to the DSMB. The DSMB had determined that they did not have any safety concerns after reviewing this information. The DSMB role is purely for safety review and they can only stop the trial with an overwhelming negative safety signal.

In PLATFORM, cangrelor had an overall higher bleed rate than placebo (16% vs 12%). The ACUITY clinically significant category had almost double the bleed rate in cangrelor versus placebo (5% vs 3%). There were slightly more patients with GUSTO Moderate and Severe/Life threatening bleeds in the cangrelor arm. On the other hand, there were slightly more TIMI major bleeds in the placebo arm.

In PCI, the various bleed rates were nearly equivalent for each of the more severe bleed categories reviewed. Overall, the cangrelor arm had more minor bleeding than clopidogrel but the differences were not as pronounced as in PLATFORM.

There was a concern about using safety information as part of the recommendation since that review is completed by the DSMB. Dr. Califf said



that he would talk to the DSMB Chair, Dr. Frans Van de Werf, about the bleeding issues already noted so that his opinion can be taken into account.

Another question was raised about how TMC could stop the trial, assuming they choose to do so. Would they stop it all at once or incrementally shut it down? Since enrollment is close to being complete, anything other than an abrupt stop would still allow continued enrollment towards the 6400 goal. Enrollment already stands at over 5200 as of April 30. Dr. Califf felt that even an “abrupt” trial termination would still take at least a week. If an incremental approach is taken, it was suggested to concentrate the site closings in the few countries that are contributing the most patients (Bulgaria, Czech Republic and the United States). There was also discussion that an abrupt closure is usually only reserved for severe safety problems, such as seen during Flolan where excess mortality was noted.

Regardless of whether TMC chooses to stop PLATFORM, even if the bleed information is taken into account, the IARC cannot force them to do so. TMC has the right to take the recommendation under advisement but does not have an obligation to follow it. The IARC will have fulfilled its role if they provide the recommendation to stop the trial for futility whatever decision TMC, in conjunction with the Principal Investigators, makes.

Dr. Califf stated that he would talk to Dr. Van de Werf over the weekend following the IARC meeting and prepare the correspondence for TMC. In an effort to provide a complete recommendation, he did ask that Cytel prepare the efficacy results for the following subgroups: age > 65 vs ≤ 65, male versus female, GP IIb/IIIa use versus not, Base anticoagulant type, patient categorization, geographic region (North America versus all others), and CK-MB assay type. The assay type is a site level variable but it is recognized that the sensitivity for detecting elevated CK-MB does differ between the methods.



CONCLUSIONS AND RECOMMENDATIONS

After reviewing all of the available data for PLATFORM, the IARC provisionally recommended that the study be terminated due to futility. Once the results of the remaining analyses are available, the conclusion will be finalized.

When the final data were received from Cytel, Dr. Califf planned to have a discussion with the DSMB Chair, Dr. Frans Van de Werf, concerning the recommendations and the potential excess clinically significant ACUTY bleeding. Depending on the outcome of the discussion with the DSMB Chair concerning the bleeding issue, there may be added emphasis placed on the excess cangrelor bleeding risk with respect to the futility recommendation.

Dr. Califf also indicated he would contact Dr. Clive Meanwell at TMC since the final recommendation was going to involve some modification to the trial, most likely through termination of enrollment.

The meeting adjourned at 1:45 p.m.



Interim Analysis Review Committee Meeting for the CHAMPION Program: PLATFORM Trial Addendum

Dr. Mehta emailed a summary document containing the results of the analyses performed after the conclusion of the IARC meeting. Per the request of Dr. Califf, the PLATFORM and PCI studies had the same subgroups analyzed to determine if cangrelor had any benefit in a specific population. As previously mentioned, the subgroups selected included: age > 65 vs ≤ 65, male versus female, GP IIb/IIIa use versus not, Base anticoagulant type, patient categorization, geographic region (North America versus all others), and CK-MB assay type. The tabled results provided by Dr. Mehta showed that no subgroups in either of the trials showed any indication of a cangrelor benefit.

Dr. Califf sent a brief response concerning his discussion with Dr. Van de Werf. Dr. Van de Werf felt that the IARC was being overly concerned about the ACUTY bleed criteria when there was not a similar signal in the other bleeding scales. Dr. Califf also asked Mr. McNulty if there was any additional mortality data to report that could influence the final decision. Mr. McNulty stated that the numbers reported to the IARC, and documented above, are accurate to the best of his knowledge.

REVISED CONCLUSIONS AND RECOMMENDATIONS

After reviewing all of the available data for PLATFORM, the IARC recommends termination of the study due to futility.



**Interim Analysis Review Committee Meeting for the
CHAMPION Program: PLATFORM Trial**

May 1, 2009

Approval of Closed Session IARC Minutes Signature Page

I have read and approve the attached Closed Session minutes.

Robert Califf, M.D. (Chairperson)

Date

Dear Drs. Harrington, Bhatt and Meanwell,

The IARC met on May 1st, 2009 and considered up to date data on the PLATFORM Trial as well as reviewing limited updated information about the PCI Trial. We considered all alternatives allowed by the initial charge and incorporated in your recent letter to us.

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We have come to the conclusion that enrollment into PLATFORM should be discontinued in an orderly process as soon as it is feasible to do so. PCI is almost complete, and therefore could be discontinued simultaneously.

The following considerations drove us to this conclusion:

1. Futility was clearly met in both trials for efficacy. We believe that you should take satisfaction that you have adequately addressed the question of whether IV P2Y12 inhibition with cangrelor at the time of PCI adds to conventional standard of care either in patients pre-treated with clopidogrel or treated with clopidogrel at the end of the procedure. Your results will permit future trials to approach this question from an enlightened point of view.
2. The enriched samples did not change this assessment, nor did any relevant subgroups including: age, sex, clinical presentation (UAP, NSTEMI, STEMI), type of CK-MB assay, region of enrollment, type of anticoagulant and use of GPI.
3. The PLATFORM Trial has a period of placebo control and indeed there is a signal for an increase in "ACUITY defined" bleeding with cangrelor compared with placebo. No significant difference is observed with other bleeding scales. This excess of bleeding with no benefit leads us to the recommendation that there is no potential benefit and some risk to new participants in the trial.
4. In the preliminary data no such signal is present in the PCI trial with its active control. However, there is also no signal of benefit and many events have accrued at this point, making continuation of no value to sites or participants.
5. We recognize the importance of availability of an IV form of P2Y12 inhibition in those who cannot take the oral medication or in those who need "bridging" for short term therapy. In constructing an argument for non-inferiority compared with oral clopidogrel, the PLATFORM data are not relevant, while the PCI trial provides ample evidence that the 2 regimens yield similar results by conventional criteria. The absence of a "classical" putative placebo argument due to the lack of adequate data comparing clopidogrel with placebo in this setting will make this an uphill climb, although it may not be impossible.
6. We recommend that you discontinue enrollment, clean up the data and consider focusing on short term use when oral drugs cannot be used or when a short half-life is highly desirable.

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We have discussed this recommendation with Prof. Van de Werf and he is in agreement.

Robert M Califf for the IARC



CANGRELOR FOR INJECTION INVESTIGATOR'S BROCHURE

Edition No. 5

Replaces Edition No. 4

Release Date: 4 May 2010

Dated: 19 August 2008

Data Cutoff Date: 3 September 2009

Data Cutoff Date: 23 May 2008

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SUMMARY OF CHANGES

The following changes have been made to this edition of the Investigator's Brochure since the previous edition (Edition 4) dated 19 August 2008.

Section	Revision Description	Reason for Change
1. Summary	Updated with Phase III information	New data available
2. Introduction	Updated with Phase III information	New data available
3. Physical, Chemical, and Pharmaceutical Properties	Reorganized/reformatted	More effective presentation of available data
4.2 Nonclinical Pharmacokinetics and Metabolism	Reorganized	Data presented in ICH –preferred order (Distribution, Metabolism, Excretion)
4.3.2 Repeated-Dose Toxicity Studies	Previous content reformatted into a table	More effective presentation of available data
4.3.3. Reproductive Toxicity Studies	Previous content reformatted into a table	More effective presentation of available data
5 Effects in Humans	Entire section reorganized. Some sections of legacy data rewritten or summarized (detailed below)	More effective presentation of legacy and new data.
5 Overview of Completed Clinical Studies With Cangrelor	Updated with Phase III information. Previous “Overview of Clinical Safety and Efficacy” incorporated into this section	New data available; more effective presentation of available data
5.2.4 Elimination	Summary shortened	More effective presentation of available data
5.2.5 Interaction Study	Summary shortened	More effective presentation of available data
5.2.6.4 Platelet Function During Infusion in PCI Patients	Updated information from Phase III PK substudy	New data available
5.3.1 Efficacy Results in Phase II Clinical Studies	Information moved to this section from “Outcomes After Infusion: section in Edition 4	More effective presentation of available data
5.3.2 Efficacy Results in Phase III Clinical Studies	Updated with Phase III information	New data available

Section	Revision Description	Reason for Change
5.3.3 Safety	Updated with Phase III information. Legacy information reorganized/rewritten. Some data moved to Appendix	New data available; more effective presentation of available data
5.6 Conclusion	Updated with Phase III information	New data available
6 Possible Risks and Adverse Events Associated With Use of Cangrelor	Rewritten	More effective presentation of available data, newly available data added.
Overall	Formatting/Editing	The entire document has been reformatted to conform with new corporate templates and edited for consistency.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ACS	Acute coronary syndromes
ADP	Adenosine diphosphate
AE	Adverse event
ALT	Alanine aminotransferase (also known as serum glutamyl pyruvate transferase, SGPT)
AR-C69712XX	Major circulating metabolite (nucleoside) of the parent compound
AR-C69931MX	Tetrasodium salt of the parent compound
AR-C69931XX	Free acid of the parent compound
AST	Aspartate aminotransferase (also known as serum glutamyl oxalate transferase, SGOT)
ATP	Adenosine triphosphate
AUC	Area under the plasma concentration time curve
AUC _{0-∞}	Area under the plasma concentration time curve to infinity
BP	Blood pressure
BT	Bleeding time
CABG	Coronary artery bypass graft (surgery)
CFR	Cyclic flow reduction
CI	Confidence interval
CL _p	Total plasma clearance
C _{max}	Maximum concentration
CNS	Central nervous system
C _{ss}	Concentration at steady state
CYP	Cytochrome P450
ECG	Electrocardiogram
f	Molar fraction
GI	Gastrointestinal
GLP	Good Laboratory Practice
GP	Glycoprotein
GTN	Nitroglycerin

Abbreviation	Definition
HR	Heart rate
IC ₅₀	Concentration required to give 50% inhibition of metabolite formation
ID ₅₀	Dose required to give 50% inhibition of platelets
IDR	Ischemia-driven revascularization
IV	Intravenous
MI	Myocardial infarction
NADPH	Nicotinamide adenine dinucleotide phosphate
NF	National Formulary
non-Q-MI	Non-Q-wave myocardial infarction
NSTEMI	Non-ST-segment elevation myocardial infarction
OR	Odds ratio
PCI	Percutaneous coronary intervention
PD	Pharmacodynamics
PhEur	European Pharmacopeia
PK	Pharmacokinetics
PRU	P2Y ₁₂ reaction units
PTCA	Percutaneous transluminal coronary angioplasty
PVC	Premature ventricular contractions
RBC	Red blood cell
SA	Stable angina
SAE	Serious adverse event
SC	Subcutaneous
SDS-PAGE	Sodium dodecylsulphate polyacrylamide gel electrophoresis
SOC	System organ class
STEMI	ST-segment elevation myocardial infarction
t _{1/2}	Half-life
TIMI	Thrombolysis in Myocardial Infarction
t-PA	Tissue plasminogen activator
UA	Unstable angina
UK	United Kingdom
USP	United States Pharmacopeia

Abbreviation	Definition
VASP PRI	Vasodilator-stimulated phosphoprotein phosphorylation index
V_{ss}	Volume of distribution at steady-state
w/v	Weight to volume

1. SUMMARY

Cangrelor is an antiplatelet agent being developed for intravenous (IV) use during coronary procedures (eg, percutaneous coronary intervention [PCI]) as well as the management of patients experiencing acute coronary syndromes (ACS). Cangrelor, also denoted as AR-C69931MX, is a substituted nucleotide that is rapidly inactivated by dephosphorylation to the nucleoside. It is a novel P2Y₁₂ receptor antagonist that effectively blocks adenosine diphosphate (ADP)-induced platelet aggregation as demonstrated in several in vitro and ex vivo studies.

The metabolite array in man is qualitatively similar to that in the rat and dog. In man, the major route of elimination is urinary. There are no interactions between cangrelor and standard aspirin, heparin, and nitroglycerin (GTN) treatments.

The drug is non-genotoxic in a standard battery of tests. The main target organ for toxicity in rats and dogs is the kidney. Renal and upper urinary tract toxicity was seen after continuous IV infusion for up to 1 month. In the rat, the toxicity seen after 1 month of dosing was shown to be reversible.

Cangrelor was not teratogenic in rat and rabbit embryo-fetal development studies. In female rats, fertility was unaffected by cangrelor. Some effects were seen on male rat fertility including changes in sperm morphology and motility after 8 weeks of treatment at the highest dose. Sperm abnormalities were reversible in the majority of rats tested following cessation of dosing and no sperm abnormalities were seen in a 4 week rat study.

Cangrelor is ultra-short acting, effectively inhibiting platelet activation and aggregation during thrombosis in damaged arteries with less associated bleeding time (BT) prolongation than the glycoprotein (GP) IIb/IIIa receptor antagonists. In the dog coronary artery, cangrelor, when administered with tissue plasminogen activator (t-PA), resulted in abolition of post-thrombolytic re-occlusion without accelerating the time to reflow. This resulted in reducing the cardiac infarct size by half.

In total, cangrelor has been studied in over 14,800 patients in seven Phase I studies, five Phase II studies and two Phase III studies, to date. In clinical pharmacology studies, the drug produced dose-related inhibition of ex vivo ADP-induced platelet aggregation. It has a rapid onset and offset of action and to exhibits dose linearity. The drug was clinically safe and well tolerated at all infusion rates.

In an open-label dose-escalation study in unstable angina (UA)/non-Q-wave myocardial infarction (MI) ([SC-931-5058](#), 39 subjects treated), administration of cangrelor caused >95% ex vivo inhibition of ADP-induced platelet aggregation at doses of 2 and 4 µg/kg/min. Cangrelor was well tolerated at doses up to 4 µg/kg/min infused for up to 72 hours, when given in addition to aspirin and unfractionated (IV) or low molecular weight (subcutaneous [SC]) heparin, plus other standard medication.

The safety of prolonged cangrelor infusions of up to 72 hours was assessed in two trials that in together enrolled 130 patients with ACS (Study [SC-931-5058](#) and [SC-931-5060](#)). These studies demonstrated that cangrelor does not effect cardiac repolarization, and was well tolerated and safe, even at a supratherapeutic dose.

Two multi-national, randomized, double-blind, double dummy, active-controlled or placebo-controlled studies assessed the safety and efficacy of cangrelor ([TMC-CAN-05-02](#) and [TMC-CAN-05-03](#)). The primary objectives of this program were to demonstrate that the efficacy of cangrelor is superior to placebo and superior to a 600 mg loading dose of clopidogrel. While both of these studies were terminated early due to the low likelihood of achieving the primary endpoint in both studies, cangrelor demonstrated greater efficacy in the clinically meaningful endpoints of death, Q-wave-MI, and ischemia-driven revascularization (IDR). In addition, it was shown to have a safety profile similar to the active comparator in both studies. Cangrelor was studied in 7036 patients in the Phase III studies, and clopidogrel/placebo was studied in 7015 patients. The incidence of adverse events (AEs) in the pooled datasets was 24.4% and 25.7%, for cangrelor and clopidogrel, respectively. The incidence of serious adverse events (SAEs) was 2.9% in both cangrelor and clopidogrel arms of study [TMC-CAN-05-02](#) (CHAMPION PCI), and 1.8% and 2.1% of cangrelor- and placebo-treated patients, respectively, in study [TMC-CAN-05-03](#) (CHAMPION Platform). There was a slight increase in minor bleeding events in cangrelor-treated patients in the Phase III studies, but this can be expected given cangrelor's potent platelet inhibition.

2. INTRODUCTION

Acute coronary syndromes (UA/stable angina [SA]/ non-ST-segment elevation MI [NSTEMI]/ ST-segment elevation MI [STEMI]) are associated with a high incidence of death and ischemic complications despite many recent improvements in the management of these conditions. Recent evolution in treatment strategies supports early cardiac intervention in combination with the use of anti-thrombotic therapies to lower the rate of procedural complications in PCI patients [[Anderson, 2007](#)]. The initial evaluation of PCI patients consists of an assessment of the risk of cardiac ischemic events (death, MI, and IDR) as well as the risk of bleeding complications from intensive medical therapy or invasive cardiac procedures. With this information in hand, the optimal treatment strategy can be determined, thereby reducing the occurrences of ischemic events and death [[Antman et al; Hills and Lange, 2009](#)].

Considerable evidence now supports the conclusion that inhibition of the platelet P2Y₁₂ receptor in patients undergoing PCI reduces platelet activation and aggregation, thereby reducing the risk of morbidity events such as MI and acute stent thrombosis – and can reduce mortality. [[Wiviott et al, 2007](#); [Vlaar et al, 2008](#), [Wallentin 2009](#)]. .

Cangrelor is a potent, P2Y₁₂ receptor antagonist that has been shown to strongly inhibit ADP-induced platelet aggregation ex vivo. The ADP P2Y₁₂ receptors are expressed on the surface of platelets and cangrelor is specific for this receptor. Since ADP plays a prominent role in platelet aggregation and activation, which are, in turn, important in arterial thrombosis, cangrelor possesses significant potential to diminish ischemic events in patients experiencing ACS.

Note: Throughout this document, the doses of the pharmaceutically acceptable tetrasodium salt (AR-C69931MX) are expressed in terms of the free acid (AR-C69931XX). The prefixes ARL and FPL [as in ARL 69931MX] are AstraZeneca internal notations used in some older study reports that have been superseded by AR [as in AR-C69931MX].

3. PHYSICAL, CHEMICAL AND PHARMACEUTICAL PROPERTIES

3.1. Drug Substance

The drug substance cangrelor is chemically similar to adenosine triphosphate (ATP), and has the following characteristics.

Chemical Name: N6-[2-(methylthio)ethyl]-2-[(3,3,3-trifluoropropyl)thio] -5'-adenylic acid, monoanhydride with (dichloromethylene) diphosphonic acid.

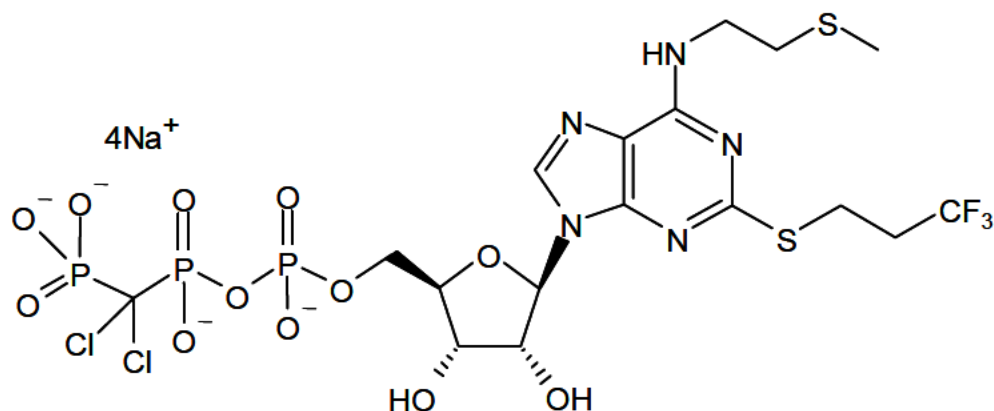
Alternative Names: AR-C69931XX = cangrelor free acid; AR-C69931MX = cangrelor tetrasodium salt.

Molecular Formula: $C_{17}H_{21}N_5Cl_2F_3Na_4O_{12}P_3S_2$

Molecular Weight: 864.3 g/mol

Chemical Structure: The chemical structure is shown in Figure 1.

Figure 1 Chemical structure of cangrelor.



Physicochemical characteristics: Cangrelor is a white to off-white hygroscopic solid.

Solubility: Cangrelor is freely soluble in water.

3.2. Drug Product

Formulation: Cangrelor is susceptible to hydrolytic degradation which led to its formulation as a lyophilized product (Cangrelor for Injection). The formulated product is supplied in 10 mL vials in order to deliver 50 mg and also contains the excipients Mannitol European Pharmacopeia/United States Pharmacopeia (PhEur/USP) and Sorbitol PhEur/USP-National Formulary (NF).

Storage: Vials of Cangrelor for Injection should be stored at controlled room temperature, 15°C to 30°C (59°F to 86°F).

Reconstitution: Cangrelor does not contain a preservative and should be not be reconstituted until immediately before infusion. Cangrelor drug substance requires reconstitution with 5.0 mL

of Sterile Water for Injection to give a solution of 10 mg/mL cangrelor. Cangrelor drug product has been formulated such that the labeled content (50 mg) may be withdrawn after reconstitution. Reconstituted vials of Cangrelor for Injection require further dilution with sodium chloride 0.9% weight per volume (w/v) infusion/injection before administration as below.

Preparation: Cangrelor infusion solutions are prepared by diluting the appropriate volume of reconstituted Cangrelor for Injection with sodium chloride 0.9% w/v infusion/injection. Instructions detailing the procedures for preparing and administering the infusion solutions are provided in individual protocols and/or pharmacy instructions. Infusion solutions are chemically stable for up to 30 hours (including administration time) at room temperature. They do not need to be protected from light after preparation or during administration.

4. NONCLINICAL STUDIES

4.1. Nonclinical Pharmacology

Cangrelor is an inhibitor of ADP-induced platelet aggregation. ADP secreted from platelet dense granules provides important autocrine and paracrine stimulation of platelet aggregation. This platelet aggregation induced by ADP is mediated, in part, by the P2Y₁₂ receptors, which are broadly expressed on the surface of platelets. ADP exerts its effects by coupling with inhibitory G-protein to inhibit adenylate cyclase, reducing the production and subsequent concentration of cyclic adenosine monophosphate. This results in platelet activation, amplification of platelet signaling effected by other agonists such as thrombin and sustaining stable platelet aggregation. Additionally, activation events result in the ability of platelets to interact with the leukocytes and the inflammatory process.

ATP is a competitive antagonist for the P2Y₁₂ receptor. Cangrelor is an ATP analogue and was therefore selected for clinical development. The results in this section summarize the nonclinical pharmacological basis for the development of cangrelor as an antiplatelet agent for use during PCI as well as in the management of ACS.

The studies described in this section demonstrate the potency, selectivity, and specificity of cangrelor as an inhibitor of ADP-induced platelet aggregation in vitro. In addition, the relationship between antiaggregatory, antithrombotic, and antihemostatic effects, as well as the effects when administered with thrombolytic drugs, were examined in vivo. Importantly, none of the metabolites of cangrelor contributes significantly to the pharmacological effects of administered drug.

Cangrelor is a potent, specific, and selective inhibitor of P2Y₁₂ receptor mediated aggregation of human washed platelets in vitro and produces dose-related, rapidly reversible inhibition of ex vivo ADP-induced platelet aggregation measured during IV infusion in the anesthetized and conscious dog.

In a model of dynamic arterial thrombosis in the anesthetized dog, cangrelor abolished thrombosis with only a modest effect on hemostasis (BT prolonged 1.6-fold). This effect was fully reversed within 10 minutes of cessation of infusion. Cangrelor infusion reduced re-occlusion and cyclical blood flow in the coronary artery of the dog following thrombolysis by t-PA and reduced the myocardial infarct size by about 50%. These findings are similar to those

made in the dog model with abciximab (Reopro[®]) when given after recombinant t-PA, where reduced re-occlusion was reported [Mickelson et al, 1990; Rote et al, 1994].

In the anesthetized dog, IV infusion of cangrelor had little or no effect on systemic hemodynamics, cardiac, respiratory, or autonomic function.

4.1.1. Actions Relevant to Proposed Therapeutic Use

4.1.1.1. In Vitro Effects on Platelet Aggregation

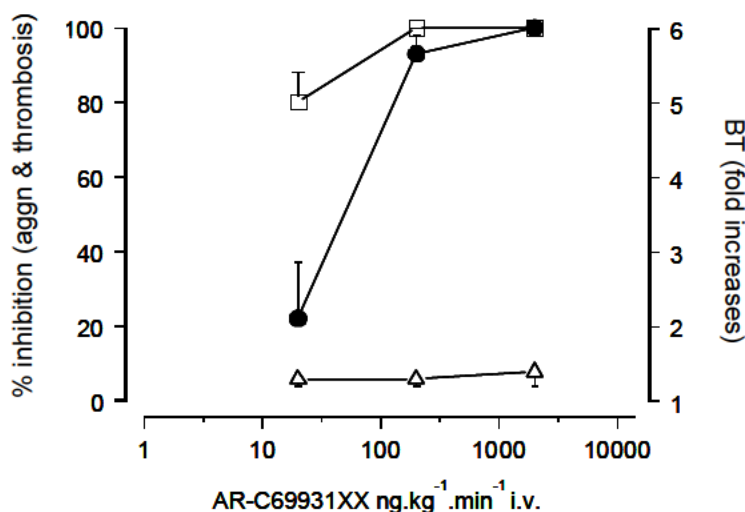
Cangrelor was shown to be a potent inhibitor of ADP-induced aggregation in human washed platelets (concentration required to give 50% inhibition of metabolite formation [IC_{50}] value 0.45 nM, n=9) [PR 30144] and in human (IC_{50} value 0.71 nM, n=4) [PR 30145], dog (IC_{50} value 0.72 nM, n=5) [PR 30146], and rat (IC_{50} value 5.1 nM, n=4) [PR 30147] whole blood in vitro.

4.1.1.2. Inhibition of Platelet Aggregation Measured Ex Vivo

Anesthetized dog - coronary artery cyclic flow reduction

In a model of dynamic arterial thrombosis in the left anterior descending coronary artery of the anesthetized dog [PR 40019], 30 minute stepped infusions of cangrelor (20, 200, 2000 ng/kg/min IV, n=6) produced dose-related inhibition of cyclic flow reduction (CFR), with little or no effect on BT (Figure 2). Measured ex vivo, full inhibition of ADP-induced platelet aggregation was necessary to achieve a full antithrombotic effect.

Figure 2: Effect of intravenous infusion of cangrelor (20, 200, 2000 ng/kg/min) on coronary artery thrombosis, bleeding time, and ADP-induced platelet aggregation measured ex vivo in the pentobarbitone-anesthetized dog



Legend:

- = coronary artery thrombosis, % inhibition compared with baseline, n=6
 - Δ = bleeding time (BT: fold increase compared with baseline), n=6
 - = ADP-induced platelet aggregation, % inhibition compared with baseline, n=5
- ADP = Adenosine diphosphate; BT = bleeding time.

Note: Values are means ± standard error of the mean.

Conscious dog

Measured ex vivo in whole blood in the conscious male Beagle dog, infusion of cangrelor (7.7 to 230 ng/kg/min IV) produced dose-related inhibition of ADP-induced platelet aggregation (dose required to give 50% inhibition of platelets [ID₅₀] 15 ng/kg/min IV, n=2) [PR 30150]. Full recovery was seen within 30 minutes of stopping the infusion even at a dose 150-fold above the ID₅₀ (n=1).

Cangrelor Additional Inhibitory Effect in Humans Receiving Clopidogrel

Ex vivo studies showed that when added to blood from patients with ACS who were taking clopidogrel, cangrelor provided an additional inhibitory effect on platelet response to ADP as determined by whole blood impedance and light transmittance aggregometry [SC-931-9064; Storey et al. 2002].

4.1.1.3. Pharmacodynamic Interaction With a Thrombolytic Drug

In a canine model of coronary arterial thrombosis, cangrelor, when administered with t-PA, improved coronary blood flow and reduced infarct size compared with saline control.

Effects on t-PA-induced thrombolysis in dog coronary artery

A fully occlusive thrombus was induced in anesthetized hound dogs by temporarily stenosing the circumflex artery and causing electrolytic damage [SC-102741]. At the start of the experimental procedure, each dog was treated with aspirin (325 mg orally) before anesthesia and by IV heparin (80 IU/kg + 17 IU/kg/hour for 2 hours). After 20 minutes of arrested blood flow (as measured by a periarterial Doppler probe), either saline (0.16 mL/min) or cangrelor (4 µg/kg/min) was infused IV for 2 hours. Approximately 10 minutes after starting the infusion, t-PA was administered (1 mg/kg IV over 20 minutes). Outcomes measured were: successful thrombolysis (≥30% baseline blood flow over the 2 hour observation period after t-PA infusion), partial thrombolysis (cyclic flow variation, ie, where there is an incidence of intermittent restoration of blood flow), total reflow duration (cumulative time when there is a measurable blood flow), time to re-occlusion, and the incidence of persistent occlusion (zero flow throughout the 2 hour period). Additional ex vivo measurements were made of infarct size (planimetry measurement of stained sections; triphenyltetrazolium chloride infused into the left anterior descending artery and Evans Blue into the left circumflex artery), blood pressure (BP), and electrocardiogram (ECG).

Animals in both treatment groups (saline or cangrelor, 10 per group), reperfused in response to t-PA with similar time to reflow. However, the saline group showed a high incidence of partial or full re-occlusion [SC-102741]. By contrast, there was virtually a full restoration of blood flow over the 2 hour observation period in the animals infused with cangrelor (4 µg/kg/min) (Table 1). The incidence of cyclic flow variation and re-occlusion was 0% in the cangrelor-treated animals and 50% and 60%, respectively, in the saline-infused dogs. As a consequence of the improved coronary blood flow restoration by adjunctive cangrelor, the resultant infarct size was halved (p=0.034) when expressed either in absolute terms or as a percent of the area at risk.

Table 1: Effects of cangrelor on t-PA-induced thrombolysis in dog coronary artery

Parameter	Mean ± SD	
	Saline (n=10)	Cangrelor (n=10)
Baseline Blood Flow (mL/min)	65.30 ± 7.47	62.33 ± 8.53
Time to Arterial Occlusion (min)	55.5 ± 14.03	62.33 ± 14.67
Incidence of Reperfusion	100%	100%
Time to Arterial Reperfusion (min)	21.50 ± 2.88	20.00 ± 6.09
Total Reflow Time (min)	75.00 ± 39.86	119.70 ± 0.67 ^a
Cyclic Flow Variation Incidence	50%	0% ^a
Reocclusion Incidence	60%	0% ^a
Area at Risk (cm ²)	48.70 ± 6.94	49.92 ± 8.41
Infarct Size (cm ²)	9.34 ± 4.37	4.70 ± 4.66 ^a

SD = standard deviation.

a. p<0.05 compared with saline control group

4.1.2. Other Actions Demonstrated or Sought (Secondary Pharmacology)

Cangrelor and its known and available metabolites have been studied in vitro and in vivo to confirm the selectivity for P2Y₁₂ receptors (compared with other P2- and P1-receptors) and specificity of action.

4.1.2.1. Studies In Vitro***Selectivity of action of cangrelor***

Cangrelor had no significant activity at other P2-receptor subtypes from a variety of species: P2Y₁; P2Y₂; P2X₁; P2X₂; P2X₇ at concentrations up to 100 μM (n=1 to 2) [PR 30136].

Specificity of action of cangrelor

Cangrelor (<100 μM, n=4) had no effect on aggregation of washed human platelets produced under ADP/P2Y₁₂ independent conditions by the thromboxane mimetic, U46619 [PR 30139], or on uptake of [³H]adenosine by human erythrocytes [PR 30138].

Studies with putative metabolites

The putative monophosphate metabolite (AR-C88558KP), the base (AR-C71301XX), and S-oxidized base (AR-C90441XX) metabolites of cangrelor had no effect on ADP-independent platelet aggregation [PR 30139], no significant activity at P2Y₁-, P2Y₂-, P2X₁-, P2X₂-, or P2X₇-receptors (n=1 to 2) [PR 30136], and no effect on the uptake of radiolabeled adenosine by human erythrocytes (n=2 to 4) [PR 30138] at concentrations of 10 to 100 μM.

4.1.2.2. Studies In Vivo

Acute effects in the conscious mouse

In conscious male CD-1 mice, a 10 minute infusion of cangrelor (58, 580 mg/kg IV) produced dose-related hypothermia, with maximal temperature reduction (3.6°C) within 30 minutes in the higher dose group (n=4) [PR 30143]. The maximal temperature reduction in an individual animal at the higher dose was 5.5°C. From 2 hours after infusion onwards, there was no significant difference in rectal temperature between the cangrelor-treated and saline-treated groups.

Central nervous system effects in the conscious mouse

Groups of 3 to 5 male CF1 mice were administered cangrelor (100, 200, 400 mg/kg IV), as a 10 minute infusion and examined for central nervous system (CNS) effects using a multi-parameter observational screen [PR 30154; Irwin, 1968]. Mainly transient stimulatory (increased motor activity) effects were observed at the lower doses and were judged to be relatively mild and free of concern. However, at the highest dose, severe symptoms of CNS depression were seen, including respiratory depression. These effects persisted at 1 hour after dosing with complete recovery at 24 hours.

Cardiovascular and respiratory effects in the anesthetized rat

In the anesthetized male rat, 30 minute stepped infusions of cangrelor (1, 10, 100, 200 µg/kg/min IV, n=3) had no obvious effect on phasic or mean BP, heart rate (HR), ECG (Lead II), respiratory flow, respiratory rate, or tidal volume [SE 9996].

Cardiovascular and respiratory effects in the anesthetized dog

When administered by stepped infusion in two pentobarbitone-anesthetized male dogs [PR 30098], cangrelor (up to 6 µg/kg/min IV) had no obvious effect on cardiovascular variables: BP, HR, cardiac output, total peripheral resistance, cardiac contractility, stroke volume, ECG, or respiratory (intratracheal pressure) variables. In a further group of three male dogs [SC-30174], infusion of cangrelor at 30 µg/kg/min IV for 6 hours also had no obvious effects on BP, HR, cardiac contractility, or ECG (12-lead).

4.2. Nonclinical Pharmacokinetics and Metabolism

Pharmacokinetics (PK) of the free acid of cangrelor (AR-C69931XX) and the nucleoside metabolite (AR-C69712XX) following IV infusion of cangrelor have been studied in male rats and dogs, and female rats, dogs, and rabbits. The metabolism and excretion of IV infusions of radiolabeled [³H]cangrelor have been investigated in male and female rats and dogs. The protein binding and blood distribution of cangrelor and AR-C69712XX have also been investigated in relevant animal species and man. Tissue distribution of [³H]cangrelor has been investigated by whole body autoradiography and quantitative tissue distribution, in pigmented and albino male rats and pregnant albino female rats.

The pharmacodynamic (PD) effect of inhibition of platelet aggregation is considered to be solely associated with the parent compound. Cangrelor is water soluble. The formulations administered to animals were prepared in sterile 0.9% (w/v) saline for injection.

Investigation of the PK and metabolism in rat, dog, and rabbit has demonstrated that cangrelor is rapidly eliminated to inactive metabolites, particularly in rat and dog. This is consistent with a

drug designed to have a short duration of action. A slower terminal elimination phase of cangrelor and the nucleoside (AR-C69712XX), characterized in the dog and rabbit, is apparent but contributes little to systemic exposure in the dog and is atypical in the rabbit. There is no evidence of retention of compound-related material from the administration of [^3H]cangrelor; radioactivity is mainly excreted in the first 24 hours after infusion. Importantly, there was no evidence of incorporation into endogenous macromolecules. The investigation of the metabolic route in the rat and dog reveals consistent findings indicative of the metabolic clearance of cangrelor to AR-C69712XX and sulfoxidation to AR-C90439XX. Approximately 60% of the dose is excreted in bile and, except for fecal exposures which are affected by microbial breakdown, further metabolism appears relatively insignificant.

Investigation of distribution in pregnant female rats indicates limited exposure to the fetus in utero.

4.2.1. Distribution

4.2.1.1. Tissue Distribution

Tritiated [^3H]cangrelor was administered by IV infusion to male rats at 48 $\mu\text{g/kg/min}$ for 30 minutes and animals were killed for autoradiography at the end of infusion, or at 10 minutes, 1, 6, and 24 hours later. A quantitative tissue distribution study was also conducted over a similar time course in male rats [SE10012]. In addition, distribution in pregnant female rats was investigated in a quantitative autoradiography study on Day 12 or Day 18 of gestation [SC-100295]. The infusion rate was the same as for the male rats, the duration was 20 minutes, and animals were examined at the end of infusion or 0.5, 6, or 24 hours later.

Autoradiographs of whole body sections of male rats, killed at the end of infusion with [^3H]cangrelor [SE 10012], indicated a widespread distribution of radioactivity, although none was evident in the CNS or testes. A quantitative tissue distribution study demonstrated highest concentrations of radioactivity in highly perfused tissues such as heart, spleen, lungs, and particularly in the excretory organs (liver and kidneys). Initially, high concentrations of radioactivity were observed in the liver, which declined by 1 hour after the end of infusion.

Autoradiography of the liver demonstrated a “speckled” distribution, consistent with concentration into the bile canaliculi. This, in conjunction with the high levels in the gastrointestinal tract, is consistent with the observed rapid biliary excretion. High concentrations of radioactivity were also observed throughout the kidney at the end of infusion, consistent with rapid urinary excretion. As concentrations of radioactivity declined, autoradiography revealed complex patterns of redistribution within the kidney with residual radioactivity highly localized to the inner cortex/outer medulla region 24 hours after the end of infusion. Although the regional distribution could not be quantified by autoradiography, in terms of the whole kidney, this residual radioactivity represented about 3% of the radioactivity originally present; for comparison the corresponding figure for liver at 24 hours was about 1%. Significant levels of radioactivity were observed in thyroid and bone marrow at the end of infusion. These decreased to low levels by 1 hour after the end of infusion. Low levels of radioactivity were also observed in the epiphysial plates of the femur up to 24 hours after the end of infusion.

Autoradiographs from pregnant female rats [SC-100295] were consistent with rapid excretion of the radiolabel in bile, feces and urine. Radioactivity in the ovaries and placenta were at a similar level to that of the heart blood. Radioactive exposure of the fetus was considerably less than that of the maternal tissues. Radioactivity, at the limit of quantification, was only detected in some fetuses 0.5 hours after the end of infusion on Day 18 of gestation.

4.2.1.2. Protein Binding and Blood Distribution

Cangrelor (20 to 400 ng/mL) was largely excluded from blood cells, and was highly (>92%) protein bound in rat, dog, and man [SE 10009]. Protein binding was less in dog plasma (about 93%) than in plasma from rat or human (97% to 98%). The nucleoside (AR-C69712XX) was less protein bound (88% to 89%) and distributed into blood cells (about 30%) in all three species.

4.2.2. Metabolism in the Dog and Rat

The metabolism of cangrelor has been investigated by analysis of samples from the excretion balance studies above. Samples from male and female rats [SC-100358; SC-100141] and dogs [SC-100357; SC-100142] were investigated for metabolite identification. Since most of the radioactivity was recovered in feces, suggesting a biliary route of elimination, an additional study was carried out on bile-duct cannulated dogs [SE 10011], together with a separate biliary excretion study in bile-duct cannulated rats [SC-100371]. The biliary excretion studies, due to their relatively short-term nature, permitted the recovery of only a proportion of the dose administered (59.3% in dog; 71.9% in rat). However, this was a sufficiently large proportion to be regarded as representative. On the basis of the assumption that the entire fecal radioactivity originated from material excreted in the bile, biliary excretion data were normalized to total fecal recovery to facilitate quantitative comparison.

Metabolism of cangrelor was qualitatively similar in both sexes of the two species. No cangrelor was detected unchanged in excreta. AR-C69931MX was completely metabolized to the nucleoside (AR-C69712XX) and oxidized products of the nucleoside and its purine base (AR-C71301XX).

Numerous other metabolites were observed in excreta. These were products of combinations of S-oxidation, purine base oxidation, deribosylation, and glucuronidation. Analysis of fecal samples indicated that the metabolites excreted in bile may have been further metabolized by the gut microflora. There was evidence that these may have mediated deribosylation, glucuronide hydrolysis, and further oxidation. The main metabolites identified in feces were the base (AR-C71301XX), the sulphoxide (AR-C90441XX) of the base, and further oxidation products of the base and its sulphoxide.

4.2.3. Excretion in the Dog and Rat

Following a 30 minute infusion of cangrelor to male [SE 10010] and female [SC-100090] rats and dogs [SE 10011; SC-100091] (12 and 3.75 µg/kg/min IV, respectively), more than 73% of the radioactivity was recovered in the excreta within 24 hours, with quantitative recovery in 7 days (Table 2). This rapid excretion is consistent with the rapid elimination of cangrelor and its major circulating metabolite from plasma. Elimination of radioactivity in both sexes of both species occurred predominantly in feces (>60%), with lesser amounts in urine (<31%), although a slightly higher proportion was found in rat urine, and rather more in males than in females.

Table 2: Recovery of radioactivity following intravenous infusion of cangrelor in the dog and rat

Recovery of radioactivity to 7 days	Dog (% radioactive dose) Dose rate = 3.75 µg/kg/min				Rat (% radioactive dose) Dose rate = 12 µg/kg/min			
	Male		Female		Male		Female	
	24 h	7 days	24 h	7 days	24 h	7 days	24 h	7 days
Urine	11.7	12.9	10.2	11.8	29.9	31.0	17.4	18.4
Feces	61.1	86.0	64.3	82.6	54.3	60.3	68.5	76.9
Total ^a	73.4	100.4	75.1	95.9	86.2	94.3	86.9	97.0

a. Totals may include small contributions from radioactivity found in cage wash and/or expired air.

Fecal excretion suggests biliary elimination to be quantitatively more important than the renal route. The rate of excretion of radioactivity was rapid, with most of the dose being eliminated within 24 hours in both male and female rats and dogs.

4.2.4. Pharmacokinetics

4.2.4.1. Cangrelor

The PK of the free acid (AR-C69931XX) following IV infusion of cangrelor to male [SE 10076] and female [SC-100124] Beagle dogs, male [SE 10075] and female [SC-100123] Sprague-Dawley rats, and female Dutch rabbits [SC-100962; SC-101314] are summarized in Table 3.

In dogs and rats, steady-state plasma concentrations (C_{ss}) were quickly attained and were stable throughout the infusion period. At the end of the infusion, plasma elimination resulted in concentrations declining by about 20-fold in 20 minutes; with an initial half-life ($t_{1/2}$) generally <1 minute. However, a more prolonged terminal elimination phase was apparent. This was best characterized in the male dog following a 4 hour infusion (Figure 3), where the terminal phase ($t_{1/2} = 5.9$ hours) represented <10% of the total area under the curve ($AUC_{[0-\infty]}$). The PK appeared to be linear across the dose ranges (6 to 60 µg/kg/min and 4.8 to 48 µg/kg/min IV in dog and rat, respectively). Plasma clearance was high in the dog and moderate in the rat. The steady-state volume of distribution, which was best characterized in the male dog following a 4 hour infusion, was 2.8 L/kg (between 2.3 and 3.5 L/kg). This parameter was underestimated in the female dog and in male and female rats, when shorter infusion durations were investigated. The terminal phase contributed little to $AUC_{(0-\infty)}$ but, because the $t_{1/2}$ was at least 2 orders of magnitude greater than the initial elimination phase, it contributed significantly to the calculation of steady-state volume of distribution.

Table 3: Pharmacokinetics of cangrelor in plasma after intravenous infusion to male and female dogs and rats and female rabbits

Parameter	Dog ^a			Rat ^b			Rabbit ^c			
	Male	Male	Female	Male	Male	Female	Female ^d	Female ^d	Female ^d	Female
Infusion rate (µg/kg/min)	6	60	60	4.8	48	48	3	6	12	36
Duration of Infusion (h)	0.5	4.0	1.0	1.0	1.0	0.5	2.0	2.0	2.0	2.0
C _{ss} (ng/mL)	110	1021	845	e	e	e	1300	2560	6240	1600
Range	99-127	947-1120	737-971	241-318	814-2810	1310-2270	1160-1420	2200-3030	4450-8230	12200-18900
CL _p (mL/min/kg)	NA	59	74	NA	25	22	NA	NA	NA	2.07
Range	NA	53-62	64-83	NA	NA	NA	NA	NA	NA	1.85-2.28
Initial t _{1/2} (min)	NA	<1	<1	NA	<1	<2	NA	NA	NA	22.7
Range	NA	NA	NA	NA	NA	NA	NA	NA	NA	17.9-26.5
Terminal t _{1/2} (h)	NA	5.9	≈1	NA	≈3	≈0.8	NA	NA	NA	3.23
Range	NA	5.6-6.2	NA	NA	NA	NA	NA	NA	NA	2.13-5.3
V _{ss} (L/kg)	NA	2.8	0.5	NA	0.7	0.3	NA	NA	NA	0.109
Range	NA	2.3-3.5	0.3-0.7	NA	NA	NA	NA	NA	NA	0.0767-0.139

CL_p = total plasma clearance; C_{ss} = steady-state plasma concentration; NA = Not applicable, not calculated; t_{1/2} = half-life; V_{ss} = volume of distribution at steady-state.

a. Includes studies [SE 10076](#) and [SC-100124](#)

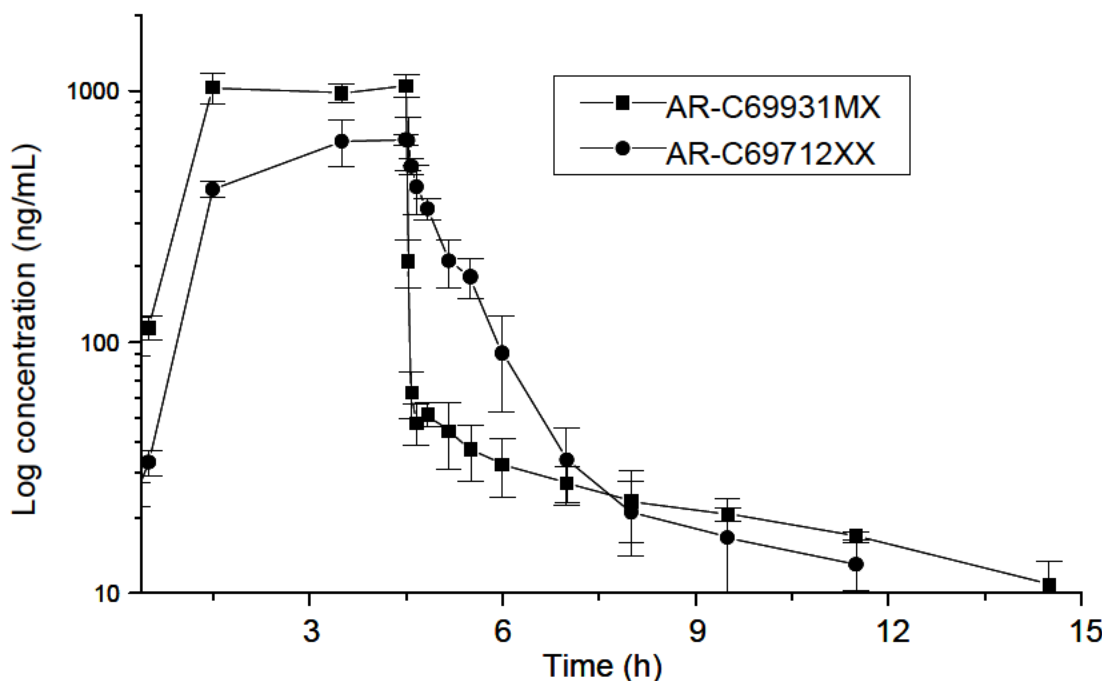
b. Includes studies [SE 10075](#) and [SC-100123](#)

c. Includes study [SC-101314](#)

d. Stepped 2 hour infusion at each of 3 doses

e. Single samples from pairs of animals at each time point investigated, range of C_{ss} reported

Figure 3: Plasma concentrations of AR-C69931XX and AR-C69712XX in the male dog receiving cangrelor by intravenous infusion (60 µg/kg/min for 4 hours)



The PK profile of cangrelor in the female rabbit was investigated to support the use of this species in reproductive toxicology studies. The findings from the PK pilot study and main study [SC-100962; SC-101314] indicated that the rabbit is atypical compared with the dog and rat. In the main study [SC-101314], the PK were investigated following a stepped, low-dose infusion at 3, 6, and 12 µg/kg/min and a high-dose infusion of 36 µg/kg/min. Although plasma concentrations were approaching steady state at the end of 2 hour infusion periods, and these were proportional to the infusion rates, the plasma exposure for a given dose was considerably higher in the rabbit than in the rat or dog. The elimination was biphasic in the rabbit, as was demonstrated in the male dog. However, the initial and terminal $t_{1/2}$ were 22.7 minutes and 3.23 hours, respectively, in the rabbit compared with <1 minute and 6 hours, respectively, in the dog. Plasma clearance was an order of magnitude lower in rabbit (2.07 mL/min/kg) than in the rat (22 to 25 mL/min/kg).

The mechanism of plasma clearance of cangrelor is dephosphorylation to the nucleoside (AR-C69712XX). The relative contribution of the liver, kidney, lung, and intestines to the plasma clearance of cangrelor was investigated in isolated perfused rat organs [SC-101599]. Determinations of efferent and afferent plasma concentrations of cangrelor [SC-101645] in the organs perfused at a target plasma concentration of 1500 ng/mL, indicated that the liver was the primary organ of elimination in the rat. An investigation of venous and arterial plasma concentrations of AR-C69931XX in infused anesthetized dog [SC-100188] indicated that up to 40% of circulating AR-C69931XX is eliminated in the pulmonary circulation. This pulmonary elimination may explain the higher plasma clearance of cangrelor in the dog, compared with the rat where there was little clearance in the isolated lung perfusions [SC-101599].

4.2.4.2. AR-C69712XX

The main plasma metabolite is the nucleoside AR-C69712XX. The PK of AR-C69712XX following IV infusion of cangrelor to male [SE 10076] and female [SC-100124] Beagle dogs, male [SE 10075] and female [SC-100123] Sprague-Dawley rats, and female Dutch rabbits [SC-100962; SC-101314] are summarized in Table 4.

The PK of AR-C69712XX was estimated assuming complete conversion of cangrelor to the nucleoside. Under these conditions, plasma clearance of AR-C69712XX can be regarded as high in the rat and dog, and moderate in the female rabbit. Although the plasma clearance of AR-C69712XX was slightly lower in female rabbit than in the rat and dog, it did not reflect the significant differences observed in the PK of AR-C69931XX in that species. In the male dog and female rabbit, a terminal phase with a similar $t_{1/2}$ to that of cangrelor was apparent. This was regarded as evidence that the elimination of AR-C69712XX may be formation rate limited during the terminal phase.

Table 4: Pharmacokinetics of AR-C69712XX, the nucleoside of cangrelor, in plasma after intravenous infusion of cangrelor to male and female dogs and rats and female rabbits

Species	Dog ^a			Rat ^b			Rabbit ^c			
Sex	Male	Male	Female	Male	Male	Female	Female ^d	Female ^d	Female ^d	Female
Infusion rate (µg/kg/min)	6	60	60	4.8	48	48	3	6	12	36
Duration of Infusion (h)	0.5	4.0	1.0	0.1	1.0	0.5	2.0	2.0	2.0	2.0
C _{ss} (ng/mL)	NA	635	270 ^b	NA	^e	^e	61.2 ^f	154 ^f	208 ^f	751 ^f
Range	NA	576-722	226-342	NA	290-509	281-307	46.3-88.3	73.9-294	151-266	685-817
CL _p (mL/min/kg) ^g	NA	69	98	NA	85	72	NA	NA	NA	29.6
Range	NA	66-71	66-126	NA	NA	NA	NA	NA	NA	26.9-33.6
Initial t _{1/2} (min)	NA	22	3.4	NA	4	5	NA	NA	NA	NA
Range	NA	17-28	2.6-3.9	NA	NA	NA	NA	NA	NA	NA
Terminal t _{1/2} (h)	NA	NA	0.7	NA	0.7	0.4	NA	NA	NA	1.61
Range	NA	1.4-14.6	0.5-0.9	NA	NA	NA	NA	NA	NA	0.87-1.98

CL_p = total plasma clearance; C_{ss} = steady-state plasma concentration; NA = Not applicable, not calculated; t_{1/2} = half-life.

a. Includes studies [SE 10076](#) and [SC-100124](#)

b. Includes studies [SE 10075](#) and [SC-100123](#)

c. Includes study [SC-101314](#)

d. Stepped 2 hour infusion at each of 3 doses

e. Single samples from pairs of animals at each time point investigated, range of C_{ss} reported

f. Not at steady state observed maximum concentration reported

g. Calculation assumes equimolar dose of AR-C69712XX to cangrelor

4.2.5. Inhibition With Cytochrome P-450 Isozymes

As part of the program to evaluate clinically relevant drug interactions, the potential of cangrelor and the major metabolites, AR-C69712MX and AR-C90439XX, to inhibit individual cytochrome P450 (CYP) isozymes was determined in vitro [SC-102858-1].

Different concentrations of cangrelor, AR-C69712MX, and AR-C90439XX, and specific inhibitors (as control incubations) were incubated at 37°C with human liver microsomes, nicotinamide adenine dinucleotide phosphate [NADPH], and seven different substrates that act as markers for individual CYP isoform (1A2-phenacetin; 2A6-coumarin; 2C9-tolbutamide; 2C19-S-mephenytoin; 2D6-dextromethorphan; 2E1-chlorzoxazone and 3A4-testosterone). The formation of the respective marker metabolites was monitored to determine the degrees of inhibition of individual isozymes. The IC₅₀ determined for each individual CYP isoform is shown in Table 5.

Table 5: Inhibition of cytochrome P450 enzymes, in vitro

CYP	IC ₅₀			
	Specific Inhibitor (controls)	Cangrelor	AR-C69712XX	AR-C90439XX
1A2	Furafylline (3.8 µM)	>100 µM	>100 µM	>100 µM
2A6	Pilocarpine (1.7 µM)	>100 µM	>100 µM	>100 µM
2C9	Sulfaphenazole (0.36 µM)	>100 µM	>100 µM	>100 µM
2C19	Omeprazole (4.1 µM)	>100 µM	58 µM	59 µM
2D6	Quinidine (0.097 µM)	>100 µM	>100 µM	>100 µM
2E1	Diethyldithioncarbamate (2.8 µM)	>100 µM	>100 µM	>100 µM
3A4	Ketoconazole (0.16 µM)	>100 µM	>100 µM	>100 µM

IC₅₀ = concentration required to give 50% inhibition of metabolite formation; CYP = cytochrome P450.

The results showed that cangrelor did not inhibit any CYP studied (IC₅₀ >100 µM). AR-C69712XX and AR-C90439XX did not inhibit CP1A2, 2A6, 2C9, 2D6, 2E1, or 3A4, and inhibition of CYP 2C19 occurred only at high concentration (IC₅₀ >50 µM) and may be of no clinical relevance.

4.3. Toxicology

Nonclinical safety studies for cangrelor were conducted in rodents and dogs, with the dosing regimens studied ranging from single IV bolus dose up to 1 month continuous IV infusion. Studies on reproductive function include histopathology of the reproductive organs and semen

analysis (sperm count and motility) in a 1 month toxicity study, fertility and embryo-fetal development studies in rats and embryo-fetal development studies in rabbits. Genotoxicity was investigated in Ames tests (with an in vitro human lymphocyte assay), a mouse micronucleus test, and an in vitro mouse lymphoma assay.

All pivotal toxicity studies were performed in compliance with the principles of the Organization for Economic Cooperation and Development Good Laboratory Practice (GLP), the United Kingdom (UK) GLP regulations, and US Food and Drug Administration GLP regulations. Some early studies do not claim GLP compliance although they were conducted in a GLP compliant environment. Some of the toxicology reports do not contain the required quality assurance statements.

4.3.1. Single Dose Toxicity Studies

The toxicity of cangrelor was studied in mice [SE 9994/2; 96031; 97094-1] and rats [SE 9993; 96030; 97093-1] after a single IV bolus dose. Early studies used groups of 2 animals but this was later repeated with groups of 5. The minimal lethal dose of cangrelor was between 200 and 400 mg/kg in rats and mice. In the early studies, histopathological examination of major organs was conducted after a 14 day observation period. In mice [SE 9994/2; 96031] there were no histopathological findings related to treatment.

In male rats [SE 9993], histopathological changes were observed in the kidney of both animals that died after receiving 800 mg/kg. The change resembled a proliferation of endothelial cells in arcuate, interlobular, and hilar arteries and coagulative necrosis of the renal tubules in the immediate vicinity. These changes may have been postmortem artifact. Basophilic tubules were seen in the kidneys of some rats. In 1 of 2 females [96030] receiving 200 mg/kg this was of moderate severity and was associated with cortical tubular degeneration, interstitial mononuclear cell infiltration, and tubules distended with colloid.

4.3.2. Repeated-Dose Toxicity Studies

Results of the repeated-dose toxicity studies conducted with cangrelor are presented in Table 6. All of the following studies, except SC-30183 and SE9861 were conducted under GLP conditions.

Table 6: Summary of repeated-dose toxicity studies

Study ID	Dose	Pertinent findings
Three Day Toxicity Study in Male Rats		
SE 9299	25, 100, or 450 mg/kg/day IV	Minor signs of toxicity at 25 mg/kg/day. At 105 mg/kg/day, changes in plasma and urine chemistry indicated possible effects on kidney and liver. One rat dosed at 450 mg/kg/day died after 3 minutes. No histopathological evidence of a direct link between cangrelor and these events.

Study ID	Dose	Pertinent findings
One Week Toxicity Study in Male Rats		
SE 9848	10, 25, 50, and 100 µg/kg/min IV	In the 25 µg/kg/min group, 1 rat showed slight inflammation of the hilar connective tissue and 1 showed moderately raised plasma urea, increased total urinary protein, and altered electrophoretic pattern of urinary proteins.
SR 97246/2 (interim kill at 1 week)	25 or 75 µg/kg/min IV	Dose-related increases of plasma ALT, AST, ALP, albumin, and total protein. Low incidence of treatment-related histopathology changes in the renal pelvis and upper ureter.
One Month Toxicity Study in Rats		
SE 9948 (male rats)	3, 12, and 48 µg/kg/min IV	Dose-related increase in plasma AST, ALT, with reduced triglyceride and cholesterol. Dose-related decrease in liver weights, focal and widespread hepatic necrosis. At 48 µg/kg/min, increased RBC and WBC count and severe pyelonephritis and ureteritis, congestion or distension and hemorrhage of the bladder. At 3 and 48 µg/kg/min, increased intensity of albumin band and appearance of additional bands of proteins, potentially related to inflammation of urinary tract.
SE 10176 (female rats)	3, 12, and 48 µg/kg/min IV	Dose-related increase in plasma AST, ALT, with reduced triglyceride and cholesterol. Dose-related decrease in liver weights. At 48 µg/kg/min, increased RBC and WBC count, inflammation of the pelvis and hilum, sometimes accompanied by urothelial hyperplasia, pelvic necrosis, ureteritis, ureteral necrosis, or urothelial hyperplasia and urothelial erosion. Increased intensity of albumin band and appearance of additional bands of proteins, potentially related to inflammation of urinary tract.
SR 97246/2	25 or 75 µg/kg/min IV	Histopathological evidence of effect on kidney and upper urinary tract after 1 month shown to be reversible in the 1-month recovery group. Recovery group showed no inflammation in renal pelvis and ureter; 5 animals had residual renal changes. Increased levels of plasma ALT, AST, albumin, and total protein shown to be reversible. Celluria and electrophoretic patterns of urinary protein completely reversed in all but 1 high-dose animal, which showed signs of recovery.

Study ID	Dose	Pertinent findings
Thirteen Day Study in the Female Dutch Rabbit		
96159-1	60 or 90 μg/kg/min IV	Conducted to support reproductive toxicity studies. Plasma concentrations of cangrelor ranged from 15900 to 55500 ng/mL at 60 μg/kg/min, and 13700 to 134000 ng/mL at 90 μg/kg/min. Results for AR-C69712XX ranged from 1830 to 3350 ng/mL at 60 μg/kg/min, and 6030 to 15100 ng/mL at 90 μg/kg/min. Dose-related toxicity demonstrated in 13% and 30% at 60 and 90 μg/kg/min, respectively. Renal dysfunction seen at both doses but most severe at 90 μg/kg/min. Cangrelor caused increased plasma ALT, AST, ALP, and GGT with most severe effects at 90 μg/kg/min. At this dose, 1 animal had marked periportal vacuolation.
Preliminary Tolerability, and One Week Study in Male Dog		
SC-30183	18, 36, or 40 μg/kg/min IV	No signs of intolerance
SE 9861	40 or 60 μg/kg/min IV	Minor inflammatory changes occurred in the renal pelvis, ureter, and urinary bladder of 1 animal at 60 μg/kg/min IV. No other significant toxicology changes.
One Month Study in Dogs		
SE 9862 (male dogs)	0, 3.75, 15, and 60 μg/kg/min IV	Dose-related increase in mean plasma concentrations in both cangrelor and AR-C69712XX. Aminotransferases raised at 60 μg/kg/min IV. Renal toxicity seen at 60 μg/kg/min IV (tubular necrosis and regeneration, pelvic and interstitial inflammation and urothelial necrosis proteinuria, raised plasma urea, raised plasma creatinine, glucosuria, and raised plasma creatinine). Two dogs receiving 60 μg/kg/min IV showed increased severity and frequency of asynchronous PVCs. Minor opthalmological changes in 3 dogs at 15 and 60 μg/kg/min IV, but no functional or behavioral perturbations.
SE 10177 (female dogs)	0, 3.75, 15, and 60 μg/kg/min IV	Dose-related increase in mean plasma concentrations in both cangrelor and AR-C69712XX. Aminotransferases raised at 15 and 60 μg/kg/min IV. Renal toxicity seen at 60 μg/kg/min IV (basophilic tubules and/or tubules distended with colloid, and inflammatory cell foci. Proteinuria, raised plasma urea, raised plasma creatinine, raised urinary β-NAG).

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; , β-NAG = β-N-acetylglucosaminidase; GGT = gamma-glutamyl transferase; IV = intravenous; PVC = Premature Ventricular Contraction; RBC = red blood cell; WBC = white blood cell.

4.3.3. Reproductive Toxicity Studies

A summary of the reproductive toxicity studies conducted with cangrelor is provided in Table 7. All of the following studies were conducted under GLP conditions.

Table 7 Summary of reproductive toxicity studies

Study ID	Dose	Pertinent findings
Dose-Finding Embryo-Fetal Development Study in the Rat (17 days)		
96178	24, 48, or 96 µg/kg/min IV or vehicle control	Plasma chemistry and histopathology changes consistent with other rat studies. Losses before and after implantation increased and fetal weight reduced at 96 µg/kg/min. Slight reduction in fetal weight at 24 and 48 µg/kg/min. 96 µg/kg/min selected as high dose in embryo-fetal development study (SR 98002)
Embryo-Fetal Development Study in the Rat (17 days)		
SR98002	3, 12, or 48 µg/kg/min IV or vehicle control	Dose-related increase in plasma concentrations at Day 7 and 17 after coitum. Slight reduction in fetal weights and increased incidence of unossified metatarsals at all dose levels of cangrelor At 48 µg/kg/min, entire litter of 1 animal was dead at C-section. This animal had impacted large intestine at necropsy. Two animals at this dose had macroscopic necropsy findings that included pale kidney(s), pale liver, and/or renal dilation and experienced reduced body weight gain and food consumption from Day 18 after coitum. Also increased incidence of incomplete ossification of skull bones and sternebrae and a slight reduction in numbers of viable fetuses at this dose.
Fertility and Early Embryo-Fetal Development Study in the Female Rat (14 days)		
SR98074-01	3, 12, or 48 µg/kg/min IV or vehicle control	No notable dose-related effects on food consumption or body weights. Clinical signs and macroscopic findings at necropsy consistent with previous studies. No effect on estrous cycles, mating performance, and losses before implantation. At 48 µg/kg/min IV, statistically significant increase in losses after implantation.

Study ID	Dose	Pertinent findings
Fertility Study in the Male Rat (8 weeks)		
SR98073/1	3, 12, or 48 μg/kg/min IV or vehicle control	<p>Dose-related incidence of blood in the urine, consistent with urinary tract toxicity seen in other rat studies.</p> <p>No effect on body weight body weight or food consumption. Decrease in body temperature observed.</p> <p>At 48 μg/kg/min, 4 of 18 males at high dose failed to produce pregnancy with partner. Five of the pregnancies at this dose experienced high loss. Abnormal sperm morphology and reduced sperm motility seen in all males at this dose, as well as reduced epididymal and vas deferens sperm counts, low epididymal weights, testicular tubular epithelial atrophy, tubular dilation. The latter were associated with epididymal oligospermia, spermatocele formation, and spermatocele degeneration.</p> <p>In the recovery group, 3 of 8 males dosed at 48 μg/kg/min showed tubular epithelial atrophy with associated effects. In 1 of 9 control males and 1 of 9 males dosed at 12 μg/kg/min, tubular epithelial atrophy was seen alone.</p>
Dose-Finding Embryo-Fetal Development Study in the Rabbit (19 Days)		
97241/1	24, 48, or 60 μg/kg/min IV or vehicle control	<p>One animal (60 μg/kg/min) died. Maternal toxicity as indicated by reduced food and water consumption and consequent reduced fecal and urine production was seen at all doses. Dose-related body weight loss, tubular dilation, degeneration, and casts. Centrilobular necrosis seen at both 48 and 60 μg/kg/min. Diffuse vacuolation seen in the liver in all doses. Litter lost due to total or partial intrauterine death or abortion increased at 48 and 60 μg/kg/min. No effect seen on fetal weight. Both 48 and 60 μg/kg/min determined as too high for definitive embryo-fetal development study in Dutch rabbits.</p>
Embryo-Fetal Development Study in the Rabbit (19 Days)		
SR 97297	4, 12, and 36 μg/kg/min IV or vehicle control	<p>Dose-related increase in plasma concentrations at Day 7 and 18 after coitum.</p> <p>Increased incidence of total intrauterine death and abortion at 12 and 36 μg/kg/min. Maternal body weight, food and water consumption, and fecal production all reduced during the dosing period in all cangrelor-treated groups, which may have influenced small reduction in fetal weight and ossification at 36 μg/kg/min. Small increase in blood vessel and skeletal variants was also observed at the high dose.</p>

C-section = Cesarean section; IV = intravenous.

4.3.4. Genotoxicity Studies

A comprehensive battery of genotoxicity studies has been completed, including bacterial and mammalian cell mutation assays and assays for cytogenetic damage using in vitro and whole animal systems. The in vitro tests were done both in the absence and presence of an exogenous metabolic activation system, derived from rat liver (S9 mix). These are described below.

In an Ames assay [SE 9940] using concentrations of up to 5000 µg/plate, the potential of cangrelor to induce point mutations was assessed using *Salmonella typhimurium* strains TA 1535, TA 1537, TA 98, TA 100, and TA 102. Prior to this study, during the early phase of development, limited Ames assays were conducted with cangrelor [SE 9389] and 2 of its metabolites, AR-C69712XX [SE 9563] and AR-C71301XX [SE 9564], using *Salmonella typhimurium* strains TA 1537, TA 98, TA 100, and TA 102. In addition, because 1 batch (4044G) contained an unknown impurity (N) not detected in previous batches, this was also tested in a limited Ames test [97036/1]. Cangrelor and its metabolic products were not mutagenic in any of the tests.

Cangrelor was not mutagenic when assayed for its ability to induce forward mutations in Mouse Lymphoma L5178Y cells at the thymidine kinase locus [96102]. Cangrelor was not clastogenic when tested for its ability to induce chromosomal aberrations in human peripheral blood lymphocytes in vitro [SE 9958]. There were no significant, reproducible increases in the frequency of structural chromosome aberrations or polyploidy that could be attributed to the test compound.

Two separate, completed, in vivo studies were designed to assess the potential of cangrelor to induce genetic damage when administered to male mice. A limited study [SE 9341] was completed during the early stages of development in which cangrelor was administered to groups of 7 male mice at 500 mg/kg as a slow IV bolus (5 minutes at 1 mL/kg/min). In the main study [96122], cangrelor was administered at 125, 250, and 500 mg/kg to groups of 9 male mice. Two animals receiving the highest dose of cangrelor died prior to the scheduled sampling times and the majority of animals exhibited adverse clinical signs. Animals were killed 24 or 48 hours later, the bone marrow extracted, and smear preparations made and stained. Polychromatic and normochromatic erythrocytes were scored for the presence of micronuclei. There was no evidence of an increase in the incidence of micronucleated polychromatic erythrocytes in either study and so it was concluded that cangrelor was nongenotoxic under the conditions of the tests.

4.3.5. Discussion

The results of animal toxicity studies predict that renal and urinary tract toxicity is the principal potential hazard associated with treatment with cangrelor. In the rat, the toxicity seen after 1 months dosing has been shown to be reversible. In respect to histopathology changes in rats, the no effect dose was 12 µg/kg/min for 1 month. In dogs, 1 week dosing at 40 µg/kg/min and 1 month dosing at 15 µg/kg/min produced no toxicologically significant changes in renal function or morphology. Female dogs were less affected, showing only minimal changes at 60 µg/kg/min after 1 month.

In Table 8, exposure to cangrelor in humans is compared with exposure in animals at a dose that was free from histopathology changes.

Table 8: Human exposure to AR-C69931XX during continuous IV infusion compared with exposure in rats and dogs at the no-effect dose

Species	Sex	Fraction unbound in Plasma	Infusion Rate (µg/kg/min) [days]	C _{ss} (ng/mL)		AUC _{0-duration} (µg/min/kg) Unbound
				Total	Unbound	
Human	Male	0.011	4	329	3.6	26.1
	Female	0.011	4	352	3.9	27.9
Rat	Male	0.013	12 [28]	328	4.3	172
	Female	0.013	12 [28]	300	3.9	157
Dog	Male	0.038	40 [7]	551	20.9	211
	Male	0.038	15 [28]	266	10.1	408
	Female	0.038	15 [28]	219	8.3	336

AUC = Area under the concentration curve; AUC for human estimated for 0 to 5 days; C_{ss} = Steady-state plasma concentration

Source: [SE9948](#); [SE10176](#); [SE9861](#); [SE9862](#); [SE10177](#); [SC-931-5014](#); [SC-931-5036](#).

Because some of the comparisons presented above offer little or no margin when comparing the highest no-effect dose in animals with the dose used clinically, the clinical significance of these findings is questionable. Attempts to correlate plasma concentrations of cangrelor or the major plasma metabolite, AR-C69712XX, to renal toxicity have not shown a causal relationship. If the duration of dosing is considered, then a large margin of safety is evident, as shown by extrapolating AUCs at the no-effect doses after 4 weeks in animals to 5 days exposure in man.

It may be speculated that the renal effects seen in animals could be due to a metabolite present in the urine. Comparison of the metabolite profile in man and animals demonstrates that they are qualitatively similar. However, the predominant route of excretion is via the urine in man and via the bile in animals. The major urinary metabolite in man is AR-C90439XX, a sulphoxide of AR-C69712XX. Table 9 illustrates the estimated 24 hour urinary excretion of AR-C90439XX at the maximum expected therapeutic dose in man, and the no-effect dose in animal safety studies.

Table 9: Estimated 24 hour urinary excretion data for AR-C90439XX following a 2 hour intravenous infusion of cangrelor

Species	Cangrelor (AR-C69931MX) (µg/kg/min)	AR-C90439XX excreted in urine in 24h (µg/kg)	References
Rat	12	122	Extrapolated from data in SE 10010 and SC-100358
Dog	15	26	Extrapolated from data in SE 10011 and SC-100357

Species	Cangrelor (AR-C69931MX) (µg/kg/min)	AR-C90439XX excreted in urine in 24h (µg/kg)	References
Dog	40	69	Extrapolated from data in SE 10011 and SC-100357
Man	4	123	Extrapolated from data in SC-931-9017

Note: All data normalized to a 2 hour infusion period.

These data demonstrate that urinary excretion is comparable, and it can be assumed that this will be the case during continuous infusion. Importantly, studies in humans have included treatment for up to 72 hours at a dose of 4 µg/kg/min with no evidence of clinically significant adverse effects on the kidney or urinary tract [[SC-931-9017](#)].

Plasma enzyme (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) changes have been documented consistently in all animal species investigated. A rat study [[SR 97246/2](#)] has demonstrated that these changes are reversible following cessation of treatment. There has been no clear association with organ damage in rats and dogs, although liver changes noted in rabbits may be associated with the compound. Notably, the plasma concentration of cangrelor and AR-C69712XX observed in rabbits is considerably higher, dose-for-dose, than in rats and dogs.

Although whole body autoradiography showed some thyroid and bone marrow exposure during dosing [[SE 10012](#)], which declined rapidly thereafter, there was no evidence to indicate any adverse effects in these tissues.

Minor ECG changes observed during the 1 month toxicity study in two male dogs, consisting of an increased severity and frequency of asynchronous premature ventricular contractions (PVCs) at 60 µg/kg/min on 2 of 3 and 1 of 3 occasions during treatment, are considered to be of no toxicological importance because asynchronous PVCs are occasionally observed in controls. Asynchronous PVCs had been noted less frequently, prior to treatment in one of the affected dogs; there were no effects reported in female dogs.

Minor changes seen in the eyes of some male dogs are considered not to be of toxicological significance. The changes were seen in the tapetum, a structure present in dogs but not in man. Furthermore, there were no changes seen in female dogs dosed with cangrelor.

Effects on fertility, ability to produce a pregnancy with female partner(s), sperm morphology and sperm motility have been noted in the male fertility study [[SR98073/1](#)] at 48 µg/kg/min. These effects were not apparent at lower doses and were reversible following cessation of dosing. In this study, semen analysis was conducted after 8 weeks of continuous treatment. In a previous 1 month toxicity study [[SE 9948](#)], semen analysis conducted after 4 weeks treatment had shown no abnormalities. Together, these studies appear to indicate that the observed effects are produced only after continuous dosing for longer than 4 weeks and importantly, the effects are reversible. It is therefore considered that this finding has no toxicological significance in relation to the proposed clinical use of cangrelor. Female fertility (estrous cycles, mating performance, preimplantation losses) was unaffected by cangrelor.

There was no indication in rat and rabbit embryo-fetal development studies that cangrelor has the potential to cause malformations. These studies provide an extremely rigorous test of the compound's potential to affect in utero development. Exposure of the pregnant animals was maintained continuously, by IV infusion, from implantation of the blastocyst until the completion of major organogenesis. During this period the steady-state plasma concentration of AR-C69931XX, compared with likely human plasma concentration, was approximately 6 times higher in rats and 60 times higher in rabbits. Data from a tissue distribution study in pregnant rats [SC-100295] using radio labeled cangrelor show that exposure of the fetus was less than maternal tissue. This is consistent with the view that cangrelor does not readily cross membranes. Evidence of delayed fetal development was noted in both rats and rabbits. Although a direct effect of the compound on the fetus cannot be ruled out, it is likely that maternal stress due to the infusion procedure or the toxicity of the compound may have contributed to the observed effects.

Overall, the findings from the toxicology studies support the dose used in the Phase III clinical studies. Relative to cangrelor, there are no reasons to specifically exclude women of childbearing potential from clinical trials.

5. EFFECTS IN HUMANS

5.1. Overview of Completed Clinical Studies with Cangrelor

A total of 14 clinical studies with cangrelor have been completed to date, with 7,655 cangrelor-treated subjects.

Under the original sponsorship of AstraZeneca, five Phase I studies (SC-931-5014, SC-931-5036, SC-931-5109, SC-931-9017, and SC-931-5037) and four Phase II studies (SC-931-5058, SC-931-5060, SC-931-5129 Part 1, and SC-931-5129 Part 2) were completed. An additional Phase II study, SC-931-5135, was terminated prematurely due to reprioritization of drug development candidates by the former Sponsor (AstraZeneca).

Under the sponsorship of The Medicines Company, two additional healthy volunteer studies (TMC-CAN-04-02 and TMC-CAN-08-01) were completed, and two Phase III studies (TMC-CAN-05-02 and TMC-CAN-05-03) were initiated but terminated early. Details of all completed clinical studies are summarized in Table 10.

Healthy volunteer studies SC-931-5014 and SC-931-5036 examined the safety and tolerability of cangrelor at increasing infusion rates of up to 4 µg/kg/min in healthy male and female volunteers, respectively. Study SC-931-9017 assessed the distribution, metabolism, and excretion of a [³H]cangrelor infusion (2 µg/kg/min). The possible interactions of aspirin, heparin, and GTN on the PK and PD of cangrelor were investigated in study SC-931-5037. Study SC-931-5109 compared the safety and tolerability of cangrelor in normal subjects to those with mild to severe renal impairment. Study TMC-CAN-04-02 was conducted to evaluate the PK and PD parameters of a bolus plus infusion dosing regimen of cangrelor in healthy volunteers. TMC-CAN-08-01 was designed to assess the safety of therapeutic and supratherapeutic doses of cangrelor on cardiac repolarization as measured by ECG.

The first study in patients with non-Q-wave myocardial infarction (non-Q-MI), SC-931-5058, determined the PK and PD of various infusion rates (up to 4 µg/kg/min) of cangrelor in patients

with UA/non-Q-MI. Study [SC-931-5060](#) further assessed the safety, tolerability, and PK of 4 µg/kg/min cangrelor in UA/non-Q-MI patients when administered as a continuous infusion for 72 hours. The effects of cangrelor were studied in patients undergoing coronary revascularization in study [SC-931-5129 Part 1](#) and [SC-931-5129 Part 2](#). Study [SC-931-5135](#) assessed the safety, tolerability, and the effect on coronary artery patency of cangrelor in patients with STEMI. The study was terminated due to changes in business priorities.

The cangrelor Phase III clinical development program (CHAMPION) was designed to demonstrate that cangrelor bolus and infusion followed by transition to oral therapy prevents platelet aggregation and is effective in preventing acute life-threatening events in patients undergoing PCI, while not increasing the risk of bleeding. This program was composed of two independent studies, CHAMPION PCI ([TMC-CAN-05-02](#)) and CHAMPION Platform ([TMC-CAN-05-03](#)).

The PCI study ([TMC-CAN-05-02](#)) planned enrollment of 9,000 patients within the following categories: SA, UA, NSTEMI, or STEMI. Patients received a dose of clopidogrel at the start of the PCI procedure and the study was designed to demonstrate superiority to a 600 mg loading dose of clopidogrel.

The Platform study ([TMC-CAN-05-03](#)) planned enrollment of 6,400 patients within the following categories: SA, UA, or NSTEMI. In contrast to PCI, STEMI patients were not enrolled in the Platform study. The other key difference was that patients did not receive a dose of clopidogrel at the start of the PCI procedure; instead, clopidogrel was given at the end of the PCI procedure. Therefore, the study was designed to demonstrate superiority to usual care. Exclusion criteria required patients to be clopidogrel-naïve, eg, no clopidogrel within 7 days prior to randomization.

The primary efficacy endpoint in both studies was the 48-hour composite of all-cause mortality, MI, or IDR. Secondary efficacy endpoints included the composite of mortality or MI at 48 hours and 30 days; the composite of mortality, MI, or IDR at 30 days, the individual components of the composite endpoints at 48 hours and 30 days, the incidence of stroke at 48 hours, acute (24 hours) and subacute (48 hours) stent thrombosis, and the incidence of all-cause mortality at 6 months and 1 year.

The CHAMPION program was designed to enroll approximately 15,400 patients; however enrollment was terminated early following the Platform 70% interim analysis, with 98% (8882) patients enrolled in PCI and 84% (5364) patients enrolled in Platform, due to the low likelihood of achieving the primary endpoint in both studies.

Table 10: Summary of completed clinical studies performed with cangrelor

Study Identifier (Phase)	Study Design	Region	Dose cangrelor	Study Treatments	Number of Subjects	Treatment Duration (h)	Status
SC-931-5014 (I)	Tolerability, safety, activity & pharmacokinetics in healthy male volunteers	UK	0.25 ng/kg/min – 4 µg/kg/min	cangrelor placebo	28 12	23	Completed 1996
SC-931-5036 (I)	Tolerability, safety, activity & pharmacokinetics in healthy female volunteers	UK	0.01 – 4 µg/kg/min	cangrelor placebo	15 8	23	Completed 1996
SC-931-9017 (I)	Metabolic profile, route of excretion in healthy male volunteers	UK	2 µg/kg/min	cangrelor	4	2	Completed 1996
SC-931-5037 (I)	Interactions with aspirin, heparin & GTN; 2-way crossover in healthy male volunteers	UK	0.05 – 2 µg/kg/min	cangrelor	12	3.75	Completed 1996
SC-931-5109 (I)	Safety, tolerability, pharmacokinetics & platelet aggregation in renally impaired patients	Germany	0.05 – 4 µg/kg/min	cangrelor	24	5	Completed 1999
TMC CAN 04-02 (I)	Randomized, open-label study of the effects of bolus plus infusion on healthy volunteers, administration with clopidogrel	US	15 or 30µg/kg bolus + 2 or 4 µg/kg/min infusion	cangrelor +/- clopidogrel	42	1 or 2	Completed 2005
TMC CAN 08-01 (I)	A double-blind, placebo-controlled, positive-controlled, randomized, crossover study to assess the effect of cangrelor at the therapeutic dose and a supratherapeutic dose level on the QT/QTc interval in healthy volunteers	US	30 µg/kg IV bolus followed by 4 µg/kg/min or 60 µg/kg IV bolus followed by 8 µg/kg/min	cangrelor placebo	71	3	Completed 2008
SC-931-5058 (II)	Safety, tolerability, activity & pharmacokinetics in UA/non-Q-MI patients	UK, Netherlands	0.05 – 2 µg/kg/min 0.2 – 4 µg/kg/min	cangrelor	39	24/72	Completed 1998

Study Identifier (Phase)	Study Design	Region	Dose cangrelor	Study Treatments	Number of Subjects	Treatment Duration (h)	Status
SC-931-5060 (II)	Double-blind, placebo controlled safety, tolerability & pharmacokinetics in UA/non-Q-MI patients	Sweden	4 µg/kg/min	cangrelor placebo	45 46	72	Completed 1999
SC-931-5129 Part 1 (II)	Double-blind, placebo controlled, safety, pharmacokinetics, platelet aggregometry & bleeding time in patients undergoing PTCA	US	1, 2, 4 µg/kg/min	cangrelor placebo	149 51	18-24	Completed 1999
SC-931-5129 Part 2 (II)	Safety, platelet aggregometry & bleeding time in patients undergoing PTCA	US	4 µg/kg/min	cangrelor abciximab	105 94	18-24 10-12	Completed 1999
SC-931-5135 (II)	Open-label, randomized paralled group safety, tolerability on coronary artery patency in ST-elevation MI patients	US, Canada	35-280 µg/min	cangrelor & Activase Activase only	85 7	24-72	Terminated Early 2001
TMC-CAN-05-02 (PCI) (III)	Randomized, double-blind, double-dummy, active control, parallel grou comparing cangrelor to clopidogrel in subjects who require percutaneous coronary intervention	Multi-national	30 µg/kg IV bolus + 4 µg/kg/min IV infusion	cangrelor clopidogrel	4374 4365	2-4	Terminated May 2009
TMC-CAN-05-03 (Platform) (III)	Randomized, double-blind, placebo-controlled, parallel group comparing treatment with cangrelor (in combination with usual care) to usual care, in subjects who require percutaneous coronary intervention	Multi-national	30 µg/kg IV bolus + 4 µg/kg/min IV infusion	cangrelor clopidogrel	2662 2650	2-4	Terminated May 2009

GTN = nitroglycerin; IV = intravenous; MI = myocardial infarction; non-Q-MI = non-Q-wave myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; QTc = QT interval corrected for heart rate; UA = unstable angina; UK = United Kingdom; US = United States.

5.2. Pharmacokinetics and Product Metabolism in Humans

5.2.1. Absorption

The absorption properties of cangrelor in humans were not evaluated due to its intended IV use.

5.2.2. Disposition

5.2.2.1. Healthy Volunteer Studies

Plasma concentrations of the parent compound (AR-C69931XX) and the primary metabolite (AR-C69712XX) were determined in healthy volunteer studies [SC-931-5014; SC-931-5036]. Results from these ascending doses studies indicated that the plasma clearance of the compound was rapid in both male and female subjects, and that it has a short initial half-life (3.5 to 6.0 minutes). Steady-state plasma concentrations were rapidly achieved following IV administration, and plasma concentrations of both parent and metabolite were found to decline in a bi-exponential manner in both studies following termination of the infusion.

Plasma clearance (53 L/hour) of the parent compound did not change significantly over the administered dose range. Steady-state concentrations of cangrelor increased linearly with dose. There was no evidence of any clinically important sex-related differences in the PK of either cangrelor or the primary metabolite (Table 11:). Assuming the molar fraction (f) of AR-C69931XX converted to AR-C69712XX was 1.0, the clearance of the primary metabolite was more rapid than that observed for the parent compound. Steady-state plasma concentrations of the primary metabolite were lower than those of the parent compound.

Table 11:: Pharmacokinetic parameter estimates and steady-state plasma concentrations of cangrelor and the primary metabolite following administration to male and female volunteers

Parameter	SC-931-5014 (male) (4 µg/kg/min) Mean (N = 6)	SC-931-5036 (female) (4 µg/kg/min) Mean (N = 3)
C _{ss} parent	329 ng/mL	350 ng/mL
C _{ss} metabolite	204 ng/mL	222 ng/mL
Clearance of parent	13.2 mL/min/kg / 53 L/h	12.7 mL/min/kg / 53 L/h
Clearance of metabolite ^a /f	22.4 mL/min/kg / 92 L/h	20.0 mL/min/kg / 108 L/h
Parent/metabolite ratio ^b	0.92	1.04
Half-life α phase of parent	3.5 min	6 min
Half-life β phase of metabolite	2.7 h	2.9 h

C_{ss} = plasma concentration at steady state; AR-C69931XX = parent compound; AR-C69712XX = metabolite; f = molar fraction.

a Estimates of metabolite clearance assume that f was approximately 1.0

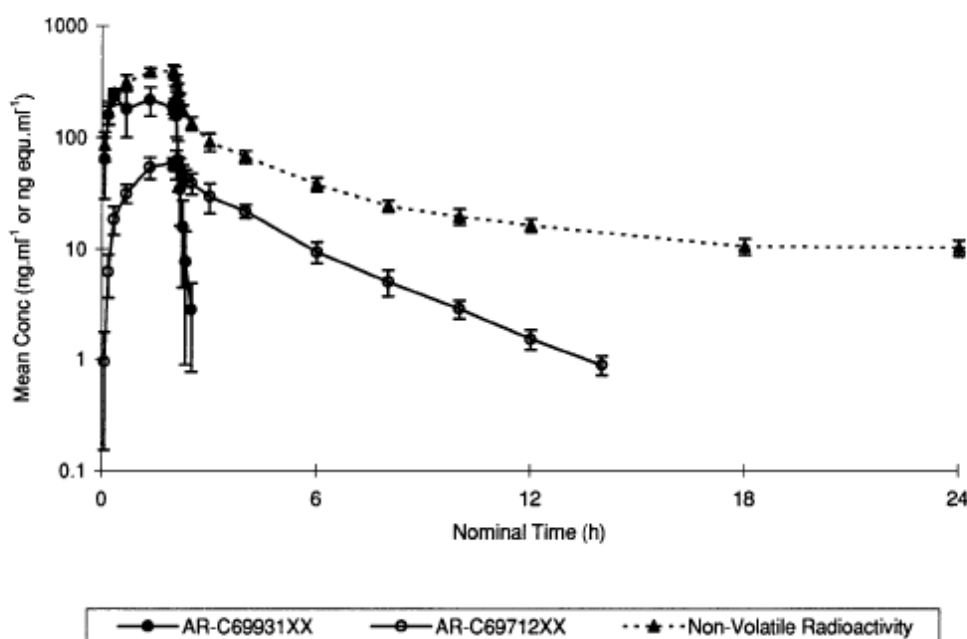
b Derived from overall mean of late plateau measurements at and above rates of 100 µg/kg /min

Source: Studies SC-931-5014 and SC-931-5036.

Radiolabelled Cangrelor Study

Additional distribution and elimination information for cangrelor infusions was generated from study [SC-931-9017](#) in which healthy male volunteers received [^3H]cangrelor IV infusions for 2 hours ($2\text{ }\mu\text{g/kg/min}$). During the infusion, the plasma concentration of radioactivity increased rapidly, reaching a plateau toward the end of the infusion period. In the first 10 hours after the end of infusion, total radioactivity declined in a bi-phasic manner, with the initial decline in total radioactivity attributable to the elimination of the cangrelor parent compound and distribution of the primary circulating metabolite (Figure 4).

Figure 4: Mean (\pm SD) plasma concentrations for AR-C69931XX ($\text{ng}\cdot\text{mL}^{-1}$), AR-C69712XX ($\text{ng}\cdot\text{mL}^{-1}$) and non-volatile radioactivity ($\text{ng equ}\cdot\text{mL}^{-1}$) over the initial 24-hour period following an intravenous infusion of AR-C6991MX at a rate of $2\text{ }\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ to healthy male volunteers ($n=4$) (Study [SC-931-9017](#))



Source: Study SC-931-9017, Figure 1.

Plasma analysis indicated that cangrelor rapidly reached steady-state. The half-life (5 minutes) was similar to that observed in volunteer studies [[SC-931-5014](#); [SC-931-5036](#)], as was the estimated terminal half-life (2.1 hours). Mean clearance was approximately 10.3 mL/kg/min .

The primary metabolite (AR-C69712XX) reached a maximum concentration of $65\text{ ng eq AR-C69931XX/mL}$ (26% of AR-C69931XX C_{max}), and remained below the concentration achieved by the parent compound until after the end of infusion.

The profile of the remainder of plasma radioactivity not accounted for by the parent compound and primary metabolite appeared to rise and decay on a similar time course to the nucleoside metabolite. A maximum concentration of 402 ng eqAR-C69931XX/mL was reached very shortly after the end of infusion.

5.2.2.2. Studies in Patients with Unstable Angina/Non Q-Wave Myocardial Infarction

The PK of cangrelor and the primary metabolite were estimated in patients with UA/non-Q-MI receiving a cangrelor infusion of up to 4 µg/kg/min in study [SC-931-5058](#). Results indicated that the parent compound was cleared very rapidly from the plasma (44.3 L/hour), at a similar rate to that observed in healthy volunteers [[SC-931-5014](#); [SC-931-5036](#)], and had a low initial volume of distribution (5.1 L). Estimates of the volume of distribution at steady state (13.4 L) suggested that the parent compound was not extensively distributed (Table 12). The population PK estimates for clearance were slightly less than the values calculated from healthy volunteer studies [[SC-931-5014](#); [SC-931-5036](#)]. Mean population PK estimates suggested that the average half-life for cangrelor in this population was less than 5 minutes, and that the majority of patients (90%) had an estimated value of less than 9 minutes.

Inter-patient variability for clearance was low at 14.4% (Table 12).

Table 12: Mean population pharmacokinetic parameters for cangrelor and the primary metabolite in patients with UA/non-Q-MI

Parameter	Mean ± SE	Inter-individual Variance (%)
Parent		
Clearance (L/h)	44.3 ± 2.16	14.4
Initial volume of distribution (L)	5.1 ± 0.53	3.46
Tissue volume (L)	8.3 ± 0.84	NE
Volume at steady state (L)	13.4	
Metabolite		
Clearance (L/h)/f	74.3 ± 4.48	30.0
Initial volume (L)/f	24.1 ± 4.14	NR
Volume of distribution at steady state (L)/f	192 ± 9.23	NE

AR-C69931XX = parent compound; AR-C69712XX = metabolite; f = molar fraction (~ 1.0); NE = not estimated; NR = not reported; SE = standard error.

Source: Study [SC-931-5058](#).

The PK profile of cangrelor was constant over the dosing interval; parameter estimates suggested that the mean C_{ss} was 375 ng/mL for the 4 µg/kg/min dose, which is slightly higher than the value observed in healthy volunteers ([Table 11](#)).

[Table 11](#):). The PK profile in this group was unaffected by changes in either the infusion rate or the infusion duration (up to 72 hours). The plasma concentrations of the metabolite declined less rapidly than those for the parent compound after the end of the infusion, and had an estimated clearance/f higher than that for the parent compound (74.3 L/hour). Estimates of the metabolic half-life were larger than those for the parent compound (2 hours), mainly due to its larger volume of distribution at steady state (192 L), which suggested that the primary metabolite was extensively distributed ([Table 12](#)).

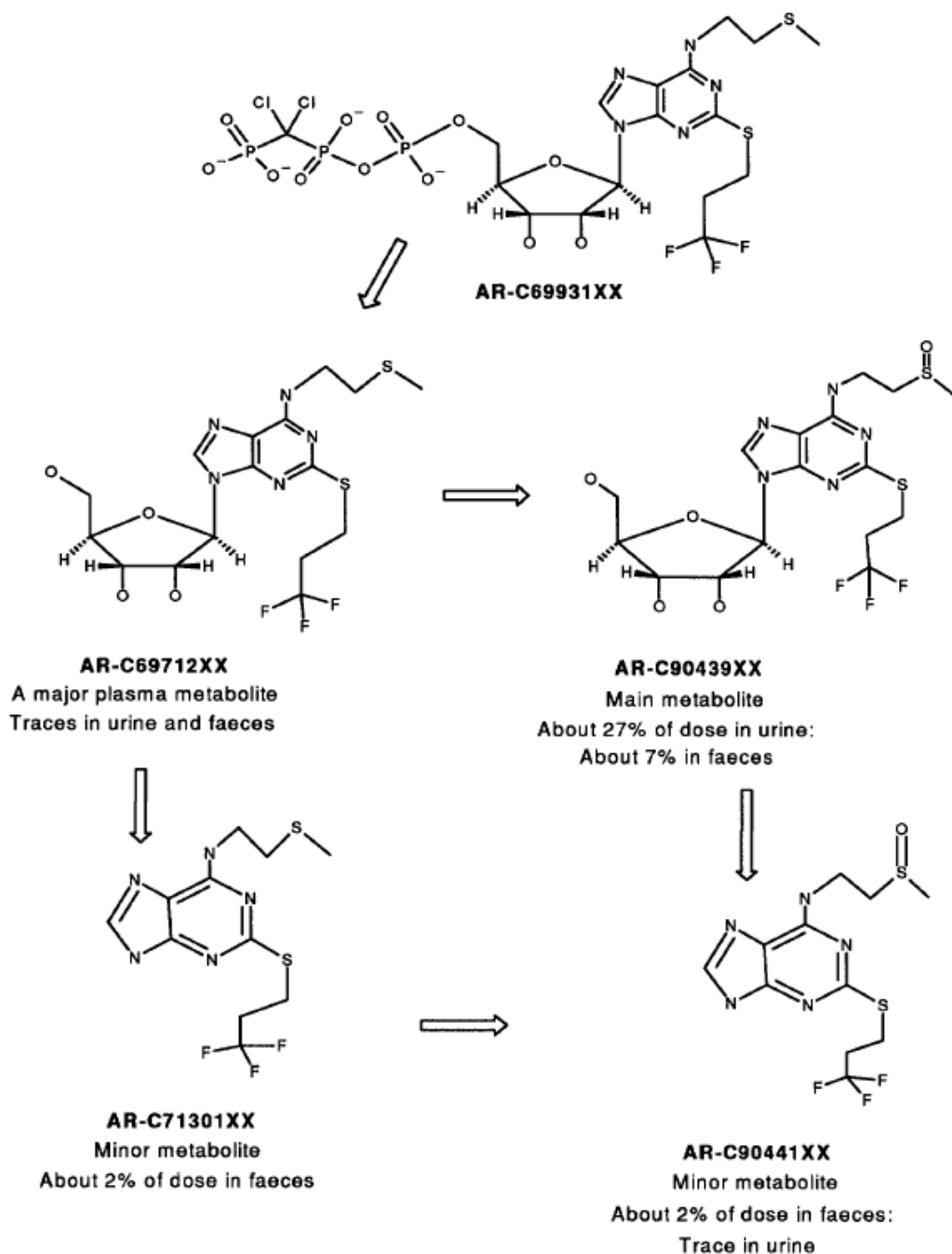
Steady-state plasma concentrations were analyzed from study [SC-931-5060](#) in which patients with UA/non-Q-MI received cangrelor infusions of 4 µg/kg/min for up to 72 hours. Mean estimates of clearance (41.0 ± 1.58 L/hour) were similar to those from study [SC-931-5058](#), with a low inter-individual variability (22.2%). Clearance estimates were not affected by the longer duration of infusion (72 hours).

5.2.3. Metabolism

The metabolic fate of the cangrelor parent compound was investigated in plasma and excreta samples from subjects following IV administration of [³H]cangrelor in study [SC-931-9017](#). This was qualitatively similar to that observed in animal studies (see [Section 4.2.2](#)). It appears that cangrelor is cleared rapidly by dephosphorylation to form the nucleoside (AR-C69712XX), as judged by the absence of significant quantities of the parent compound in excreta.

AR-C69712XX was the major circulating metabolite. The major excreted metabolite cochromatographed with AR-C90439XX, a sulphoxide of the nucleoside. In contrast to findings in the rat and dog studies, this metabolite appeared mainly in urine, accounting for 27.3% of the dose, with only 6.6% of the dose in feces. The next most abundant metabolite was a corresponding sulphoxide of the base, AR-C90441XX, which accounted for <5% of the dose in both urine and feces. Only trace amounts of the nucleoside AR-C69712XX were found in either feces or urine, although this was initially the major metabolite circulating in plasma. The remainder of the dose consisted of the substituted purine base AR-C71301XX, and other products of S-oxidation, purine base oxidation, deribosylation, and glucuronidation. No products of oxidative de-amination at C6 of the purine ring of AR-C69712XX were detected in this study, which indicated that metabolism by endogenous purine nucleoside salvage pathways did not occur.

A scheme presenting the postulated routes of metabolism of cangrelor is given in [Figure 5](#).

Figure 5: Postulated major routes of metabolism of AR-C69931MX

5.2.4. Elimination

Following IV administration of [^3H]cangrelor [SC-931-9017], 93% of total radioactivity was recovered but, contrary to findings in animal studies, 58% of this was in urine, and the remaining 35% was in feces, presumably following biliary excretion. Initial excretion was rapid, such that approximately 50% of the administered radioactivity was recovered in the first 24 hours, and

75% was recovered by 48 hours. The majority of the fecal load emerged more slowly and variably over the 72 hour period, and was attributed to delays caused by the frequency of bowel opening and latencies in gut transit time.

In study [SC-931-5109](#), healthy volunteers and subjects with renal insufficiency were administered cangrelor infusions in ascending doses (50 to 4000 ng/kg/min) for 5 hours. The primary objective was to compare the plasma concentrations of the parent compound and the major circulating metabolite and to assess the safety and tolerability by monitoring appropriate clinical and laboratory parameters. The plasma concentration-time profiles for cangrelor and its primary metabolite were comparable to those observed previously in healthy volunteers. Importantly, the PK/PD relationship for the parent compound and the major circulating metabolites appeared to be unaffected by renal impairment. [Table 13](#) shows a summary of the PK parameters.

Table 13: Summary of main pharmacokinetic parameters (results expressed as arithmetic mean \pm SD)

Group	Group Size	Maximum Infusion Rate (ng/kg/min)	Pharmacokinetic Parameter for					
			AR-C69931XX		AR-C69712XX		AR-C90439XX	
			$t_{1/2}$ (min)	CL (L/h)	$t_{1/2}$ (h)	CL/f (L/h)	$t_{1/2}$ (h)	CL/f (L/h)
Healthy Volunteers	4	2000	3.7 ± 0.2	66.3 ± 5.6	2.5 ± 0.3	112.7 ± 20.2	1.2 ± 0.1	231.3 ± 19.5
Renally Impaired	8	2000	3.9 ± 0.4	57.5 ± 8.2	2.5 ± 0.3	128.4 ± 52.9	1.3 ± 0.2	134.0 ± 52.2
Healthy Volunteers	4	4000	3.5 ± 0.1	72.9 ± 11.7^a	2.3 ± 0.1	142.8 ± 33.0	1.0 ± 0.1	287.3 ± 92.9
Renally Impaired	8	4000	3.8 ± 0.5^b	53.8 ± 17.4^b	2.6 ± 0.5	88.6 ± 30.6	1.7 ± 0.3	141.1 ± 37.0

CL = clearance; f = molar fraction; SD = standard deviation; $t_{1/2}$ = half-life.

a. n=3

b. n=7

Source: Study SC-931-5109, Table 14.2.1.4b, Table 14.2.1.5, and Table 14.2.1.6.

5.2.5. Interaction Study

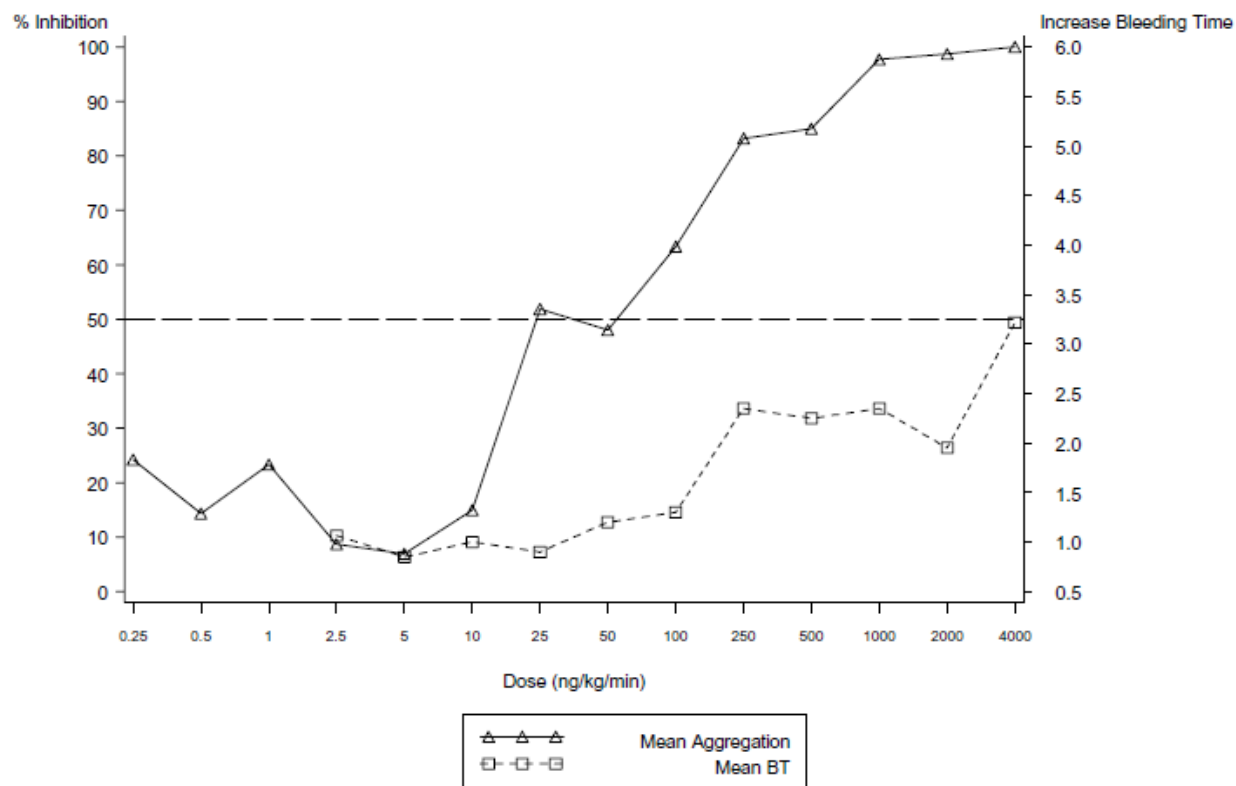
Cangrelor, administered with aspirin, heparin, and GTN, was examined in the healthy male volunteer study [SC-931-5037](#). Results indicate that the PK of cangrelor were unaffected by therapeutically relevant doses of aspirin, heparin, and GTN, with the maximum plasma concentration (C_{\max}), AUC, and total clearance similar between the two groups.

5.2.6. Pharmacodynamic Effects

5.2.6.1. Dose Escalation Studies in Healthy Volunteers

In the double-blind, placebo-controlled, ascending-dose, step-plateau infusion study conducted in healthy male volunteers [[SC-931-5014](#)], cangrelor (0.25 to 4000 ng/kg/min) was administered as four 1 hour infusions, followed by a 19 hour plateau phase at the highest dose level. A dose-related inhibition of ADP-induced platelet aggregation ex vivo was observed, with over 80% inhibition achieved at doses of 250 ng/kg/min and above. Increases in bleeding time were also observed in this dose range. Adenosine diphosphate-induced aggregation and BT responses were stable during the plateau infusion, and were generally restored to control values when measured at 20 and 60 minutes after infusion, respectively, for all dose levels. [Figure 6](#) illustrates the group mean responses at each infusion rate for the percentage inhibition of ADP-induced aggregation after 57 minutes, and the ratio of the BT after 19 hours of plateau infusion to the baseline BT. Due to the overlapping dose design, BT data means were derived from only two subjects at each intermediate level, whereas the top dose level mean was derived from six subjects.

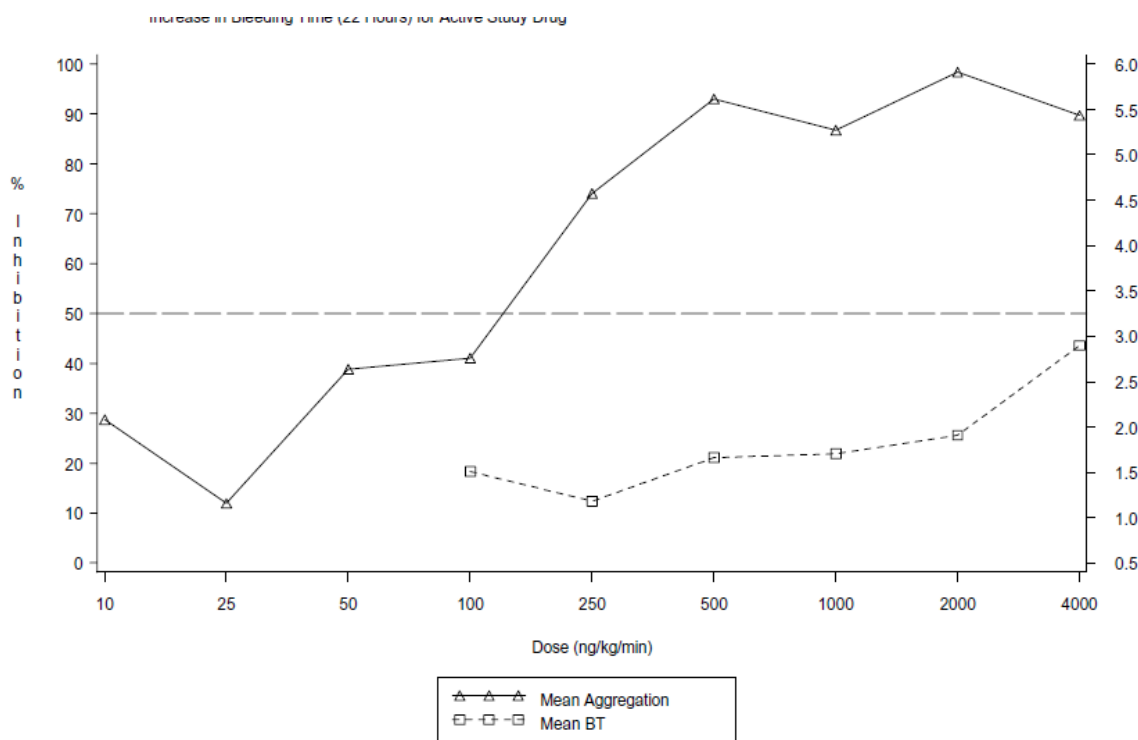
Figure 6: Comparison of percent inhibition of ADP-induced platelet aggregation (after 57 mins) and increase in bleeding time (22 hours) in male subjects (Study SC-931-5014)



Source: Study SC-931-5014, Figure F12.

In the corresponding ascending-dose, step-plateau, infusion study conducted in healthy female volunteers [SC-931-5036], (10 to 4000 ng/kg/min), cangrelor was administered as four 1 hour infusions, followed by a 19 hour plateau phase at the highest dose level. Bleeding time was increased by up to 2.9-fold at the highest dose. A dose-related inhibition of ADP-induced platelet aggregation ex vivo was observed, with over 80% inhibition achieved at doses of 500 ng/kg/min and above. Adenosine diphosphate-induced aggregation and BT responses were stable during the plateau infusion, and were generally restored to control values when measured at 20 and 60 minutes after infusion, respectively, for all dose levels. Figure 7 illustrates the group mean responses at each infusion rate for the percentage inhibition of ADP-induced aggregation after 57 minutes, and the ratio of the BT after 19 hours of plateau infusion to the baseline BT. Again, due to the overlapping dose design, BT data means are derived from only two subjects at each intermediate level, whereas the penultimate and top dose level means are derived from four and three subjects respectively. The dose-response curve for the percentage inhibition of ADP-induced platelet aggregation ex vivo in female subjects is similar to that for healthy males. There appears to be no evidence for any sex-related differences in the PD properties of cangrelor.

Figure 7: Comparison of percent inhibition of ADP-induced platelet aggregation (after 57 minutes) and increase in bleeding time (22 hours) in female subjects (Study SC 931-5036)

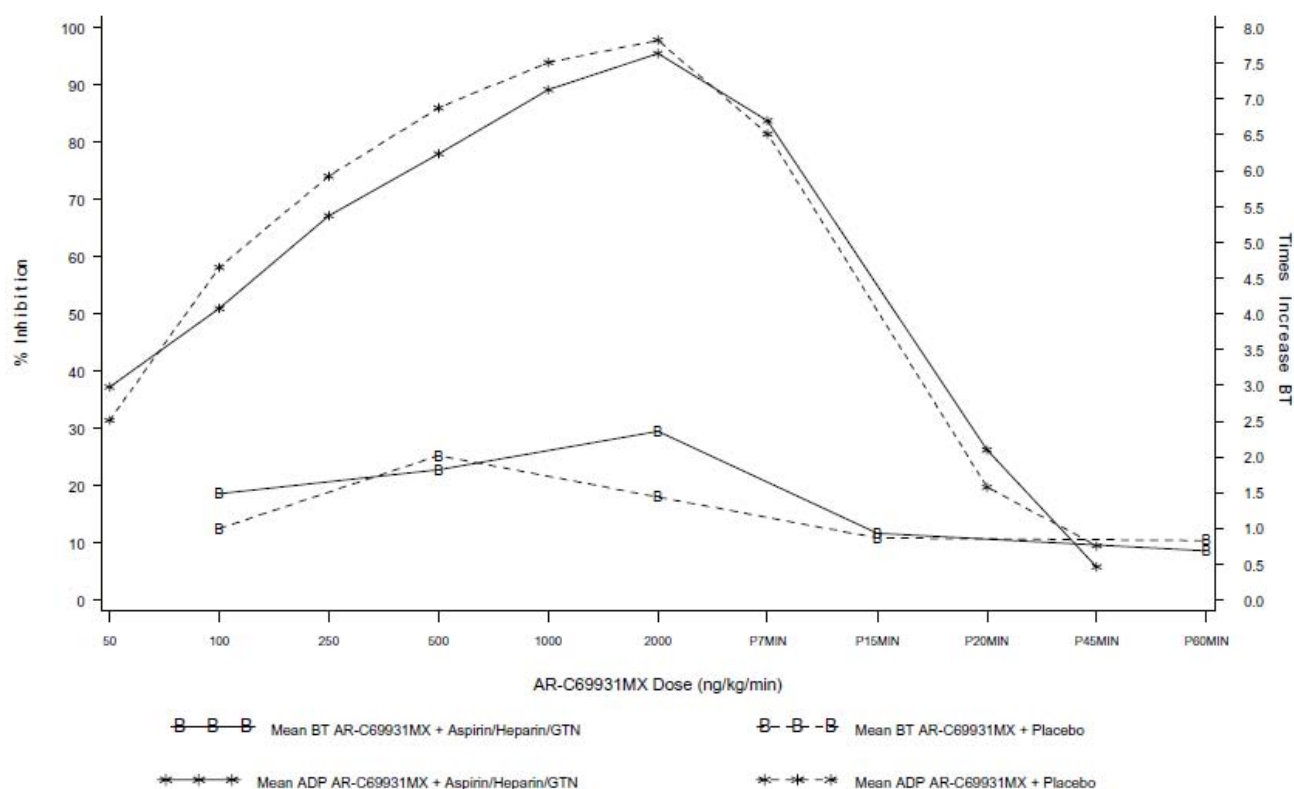


Source: Study SC-931-5036, Figure F9.

Similar assessments were made in the double-blind, placebo-controlled, two-way-crossover, incremental-dose, step-infusion interaction study conducted in healthy male volunteers receiving cangrelor alone (50, 100, 250, 500, 1000, and 2000 ng/kg/min) and in combination with aspirin, heparin, and GTN [SC-931-5037]. Figure 8 illustrates the group mean responses for the percentage inhibition of ADP-induced aggregation ex vivo measured after 15 minutes of infusion at each dose level, and at 7, 20, and 45 minutes after the end of infusion with the highest dose. Figure 7 also displays the increase in the ratio of BT following infusion with cangrelor compared with the baseline BT, and its restoration at 15 and 60 minutes after infusion. The linear portion of the infusion rate-inhibition response curve is similar to that observed for the male and female step-plateau studies (Figure 6 and Figure 7, respectively). Therefore, the percentage inhibition of ADP-induced aggregation does not appear to be influenced by the presence of aspirin, heparin, and GTN. The rapid restoration of normal platelet responsiveness was also unaffected by the presence of aspirin, heparin, and GTN, and was essentially complete 20 minutes after stopping infusion with the top dose of cangrelor. This further demonstrates that the mean ratio increase in BT was unaltered by aspirin, heparin, and GTN, and was no more than 2.4-fold at the highest

infusion rate; and that this had returned to normal values approximately 15 minutes after infusion. Therefore, aspirin, heparin, and GTN have no effect on the actions of cangrelor.

Figure 8: Percent inhibition of ADP-induced platelet aggregation and effect on bleeding time (SC-931-5037)



931= AR-C69931XX; A/H/N = aspirin/heparin/nitroglycerin.

Source: Study SC-931-5037, Figure F26.

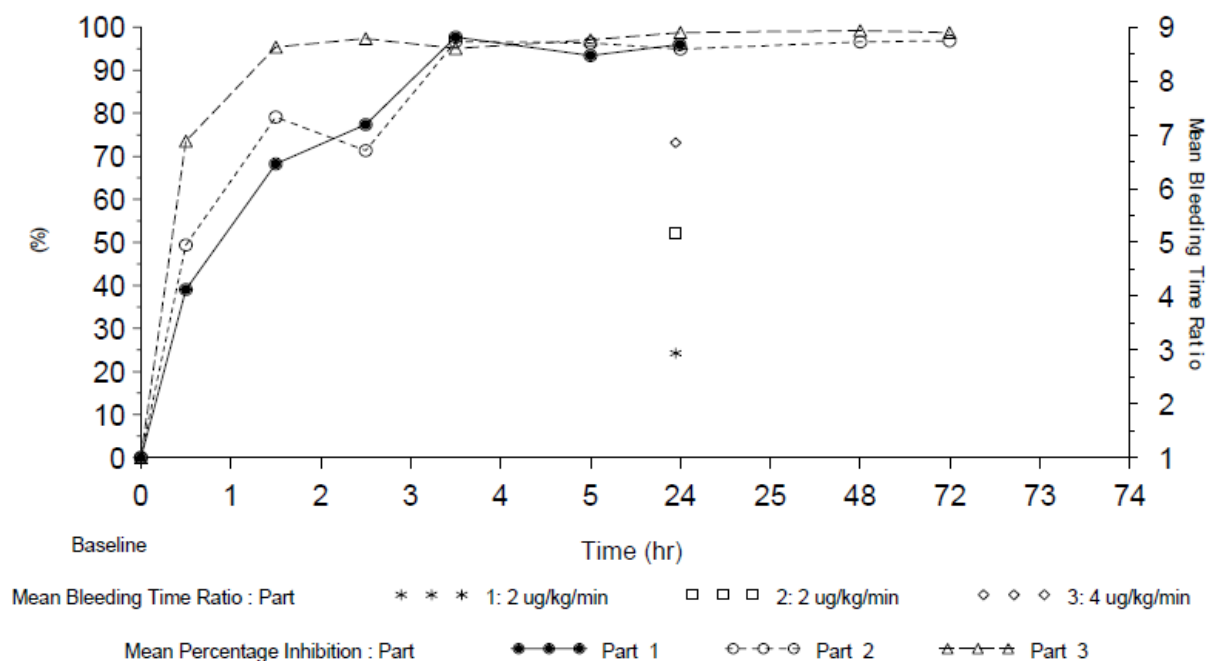
5.2.6.2. Dose Escalation Study in UA/Non-Q-MI Patients

In the dose-escalation study SC-931-5058, cangrelor was given as adjunctive therapy to aspirin, heparin, and GTN to subjects with UA/non-Q-MI. In this 3-part study, cangrelor was administered intravenously as a stepped dose titration followed by a plateau infusion phase at the top dose (Part 1, 0.05 to 2 µg/kg/min for 24 hours; Part 2, 0.05 to 2 µg/kg/min for 72 hours; and Part 3, 0.2 to 4 µg/kg/min for 72 hours). Cangrelor produced potent inhibition of ADP-induced platelet aggregation ex vivo (IC_{50} 7.72 ± 1.95 ng/mL). Mean percentage inhibition exceeded 95% by 3.5 hours after the start of the infusion, and the inhibition remained above 90% for the duration of the infusion in all parts of the study (Figure 9).

Seven of the 11 (64%) subjects in Part 1, 10 of the 13 (77%) patients in Part 2, and 12 of the 14 (86%) patients in Part 3 attained 100% inhibition of platelet aggregation at some time during the study infusion. Patients in Parts 1, 2, and 3 attained a mean inhibition of platelet aggregation of

96.0%, 96.8%, and 99.2%, respectively, during plateau. For most patients, the inhibition was rapidly reversible and the platelet aggregation response was restored by 60% within 1 hour of stopping the infusion.

Figure 9: Inhibition of ADP-induced platelet aggregation and mean bleeding time (SC-931-5058)



Note: Only values for timepoints where patient was on study infusion will be calculated.

Source: Study SC-931-5058, Figure 14.2.

Descriptive statistics of mean BT for Parts 1, 2, and 3 are depicted in Table 14. There was considerable variability in the BT measurements, with a minimum of 0.0 seconds and a maximum of 1800.0 seconds. Aggregation inhibition data are presented in Table 15.

Table 14: Summary of bleeding times (Study SC-931-5058)

Part	Dose ($\mu\text{g/kg/min}$)	Scheduled Timepoint (h:min)	Mean Bleeding Time (seconds)					
			N	Mean	SD	Median	Minimum	Maximum
1	Before Treatment	—	12	185.4	86.30	150.0	85.0	370.0
	2	23:00	11	567.6	505.03	265.0	87.0	1414.0
2	Before Treatment	—	13	157.2	104.38	120.0	0.0	395.0
	2	23:00	13	841.2	581.77	600.0	238.0	1800.0
3	Before Treatment	—	14	185.8	116.38	166.5	30.0	440.0
	4	23:00	13	961.5	664.91	865.0	0.0	1800.0

SD = standard deviation.

Source: Table 14.12 in Clinical Study Report SC-931-5058.

Table 15: Summary of mean platelet aggregation inhibition data (Study SC-931-5058)

Part	Mean % Inhibition of Aggregation at 24 Hours	% Subjects with 100% Inhibition of Aggregation during Infusion
1	96.0	64
2	94.9	77
3	98.7	86

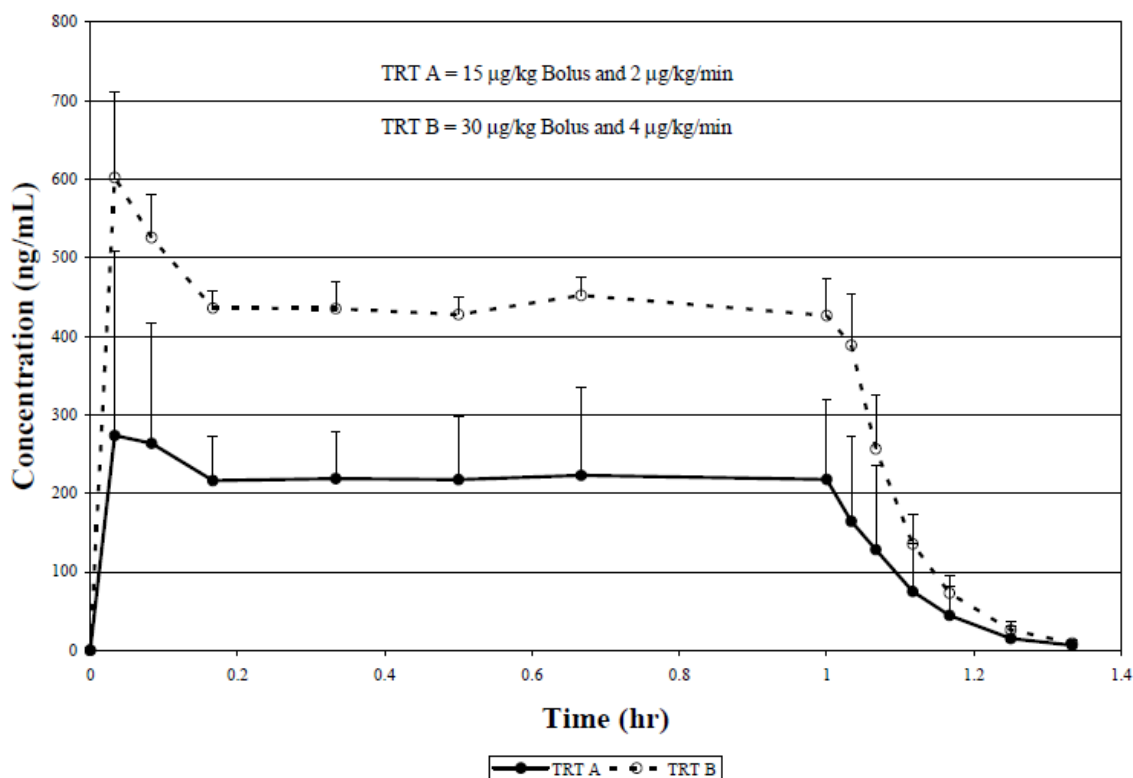
Source: Table 14.16 and Table 14.17 in Clinical Study Report SC-931-5058.

5.2.6.3. Bolus Plus Infusion Study in Healthy Volunteers

Study [TMC-CAN-04-02](#) was conducted to evaluate the PK and PD parameters of a bolus plus infusion dosing regimen of cangrelor in healthy volunteers. Two cohorts of subjects also received clopidogrel to determine the effects of concomitant therapy. Forty-two subjects were treated (12 in Group A, 10 each in Groups B through D). Groups A and B received cangrelor only (Group A, 15 µg/kg bolus + 2 µg/kg/min infusion; Group B, 30 µg/kg bolus + 4 µg/kg/min infusion). Group C received a 30 µg/kg bolus + 4 µg/kg/min infusion of cangrelor immediately followed by clopidogrel 600 mg administered orally. Group D received a single dose of clopidogrel 600 mg administered orally. Following a 2 week washout, these subjects received a second 600 mg oral dose of clopidogrel followed by a 30 µg/kg bolus + 4 µg/kg/min infusion of cangrelor. On cessation of the infusion, the Group D subjects received clopidogrel 600 mg administered orally. Groups A, B, and C received 1 hour dosing with cangrelor; Group D was administered cangrelor infusion for 2 hours.

Cangrelor plasma concentration reached steady state at 10 minutes (see [Figure 10](#)). Steady state was maintained for the duration of the infusion and dropped off rapidly when the infusion was discontinued. The PK profile was found to be linear and dose proportional. The PK data from this study were consistent with data from prior studies.

Figure 10: Plasma cangrelor concentration over time in Groups A and B (Study TMC-CAN-04-02)



TRT = treatment group

Group A: Cangrelor 15 µg/kg IV bolus + 2 µg/kg/min x 1 hour

Group B: Cangrelor 30 µg/kg IV bolus + 4 µg/kg/min x 1 hour

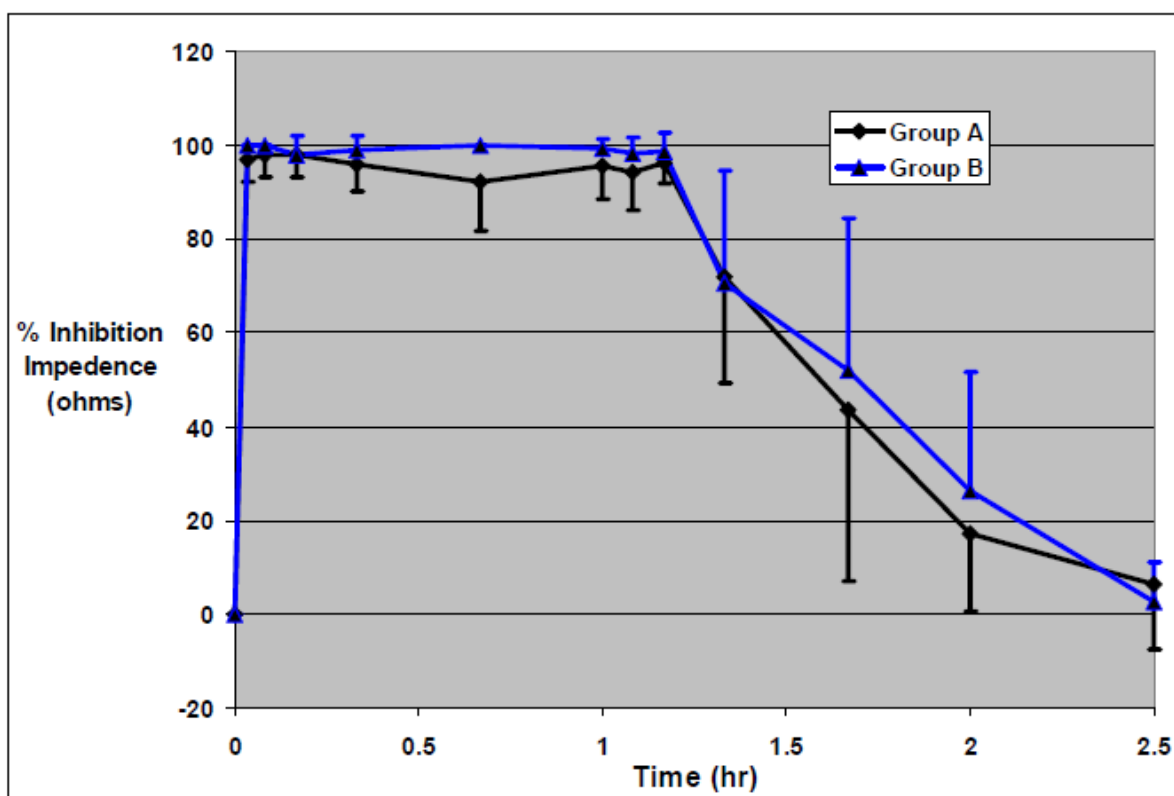
Data presented are mean ± standard deviation plasma cangrelor concentration versus nominal time

SourceStudy TMC-CAN-04-02, Figure 3.

Consistent and complete ADP-induced inhibition of aggregation, as measured by whole blood impedance aggregometry, was achieved immediately after bolus administration (see [Figure 11](#)). The degree of inhibition was maintained throughout the infusion. Full recovery of platelet function was realized approximately 60 minutes after infusion cessation.

Furthermore, clopidogrel administration at the termination of the cangrelor infusion led to the expected degree of platelet inhibition for clopidogrel as measured by whole blood impedance aggregometry.

Figure 11: Percent inhibition of platelet aggregation over time by WBIA (Groups A and B)
(Study TMC-CAN-04-02)



WBIA = whole blood electrical impedance aggregometry

Group A: Cangrelor 15 µg/kg IV bolus + 2 µg/kg/min x 1 hour

Group B: Cangrelor 30 µg/kg IV bolus + 4 µg/kg/min x 1 hour

Data presented are mean ± standard deviation.

Source: Study TMC-CAN-04-02, Figure 4.

5.2.6.4. Platelet Aggregometry and Bleeding Time

The correlation between platelet aggregometry and bleeding time was assessed in studies [SC-931-5129 Part 1](#) and [SC-931-5129 Part 2](#). In the cangrelor treatment groups in study [SC-931-5129 Part 1](#), 52% of the patients achieved 100% platelet inhibition at some point during the study, which was significantly more than placebo. A correlation was not observed between platelet inhibition and change in bleeding time in this study. In study [SC-931-5129 Part 2](#), the correlation was not applicable, as the entire cangrelor treatment group reached 100% platelet inhibition.

In study [SC-931-5135](#), the mean platelet inhibition measurements were: 69.7%, 98.4%, 100%, and 100% for the 35 + Reduced, 140 + Reduced, 280 + Reduced, and 280 Alone groups, respectively, at 1 hour after the start of AR-C69931XX infusion. While all patients in the latter three treatment groups attained 100% platelet inhibition at some point during the study, only 43% of patients in the 35+ Reduced treatment group had 100% inhibition.

5.2.6.5. Transition From Cangrelor to Clopidogrel

Study [TMC-CAN-05-02](#) (CHAMPION PCI) was a Phase III study assessing cangrelor in patients with coronary atherosclerosis who required PCI. A substudy, TMC-CAN-05-02-S1 was conducted at 15 sites to confirm that a cangrelor infusion administered prior to 600 mg clopidogrel did not have an effect on clopidogrel's platelet inhibition. Patients in the substudy were required to be clopidogrel-naïve and could not have received GP IIb/IIIa inhibition during the procedure. Platelet function parameters were measured using the VerifyNow P2Y₁₂ Assay (Accumetrics, San Diego, CA), light transmission aggregometry and vasodilator-stimulated phosphoprotein phosphorylation index (VASP PRI) [[Harrington et al. 2009](#)].

The primary endpoint, which determined if cangrelor interfered with clopidogrel treatment, was the percentage of patients in each treatment group who achieved <20% change in P2Y₁₂ reaction units (PRU) from pre-clopidogrel levels approximately 10 hours after PCI ("non-responder"), as determined by the VerifyNow P2Y₁₂ assay. If 10 hour data were not available, data was collected the morning after PCI or at discharge (whichever was sooner). The original sample size was planned for 150 patients in each arm. This provided a power of 83% to exclude 15% or more absolute increase in the non-responder rate; however, only 167 patients of the 234 enrolled were evaluable. The number of patients with <20% change in PRU from baseline was 38.1% (32 of 84 patients) in the cangrelor arm and 25.3% (21 of 83 patients) in the clopidogrel arm, with an absolute increase of 12.79% (95% confidence interval -1.18, 26.77). This result indicates that prior administration of cangrelor had no interference with clopidogrel's effect and patients were adequately transitioned from IV to oral therapy.

5.2.6.6. Platelet Function During Infusion

The platelet substudy TMC-CAN-05-02-S1 also evaluated platelet function during cangrelor infusion. The results regarding procedural platelet inhibition, which compared cangrelor's platelet inhibition during infusion versus the comparator arm are provided in Table 16. By all measures cangrelor demonstrated a high degree of platelet inhibition, which was significantly different from that comparator arm.

Table 16: Comparison of platelet function tests for cangrelor and clopidogrel-treated patients within 2 hours of PCI (during cangrelor infusion in the cangrelor arm) in Study TMC-CAN-05-02-S1)

	Cangrelor median, (1Q,3Q)	Clopidogrel median, (1Q,3Q)	P-value
VerifyNow™ PRU, n=140	93.5 (37.0,175.0)	277.0 (206.0,355.0)	<0.0001
VerifyNow™ % inhibition , n=141	71.2 % (49.6,87.1)	9.9 % (2.5,27.5)	<0.0001
Aggregometry, n=30 (final response to 20 µM ADP)	20.0 % (7.5,29.5)	67.5 % (62.0,76.0)	<0.0001

	Cangrelor median, (1Q,3Q)	Clopidogrel median, (1Q,3Q)	P-value
Aggregometry, n=30 (final response to 5 μ M ADP)	2.5% (0.0,10.5)	49% (37.0,69.0)	<0.0001
VASP-P PRI	52.5% (32.7,61.1)	84.2% (81.7,86.9)	<0.0001

ADP = adenosine diphosphate; PRI = platelet reactivity index; PRU = P2Y₁₂ reaction unit; VASP-P = vasodilator-sustained phosphoprotein phosphorylation.

5.3. Clinical Efficacy

5.3.1. Efficacy Results of Phase II Clinical Studies

Efficacy in Phase II clinical studies was assessed by determining patient outcomes.

In study [SC-931-5060](#), efficacy outcomes measured were MI, percutaneous transluminal coronary angioplasty (PTCA), coronary artery bypass graft surgery (CABG) or re-admission to the hospital due to a further episode of UA or non-Q-wave MI at the 30-day follow-up. In the cangrelor treatment arm (45 patients) there was 1 death, 2 MI, 10 PTCA, 6 CABG, and 8 “other” events. In the placebo arm (46 patients), there were no deaths, 1 MI, 6 PTCA, 9 CABG, and 5 “other” events.

Studies [SC-931-5129 Part 1](#) and [SC-931-5129 Part 2](#) were safety studies of cangrelor in patients undergoing PTCA, and assessed efficacy as cardiac events, troponin levels, BT assessments and aggregometry assessments. Bleeding time and platelet aggregometry data from these studies are discussed in [Section 5.2.6.4](#). The combined and individual outcomes of death (all cause mortality), MI/re-infarction and repeat coronary intervention (PTCA or CABG) were measured at Days 2 and 7, and at the 30-day post-infusion follow-up. The majority of combined cardiac events occurred within the first 2 days of treatment in both studies. In [SC-931-5129 Part 1](#), which compared cangrelor at 1, 2 and 4 μ g/kg/min (N = 149) with placebo (N = 51), 12% patients in the placebo group and 10%, 17% and 19% of patients in the 1, 2 and 4 μ g/kg/min cangrelor treatment groups, respectively, experienced a combined cardiac event by 30 days post-infusion. However there were no statistically significant differences among the cangrelor groups compared to placebo at 2, 7 or 30 days post-infusion. In study [SC-931-5129 Part 2](#), which compared cangrelor (N = 105) with abciximab (N = 94), 7.6% and 5.3% of patients in the cangrelor and abciximab arms, respectively, had experienced a combined cardiac event. There was 1 death in the cangrelor treatment group and no deaths in the abciximab treatment group at 30 days. MI occurred in four patients in the abciximab arm and six patients in the cangrelor arm, and two patients in the abciximab group and three patients in the cangrelor group required a repeat coronary intervention.

Study [SC-931-5135](#) compared cangrelor alone or in combination with reduced-dose Activase (alteplase) with Activase alone, in patients with STEMI. The study was terminated early after 100 of the planned 180 patients had been randomized, and only 92 patients had been treated (85 in the cangrelor group and 7 in the Activase group). Measurements of ADP-induced platelet

aggregation were made for a subset of patients in this study and are discussed in [Section 5.2.6.4](#). Efficacy was assessed by measurement of Thrombolysis in Myocardial Infarction (TIMI) grade flow, resolution of ST-segment elevation, and the combined endpoint of death, MI, and urgent coronary intervention. The proportion of patients who had TIMI Grade 3 flow following study drug infusion was 50% in the full dose Activase group, 53% to 59% in the cangrelor adjunctive therapy groups, and 18% in the cangrelor monotherapy group. By Day 30, three of the 92 patients had died, four had had another MI, 19 had undergone PTCA, CABG, and/or stent insertion, one had had a stroke, three had ECG changes, and three were rehospitalized. No conclusions regarding the efficacy of cangrelor given as an adjunct to reduced dose Activase or as monotherapy can be made since the study was terminated prematurely.

5.3.2. Efficacy Results of Phase III Clinical Studies

The primary objective of the Phase III clinical studies in the CHAMPION program was to demonstrate that the efficacy of cangrelor is superior to that of clopidogrel in patients requiring PCI as measured by the composite of all-cause mortality, MI, and IDR assessed 48 hours after randomization. This primary objective was not met in either study in the CHAMPION program.

PCI study (TMC-CAN-05-02)

This was a randomized, double-blind, double-dummy, active-controlled, parallel group clinical trial in patients who required PCI, including patients with STEMI. Patients randomized to the cangrelor group received cangrelor (30 µg/kg bolus followed immediately by 4 µg/kg/min infusion) for at least 2 hours or for the duration of the PCI procedure, whichever was longer, followed by 600 mg clopidogrel after the end of the infusion. Patients randomized to the clopidogrel group received a 600 mg loading dose of clopidogrel before the start of the PCI procedure. The primary endpoint of all-cause mortality, MI and IDR in the population that included SA and UA patients, as well as patients with NSTEMI, was observed in 290/3889 (7.5%) patients in the cangrelor group and 276/3865 (7.1%) patients in the clopidogrel group (odds ratio [OR] 1.05, 95% confidence interval [CI] 0.88-1.24, p=0.5929).

Platform study (TMC-CAN-05-03)

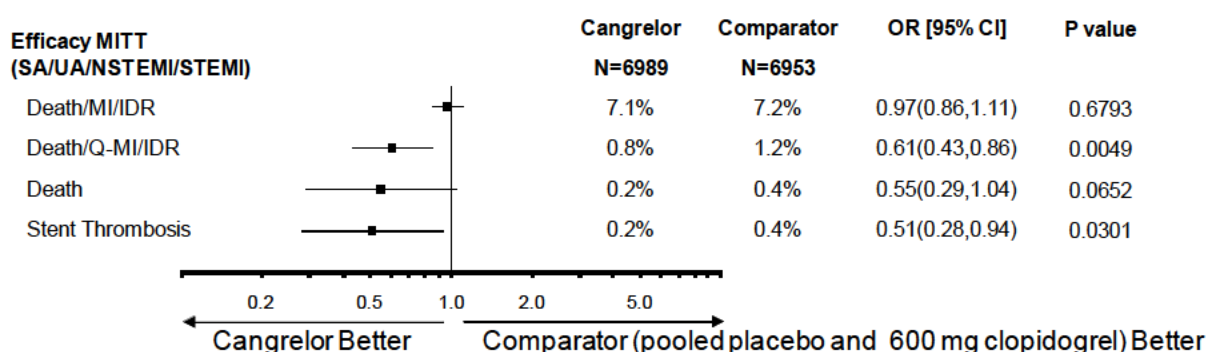
This was a randomized, double-blind, placebo-controlled, parallel group trial in patients with SA, UA, or NSTEMI who required PCI. In contrast to [TMC-CAN-05-02](#), STEMI patients were not enrolled in the Platform study. Patients were randomized to receive either placebo or cangrelor (30 µg/kg bolus followed immediately by 4 µg/kg/min infusion) prior to the procedure. Unlike [TMC-CAN-05-02](#), patients in the control group did not receive a dose of clopidogrel at the start of the PCI procedure; instead, clopidogrel was given at the end of the PCI procedure to both groups. Therefore, the study was designed to demonstrate superiority to usual care (hereafter, this group is referred to as the clopidogrel arm). The primary endpoint of all-cause mortality, MI and IDR was observed in 185/2654 (7.0%) patients randomized to cangrelor and 210/2641 (8.0%) patients randomized to clopidogrel (OR 0.87, 95% CI 0.71-1.07, p = 0.1746).

CHAMPION Pooled Dataset (all patients including STEMI patients)

When data from the two studies were pooled together, the primary endpoint for cangrelor treated patients was observed in 493/6989 (7.1%) and in 503/ 6953 (7.2%) of patients in the clopidogrel arm (OR 0.97, 95% CI 0.86 -1.11). Clinical components of the primary endpoint (death, Q-wave

MI, and IDR) were observed less frequently among patients given cangrelor (53/6989 [0.8%]) than patients in the clopidogrel arm (86/6953 [1.2%]) (OR 0.61, 95% CI 0.43-0.86). Mortality was 15/6989 (0.2%) for cangrelor and 27/6953 (0.4%) (OR 0.55, 95% CI 0.29-1.04) for placebo or clopidogrel. In addition, the incidence of stent thrombosis at 48 hours was lower in the cangrelor arm than in the clopidogrel arm (OR 0.51, 95% CI 0.28-0.94). Results are presented in Figure 12.

Figure 12: Odds ratio plot of primary, secondary and additional endpoints in pooled dataset (all patients including STEMI patients; Studies TMC-CAN-05-02 and TMC-CAN-05-03)



CI = confidence interval; IDR = ischemia-driven revascularization MI = myocardial infarction; OR = odds ratio; Q-MI = q-wave myocardial infarction.

5.4. Safety

5.4.1. Serious Adverse Events/Serious Adverse Reactions

5.4.1.1. Serious Adverse Events

Overall, cangrelor was well-tolerated in the clinical studies. The occurrence of SAEs in the cangrelor treatment groups was proportionately similar to that in the comparator groups in all phases of research.

No SAEs were reported in the healthy volunteer studies.

In the Phase II studies, a total of 84 of 621 patients experienced at least one SAE; 29 of 423 patients treated with cangrelor experienced SAEs which were considered possibly or probably related to cangrelor. The most common related SAEs were anemia, bleeding post vessel puncture, and gastrointestinal (GI) hemorrhage.

In the Phase III program there were no clinically relevant differences between the cangrelor and clopidogrel treatment groups with respect to the incidence of SAEs, as categorised by system organ class (SOC).

In [TMC-CAN-05-02](#) (CHAMPION PCI) the incidence of SAEs was 2.9% in both the cangrelor and clopidogrel groups. The most frequently reported SAEs in this study (>0.2% of patients in either treatment arm) were ventricular fibrillation (0.3% cangrelor versus 0.1% clopidogrel) and acute renal failure (0.3% versus 0.1%).

In [TMC-CAN-05-03](#) (CHAMPION Platform) the incidence of SAEs was 1.8% in patients receiving cangrelor, and 2.1% in patients who received usual care prior to PCI. The most frequently reported SAE (>0.2% of patients in either treatment arm) was cardiogenic shock (0.2% cangrelor versus 0.4% clopidogrel). SAEs in the Cardiac disorders SOC were reported for 23 and 30 patients in the cangrelor and clopidogrel arms, respectively, and SAEs in the Respiratory, thoracic, and mediastinal SOC were reported for 7 and 6 patients in the cangrelor and clopidogrel arms, respectively. Treatment-emergent SAEs that had occurred before the administration of clopidogrel were similar between the cangrelor and placebo groups in this study and are provided in Appendix 3 ([Table A3-4](#)).

5.4.1.2. Serious Adverse Reactions

The most common serious adverse reactions reported for the Phase II and III clinical program were (Preferred Term, [Frequency]): Anaemia (19), Chest pain (4), Embolism (4), Gastrointestinal haemorrhage (3) and Hypotension (3).

A summary of all serious adverse reactions reported the Phase II and III program is provided in Appendix 1 ([Table A1-1](#)).

5.4.1.3. Deaths

There were no deaths in the Phase I program, and six deaths in Phase II program (1%; N = 621). Of the six deaths, two were considered likely related to cangrelor [[SC-931-5135](#), multi-organ failure; [SC-931-5060](#), papillary muscle rupture].

In the Phase III study [TMC-CAN-05-02](#) (CHAMPION PCI), nine patients (0.2%) in each treatment arm died within the first 48 hours after randomization. None of the AEs leading to death was reported for more than two patients in any treatment arm.

Forty patients (0.9%) of the cangrelor arm and 41 patients (0.9%) of the clopidogrel arm died within 30 days after randomization. Most commonly reported AEs leading to death (>2 patients in either treatment arm) were cardiogenic shock, death, cardiac arrest, and MI.

During the 1-year period of the study, registered until 30 day database lock on completion of the last included patient, 104 patients (2.4%) in the cangrelor arm and 119 patients (2.7%) in the clopidogrel arm had died. Most frequently associated AEs (>0.2% of patients in either treatment arm) were death, MI, and cardiac arrest. A complete listing of AEs in patients who died, by SOC, is provided in Appendix 3 ([Table A3-1](#)).

In the Phase III study [TMC-CAN-05-03](#) (CHAMPION PLATFORM), 7 patients in the cangrelor treatment group died within the first 48 hours, compared with 18 patients in the clopidogrel treatment group. The most common AE resulting in death was cardiogenic shock (3 patients [0.1%] in the cangrelor group and 10 deaths [0.4%] in the clopidogrel group).

Within the first 30 days, 35 (1.3%) and 40 (1.7%) patients died in the cangrelor and clopidogrel groups, respectively. The most common AEs resulting in death in the cangrelor group were

cardiac failure (5 [0.2%]), cardiogenic shock (4 [0.2%]), and death (5 [0.2%]). In the clopidogrel treatment group, the most common AEs resulting in death were cardiogenic shock (12 [0.5%]), cardiac arrest (4 [0.2%]), and death (4 [0.2%]).

During the entire 1-year period of study, registered until 30 day database lock on completion of the last included patient, 70 (2.6%) and 79 (3.0%) patients died in the cangrelor and clopidogrel treatment arms, respectively. The only AEs resulting in death in >0.2% were cardiac failure death in the cangrelor treatment group, and cardiogenic shock and death in the clopidogrel treatment group. A complete listing of AEs in patients who died, by SOC, is provided in Appendix 3 ([Table A3-2](#)).

5.4.1.4. Withdrawals From Treatment Associated With Adverse Events

Four subjects were withdrawn from the Phase I studies due to AEs judged to be related to cangrelor. One subject was withdrawn after experiencing abnormal uterine cytology ([SC-931-5037](#)), one subject was withdrawn after losing consciousness and hyperventilating ([SC-931-5109](#)), and two subjects were withdrawn due to hypotension ([TMC-CAN-04-02](#)).

Overall, in the Phase II program, there were 44 withdrawals associated with adverse events. Twenty-one of these withdrawals were considered possibly or probably related to treatment with cangrelor. The most common treatment-associated withdrawals potentially related to cangrelor were: minor (nuisance) bleed, thrombosis coronary, and bleeding post-vessel puncture.

In the Phase III study [TMC-CAN-05-02](#) (CHAMPION PCI), 23 patients (0.5%) in the cangrelor arm and 21 patients (0.5%) in the clopidogrel arm discontinued the study due to an AE. The only AE leading to discontinuation reported for >0.1% of patients in either treatment arm was coronary artery perforation.

In the Phase III study [TMC-CAN-05-03](#) (CHAMPION Platform), 21 patients (0.8%) in the cangrelor arm discontinued the study due to an AE compared to 10 (0.4%) in the placebo arm.

5.4.2. Adverse Events/Adverse Reactions

5.4.2.1. Adverse Events Reported in Phase I Studies

In general, cangrelor was considered safe and well tolerated in the Phase I studies. The most commonly reported AEs of clinical significance were petechiae and purpura. These were usually located at the ECG chest suction electrode positions, injection sites, under the blood pressure cuff, and access sites [[SC-031-5014](#); [SC-931-5036](#); [SC-931-5037](#); [TMC-CAN-04-02](#); [TMC-CAN-08-02](#)].

Nervous system AEs were also commonly reported, primarily headache and dizziness [[SC-931-5037](#); [SC-931-5109](#); [TMC-CAN-08-01](#)]; however, headache is a frequently-observed AE in studies of this type and, in study [SC-931-5037](#), could be attributed to GTN infusion.

In study [SC-931-9017](#), one subject experienced mild asymptomatic nonspecific T-wave changes on several ECGs that were considered not to be related to study medication. A resting ECG and exercise tolerance test were found to be normal for this subject.

One subject hyperventilated in study [SC-931-5109](#), which was potentially clinically significant as another patient withdrew from this study due to hyperventilation and loss of consciousness.

5.4.2.2. Adverse Events Reported in Phase II Studies

In the dose-escalation study in UA/non-Q-MI patients [SC-931-5058], the most frequently reported AEs during treatment were injection site reaction, increased ALT levels, and purpura, reported exclusively by patients in Parts 2 and 3 of the study. Injection site reaction (preferred term) was recorded as phlebitis/cellulitis at the cannula site (2 patients) or slight bleeding at an injection site (8 patients). Purpura (preferred term) was recorded as hematomas (3 patients) or small petechia (2 patients). Events of this type are expected because of the mode of action of cangrelor. Additional AEs were reported during the follow-up period (7 days after infusion). The most commonly reported were elevated AST and ALT, reported in 7/39 (18%) and 8/39 (21%) of patients, respectively.

In the placebo-controlled study conducted in UA/non-Q-MI patients [SC-931-5060], 80% of patients in both the cangrelor and placebo treatment arms experienced at least 1 AE.

In both study SC-931-5129 Part 1 and study SC-931-5129 Part 2, the most commonly reported AEs during infusion were purpura and bleeding post vessel puncture. The safety profile of cangrelor 4 µg/kg/min compared favorably with that of abciximab in patients undergoing PTCA.

In study SC-931-5135 in patients with STEMI, platelet, bleeding, and clotting disorders were the most common AEs reported during the infusion and follow-up periods in all treatment groups. The overall incidence of AEs throughout the study (during infusion and up through Day 7 or discharge, whichever came first) was comparable in the cangrelor groups and the control group.

Presented below (Table 17) is a summary of AEs reported in studies SC-931-5058, SC-931-5060, SC-931-5109, SC-931-5129 Part 1, SC-931-5129 Part 2, and SC-931-5135. The occurrence of AEs, by body system, is reported for patients receiving cangrelor, placebo, abciximab or Activase (alteplase). The data presented below were re-coded from the original AstraZeneca COSTART terminology to MedDRA Version 7.1 terminology.

Table 17: Summary of most frequently reported (≥ 5%) adverse events by body system in early development studies

Adverse Event (AE)	Cangrelor N=448 n (%)	Placebo N=97 n (%)	Abciximab N=94 n (%)	Activase N=7 n (%)
Patients with at Least 1 AE	413 (92.2)	90 (92.8)	87 (92.6)	7 (100.0)
Vascular disorders	276 (61.6)	39 (40.2)	59 (62.8)	5 (71.4)
General disorders and administration site conditions	183 (40.8)	28 (28.9)	30 (31.9)	6 (85.7)
Cardiac disorders	131 (29.2)	36 (37.1)	19 (20.2)	5 (71.4)
Investigations	130 (29.0)	34 (35.1)	25 (26.6)	2 (28.6)
Musculoskeletal and connective tissue disorders	120 (26.8)	20 (20.6)	29 (30.9)	5 (71.4)
Surgical and medical procedures	114 (25.4)	16 (16.5)	24 (25.5)	0 (0.0)
Gastrointestinal disorders	113 (23.2)	9 (9.3)	15 (16.0)	2 (28.6)

Adverse Event (AE)	Cangrelor N=448 n (%)	Placebo N=97 n (%)	Abciximab N=94 n (%)	Activase N=7 n (%)
Nervous system disorders	58 (12.9)	11 (11.3)	11 (11.7)	1 (14.3)
Psychiatric disorders	59 (13.2)	7 (7.2)	9 (9.6)	3 (42.9)
Respiratory, thoracic, and mediastinal disorders	60 (13.4)	5 (5.2)	5 (5.3)	4 (57.1)
Renal and urinary disorders	49 (10.9)	5 (5.2)	5 (5.3)	3 (42.9)
Injury, poisoning, and procedural complications	36 (8.0)	5 (5.2)	8 (8.5)	1 (14.3)
Metabolism and nutrition disorders	30 (6.7)	4 (4.1)	6 (6.4)	3 (42.9)
Gastrointestinal signs and symptoms	26 (5.8)	3 (3.1)	3 (3.2)	0 (0.0)

AE = adverse event.

5.4.2.3. Adverse Events Reported in Phase III Studies

In the CHAMPION studies [TMC-CAN-05-02](#) and [TMC-CAN-05-03](#), the incidence of AEs was similar between patients in the cangrelor group and patients in the clopidogrel group. At least one AE was reported for 1808/7036 (25.7 %) patients in the combined cangrelor arm and 1714/7015 (24.4%) patients in the clopidogrel/placebo arm.

The incidences for any type of AE in study [TMC-CAN-05-02](#) (CHAMPION PCI) were similar between treatment arms, as shown in [Appendix 3, Table A3-3](#). In the cangrelor arm, 1175 patients (26.9%) reported at least one AE compared to 1136 patients (26.0%) in the clopidogrel arm. The incidences for any type of AE in study [TMC-CAN-05-03](#) (CHAMPION Platform) are shown in [Appendix 3, Table A3-3](#). In the cangrelor arm, 633 patients (23.8%) reported at least one AE compared to 578 patients (21.8%) in the clopidogrel arm.

In [TMC-CAN-05-03](#) (CHAMPION Platform), treatment-emergent AEs occurring before administration of clopidogrel were reported and were slightly less frequent in the cangrelor arm than in the placebo arm (2.9% vs 3.4%). A summary of AEs reported during this time period is provided in Appendix 3 ([Table A3-5](#)).

[Table 18](#) summarizes the most common AEs in the pooled CHAMPION studies. The most frequently reported AEs were back pain, chest pain, nausea and headache, which were similar between both treatment groups. Dyspnea was reported for 1.1% of patients treated with cangrelor compared to 0.4% of patients in the clopidogrel group in study [TMC-CAN-05-02](#) ($p \leq 0.0001$), and 0.6% of patients in the clopidogrel group in [TMC-CAN-05-03](#). Dyspnea was reported as serious in one patient given cangrelor and one patient given comparator treatment. Other AEs occurred with similar frequency and severity among treatment groups. All other cases were mild or moderate and all were spontaneously reversible. [Table A3-3 in Appendix 3](#) summarizes all AEs reported for more than 0.2% of patients in the pooled CHAMPION studies.

There were no clinically important differences in laboratory parameters between treatment groups.

Table 18: Summary of most common (>0.9% in cangrelor arm) adverse events by Preferred Term in pooled Studies TMC-CAN-05-02 (CHAMPION PCI) and TMC-CAN-05-03 (CHAMPION Platform)

Preferred Term	Cangrelor N=7036 n/N (%)	Clopidogrel in PCI N=4365 n/N (%)	Clopidogrel in PF N=2650 n/N (%)
Back pain	258 (3.7)	164 (3.8)	85 (3.2)
Chest pain	251 (3.6)	163 (3.7)	69 (2.6)
Nausea	183 (2.6)	145 (3.3)	66 (2.5)
Headache	153 (2.2)	97 (2.2)	68 (2.6)
Hypotension	140 (2.0)	89 (2.0)	38 (1.4)
Vomiting	107 (1.5)	78 (1.8)	31 (1.2)
Puncture site pain	88 (1.3)	52 (1.2)	29 (1.1)
Pyrexia	81 (1.2)	37 (0.8)	20 (0.8)
Dyspnoea	80 (1.1)	16 (0.4)	15 (0.6)
Hypertension	60 (0.9)	34 (0.8)	22 (0.8)

5.4.2.4. Adverse Reactions Reported in Phase III Studies

There were 228 total non-serious adverse reactions reported in the Phase III studies ([TMC-CAN-05-02](#) and [TMC-CAN-05-03](#)). The most common of these were (Preferred Term [Frequency]): nausea (24), vomiting (18), chest pain (14), hypotension (13), and dyspnoea (9). A summary of all non-serious adverse reactions reported in the Phase III studies is provided in Appendix 1 ([Table A1-2](#)).

5.4.3. Bleeding events

5.4.3.1. Bleeding Events Reported in Phase II Studies

The majority of bleeding events reported in Phase II studies were minor bleeds associated with use of the study drug. In study [SC-931-5058](#), 29 patients overall experienced a bleeding event, but the majority of these were injection site reactions. Red blood cells were found in the urine cytology of 11 patients; however, only 5 of these were recorded as AEs (haematuria). Fourteen patients were also positive for trace blood in urine.

In study [SC-931-5060](#), there were no major bleeding events, but there were more episodes of bleeding in the cangrelor treatment arm than in the placebo arm (33 and 16 events, respectively). Bleeding events were reported for 17/45 (38%) of patients in the cangrelor arm and 12/46 (26%) patients in the placebo arm. The most frequently reported bleeding events (reported by >5% of patients in either treatment group) during treatment were anaemia, purpura, bleeding post-vessel puncture, epistaxis and haematuria.

Studies [SC-931-5129 Part 1](#), [SC-931-5129 Part 2](#) and [SC-931-5135](#) analyzed bleeding events by TIMI criteria. Aggregately in these three studies, only 85 of 372 total events were categorized as

major bleeds; however, 78 of those events occurred in patients receiving cangrelor. Most of the major bleeds occurred in study [SC-931-5135](#), in which major bleeds were reported in 18% of patients. Across these three studies, the majority of bleeding events were categorized as “other bleeding.”

5.4.3.2. Bleeding Events Reported in Phase III Studies

In the pooled CHAMPION studies, the overall incidence of bleeding events (non-CABG related) in the peri-procedural setting was similar between patients treated with cangrelor and patients treated with either placebo or clopidogrel.

These studies found that major bleeding defined by the TIMI scale at 48 hours post-randomization was not increased among patients treated with cangrelor (23/7036 [0.3%]) compared to 600 mg of clopidogrel (23/7015 [0.3%]) ([Table A2-1](#)) (OR 1.0, 95% CI 0.56-1.78). Severe bleeding defined by the GUSTO scale was also similar between groups.

Major bleeding defined by the ACUITY scale at 48 hours post-randomization was higher among cangrelor-treated patients (296/7036 [4.2%]) than among patients treated with comparators (211/7015 [3.0%]) (OR 1.42, 95% CI 1.18-1.70), and was primarily attributed to hematomas >5 cm. These data are presented in Appendix 2 ([Tables A2-3](#) and [A2-5](#)). There was no difference in requirement for any blood transfusion. All reported bleeding events at 48 hours after randomization for both studies are summarized in Appendix 2 ([Tables A2-2](#), [A2-4](#), and [A2-6](#)).

In CHAMPION Platform ([TMC-CAN-05-03](#)), the time period post-administration of cangrelor and placebo, but before administration of clopidogrel, gives insight into the comparison of cangrelor versus placebo. In the cangrelor group, the bleeding rate for ACUITY-definition was numerically higher, and was primarily driven by ACUITY-major bleeding. Alternately, following the GUSTO-definition it was driven by mild bleeding, and under TIMI-definition it was driven by minor bleeding. These results are provided in Appendix 2 ([Table A2-7](#)).

5.4.4. Clinically Significant Parameters in Clinical Studies

5.4.4.1. Phase I and Phase II Clinical Studies

In the nonclinical studies with cangrelor, changes in hematology, clinical chemistry, urinalysis, and vital signs were observed. Because of these findings, these parameters were measured during the clinical trials.

Hematology: There were no clinically significant findings in either the Phase I or Phase II studies regarding hematology.

Clinical Chemistry: In two Phase II studies [[SC-931-5058](#) and [SC-931-5060](#)], increases in AST and ALT were observed. In addition, in study [SC-931-5058](#), 12 patients developed clinically-relevant abnormal clinical chemistry values, and 1 patient developed clinically relevant abnormal cardiac enzyme values.

Urinalysis: In the Phase I studies [SC-931-5036](#) and [SC-931-5037](#), positive results for urinalysis, urine cytology, sodium dodecylsulphate polyacrylamide gel electrophoresis (SDS-PAGE), and hematuria were observed. Thus urinary monitoring in the Phase I trials revealed natural

background variability in the quantity and type of cells excreted, and in SDS-PAGE, particularly in women. However no consistent or drug-related trends were observed.

A pilot study ([SC-931-5092](#)) was conducted in 25 subjects (age 44 to 80 years) with UA and/or non-Q-wave MI, to assess the incidence and range of coincidental fluctuations or abnormal findings in the array of tests to be used for monitoring the kidney and urinary tract in a subsequent study in this patient population ([SC-931-5058](#)). There was no study drug given in this pilot study. The study was intended to identify background variability in patients with UA and/or non-Q-wave MI. A high frequency of background abnormalities was observed in this population and all but one subject had at least one Class 1 abnormality in their urine cytology (epithelial cells, occasional polymorphs, and erythrocytes), two subjects had Class 2 abnormalities (inflammation/degeneration), and one subject had a Class 3 abnormality (atypia). In total, 10/25 subjects (40%) experienced a total of 17 bleeding events (bleeds as AEs, traces of blood in the dipstick urinalysis, and RBCs seen in urine cytology). Hence, renal/urinary tract safety monitoring in this patient population showed a higher frequency of abnormalities than that observed in the healthy volunteer studies. This would be anticipated for an older population with underlying medical conditions.

In study [SC-931-5058](#) conducted in UA/non-Q-MI patients, six patients developed clinically relevant abnormal urine dipstick data. Eleven patients had urine cytology that was classed as normal throughout the study. However, 72 of all samples were classed as “no significant abnormality” (Class 1). No patients had Class 2 abnormalities and only one patient had a Class 3 abnormality. There were no significant renal changes. SDS-PAGE results showed additional protein bands for 10 patients (26%), of whom 5 patients had additional bands throughout the study, including before treatment.

Vital Signs: In the healthy volunteer studies, repeated measurements of BP, 12-lead ECG, and impedance cardiodynamic monitoring did not reveal any clinically-important dose-related or drug-related effects on the cardiovascular system. The most frequently encountered cardiac abnormalities were premature atrial beats in both active and placebo subjects, and transient T-wave changes in the ECG chest leads, predominantly in subjects receiving active medication. These subjects were otherwise asymptomatic, and the abnormalities were not recognized as ST-segment changes on Holter monitoring in the step-plateau studies [[SC-931-5014](#); [SC-931-5036](#); [SC-931-5037](#)]. There were no clinically-significant changes in BP or pulse rate in the dose-escalation study in UA/non-Q-MI patients [[SC-931-5058](#)], except for one episode of hypotension and one of bradycardia in the dose group receiving a stepped dose titration infusion of cangrelor up to 2 µg/kg/min over 72 hours. Both of these events were recorded as AEs. One patient in this dose group developed an ECG abnormality (biphasic anterior T waves).

5.4.4.2. Phase III studies

For both Phase III studies, hematology and serum chemistry parameters were collected. Similar to the Phase I and II studies, there were no significant hematology findings in either study, and all parameters were similar between the cangrelor and comparator groups. Changes in the serum chemistry, specifically ALT and AST, which had been observed in the Phase II studies, were not observed in the Phase III CHAMPION program. Greater detail is provided in [Table 19](#) through [Table 22](#).

Table 19: Incidence of potentially clinically significant tests in hematology parameters (Study TMC-CAN-05-02 [CHAMPION PCI])

	Cangrelor N=4310 ^a n/N (%)	Clopidogrel N=4307 ^a n/N (%)
Hematocrit ^b ≤0.8 x LLN (%)	288 (6.7)	279 (6.5)
Hemoglobin ^b ≤0.8 x LLN (g/dL)	268 (6.2)	253 (5.9)
Platelets ≥700 (k/μL)	1 (0.0)	3 (0.1)
Platelets ≤75 (k/μL)	10 (0.2)	11 (0.3)
WBC ≥16 (k/μL)	101 (2.3)	96 (2.2)
WBC ≤2.8 (k/μL)	2 (0.0)	4 (0.1)

LLN = lower limit of normal; NSTEMI = non ST segment myocardial infarction; SA = stable angina; STEMI = ST segment myocardial infarction; UA = unstable angina; WBC = white blood cells.

a. Data from safety + SA/UA/NSTEMI/STEMI populations.

b. Adjusted for blood transfusion

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Table 20: Incidence of potentially clinically significant tests in serum chemistry parameters (Study TMC-CAN-05-02 [CHAMPION PCI])

	Cangrelor N=4310 ^a n/N (%)	Clopidogrel N=4307 ^a n/N (%)
ALT/SGPT ≥3 x ULN	46 (1.1)	42 (1.0)
AST/SGOT ≥3 x ULN	385 (8.9)	377 (8.8)
Serum Creatinine ≥2 mg/dL	89 (2.1)	81 (1.9)
Total Bilirubin ≥1.5 x ULN	141 (3.3)	125 (2.9)
Alkaline Phosphatase ≥3 x ULN	5 (0.1)	1 (0.0)

ALT/SGPT = alanine aminotransferase/serum glutamic pyruvic transaminase; AST/SGOT = aspartate aminotransferase/serum glutamic oxaloacetic transaminase; NSTEMI = non ST segment myocardial infarction; SA = stable angina; STEMI = ST segment myocardial infarction; UA = unstable angina; ULN = upper limit of normal.

a. Data from safety + SA/UA/NSTEMI/STEMI populations.

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Table 21: Incidence of potentially clinically significant tests in hematology parameters (Study TMC-CAN-05-03 [CHAMPION Platform])

	Cangrelor N=2639 ^a n/N (%)	Clopidogrel N=2616 ^a n/N (%)
Hematocrit ^b ≤ 0.8 x LLN (%)	167 (6.3)	141 (5.4)
Hemoglobin ^b ≤ 0.8 x LLN (g/dL)	156 (5.9)	130 (5.0)
Platelets ≥ 700 (k/μL)	12 (0.5)	6 (0.2)
Platelets ≤ 75 (k/μL)	3 (0.1)	4 (0.2)
WBC ≥ 16 (k/μL)	78 (3.0)	70 (2.7)
WBC ≤ 2.8 (k/μL)	2 (0.1)	0 (0.0)

LLN = lower limit of normal; NSTEMI = non ST segment myocardial infarction; SA = stable angina; STEMI = ST segment myocardial infarction; UA = unstable angina; WBC = white blood cells.

a. Data from safety + SA/UA/NSTEMI/STEMI populations.

b. Adjusted for blood transfusion

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Table 22: Incidence of potentially clinically significant tests in serum chemistry parameters (Study TMC-CAN-05-03 [CHAMPION Platform])

	Cangrelor N=2639 ^a n/N (%)	Clopidogrel N=2616 ^a n/N (%)
ALT/SGPT ≥ 3 x ULN	29 (1.1)	28 (1.1)
AST/SGOT ≥ 3 x ULN	187 (7.1)	185 (7.1)
Serum Creatinine ≥ 2 mg/dL	72 (2.7)	66 (2.5)
Total Bilirubin ≥ 1.5 x ULN	89 (3.4)	108 (4.1)
Alkaline Phosphatase ≥ 3 x ULN	1 (0.0)	3 (0.1)

ALT/SGPT = alanine aminotransferase/serum glutamic pyruvic transaminase; AST/SGOT = aspartate aminotransferase/serum glutamic oxaloacetic transaminase; NSTEMI = non ST segment myocardial infarction; SA = stable angina; STEMI = ST segment myocardial infarction; UA = unstable angina; ULN = upper limit of normal.

a. Data from safety + SA/UA/NSTEMI populations.

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5.5. Marketing Experience

Not applicable. Cangrelor has not been marketed in any country.

5.6. Conclusions

The results of the Phase I healthy volunteer studies ([SC-931-5014](#), [SC-931-5036](#)) confirm that cangrelor is an ultra-short-acting antagonist of ex vivo ADP-induced platelet aggregation in male and female subjects. Dose-related activity was observed until complete inhibition of ex vivo ADP-induced platelet aggregation was achieved.

Cangrelor was well tolerated at all dose levels. No interaction was observed between cangrelor and concomitant aspirin, heparin, and GTN ([SC-931-5037](#)). The free acid of cangrelor (AR-C69931XX) has a short half-life (5 minutes) and a rapid clearance rate (10 mL/kg/min). The metabolic profile in man is qualitatively similar to that in the rat and dog, with the parent compound being rapidly cleared by dephosphorylation to form the nucleoside metabolite AR-C69712XX. The most abundantly excreted metabolite, the nucleoside sulphoxide AR-C90439XX, is predominantly eliminated in urine in humans, in contrast to animals where this metabolite is predominantly excreted in feces ([SC-931-9017](#)).

In the dose-escalation study [SC-931-5058](#) in UA/non-Q-MI patients, cangrelor inhibited ex vivo ADP-induced platelet aggregation >95% at doses at or above 2 µg/kg/min, and showed a similar PK profile to that seen in healthy volunteers. Cangrelor infusions were well tolerated at doses up to 4 µg/kg/min. The most frequently reported AEs were injection site reactions and increased ALT. The elevations observed in AST and ALT were asymptomatic and did not result in discontinuation of drug in any patients. There were no major bleeding events reported.

In the placebo-controlled study [SC-931-5060](#) in UA/non-Q-MI patients, cangrelor was well tolerated when administered as a continuous infusion for up to 72 hours (4 µg/kg/min). The AE profile was similar for the active and placebo groups. Progressive elevations in AST and ALT were observed, but there was no difference in frequency or degree of elevation between the cangrelor and placebo-treated patients.

From the results of the clinical studies described in this brochure, special hepatic, renal, or urinary monitoring will not be required in subsequent clinical trials.

While the two Phase III studies [[TMC-CAN-05-02](#) and [TMC-CAN-05-03](#)] did not achieve their primary efficacy endpoints and were therefore terminated early, important safety and efficacy data were gained. When compared to clopidogrel, cangrelor was shown to have a similar safety profile in SAEs, AEs, and deaths. There was a small increase in minor bleeding events, but this can be expected given cangrelor's rapid and profound platelet inhibition. In addition, in meaningful clinical endpoints (death, Q-wave MI, and IDR), cangrelor was shown to have a better efficacy outcome than clopidogrel. Given these data and its unique PK profile, further efficacy research with cangrelor is warranted.

6. SUMMARY OF DATA AND GUIDANCE FOR THE INVESTIGATOR

6.1. Summary

Cangrelor is a potent, ultra-short acting and specific inhibitor of ADP-induced platelet aggregation mediated by its antagonism of the P2Y₁₂ receptor. It rapidly and reversibly inhibits

platelet activation and aggregations via the P2Y₁₂ receptor in healthy volunteers and patients undergoing PCI.

Nonclinical safety evaluation studies have not revealed any mutagenic or clastogenic activities of parent drug, its nucleoside, or base metabolites, and there is no evidence from drug metabolism studies that any of these are substrates for adenosine deaminase. Toxicology studies indicate that renal and urinary tract toxicity is the principal potential hazard associated with treatment with cangrelor; however, careful monitoring in humans revealed no drug-related renal or urinary effects. Cangrelor was shown to be neither genotoxic or teratogenic.

Cangrelor has been evaluated in 14 clinical studies, including two Phase III studies. It has been dosed with an IV bolus of both 30 µg/kg and 60 µg/kg, and at infusions ranging from 0.01 µg/kg/min to 4 µg/kg/min. The pharmacology, safety, tolerability, and efficacy of cangrelor were studied in healthy subjects as well as patients with non-Q-MI, NSTEMI, and STEMI.

In the clinical pharmacology studies, the drug produced dose-related inhibition of ex vivo ADP-induced platelet aggregation. It was confirmed to have rapid onset and offset of action and to exhibit dose linearity.

The safety database consists of 7,655 cangrelor-treated subjects/patients. The safety profile of cangrelor was shown to be similar to the active comparator in all phases of clinical research; however, there was an increased frequency of minor bleeding events in the cangrelor groups. Bleeding events were carefully monitored and are presented in [Section 5.4.3](#). More information on risks and AEs is available in [Section 6.5](#).

The primary efficacy endpoint in the Phase III studies was to demonstrate that cangrelor is superior to clopidogrel in patients requiring PCI as measured by the composite of all-cause mortality, MI, and IDR. This endpoint was not met in either study in the CHAMPION program, which resulted in early termination of the two Phase III studies. However, in the clinically meaningful composite endpoint of death, Q-wave-MI, and IDR, cangrelor was shown to have greater efficacy than clopidogrel.

6.2. General Administration

Detailed instructions for preparing and administering cangrelor infusion solutions are provided in individual protocols and/or pharmacy instructions. Infusion solutions are prepared by diluting the appropriate volume of reconstituted Cangrelor for Injection with sodium chloride 0.9% w/v infusion/injection. Cangrelor infusions are compatible with a wide range of administration systems; however to achieve the required control of infusion rate, solutions must be administered by means of a motor-driven pump rather than a gravity-fed system. Infusion solutions are chemically stable for up to 30 hours (including administration time) at room temperature. They do not need to be protected from light after preparation or during administration.

6.2.1. Use in Women

Fertility and embryo-fetal development studies were performed in animals. These give no indication of the need to exclude women of childbearing potential from participating in studies with cangrelor.

6.2.2. Use in Patients With Hepatic and Renal Impairment

Animal toxicology studies revealed a low incidence of renal and upper urinary tract toxicity, and transient elevations in transaminase levels. Extensive safety monitoring in the human volunteer and patient studies has revealed no drug-related renal, urinary tract, or liver toxicities to date.

In man, the metabolite load of cangrelor is primarily excreted in urine. Clinical studies in subjects with compromised renal function, as determined by creatinine clearance, do not indicate a necessity for dose alterations or adjustments in this patient population.

6.2.3. Use in Elderly Patients

The oldest subject in the clinical pharmacology program was 66 years of age. Two 95-year-old patients received cangrelor; one in study [TMC-CAN-05-02](#) (CHAMPION PCI) and one study [TMC-CAN-05-03](#) (CHAMPION Platform). There is no evidence for any alteration in primary metabolic inactivation rate with age.

6.2.4. Use in Children

Not tested.

6.3. Drug Interactions

The potential interaction between cangrelor and standard therapy with aspirin, heparin, and GTN therapy in clinically effective doses was evaluated in study [SC-931-5037](#). Standard triple therapy (aspirin, heparin, GTN) did not alter the dose-response for inhibition of ADP-induced platelet aggregation, extent of BT prolongation or the rapid metabolic clearance of cangrelor. There was also no evidence that the primary effects of any component of standard triple therapy were affected by cangrelor. Thus, the effects of cangrelor will remain rapidly reversible on slowing or stopping the infusion.

No interactions are expected with regularly used cardiovascular, antihypertensive, lipid lowering, antihyperglycemic, or antithrombotic drugs.

6.4. Contraindications and Precautions

6.4.1. Contraindications

Cangrelor is contraindicated in patients with:

- severe bleeding
- hypersensitivity to cangrelor or any of its excipients

6.4.2. Safety Implications of Metabolism and Excretion Data

Humans produce a metabolite array similar to rats and dogs, with the notable difference that in humans the S-oxide of the nucleoside appears predominantly in the urine. Thus, two-thirds of an administered dose of cangrelor is excreted in the urine.

6.5. Possible Risks and Adverse Events Associated With Use of Cangrelor

Cangrelor, an antiplatelet agent being developed for use during PCI and for the management of patients experiencing ACS, may be associated with increased risk of bleeding. Although bleeding with cangrelor may be expected to occur at the site of tissue damage or arterial puncture, bleeding may occur at any site and can result in death. This may be manifested as petechia, hematoma, decreases in hemoglobin or hematocrit, purpura, or ecchymosis as well as prolongation of bleeding time. Therefore, avoidance of tissue shear and trauma is necessary, and scrupulous attention should be given to vascular access and operative sites during and shortly after cangrelor infusions.

Subjects enrolled in cangrelor trials, due to their underlying cardiovascular disease, are at risk of death, myocardial infarction, recurrent myocardial infarction, stroke and other ischemic events that require revascularization. As a competitive P2Y₁₂ receptor antagonist that has been shown to inhibit ADP-induced platelet aggregation, cangrelor has significant potential to preclude thrombotic occlusion and therefore reduce the incidence of these ischemic events in patients experiencing ACS.

Adverse events from all completed Phase II and Phase III studies are summarized in [Table 17](#) (Phase II) and [Table 18](#) (Phase III). A list of expected serious adverse drug reactions is provided in [Table A1-1 in Appendix 1](#). Non-serious adverse reactions from the Phase III studies are provided in Appendix 2 ([Table A1-2](#)).

6.6. Action to be Taken in the Event of an Overdose With Cangrelor

As cangrelor has a rapid onset and offset of action in humans, the simplest method of terminating its effects is to stop drug infusion. Patients and study subjects should be regarded as having impaired platelet function during and shortly after infusion, and platelet function should be checked if considered necessary.

There is no antidote to cangrelor. However, due to its very short half-life (5 minutes), the PD effects will rapidly diminish with full restoration of platelet function within 60 minutes of cessation of the infusion.

If no complication has ensued, the amount of overdose should be calculated and recorded. Correct the infusion rate to the protocol-specified rate and continue the infusion. If the overdose has caused any complication, stop the infusion and institute the therapeutically appropriate procedures per hospital protocol. Record the occurrence as an AE.

7. REFERENCES

7.1. Literature References

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; 116:2148-e304.

Harrington RA, Stone GW, McNulty S, et al. Supplement to: Platelet inhibition with cangrelor in patients undergoing PCI. *N Engl J Med*. 2009; 361:2318-2329.

Irwin S. Comprehensive observational assessment: Ia. A systematic, quantitative procedure for assessing the behavioral and physiologic state of the mouse. *Psychopharmacologia*. 1968;13:222-257.

Lange RA, Hillis LD. Coronary revascularization in context. *N Engl J Med*. 2009; 360(10):1024-1026.

Mickelson JK, Simpson PJ, Cronin M, et al. Antiplatelet antibody [7E3 F(ab')₂] prevents rethrombosis after recombinant tissue-type plasminogen activator-induced coronary artery thrombolysis in a canine model. *Circulation*. 1990;81:617-627.

Rote WE, Mu DX, Bates ER, et al. Prevention of rethrombosis after coronary thrombolysis in a chronic canine model. I. Adjunctive therapy with monoclonal antibody 7E3 F(ab')₂ fragment. *J Cardiovasc Pharmacol*. 1994;23:194-202.

Storey RF, Wilcox RG, Heptinstall S. Comparison of the pharmacodynamic effects of the platelet ADP receptor antagonists clopidogrel and AR-C69931MX in patients with ischaemic heart disease. *Platelets*. 2002;13:407-413.

Vlaar PJ, Svilaas T, Damman K, et al. Impact of pretreatment with clopidogrel on initial patency and outcome in patients treated with primary percutaneous coronary intervention for ST-segment elevation myocardial infarction: a systematic review. *Circ*. 2008;118:1-9.

Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361:1045-1057.

Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007; 357(20):2001-2015.

7.2. Nonclinical Study Reports

Document No. 96031. ARL 69931MX: Acute intravenous toxicity study in the female mouse. Safety Assessment, Loughborough, Leicestershire, United Kingdom, 20 September, 1996.

Document No. 96030. ARL 69931MX: Acute intravenous toxicity study in the female rat. Safety Assessment, Loughborough, Leicestershire, United Kingdom, 19 September, 1996.

Document No. 96102. Mutagenicity evaluation of ARL 69931MX in the L5178Y mouse lymphoma cell thymidine kinase locus mutagenicity test. Safety Assessment, Södertälje, Sweden, 21 October, 1996.

Document No. 96122. ARL 69931MX: Induction of micronuclei in the bone marrow of treated mice. Safety Assessment, Corning Hazleton, England, 9 September, 1996.

Document No. 97036/1. AR-C69931MX: Assessment of mutagenic potential – limited Ames assay (2). Safety Assessment, Loughborough, Leicestershire, United Kingdom, 10 April, 1997.

Document No. 97093-1. Single dose toxicity of AR-C69931MX in rats after single intravenous administration. Safety Assessment, Södertälje, Sweden, 30 April, 1997.

Document No. 96159-1. AR-C69931MX: Continuous intravenous infusion toxicity study in the non-pregnant female dutch rabbit. Safety Assessment, Loughborough, Leicestershire, United Kingdom, 7 May, 1997.

Document No. 96178. AR-C69931MX: Continuous intravenous infusion dose finding embryo-fetal development study in the rat. Safety Assessment, Loughborough, Leicestershire, United Kingdom, 14 April, 1998.

Document No. 97094-1. Single dose toxicity of AR-C69931MX in mice after single intravenous administration. Safety Assessment, Södertälje, 30 April, 1997.

Document No. 97241/1. AR-C69931MX: Continuous intravenous infusion dose finding embryo-fetal development study in the rabbit. Safety Assessment, Loughborough, Leicestershire, United Kingdom, 14 April, 1998.

Document No. PR 30098. The Cardiovascular effects of intravenous ARL 69931MX in the anaesthetised dog. Astra Charnwood, 16 April, 1996.

Document No. PR 30138. General pharmacology of ARL 69931MX in vitro (3): Effect of ARL 69931MX and putative metabolites on uptake of [³H]adenosine by human erythrocytes. Astra Charnwood, 25 April, 1997.

Document No. PR 30139. General pharmacology of ARL 69931MX in vitro (4): Effect of ARL 69931MX and putative metabolites on ADP-independent aggregation of human washed platelets. Astra Charnwood, 19 May, 1998.

Document No. PR 30143. General pharmacology of ARL 69931MX in vivo (1): The Effect of Rapid Intravenous Infusion of ARL 69931MY/MX on Rectal Temperature and Renal Histology in Conscious Mouse. Astra Charnwood, 9 July, 1998.

Document No. PR 30144. The effect of ARL 69931MX and putative metabolites on ADP-induced (P2T-purinoceptor mediated) aggregation of human washed platelets. Astra Charnwood, 19 May, 1998.

Document No. PR 30145. The effect of ARL 69931MX on ADP-induced platelet aggregation in human blood in vitro. Astra Charnwood, 19 May, 1998.

Document No. PR 30146. The effect of ARL 69931MX on ADP-induced platelet aggregation in dog blood in vitro. Astra Charnwood, 19 May, 1998.

Document No. PR 30147. The effect of ARL 69931MY on ADP-induced platelet aggregation in rat blood in vitro. Astra Charwood, 19 May, 1998.

Document No. PR 30150. The effect of intravenous infusion of ARL 69931MY/MX on ADP-induced platelet aggregation measured ex vivo in blood from the conscious dog. Astra Charnwood, 3 July, 1998.

Document No. PR 30154. General pharmacology of AR-C69931MX in vivo (2): The Effect of rapid intravenous infusion of AR-C69931MX on behaviour in the conscious mouse. Astra Charnwood, 19 May, 1998.

Document No. PR 30316. General pharmacology of ARL 69931MX In Vitro (1): Effect of ARL 69931MX and putative metabolites in functional assays for activity at P2Y1-, P2Y2-, P2X1-, P2X2-, and P2X7- receptors. Astra Charnwood, 25, June, 1998.

Document No. PR40019. Assessing the antithrombotic efficacy of AR-C69931MX in a canine model of cyclic changes in coronary blood flow ("Folts model"). Astra Charnwood, 3 July 1998.

Document No. SC-30174. A Study on the Effect of Intravenously Infused AR-C69931MX on the Cardiovascular Parameters in the Anaesthetised Dog. Astra Charnwood, 25 February, 1997.

Document No. SC-30183. AR-C69931MX: Preliminary tolerability study in the conscious dog (SE 9841). Astra Charnwood, 9 July, 1998.

Document No. SC-100090. ARL 69931MX: Metabolism and excretion following intravenous infusion of [³H]ARL 69931MX to the female rat. Astra Charnwood, 3 January, 1997.

Document No. SC-100091. ARL 69931MX: Pharmacokinetics, metabolism and excretion following intravenous infusion of [³H]ARL69931MX to the female dog. Astra Charnwood, 3 January, 1997.

Document No. SC-100123. AR-C69931MX: Pharmacokinetics following intravenous infusion to the female rat. Astra Charnwood, 28 February, 1997.

Document No. SC-100124. AR-C69931MX: Pharmacokinetics following intravenous infusion to female dogs. Astra Charnwood, 27 October, 1997.

Document No. SC-100141. AR-C69931MX: Metabolite profile in excreta and plasma following intravenous infusion of [³H]AR-C69931MX to female rats (SC-100090). Astra Charnwood, 27 June, 1997.

Document No. SC-100142. AR-C69931MX: Metabolite profile in excreta and plasma following intravenous infusion of [³H]AR-C69931MX to female dogs (SC-100091). Astra Charnwood, 27 July, 1998.

Document No. SC-100188. AR-C69931MX: Pharmacokinetics and pharmacodynamics in the anaesthetised dog. Astra Charnwood, 7 October, 1997.

Document No. SC-100295. AR-C69931MX: Quantitative whole body autoradiography following intravenous infusion of [³H]AR-C69931MX to pregnant female rats. Astra Charnwood, 12 April, 1999.

Document No. SC-100357. AR-C69931MX: Metabolite profile in excreta and plasma following intravenous infusion of [3 H]AR-C69931MX to male dogs (SE 10011). Astra Charnwood, 28 February, 1997.

Document No. SC-100358. AR-C69931MX: Metabolite profile in excreta and plasma following intravenous infusion of [3 H]AR-C69931MX to male rats (SE 10010). Astra Charnwood, 5 March, 1997.

Document No. SC-100371. AR-C69931MX: Biliary excretion and metabolism following intravenous infusion of [3 H]AR-C69931MX to the rat. Astra Charnwood, 10 April, 1997.

Document No. SC-100962. AR-C69931MX: Siting study to investigate the pharmacokinetics of AR-C69931XX and AR-C69712XX following intravenous infusion of AR-C69931MX to a non-pregnant dutch rabbit. Astra Charnwood, 17 May, 1999.

Document No. SC-101314. AR-C69931MX: The pharmacokinetics of AR-C69931XX and AR-C69712XX following intravenous infusion of AR-C69931MX to non-pregnant female Dutch rabbits. AstraZeneca R&D Charnwood, 16 July, 1999.

Document No. SC-101599. AR-C69931MX: Investigation of the relative contributions of the liver, kidney, lungs and intestines to the plasma clearance of AR-C69931XX following intravenous administration of [3 H]AR-C69931MX to isolated perfused organs of male Sprague Dawley rats. BioDynamics, 12 July. 1999.

Document No. SC-101645. AR-C69931MX: Determination of AR-C69931XX in plasma perfusate samples from the organ perfusion experiments detailed in Study SC-101599. Astra Charnwood, 8 December, 1998.

Document No. SC-102741. Evaluation of P2T-receptor antagonist AR-C69931MX on the prevention of platelet aggregation and thrombosis formation in the canine coronary thrombosis model. AstraZeneca R&D Charnwood, 6 July, 1999.

Document No. SC-102858-1. AR-C69931MX: The Potential of AR-69931MX, AR-C69712XX and AR-C90439XX to inhibit human cytochrome P450 (CYP). Loughborough, Leicestershire, United Kingdom, 29 March 2000.

Document No. SE 9299. FPL 69931MX: 3-Day intravenous toxicity study in the male rat. Safety Assessment, Loughborough, Leicestershire, United Kingdom, 22 November, 1994.

Document No. SE 9341. FPL 69931MX: Screening micronucleus test in the mouse. Safety Assessment, Safeparm Laboratories Limited, Derby, United Kingdom, 24 May, 1994.

Document No. SE 9389. FPL 69931MX: Assessment of mutagenic potential – limited Ames assay. Safety Assessment, Loughborough, Leicestershire, United Kingdom, 25 April, 1994.

Document No. SE 9563. FPL 69712XX: Assessment of mutagenic potential – limited Ames assay. Safety Assessment, Loughborough, Leicestershire, United Kingdom, 9 December, 1994.

Document No. SE 9564. FPL71301XX: Assessment of mutagenic potential – limited Ames assay. Safety Assessment, Loughborough, Leicestershire, United Kingdom, 8 December, 1994.

Document No. SE 9848. ARL 69931MX: One-week continuous intravenous infusion siting toxicity study in the male rat. Safety Assessment, Loughborough, Leicestershire, United Kingdom, 3 June, 1996.

Document No. SE 9861. ARL 69931MX: Seven-day continuous intravenous infusion toxicity study in the male dog. Safety Assessment, Loughborough, Leicestershire, United Kingdom, 18 January, 1996.

Document No. SE 9862. ARL 69931MX: One month continuous intravenous infusion toxicity study in the male dog. Safety Assessment, Loughborough, Leicestershire, United Kingdom, 25 June, 1996.

Document No. SE 9940. ARL 69931MX: Assessment of mutagenic potential using the Ames strains of *Salmonella Typhimurium*. Safety Assessment, Loughborough, Leicestershire, United Kingdom, 1 December, 1995.

Document No. SE 9948. ARL 69931 MX: One-month continuous intravenous infusion toxicity study in the male rat. Safety Assessment, Loughborough, Leicestershire, United Kingdom, 2 March, 1996.

Document No. SE 9958. ARL 69931MX: In vitro cytogenic test using human peripheral blood lymphocytes. Safety Assessment, Loughborough, Leicestershire, United Kingdom, 15 March, 1996.

Document No. SE 9993. ARL 69931MX: Acute intravenous toxicity study in the male rat. Safety Assessment, Loughborough, Leicestershire, United Kingdom, 5 February, 1996.

Document No. SE 9994/2. ARL 69931MX: Acute Intravenous toxicity study in the male mouse. Safety Assessment, Loughborough, Leicestershire, United Kingdom, 6 May, 1998.

Document No. SE 9996. ARL 69931MX: Cardiovascular and respiratory assessment in the anaesthetised male rat. Safety Assessment, Loughborough, Leicestershire, United Kingdom, 12 February, 1996.

Document No. SE 10009. [³H]ARL69931MX: Binding of [³H]ARL69931MX and [³H]ARL69712XX to the plasma proteins and the blood cells, and partition in whole blood of rat, dog and human in vitro. Astra Charnwood, 8 November, 1996.

Document No. SE 10010. ARL 69931MX: Pharmacokinetics, metabolism and excretion following intravenous infusion of [³H]ARL 69931MX to the male rat. Astra Charnwood, 12 July, 1996.

Document No. SE 10011. ARL 69931MX: Pharmacokinetics, metabolism and excretion following intravenous infusion of [³H]ARL 69931MX to the male dog. Astra Charnwood, 12 July, 1996.

Document No. SE10012. ARL 69931MX: Tissue distribution following intravenous infusion of [³H]ARL69931MX to the male rat. Astra Charnwood, 8 November, 1996.

Document No. SE 10075. ARL 69931MX: Pharmacokinetics following intravenous infusion to the male rat. Astra Charnwood, 24 June, 1996.

Document No. SE 10076. ARL 69931MX: Pharmacokinetics following intravenous infusion to the male dog. Astra Charnwood, 7 August, 1996.

Document No. SE 10176. ARL 69931MX: One-month continuous intravenous infusion toxicity study in the female rat. Safety Assessment, Loughborough, Leicestershire, United Kingdom, 18 September, 1996.

Document No. SE 10177. ARL 69931MX: One-month continuous intravenous infusion toxicity study in the female dog. Safety Assessment, Loughborough, Leicestershire, United Kingdom, 18 September, 1996.

Document No. SR97246/2. AR-C69931MX: One month continuous intravenous infusion toxicity study, with assessment of recovery, in the male rat. Safety Assessment, Loughborough, Leicestershire, United Kingdom, 22 May, 1998.

Document No. SR97297. AR-C69931MX: Continuous intravenous infusion embryo-fetal development study in the rabbit. Safety Assessment, Loughborough, Leicestershire, United Kingdom, 16 November, 1998.

Document No. SR98002. Continuous intravenous infusion embryo-fetal development study in the rat. Safety Assessment, Loughborough, Leicestershire, United Kingdom, 1 February, 1999.

Document No. SR98073/1. AR-C69931MX: Continuous intravenous infusion fertility study in the male rat. Safety Assessment, Loughborough, Leicestershire, United Kingdom, 7 April, 1999.

Document No. SR98074-01. AR-C69931MX: Continuous intravenous infusion fertility and early embryo-fetal development study in the female rat. Safety Assessment, Loughborough, Leicestershire, United Kingdom, 26 February, 1999.

7.3. Clinical Study Reports

SC-100199 (Clinical Study No. CP9017). AR-C69931MX: The metabolism and disposition of [³H]AR-C69931MX in healthy male volunteers following intravenous infusion. Astra Charnwood, 13 October, 1997.

SC-931-5014. An ascending dose step-plateau infusion study to investigate the tolerability, safety, activity and pharmacokinetics of AR-C69931MX, an antiplatelet agent, in healthy male volunteers. Astra Charnwood, 14 March 1998.

SC-931-5036. An ascending dose, step-plateau infusion study to investigate the tolerability, safety, activity and pharmacokinetics of AR-C69931MX, an antiplatelet agent in healthy female volunteers. Astra Charnwood, 27 March 1998.

SC-931-5037. A double-blind placebo controlled two-way crossover study to investigate the combined effects and interactions of aspirin, heparin and glyceryl trinitrate pretreatment with stepped infusions of AR 69931MX in healthy male volunteers. Astra Charnwood, 13 May 1998.

SC-931-5058. An open multi-centre study to assess the safety, tolerability and activity of intravenous AR-C69931MX in unstable angina pectoris and/or non-Q-wave myocardial infarction. Astra Charnwood, 9 December, 1998.

SC-931-5060. A double-blind, placebo-controlled, multi-centre study to assess the safety and tolerability of intravenous AR-C69931MX and placebo in unstable angina pectoris or non-Q-wave myocardial infarction. 26 August 1999.

SC-931-5109. An open, group comparative study of the pharmacokinetics, safety and tolerability of AR-C69931MX, administered as ascending infusions (50 – 4000 ng/kg/min) for 5 hours to subjects with renal impairment and healthy controls. 9 December 1999.

SC-931-5129 Part 1. A multicentre pilot study to assess the safety and ex vivo platelet aggregation of response of intravenous AR-C69931MX in patients undergoing PTCA, with or without intracoronary stent placement (Part 1 Double-Blind vs Placebo). 16 February 2001.

SC-931-5129 Part 2. A multicentre pilot study to assess the safety and ex vivo platelet aggregation response of intravenous AR-C69931MX in patients undergoing percutaneous transluminal coronary angioplasty, with or without intracoronary stent placement. 16 February 2001.

SC-931-5135. An open study, with blinded end-point assessment, to assess the safety, tolerability, and the effect on coronary artery patency of intravenous AR-C69931MX as both monotherapy and adjunct to activase in patients with ST-elevation myocardial infarction. 16 August, 2002.

SC-931-5092. An open multicentre pilot study to assess the incidence of abnormalities in specific urine and blood parameters observed over 72 hours in patients on standard medication with unstable angina and/or non-Q-wave myocardial infarction. Astra Charnwood, 15 May 1998.

SC-931-9017. The metabolism and disposition of [^3H]AR-C69931MX (formerly ARL69931MX) in healthy male volunteers when administered intravenously at 2 $\mu\text{g/kg/min}$ for 2 hours. Astra Charnwood, 06 January 1998.

SC-931-9064. An open within-subject evaluation of the pharmacodynamic properties of clopidogrel. Astra Zeneca, 15 June 2000.

TMC-CAN-04-02. The pharmacokinetics and pharmacodynamics of cangrelor bolus plus infusion in healthy volunteers. 06 February 2009.

TMC-CAN-05-02 (PCI). Randomized, double-blind, double-dummy, active control, parallel group comparing cangrelor to clopidogrel in subjects who require percutaneous coronary intervention (in process).

TMC-CAN-05-03 (Platform). Randomized, double-blind, placebo-controlled, parallel group comparing treatment with cangrelor (in combination with usual care) to usual care, in subjects who require percutaneous coronary intervention (in process).

TMC-CAN-08-01. A double-blind, placebo-controlled, positive-controlled, randomized, crossover study to assess the effect of cangrelor at the therapeutic dose and a supratherapeutic dose level on the QT/QTc interval in healthy volunteers. 09 October 2009.

APPENDIX 1: SERIOUS ADVERSE REACTIONS

Table A1-1: Summary listing of serious adverse reactions considered probably or possibly related to cangrelor in cangrelor completed Phase II and Phase III studies

Preferred Term	Frequency (Total #)	Fatal	Life Threatening ^a
Acute pulmonary oedema	2		2
Alanine aminotransferase increased	1		
Angioneurotic oedema	1		-
Aspartate aminotransferase increased	1		
Anaemia	19		
Aneurysm	1		
Angina pectoris	2		
Angina unstable	1		
Bradycardia	2		
Cardiac arrest	1		1
Cardiogenic shock	1		1
Cellulitis	1		
Cerebral haemorrhage	1	1	
Chest discomfort	1		
Chest pain	4		1
Collapse of lung	1		
Coronary artery thrombosis	2		
Embolism	3		
Gastrointestinal haemorrhage	3		
Haemorrhage intracranial	1		
Haematoma infection	1		
Hypertensive emergency	1		
Hypotension	3		
Laryngeal oedema	1		
Liver function test abnormal	1		
Melaena	1		
Multi-organ failure	1	1	
Myocardial infarction	2		
Overdose	1		

Preferred Term	Frequency (Total #)	Fatal	Life Threatening ^a
Papillary muscle rupture	1	1	
Post procedural complication	1		
Pulmonary embolism	1		1
Pulmonary oedema	1		
Purpura	1		
Renal failure acute	1		
Retroperitoneal haemorrhage	2	1	
Stridor	1		
Thrombosis	1		
Thrombocytopenia	1		
Ventricular tachycardia	1		
Vessel puncture site haematoma	1		1
Vessel puncture site haemorrhage	6		0

Events that correlate with the mode of action for cangrelor are described in [Section 6.5](#) and include modest prolongation of bleeding time, ecchymosis and petechia.

a. Life threatening data are only available for the Phase III studies.

Report generated by: SAE_A1_1.sas (Phase III data).

Table A1-2 Summary listing of non-serious adverse drug reactions for studies TMC-CAN-02 (PCI) and TMC-CAN-03 (Platform)

Preferred Term	Frequency
Abdominal pain	1
Abdominal pain lower	3
Abdominal pain upper	2
Abdominal tenderness	1
Acute pulmonary oedema	2
Alanine aminotransferase increased	1
Anaemia	4
Angina pectoris	1
Angioneurotic oedema	1
Anxiety	1
Aspartate aminotransferase increased	4
Asthenia	1
Atrial fibrillation	2

Preferred Term	Frequency
Atrial tachycardia	1
Back pain	7
Blood bilirubin increased	6
Blood creatinine increased	2
Blood pressure increased	1
Bradycardia	6
Cardiac arrest	1
Cardiogenic shock	1
Catheter site haemorrhage	1
Catheter site pain	1
Cellulitis	1
Cerebral haemorrhage	1
Chest discomfort	2
Chest pain	14
Choking	1
Confusion postoperative	1
Constipation	1
Coronary artery occlusion	1
Diarrhoea	3
Dizziness	1
Dyspepsia	3
Dysphagia	1
Dyspnoea	9
Dysuria	1
Ecchymosis	1
Embolism	1
Flushing	1
Foreign body trauma	1
Haematoma infection	1
Haemoglobin decreased	2
Headache	3
Hepatic enzyme increased	2
Hot flush	1

Preferred Term	Frequency
Hypertension	2
Hypertensive crisis	1
Hypertensive emergency	1
Hypoaesthesia	1
Hypotension	13
Incorrect dose administered	1
Liver function test abnormal	5
Lymphadenopathy	1
Migraine	1
Musculoskeletal chest pain	1
Musculoskeletal pain	1
Nausea	24
Neck pain	1
Nodal arrhythmia	1
Oedema peripheral	1
Pain in extremity	1
Platelet count decreased	3
Pleural effusion	1
Post procedural discharge	1
Post procedural discomfort	1
Post procedural drainage	1
Procedural hypertension	1
Prothombin time prolonged	1
Pruritis	2
Pulmonary embolism	1
Puncture site pain	4
Purpura	1
Pyrexia	1
Rash	6
Rash erythematous	1
Rash pruritic	1
Reperfusion injury	4
Retroperitoneal haemorrhage	1

Preferred Term	Frequency
Skin irritation	1
Syncope vasovagal	4
Tenderness	1
Thrombosis	2
Urticaria	5
Vascular procedural complication	1
Venipuncture site swelling	2
Vertigo	1
Vessel puncture site bruise	1
Vessel puncture site haematoma	1
Vomiting	18

APPENDIX 2 BLEEDING EVENTS IN PHASE III TRIALS

Table A2-1: Summary of bleeding at 48 hour post-randomization in pooled Studies TMC-CAN-05-02 (CHAMPION PCI) and TMC-CAN-05-03 (CHAMPION Platform)

Category	Cangrelor n/N (%)	Clopidogrel n/N (%)
Pooled Studies		
Any TIMI bleeding	81 / 7036 (1.2)	65 / 7015 (0.9)
Major	23 / 7036 (0.3)	23 / 7015 (0.3)
Minor	58 / 7036 (0.8)	42 / 7015 (0.6)
PCI Study		
Any TIMI bleeding	55 / 4374 (1.3)	40 / 4365 (0.9)
Major	19 / 4374 (0.4)	14 / 4365 (0.3)
Minor	36 / 4374 (0.8)	26 / 4365 (0.6)
Platform Study		
Any TIMI bleeding	26 / 2662 (1.0)	25 / 2650 (0.9)
Major	4 / 2662 (0.2)	9 / 2650 (0.3)
Minor	22 / 2662 (0.8)	16 / 2650 (0.6)

TIMI = Thrombolysis In Myocardial Infarction.

Report generated by program (POOLED): T_BLD_CHG.SAS 23OCT09 13:20.

Table A2-2: Summary of Non-CABG related bleeding by type at 48 hour post-randomization in Studies TMC-CAN-05-02 (CHAMPION PCI) and TMC-CAN-05-03 (CHAMPION Platform)

Category	PCI Study Cangrelor N=4374 n/N (%)	PCI Study Clopidogrel N=4365 n/N (%)	Platform Study Cangrelor N=2662 n/N (%)	Platform Study Clopidogrel N=2650 n/N (%)
Access site bleeding requiring radiologic or surgical intervention	6 (0.1)	10 (0.2)	8 (0.3)	10 (0.4)
Hematoma \geq 5 cm at puncture site	84 (1.9)	75 (1.7)	115 (4.3)	71 (2.7)
Intracranial hemorrhage	1 (0.0)	0 (0.0)	2 (0.1)	1 (0.0)
Intraocular	2 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Reoperation for bleeding	1 (0.0)	1 (0.0)	0 (0.0)	1 (0.0)

Category	PCI Study Cangrelor N=4374 n/N (%)	PCI Study Clopidogrel N=4365 n/N (%)	Platform Study Cangrelor N=2662 n/N (%)	Platform Study Clopidogrel N=2650 n/N (%)
Retroperitoneal	15 (0.3)	10 (0.2)	2 (0.1)	1 (0.0)
Ecchymosis	283 (6.5)	233 (5.3)	95 (3.6)	57 (2.2)
Epistaxis	9 (0.2)	22 (0.5)	6 (0.2)	12 (0.5)
Hematoma < 5 cm at puncture site	251 (5.7)	222 (5.1)	50 (5.6)	119 (4.5)
Oozing at puncture site	400 (9.1)	316 (7.2)	125 (4.7)	91 (3.4)
Thrombocytopenia	5 (0.1)	7 (0.2)	1 (0.0)	3 (0.1)
Other	112 (2.6)	101 (2.3)	50 (1.9)	39 (1.5)
Clinically overt bleed (including bleeding seen on imaging)	864 (19.8)	747 (17.1)	440 (16.5)	319 (12.0)
Hemodynamic compromis	9 (0.2)	11 (0.3)	7 (0.3)	5 (0.2)
Transfusion	41 (0.9)	38 (0.9)	24 (0.9)	16 (0.6)
Drop in hemoglobin and/or hematocrit ^a	84 (1.9)	60 (1.4)	32 (1.2)	33 (1.2)

PCI = percutaneous coronary intervention.

a. Drop ≥ 3 g/dl for hemoglobin and/or drop $\geq 9\%$ in hematocrit recorded in bleed case report form.

Report generated by programs (PF): T_BLD.SAS 24SEP09 15:54 and (PCI): T_BLD.SAS 24SEP09 15:55

Table A2-3: Summary of bleeding at 48 hour post-randomization (Study TMC-CAN-05-02 [CHAMPION PCI])

Category	Cangrelor N=4374 n/N (%)	Clopidogrel N=4365 n/N (%)
Non-CABG related bleeding		
Any ACUTY bleeding	890 (20.3)	769 (17.6)
Major	151 (3.5)	120 (2.7)
Minor	765 (17.5)	661 (15.1)
Any GUSTO bleeding	890 (20.3)	769 (17.6)
Severe/life threatening	10 (0.2)	11 (0.3)
Moderate	36 (0.8)	30 (0.7)
Mild	853 (19.5)	736 (16.9)

Category	Cangrelor N=4374 n/N (%)	Clopidogrel N=4365 n/N (%)
Any TIMI bleeding	55 (1.3)	40 (0.9)
Major	19 (0.4)	14 (0.3)
Minor	36 (0.8)	26 (0.6)
CABG related bleeding		
Any ACUITY bleeding	10 (0.2)	8 (0.2)
Major	7 (0.2)	6 (0.1)
Minor	3 (0.1)	3 (0.1)
Any GUSTO bleeding	10 (0.2)	8 (0.2)
Severe/life threatening	0 (0.0)	0 (0.0)
Moderate	5 (0.1)	4 (0.1)
Mild	5 (0.1)	4 (0.1)
Any TIMI bleeding	0 (0.0)	0 (0.0)
Major	0 (0.0)	0 (0.0)
Minor	0 (0.0)	0 (0.0)

ACUITY = Acute Catheterization and Urgent Intervention Triage strategY; CABG = coronary artery bypass graft (surgery); GUSTO = Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries; TIMI = Thrombolysis In Myocardial Infarction.

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Table A2-4: Summary of non-CABG and CABG related bleeding by type at 48 hour post-randomization (Study TMC-CAN-05-02 [CHAMPION PCI])

Category	Cangrelor N=4374 n/N (%)	Clopidogrel N=4365 n/N (%)
Non-CABG related bleeding		
Access site bleeding requiring radiologic or surgical intervention	6 (0.1)	10 (0.2)
Hematoma \geq 5 cm at puncture site	84 (1.9)	75 (1.7)
Intracranial hemorrhage	1 (0.0)	0 (0.0)
Intraocular	2 (0.0)	0 (0.0)
Reoperation for bleeding	1 (0.0)	1 (0.0)
Retroperitoneal	15 (0.3)	10 (0.2)
Ecchymosis	283 (6.5)	233 (5.3)
Epistaxis	9 (0.2)	22 (0.5)

Category	Cangrelor N=4374 n/N (%)	Clopidogrel N=4365 n/N (%)
Hematoma < 5 cm at puncture site	251 (5.7)	222 (5.1)
Oozing at puncture site	400 (9.1)	316 (7.2)
Thrombocytopenia	5 (0.1)	7 (0.2)
Other	112 (2.6)	101 (2.3)
Clinically overt bleed (including bleeding seen on imagining)	864 (19.8)	747 (17.1)
Hemodynamic compromise	9 (0.2)	11 (0.3)
Transfusion	41 (0.9)	38 (0.9)
Drop in hemoglobin and/or hematocrit ^a	84 (1.9)	60 (1.4)
CABG related bleeding		
Access site bleeding requiring radiologic or surgical intervention	0 (0.0)	0 (0.0)
Hematoma ≥ 5 cm at puncture site	1 (0.0)	1 (0.0)
Intracranial hemorrhage	0 (0.0)	0 (0.0)
Intraocular	0 (0.0)	0 (0.0)
Reoperation for bleeding	0 (0.0)	0 (0.0)
Retroperitoneal	0 (0.0)	0 (0.0)
Ecchymosis	1 (0.0)	1 (0.0)
Epistaxis	0 (0.0)	0 (0.0)
Hematoma < 5 cm at puncture site	0 (0.0)	0 (0.0)
Oozing at puncture site	0 (0.0)	3 (0.1)
Thrombocytopenia	1 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)
Clinically overt bleed (including bleeding seen on imagining)	2 (0.0)	3 (0.1)
Hemodynamic compromise	0 (0.0)	0 (0.0)
Transfusion	5 (0.1)	4 (0.1)
Drop in hemoglobin and/or hematocrit ^a	7 (0.2)	3 (0.1)

CABG = coronary artery bypass graft (surgery).

a. Drop ≥3g/dl for hemoglobin and/or drop ≥9% in hematocrit recorded in Bleed case report form.

Report generated by program (PCI): T_BLD.SAS 24SEP09 15:55

Table A2-5: Summary of bleeding at 48 hour post-randomization (Study TMC-CAN-05-03 [CHAMPION Platform])

Category	Cangrelor N=2662 n/N (%)	Clopidogrel N=2650 n/N (%)
Non-CABG related bleeding		
Any ACUITY bleeding	450 (16.9)	326 (12.3)
Major	145 (5.4)	91 (3.4)
Minor	320 (12.0)	246 (9.3)
Any GUSTO bleeding	450 (16.9)	326 (12.3)
Severe/life threatening	9 (0.3)	6 (0.2)
Moderate	18 (0.7)	13 (0.5)
Mild	427 (16.0)	308 (11.6)
Any TIMI bleeding	26 (1.0)	24 (0.9)
Major	4 (0.2)	9 (0.3)
Minor	22 (0.8)	15 (0.6)
CABG related bleeding		
Any ACUITY bleeding	2 (0.1)	2 (0.1)
Major	2 (0.1)	2 (0.1)
Minor	0 (0.0)	0 (0.0)
Any GUSTO bleeding	2 (0.1)	2 (0.1)
Severe/life threatening	0 (0.0)	0 (0.0)
Moderate	2 (0.1)	0 (0.0)
Mild	0 (0.0)	2 (0.1)
Any TIMI bleeding	0 (0.0)	1 (0.0)
Major	0 (0.0)	0 (0.0)
Minor	0 (0.0)	1 (0.0)

ACUITY = Acute Catheterization and Urgent Intervention Triage strategY; CABG = coronary artery bypass graft (surgery); GUSTO = Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries; TIMI = Thrombolysis In Myocardial Infarction.

Report generated by program: T_BLD.SAS 24SEP09 15:54

Table A2-6: Summary of non-CABG and CABG related bleeding by type at 48 hour post-randomization (Study TMC-CAN-05-03 [CHAMPION Platform])

Category	Cangrelor N=2662 n/N (%)	Clopidogrel N=2650 n/N (%)
Non-CABG related bleeding		
Access site bleeding requiring radiologic or surgical intervention	8 (0.3)	10 (0.4)
Hematoma \geq 5 cm at puncture site	115 (4.3)	71 (2.7)
Intracranial hemorrhage	2 (0.1)	1 (0.0)
Intraocular	0 (0.0)	0 (0.0)
Reoperation for bleeding	0 (0.0)	1 (0.0)
Retroperitoneal	2 (0.1)	1 (0.0)
Ecchymosis	95 (3.6)	57 (2.2)
Epistaxis	6 (0.2)	12 (0.5)
Hematoma < 5 cm at puncture site	150 (5.6)	119 (4.5)
Oozing at puncture site	125 (4.7)	91 (3.4)
Thrombocytopenia	1 (0.0)	3 (0.1)
Other	50 (1.9)	39 (1.5)
Clinically overt bleed (including bleeding seen on imaging)	440 (16.5)	319 (12.0)
Hemodynamic compromise	7 (0.3)	5 (0.2)
Transfusion	24 (0.9)	16 (0.6)
Drop in hemoglobin and/or hematocrit*	32 (1.2)	33 (1.2)
CABG related bleeding		
Access site bleeding requiring radiologic or surgical intervention	0 (0.0)	0 (0.0)
Hematoma \geq 5 cm at puncture site	0 (0.0)	0 (0.0)
Intracranial hemorrhage	0 (0.0)	0 (0.0)
Intraocular	0 (0.0)	0 (0.0)
Reoperation for bleeding	1 (0.0)	0 (0.0)
Retroperitoneal	0 (0.0)	0 (0.0)
Ecchymosis	0 (0.0)	0 (0.0)
Epistaxis	0 (0.0)	0 (0.0)
Hematoma < 5 cm at puncture site	0 (0.0)	0 (0.0)

Category	Cangrelor N=2662 n/N (%)	Clopidogrel N=2650 n/N (%)
Oozing at puncture site	0 (0.0)	0 (0.0)
Thrombocytopenia	1 (0.0)	0 (0.0)
Other	0 (0.0)	1 (0.0)
Clinically overt bleed (including bleeding seen on imaging)	1 (0.0)	1 (0.0)
Hemodynamic compromise	0 (0.0)	0 (0.0)
Transfusion	2 (0.1)	0 (0.0)
Drop in hemoglobin and/or hematocrit	1 (0.0)	2 (0.1)

CABG = coronary artery bypass graft (surgery).

Report generated by program: T_BLD.SAS 24SEP09 15:54

Table A2-7: Summary of bleeding events^a that occurred post-randomization and before administration of clopidogrel in study TMC-CAN-05-03 (CHAMPION Platform)

Category	Cangrelor N=2662 n/N (%)	Placebo N=2650 n/N (%)
Non-CABG related bleeding		
Any ACUITY bleeding	15 (0.6)	8 (0.3)
Major	8 (0.3)	0 (0.0)
Minor	7 (0.3)	8 (0.3)
Any GUSTO bleeding	15 (0.6)	8 (0.3)
Severe/life threatening	0 (0.0)	0 (0.0)
Moderate	1 (0.0)	0 (0.0)
Mild	14 (0.5)	8 (0.3)
Any TIMI bleeding	2 (0.1)	0 (0.0)
Major	0 (0.0)	0 (0.0)
Minor	2 (0.1)	0 (0.0)
CABG related bleeding		
Any ACUITY bleeding	0 (0.0)	0 (0.0)
Major	0 (0.0)	0 (0.0)
Minor	0 (0.0)	0 (0.0)
Any GUSTO bleeding	0 (0.0)	0 (0.0)

Category	Cangrelor N=2662 n/N (%)	Placebo N=2650 n/N (%)
Severe/life threatening	0 (0.0)	0 (0.0)
Moderate	0 (0.0)	0 (0.0)
Mild	0 (0.0)	0 (0.0)
Any TIMI bleeding	0 (0.0)	0 (0.0)
Major	0 (0.0)	0 (0.0)
Minor	0 (0.0)	0 (0.0)

ACUTY = Acute Catheterization and Urgent Intervention Triage strategY; CABG = coronary artery bypass graft (surgery); GUSTO = Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries; TIMI = Thrombolysis In Myocardial Infarction.

a. Data from safety + SA/UA/NSTEMI/STEMI populations.

Report generated by program: T_BLD_PLACEBO.SAS 15APR10 10:56

APPENDIX 3 ADVERSE EVENTS IN PHASE III TRIALS

Table A3-1: Summary of AEs with fatal outcome by system organ class, in patients in the cangrelor arm who had died at 1 year (safety population; Study TMC-CAN-05-02 [CHAMPION PCI])

System Organ Class	Number of Events
General disorders and administration site conditions	26
Cardiac disorders	43
Gastrointestinal disorders	2
Respiratory, thoracic and mediastinal disorders	6
Investigations	1
Nervous system disorders	5
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	9
Renal and urinary disorders	3
Injury, poisoning and procedural complications	2
Infections and infestations	3
Missing SOC term	2
Report generated by program (PCI): T_AE_DEATH.SAS 24SEP09 16:15	

Table A3-2: Summary of AEs with fatal outcome by system organ class, in patients in the cangrelor arm who had died at 1 year (safety population; Study TMC-CAN-05-03 [CHAMPION Platform])

System Organ Class	Number of Events
Cardiac disorders	30
General disorders and administration site conditions	15
Nervous system disorders	6
Gastrointestinal disorders	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	8
Respiratory, thoracic and mediastinal disorders	3
Vascular disorders	1
Injury, poisoning and procedural complications	1
Infections and infestations	2
Missing SOC term	2
Report generated by program: T_AE_DEATH.SAS 24SEP09 16:00	

Table A3-3: Summary of common (>0.2% on cangrelor arm) adverse events by Preferred Term in pooled Studies TMC-CAN-05-02 (CHAMPION PCI) and TMC-CAN-05-03 (CHAMPION Platform)

Preferred Term	Cangrelor N=7036 n/N (%)	Clopidogrel in PCI N=4365 ^a n/N (%)	Clopidogrel in PF N=2650 ^b n/N (%)
Back pain	258 (3.7)	164 (3.8)	85 (3.2)
Chest pain	251 (3.6)	163 (3.7)	69 (2.6)
Nausea	183 (2.6)	145 (3.3)	66 (2.5)
Headache	153 (2.2)	97 (2.2)	68 (2.6)
Hypotension	140 (2.0)	89 (2.0)	38 (1.4)
Vomiting	107 (1.5)	78 (1.8)	31 (1.2)
Puncture site pain	88 (1.3)	52 (1.2)	29 (1.1)
Pyrexia	81 (1.2)	37 (0.8)	20 (0.8)
Dyspnoea	80 (1.1)	16 (0.4)	15 (0.6)
Hypertension	60 (0.9)	34 (0.8)	22 (0.8)
Ventricular tachycardia	48 (0.7)	35 (0.8)	11 (0.4)
Chest discomfort	45 (0.6)	24 (0.5)	11 (0.4)
Bradycardia	39 (0.6)	35 (0.8)	15 (0.6)
Atrial fibrillation	34 (0.5)	18 (0.4)	9 (0.3)
Pain in extremity	34 (0.5)	24 (0.5)	14 (0.5)
Angina pectoris	31 (0.4)	34 (0.8)	17 (0.6)
Syncope vasovagal	30 (0.4)	26 (0.6)	4 (0.2)
Anxiety	29 (0.4)	22 (0.5)	3 (0.1)
Pain	27 (0.4)	13 (0.3)	8 (0.3)
Dizziness	26 (0.4)	21 (0.5)	9 (0.3)
Coronary artery dissection	25 (0.4)	15 (0.3)	7 (0.3)
Dyspepsia	24 (0.3)	22 (0.5)	8 (0.3)
Abdominal pain	22 (0.3)	10 (0.2)	8 (0.3)
Ventricular fibrillation	21 (0.3)	6 (0.1)	7 (0.3)
Diarrhoea	20 (0.3)	13 (0.3)	3 (0.1)
Musculoskeletal pain	20 (0.3)	23 (0.5)	13 (0.5)
Procedural pain	20 (0.3)	11 (0.3)	0 (0.0)
Insomnia	18 (0.3)	6 (0.1)	15 (0.6)
Blood creatinine increased	17 (0.2)	6 (0.1)	3 (0.1)

Preferred Term	Cangrelor N=7036 n/N (%)	Clopidogrel in PCI N=4365 ^a n/N (%)	Clopidogrel in PF N=2650 ^b n/N (%)
Blood pressure increased	17 (0.2)	9 (0.2)	2 (0.1)
Cardiac failure congestive	16 (0.2)	9 (0.2)	4 (0.2)
Hypokalaemia	16 (0.2)	7 (0.2)	2 (0.1)
Red blood cell sedimentation rate increased	15 (0.2)	16 (0.4)	0 (0.0)
Renal failure acute	15 (0.2)	8 (0.2)	1 (0.0)

AE = adverse event; NSTEMI = non-ST segment myocardial infarction; PCI = percutaneous coronary intervention; PF = Platform; SA = stable angina; STEMI = ST segment myocardial infarction; UA = unstable angina.

a. Adverse event data from safety + SA/UA/NSTEMI/STEMI populations.

b. Adverse event data from safety + SA/UA/NSTEMI populations.

Table A3-4 Summary of treatment-emergent serious adverse events that occurred post-randomization and before administration of clopidogrel in study TMC-CAN-05-03 (CHAMPION Platform)

System Organ Class/Preferred Term	Cangrelor (N=2662) ^a n (%)	Placebo (N=2650) ^a n (%)
Patients with at least one SAE	8 (0.3)	11 (0.4)
Cardiac disorders	6 (0.2)	6 (0.2)
Cardiac arrest	1 (0.0)	0 (0.0)
Cardiac failure congestive	2 (0.1)	1 (0.0)
Cardiogenic shock	2 (0.1)	1 (0.0)
Coronary artery occlusion	0 (0.0)	1 (0.0)
Coronary artery thrombosis	0 (0.0)	1 (0.0)
Left ventricular failure	0 (0.0)	1 (0.0)
Ventricular fibrillation	1 (0.0)	1 (0.0)
Respiratory, thoracic and mediastinal disorders	1 (0.0)	3 (0.1)
Pulmonary oedema	1 (0.0)	3 (0.1)
Vascular disorders	1 (0.0)	2 (0.1)
Hypertension	0 (0.0)	1 (0.0)
Hypotension	1 (0.0)	1 (0.0)

SAE = serious adverse event; NSTEMI = non-ST segment myocardial infarction; SA = stable angina; STEMI = ST segment myocardial infarction; UA = unstable angina

Data from safety + SA/UA/NSTEMI populations.

Report generated by program: AE_YS.SAS 09APR10 16:23.

Table A3-5 Summary of treatment-emergent adverse events that occurred post-randomization and before administration of clopidogrel in study TMC-CAN-05-03 (CHAMPION Platform)

System Organ Class/Preferred Term	Cangrelor (N = 2662) ^a n (%)	Placebo (N = 2650) ^a n (%)
Patients with at least one AE	76 (2.9)	84 (3.4)
Cardiac disorders	25 (0.9)	35 (1.3)
Angina pectoris	3 (0.1)	4 (0.2)
Angina unstable	1 (0.0)	0 (0.0)
Atrial fibrillation	1 (0.0)	0 (0.0)
Atrial flutter	0 (0.0)	1 (0.0)
Atrioventricular block	1 (0.0)	1 (0.0)
Antioventricular block third degree	1 (0.0)	0 (0.0)
Bradycardia	3 (0.1)	8 (0.3)
Cardiac arrest	1 (0.0)	0 (0.0)
Cardiac failure congestive	2 (0.1)	1 (0.0)
Cardiogenic shock	2 (0.1)	1 (0.0)
Coronary artery dissection	5(0.2)	5 (0.2)
Coronary artery embolism	0 (0.0)	1 (0.0)
Coronary artery occlusion	3 (0.1)	5 (0.2)
Coronary artery thrombosis	1 (0.0)	1 (0.0)
Left ventricular failure	0 (0.0)	1 (0.0)
Nodal rhythm	1 (0.0)	0 (0.0)
Sinus bradycardia	0 (0.0)	1 (0.0)
Ventricular extrasystoles	0 (0.0)	1 (0.0)
Ventricular fibrillation	2 (0.1)	5 (0.2)
Gastrointestinal disorders	10 (0.4)	7 (0.3)
Abdominal pain	1 (0.0)	0 (0.0)
Nausea	8 (0.3)	5 (0.2)
Vomiting	4 (0.2)	3 (0.1)
General disorders and administration site conditions	17 (0.6)	20 (0.8)
Asthenia	1 (0.0)	0 (0.0)

System Organ Class/Preferred Term	Cangrelor (N = 2662) ^a n (%)	Placebo (N = 2650) ^a n (%)
Chest discomfort	3 (0.1)	5 (0.2)
Chest pain	12 (0.5)	11 (0.4)
Chills	0 (0.0)	1 (0.0)
Paradoxical drug reaction	0 (0.0)	1 (0.0)
Puncture site pain	0 (0.0)	2 (0.1)
Pyrexia	1 (0.0)	0 (0.0)
Injury, poisoning and procedural complications	4 (0.2)	4 (0.2)
Device breakage	1 (0.0)	0 (0.0)
Incorrect dose administered	1 (0.0)	0 (0.0)
Post procedural headache	1 (0.0)	0 (0.0)
Procedural hypertension	0 (0.0)	1 (0.0)
Procedural hypotension	0 (0.0)	1 (0.0)
Vascular procedure complication	0 (0.0)	2 (0.1)
Investigations	1 (0.0)	0 (0.0)
Blood pressure increased	1 (0.0)	0 (0.0)
Metabolism and nutrition disorders	0 (0.0)	1 (0.0)
Hyopglycaemia	0 (0.0)	1 (0.0)
Musculoskeletal and connective tissue disorders	3 (0.1)	5 (0.2)
Back pain	2 (0.1)	2 (0.1)
Musculoskeletal pain	1 (0.0)	2 (0.1)
Pain in extremity	0 (0.0)	2 (0.1)
Nervous system disorders	4 (0.2)	3 (0.1)
Headache	0 (0.0)	1 (0.0)
Hypoesthesia	1 (0.0)	1 (0.0)
Lethargy	0 (0.0)	1 (0.0)
Paraesthesia	1 (0.0)	0 (0.0)
Syncope vasovagal	2 (0.1)	1 (0.0)
Psychiatric disorders	4 (0.2)	1 (0.0)
Anxiety	3 (0.1)	1 (0.0)

System Organ Class/Preferred Term	Cangrelor (N = 2662) ^a n (%)	Placebo (N = 2650) ^a n (%)
Panic attack	1 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	6 (0.2)	4 (0.2)
Dyspnoea	3 (0.1)	1 (0.0)
Pulmonary oedema	3 (0.1)	3 (0.1)
Skin and subcutaneous tissue disorders	4 (0.2)	3 (0.1)
Dermatitis allergic	0 (0.0)	1 (0.0)
Pruritis	1 (0.0)	1 (0.0)
Rash	2 (0.1)	1 (0.0)
Skin ulcer	1 (0.0)	0 (0.0)
Vascular disorders	16 (0.6)	13 (0.5)
Embolism	1 (0.0)	1 (0.0)
Hypertension	4 (0.2)	2 (0.1)
Hypotension	8 (0.3)	7 (0.3)
Reperfusion injury	3 (0.1)	2 (0.1)
Shock	0 (0.0)	1 (0.0)
Thrombosis	1 (0.0)	0 (0.0)

AE = adverse event.

a. Data from safety + SA/UA/NSTEMI populations.

Report generated by program: AE_YS.SAS 09APR10 16:23.



CANGRELOR FOR INJECTION INVESTIGATOR'S BROCHURE

Edition No. 6

Replaces Edition No. 5

Release Date: 20 June 2011

Dated: 4 May 2010

Data Cutoff Date: 30 April 2011

Data Cutoff Date: 23 September 2009

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SAMPLE INFORMED CONSENT

STUDY NAME: **CHAMPION PHOENIX: A clinical trial comparing cangrelor to clopidogrel standard of care therapy in subjects who require percutaneous coronary intervention.**

PROTOCOL NUMBER: [TMC-CAN-10-01]

INVESTIGATOR: [Investigator to add]

Introduction

You are being asked to take part in a research study. Taking part in this study is completely voluntary. This study will be run by Dr. [Investigator] at [Name of Hospital]. It is important that you read and understand this consent form. Please read it carefully. Take time to ask the research doctor or staff as many questions about this research study as you would like. If there are any words or information that you do not understand, the research doctor or staff will explain them to you. Reading this form and talking to the research doctor or staff should help you decide whether or not to take part in this research study. If you do decide to participate, you must sign and date this form before your participation in this research study begins. You will be consenting to participate in this study before your doctor will know if you are eligible. Your doctor will need to review pictures of your heart vessels. You are eligible for this study if your doctor determines that you need a procedure to open clogged vessels in your heart. Your doctor will let you know if you are eligible to participate.

Background and Purpose

You are being asked to be a volunteer in this research study because you are having signs and symptoms of coronary heart disease. This may be a serious heart problem where the heart does not get enough oxygen. This condition may be caused by a partial blockage in one or more of the blood vessels in your heart.

This research study involves the use of an investigational drug called cangrelor, which is being tested for its ability to prevent blood clots in patients having a balloon procedure known as a percutaneous coronary intervention (PCI) to open blocked blood vessels in the heart. This study also uses the FDA-approved drug clopidogrel (Plavix®). Plavix is approved to treat heart attacks and strokes. The initial dose of Plavix that you will receive when you have a PCI can be up to two times the approved dose depending on your institution's standard of care. The purpose of this study is to compare the safety and effectiveness of cangrelor combined with Plavix to the safety and effectiveness of Plavix alone. Cangrelor has not been approved by the US Food and Drug Administration (FDA); therefore, the use of cangrelor is experimental in this study.

This research study will enroll approximately 10,900 people at approximately 200 sites globally.

Description of the Study

Your doctor will also perform a complete medical evaluation to find out if you can participate in this research study. It will include medical history, a physical exam, demographic questions, blood tests, a urine sample and an electrical tracing of the heartbeat (ECG). For the blood tests, about 4 teaspoons (approx 20 mLs or ¾ ounce) of blood will be drawn by a trained person through a single needle puncture of a vein. All of these evaluations are usually conducted as part of the standard patient care. Standard of care means that you would have these tests or procedures performed whether you are in the study or not. In addition to the normal blood tests that you will have as part of your standard of care, you will have 4ml (approximately 1 teaspoon) of blood drawn for the study which will be sent to a central lab. You should tell your doctor about your medical history, including all medicines that you are taking (even herbal treatments or over-the-counter products) and if you are taking part in any other studies. You should also tell your doctor if you are pregnant, or if you think that you may be pregnant. Females of childbearing age must receive a pregnancy test that is confirmed to be negative before participating in this study.

Study Procedures

If you qualify and wish to continue, you will be randomly assigned (by chance) to 1 of 2 study groups:

- **Cangrelor Group** - during the PCI procedure you will get cangrelor through an IV (intravenous) catheter (plastic tubing) inserted into your vein that will slowly inject the cangrelor into your body for at least 2 hours. However, your physician may choose to continue the infusion for up to a total of 4 hours if the duration of the PCI procedure is longer than 2 hours. Per your institutions' standard of care you will receive 2 - 4 placebo capsules (capsules containing no medication) at the time of the PCI procedure. Finally, you will receive four (4) 150 mg capsules of Plavix (600 mg total) immediately after the cangrelor drip is stopped.
- **Placebo Group** - during the PCI procedure you will get placebo (a medically inactive substance) through an IV catheter inserted into your vein that will slowly inject into your body for at least 2 hours. However, your physician may choose to continue the infusion for up to a total of 4 hours if the duration of the PCI procedure is longer than 2 hours. Per your institutions' standard of care, you will receive 2 - 4 150 mg capsules of Plavix at the time of the PCI. Finally, you will receive four (4) placebo capsules immediately after the placebo drip is stopped.
- You will have an equal chance of getting either of the intravenous study drugs (cangrelor or placebo). Neither you nor the research study doctor will know which study drug you are getting. However, in the event of a medical emergency, the research doctor will be able to find out which study drug you are taking.

During your hospitalization, you will need to have at least 2 more ECG's and 4 blood samples taken [about 5 teaspoons (approx 25 mLs or 1 ounce)]. Three of the blood samples (4 mls each) will be drawn and sent to the central lab for analysis. As a part of standard medical treatment you may also receive Aspirin and other medications to prevent complications related to your procedure based on your physician's judgment. The day after the procedure, medication to prevent blood clots from forming and Aspirin will be prescribed for you. These need to be taken for at least one month or more based up on your physician's judgment.

Follow-Up

You will get follow-up phone calls in about 2 days (if you are no longer in hospital) and 1 month after the PCI procedure to see how you are doing and if there are any changes in your medical history and condition since the previous contact. You will be asked to inform the research staff if there are any changes in your contact information during the follow-up period.

Length of Participation

Your participation in this research study will begin when you sign this consent form and continue for approximately 35 days after your procedure.

Withdrawal from Study

You can end your participation in this study at any time. Your doctor may also decide to end your participation in the study early, if:

- new information about the treatment suggests that it will not work
- new information about the treatment suggests that it will be unsafe for you
- you do not follow the study rules
- you have a new injury or illness

If you or your doctor decides to stop your participation in the study, you may be asked to have additional laboratory tests and examinations that your doctor thinks are necessary.

Risks/Benefits

Cangrelor: Cangrelor has been administered to approximately 7,600 people in other studies. The most common side effect seen with cangrelor is bleeding. As with any blood-thinning medication, bleeding can occur at or into any place in the body including at the site of needle sticks, in the digestive system, inside the belly, or into the urine. This may be manifested as but not limited to bruising, hematoma, decreases in hemoglobin or hematocrit (both signs of blood loss seen in laboratory examinations), purpura (red or purple discoloration on the skin caused by bleeding underneath the skin which can be small or large), as well as prolongation of bleeding time; rarely (< 1/1000), bleeding can occur inside the eyes or the brain. Bleeding events may be severe and result in other complications, including death.

The other common side effects reported include: Back pain, chest pain, nausea (uneasiness of the stomach), headache, low blood pressure, vomiting, puncture site pain, fever, shortness of breath, and high blood pressure.

Serious side effects have been reported very rarely which included heart attacks, multiple organ failure, or that a clot can form inside the lung or coronary arteries.

Clopidogrel Risks

Clopidogrel (Plavix®) is an approved prescription medication used in the treatment of heart attacks and strokes. The initial dose you will receive in this trial is two times the approved dose; however, it is currently used in the treatment of subjects undergoing a PCI.

As a medication that affects the function of blood platelets, the most common side effects associated with clopidogrel are bleeding. Severe bleeding events that resulted in death have occurred in 0.2% of patients treated. In extremely rare cases (about 4 in a million), a serious bleeding problem called thrombotic thrombocytopenic purpura (TTP) can occur which is a rare disorder which affects the ability for your blood to clot.

The most common side effects of clopidogrel reported in clinical trials more than 54,000 patients at the approved doses were headache, dizziness, stomach pain, chest pain, a drop in your blood cells (which could lead to an increased risk of infection), diarrhea, indigestion, an increase in cholesterol levels, rash, nausea, or a drop in the number of platelets (small particles in the blood that help with blood clotting).

Reproductive Risks

The effects of cangrelor on the unborn child are unknown. There is no information on the long-term effects of cangrelor on either male or female fertility. Similarly, there are no adequate and well controlled studies of Clopidogrel on pregnant women. Do not participate in this study if you are pregnant or if you think you might be pregnant. Be sure to tell your doctor if you think you may be pregnant, or if you are unsure.

Unknown Risks

You might have side effects or discomforts that are not listed in this form. Some side effects may not be known yet. New ones could happen to you. Tell the research doctor or staff right away if you have any problems.

Benefits associated with participation in this research study

You may or may not receive personal benefits from taking part in the study; however, in the future, other people [with heart disease, undergoing heart procedures] may benefit from the information we learn from this study.

Alternative Treatments

You will receive the standard treatments for your condition if you decide not to take part in this study, depending on what your doctor feels best for you in this condition.

Costs

The regular cost of treatment for your condition and your procedure will be billed to you or your insurance carrier. You will receive the study drug and the medical testing needed for this research study for free.

Compensation

You will not be paid for your participation in this study.

Research related injury

If you have any adverse reaction (side effect) from the study or changes in your physical or mental condition during the course of your participation in this research study, you should immediately seek treatment and contact the research staff or study doctor at (phone #.....) as soon as you are able.

If you are injured as a result of participating in this study, The Medicines Company, the Sponsor of the study, will provide for medical treatment to the extent that the injuries resulted from: (a) cangrelor, the drug being studied in the trial, so long as it was administered according to the study protocol, or (b) procedures your doctor performed as part of the study, so long as they were performed according to the study protocol. The costs of treatment will be paid by the Sponsor to the extent they are not covered by your health insurance. No further compensation for research-related injury is available.

Privacy and Confidentiality**Purpose for collecting Protected Health Information**

If you join in this study, you are giving permission for your health information to be collected. Record of your participation in this study will be kept confidential except as required by law, but strict confidentiality cannot be guaranteed. The study doctor, the sponsor, representatives of sponsor, the Food and Drug Administration (FDA), other governmental agencies in the US and other countries, and the IRB (institutional review board or group of people at your medical center who are responsible for reviewing research and protecting your rights.) will be able to inspect and have access to confidential data.

You will not be identified by name, street address, social security number, etc. in any information used outside of the medical center. If the study results are published, no information will be included that can identify you. The information that will be collected could be a part of your medical record filed at [Hospital Name]. You may ask for your medical records at any time. Your agreement to allow the research staff to use your information begins when you sign this document and does not have an expiration date. If you do not agree to allow the use and sharing of your health information, you cannot take part in this study.

The following health information will be collected from you for this study:

- [Your [initials, age, gender, race]
- The dates that you were admitted and discharged from the hospital, relating to this study.
- Any past illnesses or risk factors that may have helped lead to your diagnosis of [heart] disease
- Your medication, schedule for taking medication, and any changes
- Your present health and medical condition
- Information about your heart procedure(s)
- Any changes in your health and medical condition for a period of approximately [x] days after your heart procedure(s)

Access to your Protected Health Information

Your personal health information is protected by The Health Insurance Portability and Accountability Act of 1996 (HIPAA). The research staff at the medical center will use your Protected Health Information to treat you correctly, manage the medical center, and perform research. To make sure that your information is kept confidential, you will be assigned a code number. All information needed for the study will be recorded and tracked using that code.

You should know that by signing this form, you are giving permission for employees or other people connected with the groups listed below to see your medical records. This makes it possible for your safety to be assured, for the research procedures and result of the study to be verified as reliable, and for information to be sent to health care insurers. To the extent that the law allows, your original medical records or copies may be given to the following groups:

- The Medicines Company (the company that sponsors this study) or individuals associated with The Medicines Company
- Members, consultants and staff of the Institutional Review Board at your medical center
- Billing or quality assurance staff at your medical center
- The Joint Commission of Accreditation of Health Care Organizations
- The Food and Drug Administration or other authorities

Your Protected Health Information will be kept as confidential as possible, but the medical center cannot promise complete privacy. Laws stop the medical center from using your Protected Health Information in any way other than described in this form. Once your information leaves the medical center, we will not be able to control how it is used because laws no longer protect the information. If your research records are kept with your medical records, only the information that is needed for the research will be sent to the groups listed above. This information will show why you have been asked to participate in this research study.

The use and sharing of your health information from this study will continue for an indefinite time. However, you have the right to stop allowing the use or sharing of your health data. You can do this at any time by writing to the study doctor. If you do this, the collecting of any new health data from you will stop, except if needed to follow-up on a side effect you were having in the study. Any data that is collected before you wrote your letter may continue to be used.

QUESTIONS ABOUT RESEARCH

If you have any questions about the research, you should contact **Dr. Name** at **phone #**. During non-business hours you should contact **Dr. Name** at **phone #**.

If you have questions about your rights as a participant in this research, you should contact **Name** at the **Organization/IRB at phone #**. You will receive a copy of this form.

Statement of Consent:

I understand that this study involves research. I have read this informed consent. My questions have been answered. I will be given a copy of this document. I know that taking part in this study is voluntary. I may refuse to be in the study without losing any benefits I would otherwise receive. The study and its risks and benefits, alternative treatments, procedures and purpose have been explained to me. By signing this form, I have not lost any legal rights. I allow access of my medical records to government agencies and The Medicines Company or their designees for this purpose. My identity will be kept confidential if the data collected from this study is used for publication or educational purposes.

I will be told about new findings the investigators learn during the study that may affect my willingness to stay in the study. If I want to have this information sent to my personal doctor, I should tell [Dr. investigator].

Statement of Consent:

By signing below, you (the participant) acknowledge that you have read, or have had read to you, this informed consent document, have talked with research personnel about this study, have been given the opportunity to ask questions and have them satisfactorily answered, and voluntarily consent to participate **in this study** as described in this form.

Printed name of Patient

Signature of Patient Date/Time

Signature of Patients' Legally Authorized Representative (if applicable) Date/Time

I explained the study to the patient and witnessed their consent to the study:

Investigator/Designee Name

Investigator/Designee Signature Date/Time

CONSENT TO PARTICIPATE IN RESEARCH

A Clinical Trial Comparing Cangrelor Treatment Strategy to Clopidogrel Standard of Care Treatment Strategy In Subjects Who Require Percutaneous Coronary Intervention

Champion PHOENIX

Principal Investigator: Matthew Price, MD

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Research Site(s): Division of Cardiovascular Diseases. Scripps Clinic/Scripps Green Hospital
10666 North Torrey Pines Road, La Jolla, CA 92037

Sponsor: The Medicines Company

Before you start reading about this research, please read the California Experimental Subjects' Bill of Rights, which is page 10 of this form.

This is a clinical trial (a type of research study or medical experiment). Clinical trials include only patients who choose to take part. Please take your time to make your decision. Discuss it with your friends and family. Be sure to ask questions about anything you do not understand.

Why is this research being done?

You have been asked to participate in a study because you have chest pain or other symptoms of heart disease. Your symptoms are caused by a blockage in the arteries supplying blood to part of your heart muscle. To open this blockage, your doctors agree that you should undergo an angiogram and possible angioplasty in a procedure called cardiac catheterization. The doctor can look at blood vessels in your heart to see if they are blocked by using an x-ray machine and angioplasty uses small balloons and other devices to unblock the artery if necessary. During angioplasty, drugs are given to thin the blood and prevent clotting. Drugs can also be given before the procedure or immediately after the procedure to help thin the blood and prevent clotting.

This research study involves the use of an investigational drug called cangrelor, which is being tested for its ability to prevent blood clots in patients having a balloon procedure known as a percutaneous coronary intervention (PCI) to open blocked blood vessels in the heart. This study also uses the FDA-approved drug clopidogrel (Plavix®). Plavix is approved to treat heart attacks and strokes. The initial dose of Plavix that you will receive when you have a PCI can be up to two times the approved dose depending on your institution's standard of care. The purpose of this study is to compare the safety and effectiveness of cangrelor combined with Plavix to the safety and effectiveness of Plavix alone. Cangrelor has not been approved by the US Food and Drug Administration (FDA); therefore, the use of cangrelor is experimental in this study.

The sponsor, the company that pays Scripps and the study doctor to do the study, is The Medicines Company. This research study will enroll approximately 10,900 people at approximately 200 sites globally; approximately 75 will be enrolled at Scripps. Approximately 7,600 have already received this drug in studies like this one.

What makes this different from usual treatment?

Cangrelor is an experimental drug that has not been approved by the US Food and Drug Administration (FDA) for general use.

Neither you nor your doctor will know whether you are being given cangrelor or Plavix. You will be given an intravenous infusion (IV) (a liquid drug solution dripped down a tube and into a thin needle in your vein) with cangrelor or placebo during your angioplasty or stent placement procedure. Placebo looks like the study drug but does not contain cangrelor or Plavix. The infusion will be given for at least 2 hours; however, your physician may choose to continue the infusion for up to a total of 4 hours if the duration of the PCI procedure is longer than 2 hours. Prior to the start of the infusion, you will also be required to take 2 to 4 capsules of either Plavix or placebo. The number of pills you receive will depend on your doctor's decision what is best for your procedure. When the infusion stops you will take another 4 capsules of either Plavix or placebo. One of these two sets of 4 capsules will have contained active Plavix so all subjects will have received Plavix by the completion of study drug administration.

To make sure you cannot tell which drug you will receive, you will have an equal chance (like flipping a coin) of being in one of two groups. **Group A:** You will receive placebo (pills), Cangrelor (IV), Plavix (pills) **Group B:** You will receive Plavix (pills), placebo (IV), placebo (pills).

How long will I be in the study?

If the study suits you and you agree to join, you will be in it for approximately 35 days after your procedure.

What will happen to me during the study?

Sign Consent: After reading this form and having any questions answered that you might have, you will sign this form if you are interested in joining this study.

All these procedures are part of Standard of Care for your condition and would be done even if you did not join the study. They are:

- A pregnancy test is required for all women of childbearing age

- **EKG:** Self-stick pads will be placed on your chest and legs. Wires will be attached to the pads and to a machine that will record the electrical activity of your heart. An electrocardiogram (EKG) is a tracing of your heart's activity.
- **Vital Signs:** Your blood pressure, heart rate, temperature and weight (vital signs) will be measured
- **Angiogram** (procedure to look at the blood vessels in your heart)
- **Blood tests** (About 5 teaspoons of blood will be drawn from your vein to look at your heart, and body functions), every 6 hours until discharge

The following procedures will be performed if you join this study. They are:

- A separate IV will be started for the study drug.
- If an ECG was done more than 7 days before your procedure, another ECG will be done.
- If blood tests for cardiac enzymes (substance released from heart muscles that indicates heart attack) were drawn more than 72 hours before your procedure they will be drawn again.
- Another teaspoon of blood will be drawn from the access site during your procedure to look at your heart function.

During your angiogram: Your doctor will put a plastic tube, called a sheath, in the blood vessel in your groin. Your groin is the area of your leg right below your hip bone. Once the sheath is in, your doctor will be able to put long narrow tubes, called catheters, through the sheath and into the blood vessel in your groin. The catheter is passed up the blood vessel into the heart's blood vessels. Your doctor will then inject dye through the catheter. The dye will allow your doctor to look at any blockages in your heart's blood vessels under the x-ray machine.

If there is a blockage in one of your heart's blood vessels, doctors can open up that blockage by putting a balloon or stent inside the blood vessel. The stent is made of stainless steel and looks like a chain linked fence. The stent is able to keep your blood vessel open and allow blood to flow through.

If you agree to participate and if your doctor performs angioplasty and/or stenting to open your blood vessel, you will be assigned by chance (like flipping a coin) to one of the following treatments:

- Cangrelor through an IV line plus 2-4* placebo capsules that look like Plavix
- OR
- Placebo (salt water) through an IV line to mimic cangrelor plus 2-4* capsules of Plavix

**The number of capsules you will receive in either treatment group depends on your doctor's decision what is best for your procedure.*

These drugs will be given during the procedure. You will have an equal chance of getting either of the study drugs (cangrelor or placebo). Additionally, you will also receive 4 capsules of either placebo or Plavix after the procedure. You won't know which you get and neither will the study doctor or staff. However, in the event of a medical emergency, the research doctor will be able to find out which study drug you are taking.

After the procedure and prior to discharge you will need to have at least 2 more ECG's and 4 blood samples taken, about 5 teaspoons. Three of the blood samples will be drawn and sent to the central lab for analysis. As a part of standard medical treatment you may also receive Aspirin and other medications to prevent complications related to your procedure based on your physician's judgment. The day after the procedure, medication to prevent blood clots from forming and Aspirin will be prescribed for you. These need to be taken for at least one month or more based up on your physician's judgment.

Follow-Up: You will be contacted 2 days after your procedure on the telephone as well as 30 days after your procedure. During these contacts, you will be interviewed about your health and any changes in your medication since your last visit and/or contact. If you move or change your telephone number, please notify the study doctor/ or the study staff so he/she will be able to contact you at these times.

The study procedures are broken up into six parts: Before Angiogram, During Procedure, After Procedure/ Discharge, 2 Day follow-up and 30 Day follow-up. Please refer to the visit schedule below.

Visit Schedule

Test	Before Procedure	During Procedure	After Procedure/Discharge	2 Day Telephone Follow Up	30 Day Telephone Follow Up
Answer questions about your health.	X			X	X
Doctor Examines you	X		X		
Vital Signs	X		X		
ECG	X		X		
Blood Samples	X	X	X		
Randomization of Study Drugs		X			
Administration of Study Drugs		X	X		

Could I experience any side effects or discomforts?

Risks associated with an angiogram, Standard of Care:

All angiograms and stent procedures can cause reactions or side effects. If you have an angiogram you may get any of the following:

Likely

- chest pain or discomfort
- bruising
- pain at the access site, the site where the catheters were inserted in the body, usually the groin

These side effects are usually mild and go away either on their own or with medication.

Less likely

- renewed formation of a narrowing in the treated vessel
- coronary spasms

These side effects can be serious. If you get any of these, you may need treatment, which could include medication or another angiogram.

Not very likely

- Irregular heart beat
- Unnatural connection between vein and artery
- Injury or tearing of blood vessel possibly requiring surgical repair
- Part of the wall of the artery cracks during the procedure and may block part or all of the artery reducing blood flow to the heart which may lead to a heart attack
- Side effects due to contrast dye or heparin
- Air, tissue, or clots which can block the vessel
- Bleeding that could require a blood transfusion
- High or low blood pressure
- Infection
- Inadequate supply of blood to the heart
- Bruising which resides on a blood vessel
- Movement of the stent as it is sliding from the balloon into the blood vessel
- Plugging of the stent with blood clots
- Stroke or other neurologic event
- Total blockage of the vessel
- Collection of blood or fluid in the lining of the heart
- Worsening of heart, lung and kidney function, which could lead to heart, lung failure, or kidney failure
- Fluid in the lung tissues
- Allergic reaction to the contrast dye (including kidney failure), to the stent materials, or to the drugs which prevent blood clots
- Low blood pressure resulting in inadequate blood flow to the body
- Increased risk of non-Q wave myocardial infarction called a heart attack, if multiple stents implanted
- Emergency surgery
- Death

Risks with being in this research study:

All drug treatments whether a part of this study or not, have the potential to cause side effects. All side effects should be reported to your study doctor or staff member at every visit or by phone between visits.

Cangrelor Risks

Cangrelor has been given to about 7,600 people in other studies. Below are the known side effects associated with the study medication, Cangrelor.

Likely

- Bleeding

Less likely

- Bruising

- Oozing at puncture site
- Drop in red blood cell count, which can cause tiredness
- Back pain
- Chest pain
- Nausea
- Headache
- Low blood pressure
- Vomiting
- Puncture site infection
- Fever
- Shortness of breath

Not very likely

- High blood pressure
- Dangerous, rapid heart rate
- Chest discomfort
- Slow heartbeat less than 60
- Irregular heart beat
- Pain in arms or legs
- Fainting
- Anxiety
- Dizziness
- Tearing of coronary artery
- Upset stomach
- Abdominal pain
- Dangerous, rapid irregular heartbeat
- Diarrhea
- Pain in your muscles or bones
- Sleeplessness
- Failure of heart's pumping ability
- Low potassium in the blood
- Kidney failure
- Bleeding into digestive system, abdomen and urine
- Death due to serious bleeding

You will be carefully monitored before, during and after your procedure and any side effects you may experience will be treated.

Medications

There are possible risks from the medications Clopidogrel (Plavix ®) and aspirin, the FDA approved medications used to prevent your blood from clotting. For example, there is a small risk of bleeding from an ulcer, if you have one. You could also bleed at the puncture site in your groin or arm.

- **Tell your study doctor about any unusual bleeding that you experience**
- **Tell your regular doctor or dentist that you are taking blood-thinning medication before any procedure**

Blood thinning medications such as aspirin and clopidogrel can cause diarrhea, nausea, digestive problems, vomiting, lack of appetite, and skin rash. In rare cases, the number of white blood cells decreases. If the number decreases markedly, you could be less able to fight an infection. TTP (thrombotic thrombocytopenic purpura) is a rare but possible side effect of clopidogrel. TTP is a rare disease in which small blood clots form suddenly throughout the body.

Reproductive Risks

The effects of Cangrelor on the unborn child are unknown. There is no information on the long-term effects of Cangrelor on either male or female fertility. Similarly, there are no adequate and well controlled studies of Clopidogrel on pregnant women. Do not participate in this study if you are pregnant or if you think you might be pregnant. Be sure to tell your doctor if you think you may be pregnant, or if you are unsure.

If you are female, you will have a pregnancy test. You can't be in the study if you are pregnant or plan to get pregnant. You can't be in the study if you are nursing a baby. The drugs used could hurt a baby.

Unknown Risks

You might have side effects or discomforts that are not listed in this form. Some side effects may not be known yet. New ones could happen to you. Tell the research doctor or staff right away if you have any problems.

Is there anything else I should know?

- You may not be enrolled in this study even if you sign this consent form.
- If you have been in another research study in the last month, you should tell the study doctor.
- You cannot give the drug to anyone else and you should keep it away from children.

Blood Sampling: It may hurt when the needle pokes your skin. You could be sore and bruised for a day or two. You could get an infection, but that's not likely. If you have ever felt dizzy or fainted while having blood drawn, you should tell the person drawing your blood. If you lie down, you might not get dizzy.

Will I benefit from participating?

You may or may not benefit from taking part in the study. However, in the future, other people [with heart disease, undergoing heart procedures] may benefit from the information we learn from this study.

Will I be paid?

No, you will not be paid to be in the study.

Will it cost anything to be in the study?

The regular cost of treatment for your condition and your procedure will be billed to you or your insurance carrier. You will receive the study drug and the medical testing needed for this research study for free.

What if I end the study early?

Being in this study is absolutely voluntary. If you do not want to be treated in this study or if you decide to stop the study before you complete your follow-up, your decision to do so will have no effect on your further treatment. Also, the study may be stopped for other reasons or your doctor may have you not be

in the study, with or without your consent, for medical reasons. If you quit the study or are taken out early, you may be asked to do tests to be sure you are as healthy as you were when you started. You can quit the study whenever you want to.

You must write to the study doctors at the address below and tell them you no longer want to be part of the research:

Matthew Price, MD
Scripps Clinic, Department of Cardiovascular Diseases
10666 North Torrey Pines Road, Rm S-1056
La Jolla, CA 92037

The study doctors or the sponsor can take you out of the study:

- If you do not follow the study requirements
- If the study is cancelled by the sponsor or the FDA
- The study doctors think it is necessary for your health or safety

What treatments could I take instead of joining this study?

You will receive the standard treatments for your condition if you decide not to take part in this study, depending on what your doctor feels best for you in this condition.

What are my rights?

- You can call the staff to ask any questions about this study. The telephone number is listed at the top of this form.
- You can decide not to be in this study or you can quit after starting. Whatever you do, your medical care at Scripps will not be affected.
- If you have any questions about your rights, call the Scripps Office for the Protection of Research Subjects at (858) 652-5500. You should also read the *Experimental Subject's Bill of Rights*, which is toward the end of this form.
- You do not have to be in this study. You still have all your legal rights whether you join the study or not.
- You have the right to be told about any new information that might make you change your mind about staying in the study

What are my responsibilities if I join?

If you are in this study, you are expected to:

- Follow the instructions of the research staff
- Report any serious or unusual side effects to the study doctor
- Take study drugs as directed
- Keep your study appointments

What about confidentiality?

The study doctor and the sponsor will keep your personal information confidential whenever they can. We can't promise that no one will see it. Your identity as a participant in this study will remain strictly confidential. Authorized representatives of this institution, the FDA and the sponsor, The Medicine's Company can view your medical files to ensure that the information provided to them is correct. Information received and processed by The Medicines Company, or its representatives will not include your name or personal data. You will only be identified in the study under a study specific code. If the

study results are published, no information will be included that can identify you. For more information, see the **Authorization to use your Private Health Information** at the end of this consent form.

What if I get hurt while in the study?

You can call Dr. Matthew Price at 858-554-9859 Monday through Friday, 8:00 a.m. to 5:00 p.m. if you get sick or injured while in this study. If you get sick or injured at night or on a weekend, call (858) 455-9100 ask for the doctor on call for the Division of Cardiology.

If you need medical or urgent care during the study, it will be provided. You or your medical insurance will be billed for any treatment given.

Scripps and the sponsor of the study do not plan to pay for anything else. You are not giving up any of your legal rights by being in this study

Will Scripps, the study doctor or sponsor benefit from this study?

Scripps and the study doctors are being paid by The Medicines Company to do this study. You have the right to ask and be told about any financial interests they might have in this study. The investigators have no financial conflict of interest to report.

I agree to participate.

I have read and understood the explanation of the study. The study has also been explained to me by Dr. Price or his designee. I have had a chance to ask questions and have them answered to my satisfaction. I agree to take part in this study. I have not been forced or made to feel obligated to take part.

*I have read the attached **Experimental Subject's Bill of Rights** and the **Authorization to use my Private Health Information** that contains some important information about research studies. I must sign this consent form, the **Experimental Subject's Bill of Rights** and the **Authorization to use my Private Health Information**. I will be given a signed copy of each to keep.*

Printed Name of Subject

Signature of Subject

Date

Signature of person conducting the informed consent discussion

Date

Role of person named above in the research project

EXPERIMENTAL SUBJECT'S BILL OF RIGHTS*

If I am asked to consent to be a subject in a research study involving a medical experiment, or if I am asked to consent for someone else, I have the right to:

Learn the nature and purpose of the experiment (also called "study" or "clinical trial").

Receive an explanation of the procedures to be followed in the study, and any drug or device to be used.

Receive a description of any discomforts and risks that I could experience from the study.

Receive an explanation of any benefits I might expect from the study.

Learn about the risks and benefits of any other available procedures, drugs or devices that might be helpful to me.

Learn what medical treatment will be made available to me if I should be injured because of the study.

Ask any questions about the study or the procedures involved.

Quit the study at any time, and my decision will not be used as an excuse to withhold necessary medical treatment.

Receive a copy of the signed and dated consent form.

Decide to consent or not to consent to a study without feeling forced or obligated.

If I have questions about a research study, I can call the contact person listed on the consent form. If I have concerns about the research staff, or need more information about my rights as a subject, I can contact the Scripps Office for the Protection of Research Subjects, which protects volunteers in research studies. I may telephone the Office at **(858) 652-5500**, 8:00 a.m. to 4:00 p.m. weekdays, or I may write to the Scripps Office for the Protection of Research Subjects, 11025 North Torrey Pines Road, Suite 200, La Jolla, CA, 92037.

By signing this document, I agree that I have read and received a copy of this Bill of Rights.

Signature of Subject or Legal Representative

Date

*California Health & Safety Code, Section 24172



Authorization to use your Private Health Information

Name of Study: Champion PHOENIX

Principal Investigator: Matthew Price, MD

IRB Study Number: 11-5664

What is private health information?

Private health information is any information that can be traced back to you. We need your authorization (permission) to use your private health information in this research study. The private health information that we will use and share for this study includes:

- Your past and present health information, including progress notes and history and physical in your medical record
- Information that can be used to contact you, such as your home address, phone number(s), and/or emergency contacts if you can not be reached any other way
- Results of your medical tests including cardiac stenting procedures, treadmill exercise tests, EKG's, physical exams, and laboratory (blood and urine) tests
- Research records
- Records about phone calls made as part of this research
- Records about your study visits

Who else will see my information?

In addition to the Principal Investigator, this information may be shared with:

- the sponsor of the research study, The Medicine Company and any groups or companies that work with the sponsor.
- government agencies, such as the US Food and Drug Administration and agencies like it in other countries, or agencies of the Department of Health and Human Services, and
- Scripps committees that review research to help protect people who join research studies.

Once we have shared your information we cannot be sure that it will stay private. If **you** share your information with people outside the research team, it will no longer be private. Your name will not be used in any report that is written.

How long will Scripps use and share my information?

- Your information will be used and shared until the research is completed, which we think will be in 2021.

What if I change my mind about sharing my research information?

If you decide not to share your information anymore:

- The sponsor and the research team can continue to use any of the private information that they already have.
- You will no longer be a part of the research study.
- You will still get the same medical care that you've always had at Scripps.
- You must write to the investigator and tell him that you no longer want to share your information. Write to the investigator at:

Matthew Price, MD
Scripps Clinic Torrey Pines
Division of Cardiovascular Diseases
10666 N. Torrey Pines Road
La Jolla, CA 92037

Do I have the right to see and copy my research information?

You cannot see your research information while the study is going on, unless it is also being used for your health care. Once the study is over, you can ask to see any research information that is in your Medical Record that is kept at Scripps.

If you agree to share your information you should sign this form below. You will be given a copy of this form.

I agree to share my information as described in this form

Print your name

Sign your name

Date

If you have questions or concerns about your privacy and the use of your personal medical information, contact the investigator at the telephone number listed in the consent form.

Attachment 6: Austrian ICD

PATIENTENINFORMATION UND EINWILLIGUNGSERKLÄRUNG

TITEL DER STUDIE:

CHAMPION Phoenix: Eine klinische Studie zum Vergleich von Cangrelor mit Clopidogrel als Standardbehandlung bei Patienten, die eine perkutane Koronarintervention benötigen

PRÜFPLANNUMMER: TMC-CAN-10-01

PRÜFARZT: Prim. Prof. Dr. Kurt Huber

Sehr geehrte Patientin, sehr geehrter Patient,

Sie haben die Möglichkeit, an einer klinischen Studie teilzunehmen. Die Teilnahme an dieser Studie ist vollkommen freiwillig. Diese Studie wird von Prim. Prof. Dr. Kurt Huber im Krankenhaus Wilhelminenspital durchgeführt. Es ist wichtig, dass Sie diese Patienteninformation lesen und verstehen. Bitte lesen Sie sie aufmerksam durch. Nehmen Sie sich Zeit, um dem Prüfarzt oder dem Studienpersonal so viele Fragen über die klinische Studie zu stellen, wie Sie möchten. Bitte wenden Sie sich an den Prüfarzt oder das Studienpersonal, wenn Sie die Bedeutung bestimmter Begriffe nicht kennen oder Fragen zum Inhalt haben. Das Lesen dieser Patienteninformation und das Gespräch mit dem Prüfarzt oder dem Studienpersonal sollen Ihnen helfen zu entscheiden, ob Sie an der klinischen Studie teilnehmen möchten oder nicht. Wenn Sie sich für eine Teilnahme entscheiden, müssen Sie vor Ihrer Teilnahme an der klinischen Studie die Einwilligungserklärung unterzeichnen und datieren. Sie werden in die Teilnahme an der Studie einwilligen, bevor Ihr Prüfarzt weiß, ob Sie dafür geeignet sind. Ihr Prüfarzt muss Bilder Ihrer Blutgefäße im Herzen überprüfen. Sie sind für die Studie geeignet, wenn Ihr Prüfarzt feststellt, dass die blockierten Gefäße in Ihrem Herzen operativ geöffnet werden müssen. Ihr Prüfarzt wird Ihnen mitteilen, ob Sie für eine Studienteilnahme geeignet sind.

Hintergrund und Ziel der Studie

Sie werden gebeten, freiwillig an dieser klinischen Studie teilzunehmen, weil Sie Anzeichen und Symptome einer koronaren Herzkrankheit aufweisen. Dabei kann es sich um ein schwerwiegendes Herzproblem handeln, bei dem das Herz nicht ausreichend mit Sauerstoff versorgt wird. Diese Erkrankung kann durch eine teilweise Blockierung eines oder mehrerer

PATIENT INFORMATION AND CONSENT

STUDY TITLE:

CHAMPION Phoenix: A clinical trial comparing cangrelor with clopidogrel as a standard treatment in patients requiring percutaneous coronary intervention

PROTOCOL NUMBER: TMC-CAN-10-01

INVESTIGATOR: Principal Prof. Kurt Huber

Dear patient, dear patient,

You have the opportunity to participate in a clinical trial. Participation in this study is completely voluntary. This study will be performed by Principal Professor Kurt Huber at Hospital Wilhelminenspital. It is important that you read and understand this patient information. Please read them carefully. Take time to ask the investigator or the study staff as many questions about the clinical trial as you like. Please contact the investigator or the study staff, if you do not know the meaning of certain terms or have questions about the content. Reading this patient information and conversing with the investigator or the study staff will help you to decide if you wish to participate in the clinical trial or not. If you decide to participate, you must sign and date the informed consent form prior to participation in the clinical trial. You will agree to participate in the study before your investigator knows if you are suitable. Your investigator must review the images of the blood vessels in the heart. You are eligible for the study if your investigator finds that the blocked vessels in your heart must be opened surgically. Your investigator will tell you whether you qualify for participation in the study.

Background and purpose of the study

You are being asked to participate voluntarily in this clinical trial because you have signs and symptoms of coronary heart disease. It may be a serious heart problem in which the heart does not receive enough oxygen. This condition may be caused by partial blockage of one or more blood vessels in your heart.

Blutgefäße in Ihrem Herzen verursacht werden.

In dieser klinischen Studie wird ein in der Erprobung befindliches Medikament namens Cangrelor angewendet. Es soll untersucht werden, ob Cangrelor in der Lage ist, die Bildung von Blutgerinnseln bei Patienten zu verhindern, bei denen eine Ballondilatation (eine sogenannte perkutane Koronarintervention oder PKI) durchgeführt wurde, um blockierte Blutgefäße im Herzen wieder durchgängig zu machen. Im Rahmen dieser Studie wird auch das von der US-amerikanischen „Food and Drug Administration“ (FDA) zugelassene Arzneimittel Clopidogrel (Plavix®) angewendet. Plavix ist für die Behandlung von Herzinfarkten und Schlaganfällen zugelassen. Die Anfangsdosis Plavix, die Sie erhalten, wenn bei Ihnen eine PKI durchgeführt wird, kann bis zum Zweifachen der zugelassenen Dosis betragen, abhängig von der in Ihrer Einrichtung angewendeten Standardbehandlung.

In dieser Studie soll die Sicherheit und Wirksamkeit einer Kombinationstherapie von Cangrelor und Plavix mit der Sicherheit und Wirksamkeit einer Behandlung mit Plavix alleine verglichen werden. Cangrelor wurde bisher nicht von der US-amerikanischen „Food and Drug Administration“ (FDA) zugelassen; daher ist die Anwendung von Cangrelor in dieser Studie experimentell.

In diese klinische Studie werden etwa 10.900 Patienten an etwa 200 Prüfzentren weltweit aufgenommen.

Beschreibung der Studie

Ihr Prüfarzt wird auch eine vollständige medizinische Untersuchung durchführen, um festzustellen, ob Sie an der klinischen Studie teilnehmen können. Dies umfasst Ihre Krankengeschichte, eine körperliche Untersuchung, Fragen zu Ihrer ethnischen Zugehörigkeit, Ihrem Alter und Geschlecht, Blutuntersuchungen, eine Urinprobe und eine elektrische Aufzeichnung Ihres Herzschlags (EKG). Für die Blutuntersuchungen werden Ihnen von einer Fachkraft etwa 4 Teelöffel (ca. 20 ml) Blut durch einen Einstich in eine Vene entnommen. Die Blutproben werden verwendet, um die Hämatologie sowie die Biomarker für die myokardiale Infarktbildung (Troponin I und T) zu analysieren. Alle diese Beurteilungen werden im Labor des Krankenhauses durchgeführt. Alle diese Untersuchungen werden für gewöhnlich im Rahmen

In this clinical study an investigational drug called cangrelor is used. It will be investigated whether cangrelor is able to prevent blood clots in patients in whom a balloon dilation (a so-called percutaneous coronary intervention or PKI) was performed to make blocked blood vessels in the heart consistent again. This study will also use the U.S. 'Food and Drug Administration' (FDA) approved drug clopidogrel (Plavix®). Plavix is used for the treatment of heart attacks and strokes. The initial dose of Plavix, which you get when you get a PKI, can be up to twice the approved dose dependent upon the standard treatment applied in your facility.

This study will evaluate the safety and efficacy of combination therapy with cangrelor and Plavix compared to the safety and efficacy of treatment with Plavix alone. Cangrelor has not yet been licensed by the U.S. "Food and Drug Administration" (FDA), so the use of cangrelor in this study is experimental.

In this clinical study about 10,900 patients at 200 clinical sites will be enrolled worldwide.

Description of the study

Your investigator will perform a complete medical examination to determine if you can participate in the clinical trial. This includes your medical history, physical examination, questions about your ethnicity, age and gender, blood tests, a urine sample and an electric recording of your heart (ECG). For the blood tests about 4 teaspoons (20 ml) of blood will be removed from you through a puncture into a vein by a specialist. The blood samples will be analyzed for hematology and biomarkers of myocardial infarction (troponin I and T). All of these tests will be performed in the hospital laboratory. All of these investigations are usually performed in the context of standard of care. Standard of care means that these studies and measures would be carried out in any case regardless of whether you are participating in the study or not. In addition to the regular blood tests

der Standardversorgung durchgeführt. Standardversorgung bedeutet, dass diese Untersuchungen und Maßnahmen auf jeden Fall durchgeführt würden, unabhängig davon, ob Sie an der Studie teilnehmen oder nicht. Zusätzlich zu den normalen Blutuntersuchungen, die im Rahmen Ihrer Standardversorgung durchgeführt werden, werden für die Studie 4 ml (etwa 1 Teelöffel) Blut entnommen, die an ein amerikanisches Zentrallabor geschickt werden. Bei dieser Probe wird eine weitere Analyse vorgenommen, und zwar die CK-MB Bestimmung, die bei der Diagnose des Herzinfarktes hilft. Der Zugang zu den Proben ist nur berechtigtem Laborpersonal gestattet. Die Proben werden xxxxx Tage nach der Analyse zerstört. Sie sollten Ihren Prüfarzt über Ihre Krankengeschichte – einschließlich aller Medikamente, die Sie derzeit einnehmen (auch pflanzliche Heilmittel oder frei verkäufliche Produkte) – sowie über Ihre Teilnahme an anderen Studien informieren.

Studienablauf

Wenn Sie für die Studienteilnahme geeignet sind und weiterhin teilnehmen möchten, werden Sie nach dem Zufallsprinzip einer von zwei Studiengruppen zugeteilt, entweder der Cangrelor und Plavix- oder der Placebo und Plavix-Gruppe. Der Grund für die Verabreichung von Placebo ist, die Behandlung zu verblinden, damit weder Sie noch Ihr Prüfarzt wissen, ob Sie das Studienmedikament Cangrelor erhalten haben, bevor Sie die Plavix Standardbehandlung verabreicht bekommen. Dies ist wichtig, damit Ihre Erwartungen nicht das Ergebnis beeinflussen:

- **Cangrelor-Gruppe** – während der PKI wird Ihnen Cangrelor langsam über mindestens 2 Stunden durch einen intravenösen (IV-) Katheter (Plastikröhrchen) in eine Vene verabreicht. Ihr Prüfarzt kann die Infusion jedoch auf bis zu insgesamt 4 Stunden verlängern, wenn die PKI länger als 2 Stunden dauert. Gemäß der Standardversorgung in Ihrer Einrichtung erhalten Sie zum Zeitpunkt der PKI 2 bis 4 Placebo-Kapseln (Kapseln, die keinen Wirkstoff enthalten). Abschließend erhalten Sie unmittelbar nach Ende der Cangrelor-Infusion vier (4) Kapseln Plavix zu je 150 mg (insgesamt 600 mg).

- **Placebo-Gruppe** – während der PKI wird Ihnen ein Placebo (eine wirkstofffreie Substanz) langsam über mindestens 2 Stunden durch einen IV-Katheter in eine Vene

as part of your standard care, 4 ml (about 1 teaspoon) of blood are taken for the study which are sent to a central American lab. On this sample a further analysis is carried out, namely a CK-MB determination that helps in the diagnosis of myocardial infarction. Access to the sample is only by qualified laboratory personnel. The samples are destroyed xxxxx days after the analysis. You should inform your investigator about your medical history - including any medications you are currently taking (including herbal remedies or OTC products) - as well as your participation in other studies.

Study procedure

If you are eligible for study participation and wish to participate, you will be randomly assigned to one of two study groups, either the cangrelor and Plavix or placebo and Plavix groups. The reason for the administration of placebo is blinding of the treatment, so neither you nor your investigator know whether you have received the study drug cangrelor before the standard treatment Plavix gets administered. This is important so that your expectations do not influence the result:

- **Cangrelor group** – During the PKI you will be administered cangrelor slowly into a vein over at least 2 hours through an intravenous (IV) catheter (plastic tube). However, your investigator can extend the infusion up to 4 hours in total when the PKI takes longer than 2 hours. According to the standard of care in your facility, you will receive at the time of PKI 2-4 placebo capsules (capsules containing no active ingredient). Finally, you will receive immediately after the end of the cangrelor infusion four (4) capsules, containing 150 mg of Plavix (total 600 mg).

- **Placebo group** - During the PKI you will be administered a placebo (a drug-free substance) slowly into a vein over at least 2 hours through an IV catheter. However, your investigator

verabreicht. Ihr Prüfarzt kann die Infusion jedoch auf bis zu insgesamt 4 Stunden verlängern, wenn die PKI länger als 2 Stunden dauert. Gemäß der Standardversorgung in Ihrer Einrichtung erhalten Sie zum Zeitpunkt der PKI 2 bis 4 Kapseln Plavix zu je 150 mg. Abschließend erhalten Sie unmittelbar nach Ende der Placebo-Infusion vier (4) Placebo-Kapseln.

Die Wahrscheinlichkeit der Zuteilung ist für beide intravenös verabreichten Studienmedikamente (Cangrelor oder Placebo) gleich hoch. Weder Sie noch der Prüfarzt werden wissen, welchem Studienmedikament Sie zugeteilt wurden. In einem Notfall kann der Prüfarzt jedoch in Erfahrung bringen, welches Studienmedikament Sie erhalten.

Während Ihres Krankenhausaufenthalts müssen mindestens 2 weitere EKGs aufgezeichnet und 4 Blutproben [etwa 5 Teelöffel (ca. 25 ml)] entnommen werden. Drei der Blutproben (jeweils 4 ml) werden entnommen und zur Analyse an ein Zentrallabor geschickt. Im Rahmen der medizinischen Standardbehandlung können Sie auch Aspirin oder andere Medikamente erhalten, um Komplikationen in Zusammenhang mit dem Eingriff vorzubeugen. Dies liegt im Ermessen Ihres Prüfarztes. Am Tag nach dem Eingriff werden Ihnen Medikamente zur Vorbeugung von Blutgerinnseln sowie Aspirin verordnet. Diese Medikamente müssen nach Ermessen Ihres Prüfarztes mindestens einen Monat oder länger eingenommen werden.

Nachbeobachtung

Sie werden etwa 2 Tage (sofern Sie nicht länger im Krankenhaus sind) und 1 Monat nach der PKI telefonisch kontaktiert, damit festgestellt werden kann, wie es Ihnen geht und ob es seit dem letzten Kontakt Veränderungen in Ihrer Krankengeschichte und Ihrer Erkrankung gab. Sie werden gebeten, das Studienpersonal zu informieren, wenn sich Ihre Kontaktinformationen während der Nachbeobachtungsphase ändern.

Dauer der Studienteilnahme

Ihre Teilnahme an dieser klinischen Studie beginnt, wenn Sie diese Einwilligungserklärung unterzeichnen, und dauert bis etwa 35 Tage nach Ihrem Eingriff.

Abbruch der Studienteilnahme

Sie können Ihre Teilnahme an dieser Studie jederzeit beenden. Ihr Prüfarzt kann ebenfalls

can extend the infusion up to 4 hours in total when the PKI takes longer than 2 hours. According to the standard of care in your facility, you will receive at the time of PKI 2-4 capsules each with Plavix 150 mg. Finally, you will receive immediately after the end of the placebo infusion, four (4) placebo capsules.

The probability of allocation is equal for both intravenous study medications (cangrelor or placebo). Neither you nor the investigator will know which study drug you have been allocated. In an emergency, however, the investigator can find out which study drug you received.

During your hospital stay at least 2 more ECGs must be recorded and 4 blood samples [about 5 teaspoons (25 ml)] are removed. Three blood samples (4 ml each) will be removed and sent for analysis to a central laboratory. Under standard medical treatment, you can also obtain aspirin or other medicines in order to prevent complications related to the procedure. This is at your investigator's discretion. The day after surgery you will be prescribed drugs to prevent blood clots and aspirin. These drugs need to be taken at your investigator's discretion at least a month or more.

Follow-up

You will be contacted by phone about 2 days (if you are no longer in the hospital) and 1 month after the PKI so that it can be determined how you are and whether there were changes in your medical history and your condition since the last contact. You are asked to contact the study staff if your contact information changes during the follow-up period.

Duration of study participation

Your participation in this clinical trial starts when you sign this consent sign and lasts until about 35 days after your procedure.

Discontinuation of study participation

You can always cancel your participation in this study. Your investigator may also decide to

beschließen, Ihre Studienteilnahme vorzeitig zu beenden, wenn:

- neue Erkenntnisse über die Behandlung darauf hindeuten, dass diese nicht wirkt
- neue Erkenntnisse über die Behandlung darauf hindeuten, dass diese für Sie nicht sicher ist
- Sie sich nicht an die Studienvorschriften halten
- bei Ihnen neue Gesundheitsschäden oder Erkrankungen auftreten

Wenn Sie oder Ihr Prüfarzt beschließen, Ihre Studienteilnahme zu beenden, können Sie gebeten werden, zusätzliche Laboruntersuchungen und andere Untersuchungen zu absolvieren, die Ihr Prüfarzt für notwendig erachtet.

Risiken und Nutzen

Cangrelor: Cangrelor wurde im Rahmen anderer Studien etwa 7600 Personen verabreicht. Die am häufigsten in Zusammenhang mit Cangrelor beobachtete Nebenwirkung sind Blutungen. Wie bei allen blutverdünnenden Medikamenten kann es zu Blutungen am oder im Körper kommen, z. B. an Einstichstellen, im Verdauungssystem, im Bauch oder es kann Blut im Urin auftreten. Anzeichen dafür sind insbesondere blaue Flecken, Blutergüsse (Hämatome), Absinken des Hämoglobins oder des Hämatokrits (beides Anzeichen für Blutverlust, erkennbar in den Laborbefunden), punktförmige oder flächige rote oder violette Verfärbungen der Haut, die durch Blutungen unter der Haut entstehen (Purpura), sowie Verlängerung der Gerinnungszeit; in seltenen Fällen ($< 1/1000$) kann es zu Blutungen in den Augen oder im Gehirn kommen. Blutungsereignisse können schwerwiegend sein und zu weiteren Komplikationen bzw. sogar zum Tod führen.

Weitere häufig berichtete Nebenwirkungen sind: Rückenschmerzen, Brustschmerzen, Übelkeit, Kopfschmerzen, niedriger Blutdruck, Erbrechen, Schmerzen an der Einstichstelle, Fieber, Kurzatmigkeit und hoher Blutdruck.

Zu den schwerwiegenden, aber sehr selten auftretenden Nebenwirkungen gehören Herzinfarkt, das Versagen mehrerer Körperorgane (multiples Organversagen) sowie Gerinnselbildung in der Lunge oder den Koronararterien

Risiken in Zusammenhang mit Clopidogrel

Clopidogrel (Plavix®) ist ein zugelassenes verschreibungspflichtiges Medikament zur

terminate your participation in the study early if:

- new findings suggest that the treatment does not work
- new findings suggest that the treatment is not for safe for you
- you do not adhere to the study requirements
- new health problems or illnesses occur for you

If you or your investigator decides to terminate your participation in the study, you may be asked to complete additional laboratory tests and other examinations that your investigator considers necessary.

Risks and benefits

Cangrelor: Cangrelor was administered to approximately 7600 persons in other studies. The most frequently observed side effect with cangrelor is bleeding. As with all blood-thinning medicines it can cause bleeding on or in the body, for example, at injection sites, in the digestive system, in the stomach, or in the urine. Signs are particularly bruises, bruising (hematoma), decrease in hemoglobin or hematocrit (both signs of blood loss, recognizable in the laboratory findings), point or area red or purple discoloration of the skin caused by bleeding under the skin (purpura), and extension of the clotting time and, only in rare cases ($< 1/1000$), it can cause bleeding in the eyes or in the brain. Bleeding events may be severe and can lead to complications or even death.

Other commonly reported side effects are back pain, chest pain, nausea, headache, low blood pressure, vomiting, pain at the injection site, fever, shortness of breath and high blood pressure.

The serious, but very infrequent, side effects include heart attack, the failure of multiple body organs (multiple organ failure), and clot formation in the lung or the coronary arteries.

Risks associated with clopidogrel

Clopidogrel (Plavix®) is a prescription medication approved for the treatment of heart attacks and

Behandlung von Herzinfarkten und Schlaganfällen. Die Anfangsdosis, die Sie in der Studie erhalten werden, entspricht dem Zweifachen der zugelassenen Dosis. Diese Dosis wird jedoch derzeit zur Behandlung von Patienten angewendet, die sich einer PKI unterziehen.

Da es sich bei Clopidogrel um ein Medikament handelt, das sich auf die Funktion der Blutplättchen auswirkt, sind die häufigsten Nebenwirkungen Blutungen. Bei 0,2% der Patienten traten schwerwiegende Blutungsereignisse auf, die zum Tod führten. In extrem seltenen Fällen (bei etwa 4 von einer Million Patienten) kann ein schwerwiegendes Blutungsereignis – eine sogenannte thrombotische thrombozytopenische Purpura (TTP) – auftreten. Dabei handelt es sich um eine seltene Erkrankung, die die Gerinnungsfähigkeit des Blutes beeinträchtigt.

Die Nebenwirkungen, die in klinischen Studien mit 54.000 Patienten am häufigsten in Zusammenhang mit Clopidogrel in zugelassenen Dosierungen berichtet wurden, sind Kopfschmerzen, Schwindel, Magenschmerzen, Brustschmerzen, verminderte Anzahl der Blutzellen (was zu einem erhöhten Infektionsrisiko führen könnte), Durchfall, Verdauungsstörungen, erhöhter Cholesterinspiegel, Hautausschlag, Übelkeit oder verminderte Anzahl der Blutplättchen (kleine Blutbestandteile, die die Blutgerinnung unterstützen).

Informationen für gebärfähige Frauen – Schwangerschaftstest

Sie müssen Ihren Prüfarzt auch informieren, wenn Sie schwanger sind oder stillen oder wenn Sie den Verdacht haben, schwanger zu sein. Gebärfähige Frauen (Frauen, die schwanger werden können) müssen einen Blut- oder Urin-Schwangerschaftstest durchführen lassen, der negativ ausfallen muss, bevor sie an dieser Studie teilnehmen können. Schwangere und stillende Frauen dürfen NICHT an dieser klinischen Studie teilnehmen.

Risiken für die Fortpflanzung

Es ist nicht bekannt, welche Auswirkungen Cangrelor auf ein ungeborenes Kind haben kann. Es gibt keine Informationen zu den Langzeitauswirkungen von Cangrelor auf die Fruchtbarkeit von Männern und Frauen. Ebenso gibt es keine ausreichenden und gut kontrollierten Studien zur Anwendung von Clopidogrel bei schwangeren Frauen. Nehmen Sie nicht an der Studie teil,

strokes. The initial dose that you will be given in the study corresponds to twice the approved dose. This dose, however, is currently used to treat patients who undergo a PKI

Since clopidogrel is a drug that affects the function of platelets, the most common side effects are bleeding. In 0.2% of patients serious bleeding events occurred that led to death. In extremely rare cases (about 4 in a million patients), a serious bleeding event – so called thrombotic thrombocytopenic purpura (TTP) - occurred. This is a rare disease that affects the clotting ability of the blood.

The side effects in the clinical trials with 54,000 patients most associated with clopidogrel at approved doses are headache, dizziness, stomach pain, chest pain, decreased number of blood cells (which could lead to an increased risk of infection), diarrhea, indigestion, high cholesterol, rash, nausea, or decreased number of platelets (small blood components that help blood clotting).

Information for women of childbearing age - pregnancy test

You must also tell your investigator if you are pregnant or nursing or if you suspect you may be pregnant. Women of childbearing potential (women who can become pregnant) have to perform a blood or urine pregnancy test, which must be negative, before they can participate in this study. Pregnant and lactating women may NOT participate in this clinical trial.

Reproductive risks

It is not known whether cangrelor can have an impact on an unborn child. There is no information on the long-term effects of cangrelor on fertility of men and women. Similarly, there are no adequate and well-controlled studies of the use of clopidogrel in pregnant women. Do not take part in the study if you are pregnant or suspect you may be pregnant. Be sure to inform your investigator if you suspect you may be pregnant or if you are uncertain in this

wenn Sie schwanger sind oder den Verdacht haben, schwanger zu sein. Informieren Sie unbedingt Ihren Prüfarzt, wenn Sie vermuten, schwanger zu sein oder wenn Sie diesbezüglich unsicher sind.

Unbekannte Risiken

Es könnten auch Nebenwirkungen oder Beschwerden bei Ihnen auftreten, die nicht in dieser Einverständniserklärung aufgeführt sind. Möglicherweise sind einige Nebenwirkungen zum jetzigen Zeitpunkt noch nicht bekannt. Bei Ihnen könnten auch neue Nebenwirkungen auftreten. Bitte informieren Sie umgehend den Prüfarzt oder das Studienpersonal, wenn bei Ihnen Probleme auftreten.

Nutzen im Zusammenhang mit der Teilnahme an dieser klinischen Studie

Die Teilnahme an dieser Studie bringt Ihnen nicht unbedingt einen persönlichen Nutzen; andere Patienten [mit einer Herzerkrankung, die sich einem Eingriff am Herzen unterziehen] können jedoch möglicherweise in Zukunft von den Informationen aus der Studie profitieren.

Andere Behandlungsmöglichkeiten

Wenn Sie sich gegen eine Studienteilnahme entscheiden, erhalten Sie die Standardbehandlung für Ihre Erkrankung, je nachdem, welche Behandlung Ihr Arzt für Ihren Zustand als am besten erachtet. Die Standardbehandlung für Ihre Erkrankung ist Plavix, die identisch mit der Placebo-Gruppe in dieser Studie ist.

Kosten

Die normalen Behandlungskosten für Ihre Erkrankung und den Eingriff werden Ihnen oder Ihrer Krankenversicherung in Rechnung gestellt. Das Studienmedikament und die für die klinische Studie erforderlichen medizinischen Untersuchungen sind für Sie kostenfrei.

Vergütung

Sie werden für Ihre Teilnahme an dieser Studie nicht bezahlt.

Studienbedingte Gesundheitsschäden

Wenn bei Ihnen infolge der Studienteilnahme Nebenwirkungen auftreten oder sich Ihr körperlicher oder geistiger Gesundheitszustand während Ihrer Teilnahme an der klinischen Studie verändert, müssen Sie sich umgehend in

respect.

Unknown risks

You could also experience side effects or symptoms not listed in this consent. Some side effects may not yet be known at this time. You could experience new side effects. Please immediately inform the investigator or study staff if you have problems.

Benefits associated with participation in this clinical study

Participation in this study will not necessarily bring a personal benefit; other patients [with heart disease, who undergo heart interventions], however, may be able to benefit in the future from the information from the study.

Other treatment options

If you choose not to participate in the study, you will receive the standard treatment for your condition, depending on which treatment your doctor deems best for your condition. The standard treatment for your condition is Plavix, identical with the placebo group in this study.

Costs

The normal cost of treatment for your condition and the procedure will be billed to your health insurance penalty. The study drug and the medical examinations required for this clinical study are free of charge

Payment

You will not be paid for your participation in this study.

Study-related health injury

If as a result of study participation side effects occur or your physical or mental health changes during your participation in the clinical study, you have to go immediately and seek treatment and as soon as possible contact the study staff or the investigator

ärztliche Behandlung begeben und so bald wie möglich das Studienpersonal oder den Prüfarzt unter der Telefonnummer 01/ 491 50-2344 kontaktieren.

Versicherung

Als Teilnehmer dieser klinischen Studie besteht für Sie der gesetzlich vorgeschriebene Versicherungsschutz (Personenschadenversicherung nach § 32 des Österreichischen Arzneimittelgesetzes [AMG]), der alle Schäden abdeckt, die an Ihrem Leben und Ihrer Gesundheit durch die an Ihnen durchgeführten Maßnahmen der Studie verursacht werden können. Diese Versicherung deckt keine Schäden, die aufgrund von Veränderungen im Erbgut Ihrer Fortpflanzungszellen entstanden sind. Die Versicherung wurde bei Lloyd's, Kantgasse 3 in Wien 1010, Telefonnummer 01/ 71 30 713 unter der Versicherungsnummer 10ME222515KA103 abgeschlossen. Sie erhalten auf Anfrage Einsicht in die Versicherungsunterlagen. Im Schadensfall können Sie sich direkt an den Versicherer wenden, um den Schaden zu melden. Für den Versicherungsvertrag ist österreichisches Recht anwendbar, die Versicherungsansprüche sind in Österreich einklagbar. Wenn Sie Hilfe benötigen, können Sie sich auch an die Patientenanwaltschaft oder die Patientenvertretung wenden. Um Ihren Versicherungsschutz nicht zu gefährden, sollten Sie die folgenden Verpflichtungen einhalten.

- Sie dürfen sich während Ihrer Teilnahme an der klinischen Studie ohne vorherige Zustimmung Ihres behandelnden Prüfarztes keiner anderen medizinischen Behandlung unterziehen. Davon ausgenommen sind Notfälle. Dies gilt auch für die Einnahme zusätzlicher Medikamente.
- Sie müssen den behandelnden Prüfarzt – oder das oben genannte Versicherungsunternehmen – umgehend über jegliche Gesundheitsschäden informieren, die infolge Ihrer Teilnahme an der klinischen Studie auftreten.
- Sie müssen sich bei der Einnahme des Studienmedikaments an die Anweisungen des Prüfarztes halten.
- Ihr Gesundheitsschaden darf nicht vorsätzlich verursacht sein.
- Sie müssen den medizinischen Rat des Prüfarztes befolgen.

Datenschutz und Vertraulichkeit

by phone 01/491 50-2344.

Insurance

As a participant in this clinical trial there exists for you the statutory insurance coverage (personal injury insurance according to § 32 of the Austrian Medicines Law [AMG]), which covers all damage to your life and your health that may be caused by the actions you performed in the study. This insurance does not cover damage caused by alterations in the genetic material of your reproductive cells. The insurance was completed at Lloyd's, Kantgasse 3 in Vienna 1010, telephone 01/71 30 713 under the insurance policy number 10ME222515KA103. You can get on request information on the insurance documents. In event of injury you can contact directly the insurance company to report the injury. The insurance contract is subject to Austrian law applicable to insurance claims enforceable in Austria. If you need help, you can also contact the contact patient advocate or the patient representative. In order not to compromise your insurance coverage you should comply with the following obligations.

- You may not undergo any other medical treatment during your participation in the clinical trial without permission from your treating investigator. The exceptions are emergencies. This also applies to taking additional medication.
- You must inform the treating investigator - or the above insurance companies - promptly of any adverse health effects that occur as a result of your participation in the clinical trial.
- You must take the study drug according to the instructions of the investigator.
- You should not cause harm to your health intentionally.
- You must follow the medical advice of the investigator.

Privacy and confidentiality

Ziel der Erhebung geschützter Gesundheitsinformationen

Wenn Sie an der Studie teilnehmen, erteilen Sie Ihre Genehmigung zur Erhebung Ihrer indirekt personenbezogenen Daten. Die Unterlagen zu Ihrer Studienteilnahme werden vertraulich behandelt, sofern nicht gesetzlich anderweitig vorgeschrieben; strikte Vertraulichkeit kann jedoch nicht garantiert werden. Der Prüfartz, der Studienauftraggeber, Vertreter des Studienauftraggebers, die US-amerikanische „Food and Drug Administration“ (FDA), die Europäische Arzneimittelagentur (EMA), andere Regierungsbehörden in den USA und in anderen Ländern sowie die Ethikkommission (eine Gruppe von Personen an Ihrem Prüfzentrum, die für die Überwachung der klinischen Studie und für den Schutz Ihrer Rechte verantwortlich ist) können vertrauliche Daten prüfen und darauf zugreifen.

Ihr Name, Ihre Adresse, Ihre Sozialversicherungsnummer und ähnliche Angaben werden in keiner Information erscheinen, die außerhalb des Prüfzentrums verwendet wird. Wenn die Studienergebnisse veröffentlicht werden, werden diese keine Informationen enthalten, anhand derer Sie identifiziert werden können. Die erhobenen Informationen könnten in Ihre Krankenakte im Krankenhaus aufgenommen werden. Sie können jederzeit in Ihre Krankenakte Einsicht nehmen. Ihre Genehmigung zur Verwendung Ihrer Informationen durch das Studienpersonal tritt in Kraft, sobald Sie dieses Dokument unterzeichnen. Wenn Sie mit der Verwendung und Weitergabe Ihrer Gesundheitsinformationen nicht einverstanden sind, können Sie nicht an dieser Studie teilnehmen.

Folgende Gesundheitsinformationen werden im Rahmen dieser Studie über Sie erhoben:

- Initialen, Alter, Geschlecht, ethnische Abstammung
- Die Daten Ihrer Aufnahme und Entlassung aus dem Krankenhaus in Zusammenhang mit dieser Studie
- Frühere Erkrankungen oder Risikofaktoren, die bei Ihnen möglicherweise zur Diagnose einer [Herz-] Erkrankung beigetragen haben
- Ihre Medikamente, deren Einnahmeplan sowie etwaige Änderungen
- Informationen zu Ihrem derzeitigen Gesundheitszustand und Ihrer Erkrankung
- Informationen zum Eingriff (bzw. den Eingriffen)

The aim of the survey of protected health information

If you participate in the study, you give your permission to collect your indirect personal data. The documents relating to your participation in the study will be confidentially treated, unless otherwise required by law; strict confidentiality, however, can not be guaranteed. The investigator, the study sponsor, representatives of the study sponsor, the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), other government agencies in the U.S. and in other countries, as well as the ethics committee (a group of people at your test center responsible for monitoring the clinical trial and the protection of your rights) may examine confidential data and access it.

Your name, your address, your social security number and similar information are information not to be used outside of the test center. If the study results are published, this information will not included, based on which you can be identified. The information collected could be recorded in your medical record in hospital. You can at any time inspect your medical record. Your permission to use the information by the study personnel will enter into force as soon as you sign this document. If you do not agree with the use and disclosure of your health information not agree, you can not participate in this study.

The following health information about you is collected during this study:

- initials, age, gender, ethnicity
- the data about your admission and discharge from the hospital in connection with this study
- previous disease or risk factors that have contributed to a diagnosis of a [heart] disease
- your medications, their dosing schedule and any changes
- information about your current health and your condition
- information about the intervention (or interventions) on your heart
- changes in your health and your condition within a period of about 30 days (+ 5 days) after the

an Ihrem Herzen

- Veränderungen Ihres Gesundheitszustands und Ihrer Erkrankung innerhalb eines Zeitraums von etwa 30 Tagen (+ 5 Tage) nach dem Eingriff (bzw., den Eingriffen) an Ihrem Herzen

Zugriff auf Ihre geschützten Gesundheitsinformationen

Um sicherzustellen, dass Ihre Informationen vertraulich bleiben, wird Ihnen eine Codenummer zugeteilt. Dieser Code wird verwendet, um alle im Rahmen der Studie erforderlichen Informationen zu kennzeichnen und zurückzufolgern. Ihre medizinischen Informationen werden vom Prüfarzt und vom Studienpersonal vertraulich behandelt und nur dann weitergeleitet, wenn es das Gesetz verlangt, z. B. zur Benachrichtigung der Behörden im Falle schwerwiegender Nebenwirkungen.

Die im Rahmen dieser Studie erhobenen Daten (die keine Informationen enthalten werden, anhand derer Sie identifiziert werden können) werden an den Studienauftraggeber und/oder seine Vertreter weitergeleitet und können veröffentlicht und/oder an die Zulassungsbehörden in Österreich oder in anderen Ländern, in denen ein Antrag auf Zulassung von Cangrelor gestellt wurde, sowie an die zuständige Ethikkommission weitergeleitet werden.

Ihre Originalkrankenakte kann, soweit es das Gesetz erlaubt, überprüft werden von

- o The Medicines Company (dem Unternehmen, das die Studie in Auftrag gegeben hat) und/oder seinen Vertretern
- o den Zulassungsbehörden zum Zwecke der Bewertung von Verfahren und/oder von Daten der klinischen Studie.
- o der Ethikkommission, die diese Studie überwacht.

Diese Personen sind zur Verschwiegenheit verpflichtet.

Wenn Sie diese Einwilligungserklärung unterzeichnen, erteilen Sie Ihre Genehmigung zur Verwendung der im Lauf der Studie erhobenen indirekt personenbezogenen Daten (anhand derer Sie nicht durch rechtliche zulässige Verfahren identifiziert werden können) durch den Studienauftraggeber, Unternehmen, die mit dem Studienauftraggeber zusammenarbeiten, Vertragspartner des Sponsors und vom Studienauftraggeber beauftragte Dienstleister sowie das Versicherungsunternehmen, bei dem die Personenschadenversicherung gemäß Art. 32

intervention (or interventions) on your heart

Access to your protected health information

To ensure that your information remains confidential, you will be assigned a code number. This code is used by all required as part of the study to identify and trace information. Your medical information will be handled by the investigator and study staff confidentially and only forwarded if required by law, such as to inform authorities in the event serious side effects.

The data collected in this study (which will not contain information by which you can be identified) will be forwarded to the study sponsor and/or its agents and may be published and/or to the regulatory authorities in Austria or other countries in which an application for approval of cangrelor will be submitted, and will be forwarded to the relevant ethics committee.

Your original medical record may, where permitted by law, be checked by

- o The Medicines Company (the company that commissioned the study) and/or its representatives
- o the regulatory authorities for the purpose of evaluation of methods and/or the data of the clinical trial
- o the Ethics Committee, which oversees the study.

These individuals are bound to secrecy.

When you sign this consent form, you give your permission for the evidence to be collected in the course of the study indirect personal data (based on which you can not be identified by legal methods allowed) by the study contracting companies that cooperate with the study sponsor, contractors appointed by the sponsor and study customer service, and the insurance company, in which the personal injury insurance in accordance with Article 32 Paragraph 1 item. 11 AMG has been completed. When you sign the consent form, you also expressly consent to disclosure of such indirect personal

Abs. 1 Ziff. 11 AMG abgeschlossen wurde. Wenn Sie die Einwilligungserklärung unterzeichnen, stimmen Sie außerdem ausdrücklich der Weitergabe derartiger indirekt personenbezogener Informationen an die oben genannten Stellen zu, einschließlich der Weitergabe von Daten in Länder außerhalb des EWR.

Die Verwendung und Weitergabe Ihrer Gesundheitsinformationen aus dieser Studie kann über einen unbestimmten Zeitraum erfolgen. Sie haben jedoch das Recht, die Einwilligung zur Verwendung oder Weitergabe Ihrer Gesundheitsinformationen zu widerrufen, indem Sie sich schriftlich an den Prüfarzt wenden. In diesem Fall werden keine neuen Gesundheitsinformationen mehr erhoben, es sei denn, dies ist im Rahmen der Nachbeobachtung einer Nebenwirkung erforderlich, die während der Studie bei Ihnen aufgetreten ist. Alle Daten, die vor Ihrem schriftlichen Widerruf erhoben wurden, können weiterhin verwendet werden.

FRAGEN ZUR STUDIE

Wenn Sie Fragen zur Studie haben, wenden Sie sich bitte an Herrn Prim. Prof. Dr. Kurt Huber unter 01/ 491 50-2309. Außerhalb der Sprechzeiten rufen Sie bitte die 24-Stunden Notfallnummer 01/ 491 50 - 2344 an.

Wenn Sie Fragen zu Ihren Rechten als Teilnehmer an dieser Studie haben, wenden Sie sich bitte an den Wiener Pflege-, Patientinnen- und Patientenanwalt, Schönbrunner Straße 108 in Wien 1050 unter der Telefonnummer 01/ 587 12 04. Sie erhalten ein Exemplar dieser Patienteninformation und Einwilligungserklärung.

Einwilligungserklärung:

- Mir ist bekannt, dass diese Studie der Forschung dient.
- Ich habe diese Patienteninformation und Einwilligungserklärung gelesen und hatte Zeit, darüber nachzudenken.
- Alle Fragen wurden zu meiner Zufriedenheit beantwortet. Ich erhalte ein Exemplar dieses Dokuments für meine Unterlagen.
- Mir ist bekannt, dass eine Teilnahme an dieser Studie freiwillig ist.
- Ich erkläre mich damit einverstanden, den Studienablauf einzuhalten und dem Prüfarzt, den Pflegekräften und dem Studienpersonal auf Verlangen die erforderlichen Informationen zur Verfügung zu stellen.
- Ich kann meine Einwilligung zur Teilnahme an der

information to the above offices, including transfer of data to countries outside the EWR.

The use and disclosure of your health information from this study can occur for an indefinite period. However, you have the right to revoke consent for use or disclosure of your health information by yourself writing to the investigator. In this case, no more new health information will be collected, unless it is required in the context of following a side effect that occurred to you during the study. All data collected prior to your written revocation may still be used.

QUESTIONS ABOUT THE STUDY

If you have questions about the study, please contact Principal Professor Kurt Huber at 01/491 50-2309. Outside of office hours please call the 24-hour emergency number 01/491 50-2344.

If you have questions about your rights as a participant in this study, please contact the Vienna Nursing and Patient Advocate, Schönbrunnerstraße 108 Vienna 1050 by phone 01/587 12 04. You will receive a copy of this patient information and consent form.

Informed Consent:

- I am aware that this study serves research.
- I have read this patient information and consent and have had time to think about it.
- All questions have been answered to my satisfaction. I have received a copy of this document for my records.
- I understand that participation in this study is voluntary.
- I hereby agree to comply with the study process and to provide the required information at the request of the investigator, caregivers and the study staff.
- I can revoke my consent to participate in the study at any time without giving reasons, without losing entitled benefits.
- I was informed about the study and its objectives,

Studie jederzeit ohne Angabe von Gründen widerrufen, ohne mir zustehende Leistungen zu verlieren.

- Ich wurde über die Studie und ihre Ziele, den Studienablauf, die Risiken und den möglichen Nutzen, sowie über andere Behandlungsmöglichkeiten informiert.
- Ich gestatte die in diesem Dokument beschriebene Verwendung und Offenlegung meiner personenbezogenen Gesundheitsinformationen. Meine Identität wird vertraulich behandelt, wenn die im Rahmen dieser Studie erhobenen Daten veröffentlicht oder für Lehrzwecke verwendet werden. Bei der Verwendung der Daten werden die Regelungen des Datenschutzgesetzes eingehalten.

Der Prüfarzt wird mich über neue Erkenntnisse informieren, die sich im Verlauf der Studie ergeben und Einfluss auf meine Bereitschaft zur Fortsetzung der Studienteilnahme haben können. Wenn ich möchte, dass diese Informationen an meinen Hausarzt weitergeleitet werden, muss ich meinen behandelnden Prüfarzt in dieser Studie informieren.

Einwilligungserklärung:

Wenn Sie dieses Dokument unterzeichnen, bestätigen Sie (der Studienteilnehmer), dass Sie diese Patienteninformation und Einwilligungserklärung gelesen haben bzw. sie Ihnen vorgelesen wurde, dass Sie mit dem Studienpersonal über die Studie gesprochen haben, dass Sie Gelegenheit hatten, Fragen zu stellen und alle Fragen zufriedenstellend beantwortet wurden und dass Sie freiwillig in die Teilnahme an dieser Studie, wie in diesem Dokument beschrieben, einwilligen.

the study procedure, the risks and potential benefits, as well as information about other treatment options.

- I authorize the use and disclosure described in this document of my personal health information. My identity will be treated confidentially if the data collected in this study are published or used for teaching purposes. When using the data, the regulations of the Data Protection Act will be observed.

The investigator will notify me of new information, which in the course of the study arises and can affect my willingness to continue participation in the study. If I want this information to be passed on to my family doctor, I must inform my treating investigator in this study.

Informed Consent:

When you sign this document, you acknowledge (the study participant) that you have read this patient information and consent form or you will have read them, that you have spoken with the study staff about the study, that you have the opportunity to ask questions and all questions were answered satisfactorily, and that you voluntarily participate in this study, as in this document described.

Attachment 7: German ICD

The Medicines Company TMC-CAN-10-01
Information Leaflet and Informed Consent Form for
the Participation in a Clinical Study, V1.0GER2.1
Germany, Final Version 2.1, 04 July 2011

Prof. Dr. med. Peter Radke
Universitaetsklinikum Schleswig-Holstein
Medizinische Klinik 2
Ratzeburger Allee 160, 23538 Luebeck Germany

PATIENTENINFORMATION UND EINWILLIGUNGSERKLÄRUNG

TITEL DER STUDIE:

CHAMPION Phoenix: Eine klinische Studie zum
Vergleich von Cangrelor mit Clopidogrel als
Standardbehandlung bei Patienten, die eine
perkutane Koronarintervention benötigen

PRÜFPLANNUMMER: TMC-CAN-10-01

PRÜFARZT: Prof. Dr. Med. Peter Radke
(address & phone number)

Einleitung

Sehr geehrte Patientin, sehr geehrter Patient,
Sie wurden gefragt, ob Sie daran interessiert sind,
an einer klinischen Studie teilzunehmen, die im
Folgenden beschrieben wird. Die Teilnahme an
dieser Studie ist vollkommen freiwillig. Sie können
die Teilnahme auch ablehnen, ohne dass Ihnen
hierdurch Nachteile bei Ihrer medizinischen
Betreuung entstehen. Diese Studie wird von Ihrem
Prüfarzt durchgeführt. Es ist wichtig, dass Sie diese
Patienteninformation lesen und die darin
enthaltenen Informationen auch verstehen. Bitte
lesen Sie das Dokument daher aufmerksam durch.
Nehmen Sie sich Zeit, um dem Prüfarzt oder dem
Studienpersonal so viele Fragen über die klinische
Studie zu stellen, wie Sie möchten. Bitte wenden
Sie sich an den Prüfarzt, wenn Sie die Bedeutung
bestimmter Begriffe nicht kennen oder inhaltliche
Fragen haben. Das Lesen dieser
Patienteninformation und das Gespräch mit dem
Prüfarzt oder dem Studienpersonal sollen Ihnen
helfen zu entscheiden, ob Sie an der klinischen
Studie teilnehmen möchten oder nicht. Wenn Sie
sich für eine Teilnahme entscheiden, müssen Sie
vor Ihrer Teilnahme an der klinischen Studie die
Einwilligungserklärung unterzeichnen und
datieren. Die Einwilligung in die Studienteilnahme
findet statt, bevor der Prüfarzt Ihre Eignung für die

The Medicines Company TMC-CAN-10-01
Information Leaflet and Informed Consent Form for
the Participation in a Clinical Study, V1.0GER2.1
Germany, Final Version 2.1, 04 July 2011

Prof. Dr. med. Peter Radke
Universitaetsklinikum Schleswig-Holstein
Medizinische Klinik 2
Ratzeburger Allee 160, 23538 Luebeck Germany

PATIENT INFORMATION AND CONSENT

STUDY TITLE:

CHAMPION Phoenix: A clinical trial comparing
cangrelor with clopidogrel as a standard treatment
in patients requiring percutaneous coronary
intervention

PROTOCOL NUMBER: TMC-CAN-10-01

INVESTIGATOR: Prof. Dr. Med. Peter Radke
(address & phone number)

Introduction

Dear patient, dear patient,
You were asked if you are interested in participating
in a clinical trial that is described below.
Participation in this study is completely voluntary.
You can also refuse to participate, without thereby
suffering disadvantages in your medical care. This
study will be carried out by your investigator. It is
important that you read this patient information and
understand the information contained therein.
Please read the document carefully. Take time to
ask the investigator or the study staff as many
questions about the clinical trial as you like. Please
contact the investigator or the study staff, if you do
not know the meaning of certain terms or have
substantive questions. Reading this patient
information and conversing with the investigator or
the study staff will help you to decide if you wish to
participate in the clinical trial or not. If you decide
to participate, you must sign and date the informed
consent form prior to participation in the clinical
trial. Consent for study participation takes place
before the investigator has checked your eligibility
for the study. Your investigator must check the
image recordings of your coronary arteries. You are
eligible for the study if your investigator finds that
certain closed coronary arteries must be opened
surgically. Your investigator will tell you whether

Studie überprüft hat. Ihr Prufarzt muss hierfür Bildaufnahmen Ihrer Herzkranzgefasse überprüfen. Sie sind für die Studie geeignet, wenn Ihr Prüfarzt feststellt, dass bestimmte verschlossene Herzkranzgefasse operativ geöffnet werden müssen. Ihr Prüfarzt wird Ihnen mitteilen, ob Sie für eine Studienteilnahme geeignet sind.

Hintergrund und Ziel der Studie

Sie werden gebeten, auf freiwilliger Basis an dieser klinischen Studie teilzunehmen, weil bei Ihnen Anzeichen und Symptome einer koronaren Herzkrankheit vorliegen. Diese können auf ein schwerwiegendes Herzproblem hinweisen, bei dem das Herz nicht ausreichend mit Sauerstoff versorgt wird. Diese Störung kann durch eine teilweisen Verschluss eines oder mehrerer Herzkranzgefasse verursacht werden.

In dieser klinischen Studie wird ein in der Phase der Arzneimittelpfung befindliches Medikament namens Cangrelor angewendet. Es soll untersucht werden, ob Cangrelor die Blutgerinnselbildung bei Patienten zu verhindern kann, bei denen eine Ballondilatation (eine sogenannte perkutane Koronarintervention oder PKI) durchgeführt wurde, um verschlossene Herzkranzgefasse zu öffnen. Im Rahmen dieser Studie wird auch das von der Europäischen Union zugelassene Arzneimittel Clopidogrel (Plavix®) angewendet. Plavix ist für die Behandlung von Herzinfarkten und Schlaganfällen zugelassen. Wenn bei Ihnen eine PKI durchgeführt wird, kann die Anfangsdosis Plavix bis zum Zweifachen der zugelassenen Dosis betragen. Die Dosis hängt davon ab, welches der übliche Standard an Ihrer Einrichtung ist. In dieser Studie soll die Sicherheit und Wirksamkeit einer Kombinationstherapie von Cangrelor und Plavix mit der Sicherheit und Wirksamkeit einer Behandlung mit Plavix alleine verglichen werden. Cangrelor ist bisher nicht von der Europäischen Arzneimittelagentur (EMA) zugelassen; daher ist die Anwendung von Cangrelor in dieser Studie experimentell.

In diese klinische Studie werden etwa 10.900 Patienten an etwa 200 Prüfzentren weltweit aufgenommen.

Beschreibung der Studie

Ihr Prüfarzt wird auch eine vollständige medizinische Untersuchung durchführen, um festzustellen, ob Sie an der klinischen Studie teilnehmen können. Dies umfasst Ihre Krankengeschichte, eine körperliche Untersuchung, demographische, Blutuntersuchungen, Abgabe einer

you qualify for participation in the study.

Background and purpose of the study

You are being asked on a voluntary basis to participate in this clinical trial because you have signs and symptoms of coronary heart disease. These may indicate a serious heart problem in which the heart does not receive enough oxygen. This condition may be caused by partial blockage of one or more coronary arteries.

In this clinical study an investigational drug called cangrelor is used. It will be investigated whether cangrelor can prevent the formation of blood clots in patients in whom a balloon dilation (a so-called percutaneous coronary intervention or PKI) was performed to open blocked coronary arteries. This study will also use the European Union approved drug clopidogrel (Plavix®). Plavix is used for the treatment of heart attacks and strokes. When you get a PKI, the starting dose of Plavix can be up to twice the approved dose. The dose depends upon the usual standard in your facility. This study will evaluate the safety and efficacy of combination therapy with cangrelor and Plavix compared to the safety and efficacy of treatment with Plavix alone. Cangrelor is not yet licensed by the European Medicines Agency (EMA); hence the use of cangrelor in this study is experimental.

In this clinical study about 10,900 patients at 200 clinical sites will be enrolled worldwide.

Description of the study

Your investigator will perform a complete medical examination to determine if you can participate in the clinical trial. This includes your medical history, physical examination, demographics, blood tests, provision of a urine sample and an electric recording of your heart (ECG). For the blood tests

Urinprobe und eine elektrische Aufzeichnung Ihres Herzschlags (EKG). Für die Blutuntersuchungen werden Ihnen von einer Fachkraft etwa 20 ml Blut durch einen Einstich in eine Vene entnommen. Alle diese Untersuchungen werden für gewöhnlich im Rahmen der Standardversorgung durchgeführt. Standardversorgung bedeutet, dass diese Untersuchungen und Maßnahmen auf jeden Fall durchgeführt würden, unabhängig davon, ob Sie an der Studie teilnehmen oder nicht. Zusätzlich zu den normalen Blutuntersuchungen, die im Rahmen Ihrer Standardversorgung durchgeführt werden, werden für die Studie 4 ml Blut entnommen, die an ein Zentrallabor geschickt werden. Sie sollten Ihren Prüfarzt über Ihre Krankengeschichte – einschließlich aller Medikamente, die Sie derzeit einnehmen (auch pflanzliche Heilmittel oder frei verkäufliche Produkte) – sowie über Ihre Teilnahme an anderen Studien informieren. Sie müssen Ihren Prüfarzt auch dann informieren, wenn Sie schwanger sind oder den Verdacht haben, schwanger zu sein. Gebarfähige Frauen müssen einen Schwangerschaftstest durchführen, der negative ausfallen muss, bevor sie an dieser Studie teilnehmen können.

Studienablauf

Wenn Sie für die Studienteilnahme geeignet sind und weiterhin teilnehmen möchten, werden Sie nach dem Zufallsprinzip (wie beim Werfen einer Münze) einer von zwei Studiengruppen zugeteilt:

- **Cangrelor-Gruppe** – während der PKI wird Ihnen Cangrelor langsam über mindestens 2 Stunden durch einen intravenösen (IV-) Katheter (Plastikröhrchen) in eine Vene verabreicht. Ihr Prüfarzt kann die Infusion jedoch auf bis zu insgesamt 4 Stunden verlängern, wenn die PKI länger als 2 Stunden dauert. In Abhängigkeit von der Standardversorgung in Ihrer Einrichtung erhalten Sie zum Zeitpunkt der PKI 2 bis 4 Placebo-Kapseln (Kapseln, die keinen Wirkstoff enthalten). Abschließend erhalten Sie unmittelbar nach Ende der Cangrelor-Infusion vier (4) Kapseln Clopidogrel zu je 150 mg (insgesamt 600 mg).

- **Placebo-Gruppe** – Gemäß der Standardversorgung in Ihrer Einrichtung erhalten Sie zum Zeitpunkt der PKI 2 bis 4 Kapseln Clopidogrel. Während der PKI wird Ihnen eine Placebo-Infusion (eine Infusion, die keinen Wirkstoff enthält) langsam über mindestens 2 Stunden durch einen IV-Katheter in eine Vene

about 20 ml of blood will be removed from you through a puncture into a vein by a specialist. All of these investigations are usually performed in the context of standard of care. Standard of care means that these studies and measures would be carried out in any case regardless of whether you participate in the study or not. In addition to the regular blood tests as part of your standard care, 4 ml of blood are taken for the study which are sent to a central lab. You should inform your investigator about your medical history - including any medications you are currently taking (including herbal remedies or OTC products) - as well as your participation in other studies. You must inform your investigator if you are pregnant or suspect you may be pregnant. Women of child-bearing potential must undergo a pregnancy test, which must turn out negative, before they participate in this study.

Study procedure

If you are eligible for study participation and wish to participate, you will be randomly assigned (like tossing a coin) to one of two study groups,

- **Cangrelor group** – During the PKI you will be administered cangrelor slowly into a vein over at least 2 hours through an intravenous (IV) catheter (plastic tube). However, your investigator can extend the infusion up to 4 hours in total when the PKI takes longer than 2 hours. As a function of the standard of care in your facility, you will receive at the time of PKI 2-4 placebo capsules (capsules containing no active ingredient). Finally, you will receive immediately after the end of the cangrelor infusion four (4) capsules, containing 150 mg of clopidogrel (total 600 mg).

- **Placebo group** - According to the standard of care at your facility, you will receive at the time of PKI 2-4 capsules clopidogrel. During the PKI you will be administered a placebo (an infusion, which contains no active ingredient) slowly into a vein over at least 2 hours through an IV catheter. However, your investigator can extend the infusion

verabreicht. Ihr Prüfarzt kann die Infusion jedoch auf bis zu insgesamt 4 Stunden verlängern, wenn die PKI länger als 2 Stunden dauert. Abschließend erhalten Sie unmittelbar nach Ende der Placebo-Infusion vier (4) Placebo-Kapseln (Kapseln, die keinen Wirkstoff enthalten).

In dieser Studie wird das Studienmedikament Cangrelor mit dem bereits zugelassenen Medikament Clopidogrel verglichen. Um sicherzustellen, dass jede beobachtete Besserung in Ihrem Zustand tatsächlich das Ergebnis der möglicherweise höheren Wirksamkeit des Studienmedikaments ist und nicht durch andere Faktoren beeinflusst wurde, ist es notwendig, dass weder Sie noch der Prüfarzt werden wissen, welchem Studienmedikament Sie zugeteilt wurden. In einem Notfall kann der Prüfarzt jedoch in Erfahrung bringen, welches Studienmedikament Sie erhalten. Aufgrund der Tatsache, dass Cangrelor als Infusion in eine Vene verabreicht wird, während Clopidogrel über den Mund (oral) eingenommen wird, konnte leicht erkannt werden, welchem Studienmedikament Sie zugeteilt wurden. Um dies zu verhindern, erhalten Sie in jedem Fall eine Infusion sowie Kapseln zur oralen Einnahme. Nur eine Behandlung enthält jedoch einen Wirkstoff (Cangrelor oder Clopidogrel). Die andere Behandlung ist ein Placebo (eine wirkstofffreie Substanz, die in dieser Studie Angewendet wird, um die Verblindung der Studie aufrechtzuerhalten). Die Wahrscheinlichkeit der Zuteilung zu Cangrelor oder Clopidogrel ist gleich hoch.

Während Ihres Krankenhausaufenthalts müssen mindestens 2 weitere EKGs aufgezeichnet und 4 Blutproben (etwa 25 ml) abgenommen werden. Drei der Blutproben (jeweils 4 ml) werden nach der Entnahme zur Analyse an ein Zentrallabor geschickt. Im Rahmen der medizinischen Standardbehandlung können Sie auch Aspirin oder andere Medikamente erhalten, um Komplikationen in Zusammenhang mit dem Eingriff vorzubeugen. Dies liegt im Ermessen Ihres Prüfarztes. Am Tag nach dem Eingriff werden Ihnen Medikamente zur Vorbeugung von Blutgerinnseln sowie Aspirin verordnet. Diese Medikamente müssen nach Ermessen Ihres Prüfarztes mindestens einen Monat oder länger eingenommen werden.

Nachbeobachtung

Sie werden etwa 2 Tage (sofern Sie nicht länger im Krankenhaus sind) und 1 Monat nach der PKI telefonisch kontaktiert, damit festgestellt

up to 4 hours in total when the PKI takes longer than 2 hours. According to the standard of care in your facility, you will receive at the time of PKI 2-4 capsules each with Plavix 150 mg. Finally, you will receive immediately after the end of the placebo infusion, four (4) placebo capsules (capsules, which contain no active ingredient).

In this study, the investigational drug cangrelor is compared with the already approved drug clopidogrel. To ensure that any observed improvement in your condition is actually the result of the possibly higher efficacy of the study drug and is not influenced by other factors, it is necessary that neither you nor the investigator will know which study drug you have been allocated. In an emergency, however, the investigator can find out which study drug you received. Due to the fact that cangrelor is administered as an infusion into a vein, while clopidogrel is taken by mouth (oral), it could be easily detected, which study drug you have been allocated. To prevent this, you will always receive an infusion and capsules for oral administration. However, only one treatment contains an active ingredient (cangrelor or clopidogrel). The other treatment is a placebo (an inactive substance, we used to maintain the blinding of the study). The probability of assignment to cangrelor or clopidogrel is the same.

During your hospital stay at least 2 more ECGs must be recorded and 4 blood samples [about (25 ml) removed. Three blood samples (4 ml each) will be removed and sent after removal for analysis to a central laboratory. Under standard medical treatment, you can also obtain aspirin or other medicines in order to prevent complications related to the procedure. This is at your investigator's discretion. The day after surgery you will be prescribed drugs to prevent blood clots and aspirin. These drugs need to be taken at your investigator's discretion at least a month or more.

Follow-up

You will be contacted by phone about 2 days (provided you are no longer in the hospital) and 1 month after the PKI so that it can be determined

werden kann, wie es Ihnen geht und ob es seit dem letzten Kontakt Änderungen bei Ihrer Krankengeschichte und Ihrer Erkrankung gab. Sie werden gebeten, das Studienpersonal zu informieren, wenn sich Ihre Kontaktinformationen während der Nachbeobachtungsphase ändern.

Dauer der Studienteilnahme

Ihre Teilnahme an dieser klinischen Studie beginnt, wenn Sie diese Einwilligungserklärung unterzeichnen, und dauert bis etwa 35 Tage nach Ihrem Eingriff.

Abbruch der Studienteilnahme

Sie können Ihre Teilnahme an dieser Studie jederzeit beenden. Dies hat keinen Einfluss auf Ihre medizinische Versorgung. Ihr Prüfarzt kann ebenfalls beschließen, Ihre Studienteilnahme vorzeitig zu beenden, wenn:

- neue Erkenntnisse auf eine mangelnde Wirksamkeit der Behandlung hindeuten
- neue Erkenntnisse auf eine mangelnde Sicherheit der Behandlung hindeuten
- Sie sich nicht an die Studienvorschriften halten
- bei Ihnen neue Gesundheitsschädigung oder Erkrankungen auftritt

Wenn Sie oder Ihr Prüfarzt beschließen, Ihre Studienteilnahme zu beenden, können Sie gebeten werden, zusätzliche Laboruntersuchungen und andere Untersuchungen durchführen zu lassen, die Ihr Prüfarzt für notwendig erachtet.

Risiken und Nutzen

Cangrelor: Cangrelor wurde im Rahmen anderer Studien etwa 7600 Personen verabreicht. Die am häufigsten in Zusammenhang mit Cangrelor beobachtete Nebenwirkung sind Blutungen (betrifft mehr als 1 von 10 Patienten). Wie bei allen blutverdünnenden Medikamenten kann es zu Blutungen am oder im Körper kommen, z. B. an Einstichstellen, im Verdauungssystem, im Bauch oder es kann Blut im Urin auftreten. Anzeichen dafür sind insbesondere Blutergüsse (blaue Flecken) und innere Einblutungen ins Gewebe (Hämatome), Absinken des roten Blutfarbstoffs (Hämoglobin) oder des Hämatokrits (beides Anzeichen für Blutverlust und aus den Laborbefunden ersichtlich), punktförmige oder flächige rote oder violette Verfärbungen der Haut, die durch Blutungen unter der Haut entstehen (Purpura), sowie Verlängerung der Gerinnungszeit; in seltenen Fällen (< 1/1000) kann es zu Blutungen in den Augen oder im Gehirn kommen. Blutungsereignisse können schwerwiegend sein und zu weiteren

how you are and whether there were changes in your medical history and your condition since the last contact. You are asked to contact the study staff if your contact information changes during the follow-up period.

Duration of study participation

Your participation in this clinical trial starts when you sign this consent sign and lasts until about 35 days after your procedure.

Discontinuation of study participation

You can always cancel your participation in this study. This does not affect your medical care. Your investigator may also decide to terminate your participation in the study early if:

- new findings suggest a lack of effectiveness of the treatment
- new findings suggest a lack of safety of the treatment
- you do not adhere to the study requirements
- new damage to health or illnesses occur for you

If you or your investigator decides to terminate your participation in the study, you may be asked for additional laboratory tests and other examinations to be carried out that your investigator considers necessary.

Risks and benefits

Cangrelor: Cangrelor was administered to approximately 7600 persons in other studies. The most frequently observed side effect with cangrelor is bleeding (affects more than 1 in 10 patients). As with all blood-thinning medicines it can cause bleeding on or in the body, for example, at injection sites, in the digestive system, in the stomach, or in the urine. Signs are particularly bruises (bruising) and internal bleeding into the tissue (hematoma), decrease in red blood color (hemoglobin) or hematocrit (both signs of blood loss and recognizable in the laboratory findings), point or area red or purple discoloration of the skin caused by bleeding under the skin (purpura), and extension of the clotting time; only in rare cases (<1/1000), bleeding in the eyes or in the brain occurs. Bleeding events may be severe and can lead to complications or even death.

Komplikationen bzw. sogar zum Tod führen.

Weitere häufig (<1/10) berichtete Nebenwirkungen sind: Rückenschmerzen, Schmerzen im Brustraum, Übelkeit, Kopfschmerzen, niedriger Blutdruck, Erbrechen, Schmerzen an der Einstichstelle, Fieber, Kurzatmigkeit und hoher Blutdruck.

Zu den schwerwiegenden, aber sehr selten (<1/10.000) auftretenden Nebenwirkungen gehören Herzinfarkt, das Versagen mehrerer Körperorgane (multiple Organversagen) sowie Gerinnselbildung in der Lunge oder den Koronararterien

Risiken in Zusammenhang mit Clopidogrel

Clopidogrel (Plavix®) ist ein zugelassenes verschreibungspflichtiges Medikament zur Behandlung von Herzinfarkten und Schlaganfällen. Die Anfangsdosis, die Sie in der Studie erhalten werden, entspricht dem Zweifachen der zugelassenen Dosis. Diese Dosis wird jedoch derzeit zur Behandlung von Patienten angewendet, die sich einer PKI unterziehen.

Da es sich bei Clopidogrel um ein Medikament handelt, das sich auf die Funktion der Blutplättchen auswirkt, sind die häufigsten Nebenwirkungen Blutungen. Bei 0,2% der Patienten traten schwerwiegende Blutungsereignisse auf, die zum Tod führten. In extrem seltenen Fällen (bei etwa 4 von einer Million Patienten) kann ein schwerwiegendes Blutungsereignis – eine sogenannte thrombotische thrombozytopenische Purpura (TTP) – auftreten. Dabei handelt es sich um eine seltene Erkrankung, die die Gerinnungsfähigkeit des Blutes beeinträchtigt.

Die Nebenwirkungen, die in klinischen Studien mit 54.000 Patienten am häufigsten in Zusammenhang mit Clopidogrel in zugelassenen Dosierungen berichtet wurden, sind Kopfschmerzen, Schwindel, Magenschmerzen, Schmerzen im Brustraum, verminderte Anzahl der Blutzellen (was zu einem erhöhten Infektionsrisiko führen könnte), Durchfall, Verdauungsstörungen, erhöhter Cholesterinspiegel, Hautausschlag, Übelkeit oder verminderte Anzahl der Blutplättchen (kleine Blutbestandteile, die die Blutgerinnung unterstützen).

Risiken für die Fortpflanzung

Es ist nicht bekannt, welche Auswirkungen Cangrelor auf ein ungeborenes Kind haben kann. Es gibt keine Informationen zu den Langzeitauswirkungen von Cangrelor auf die Fruchtbarkeit von Männern und Frauen. Ebenso gibt

Other commonly (<1/10) reported side effects are: back pain, chest pain, nausea, headaches, low blood pressure, vomiting, pain at the injection site, fever, shortness of breath and high blood pressure.

The serious, but very infrequent (<1/10,000), side effects include heart attack, the failure of multiple body organs (multiple organ failure), and clot formation in the lung or the coronary arteries.

Risks associated with clopidogrel

Clopidogrel (Plavix®) is a prescription medication approved for the treatment of heart attacks and strokes. The initial dose that you will be given in the study corresponds to twice the approved dose. This dose, however, is currently used to treat patients who undergo a PKI

Since clopidogrel is a drug that affects the function of platelets, the most common side effects are bleeding. In 0.2% of patients serious bleeding events occurred that led to death. In extremely rare cases (about 4 in a million patients), a serious bleeding event – so called thrombotic thrombocytopenic purpura (TTP) - occurred. This is a rare disease that affects the clotting ability of the blood.

The side effects in the clinical trials with 54,000 patients most associated with clopidogrel at approved doses are headache, dizziness, stomach pain, chest pain, decreased number of blood cells (which could lead to an increased risk of infection), diarrhea, indigestion, high cholesterol, rash, nausea, or decreased number of platelets (small blood components that help blood clotting).

Reproductive risks

It is not known whether cangrelor can have an impact on an unborn child. There is no information on the long-term effects of cangrelor on fertility of men and women. Similarly, there are no adequate and well-controlled studies of the use of clopidogrel

es keine ausreichenden und gut kontrollierten Studien zur Anwendung von Clopidogrel bei schwangeren Frauen. Nehmen Sie nicht an der Studie teil, wenn Sie schwanger sind oder den Verdacht haben, schwanger zu sein. Informieren Sie unbedingt Ihren Prüfarzt, wenn Sie vermuten, schwanger zu sein oder wenn Sie diesbezüglich unsicher sind.

Unbekannte Risiken

Es könnten auch Nebenwirkungen oder Beschwerden bei Ihnen auftreten, die nicht in dieser Patienteninformation aufgeführt sind. Möglicherweise sind einige Nebenwirkungen zum jetzigen Zeitpunkt noch nicht bekannt. Bei Ihnen könnten auch neue Nebenwirkungen auftreten. Bitte informieren Sie umgehend den Prüfarzt oder das Studienpersonal, wenn bei Ihnen Probleme auftreten.

Nutzen im Zusammenhang mit der Teilnahme an dieser klinischen Studie

Die Teilnahme an dieser Studie bringt Ihnen nicht unbedingt einen persönlichen Nutzen; andere Patienten [mit einer Herzerkrankung, die sich einem Eingriff am Herzen unterziehen] können jedoch möglicherweise in Zukunft von den Informationen aus der Studie profitieren.

Andere Behandlungsmöglichkeiten

Wenn Sie sich gegen eine Studienteilnahme entscheiden, erhalten Sie die Standardbehandlung für Ihre Erkrankung, je nachdem, welche Behandlung Ihr Arzt für Ihren Zustand als am besten erachtet.

Kosten

Die normalen Behandlungskosten für Ihre Erkrankung und den Eingriff werden Ihnen oder Ihrer Krankenversicherung in Rechnung gestellt. Der Auftraggeber dieser Studie, The Medicines Company, trägt die Kosten für das Studienmedikament und für die klinische Studie erforderlichen medizinischen Untersuchungen.

Vergütung

Sie werden für Ihre Teilnahme an dieser Studie nicht bezahlt.

Studienbedingte Gesundheitsschäden

In einer klinischen Arzneimittelstudie sind alle Teilnehmer gemäss den Bestimmungen des deutschen Arzneimittelgesetzes versichert. Der Umfang des Versicherungsschutzes, der vom

in pregnant women. Do not take part in the study if you are pregnant or suspect you may be pregnant. Be sure to inform your investigator if you suspect you may be pregnant or if you are uncertain in this respect.

Unknown risks

You could also experience side effects or symptoms not listed in this patient information. Some side effects may not yet be known at this time. You could experience new side effects. Please immediately inform the investigator or study staff if you have problems.

Benefits associated with participation in this clinical study

Participation in this study will not necessarily bring a personal benefit; other patients [with heart disease, who undergo heart interventions], however, may be able to benefit in the future from the information from the study.

Other treatment options

If you choose not to participate in the study, you will receive the standard treatment for your condition, depending on which treatment your doctor deems best for your condition.

Costs

The normal cost of treatment for your condition and the procedure will be billed to your health insurance penalty. The sponsor of this study, The Medicines Company, bears the cost of the study drug and the medical examinations required for this clinical study.

Payment

You will not be paid for your participation in this study.

Study-related health injury

In a clinical drug trial, all participants are insured pursuant to the provisions of the German Medicines Act. The scope of insurance coverage, to which the sponsor of the study, The Medicines Company,

Auftraggeber der Studie, The Medicines Company, vereinbart wurde, ist aus den Versicherungsunterlagen ersichtlich, die Sie ausgehandelt bekommen.

Wenn Sie vermuten, dass durch die Teilnahme an der Studie Ihre Gesundheit geschädigt oder ein bestehendes Leiden verstärkt wurde, müssen Sie dies unverzüglich dem Versicherer

(Name und Adresse, Telefon, Fax, Versicherungsnummer)

direkt anzeigen (gegebenenfalls mit Unterstützung durch Ihren Prufarzt), um Ihren Versicherungsschutz nicht zu gefährden. Falls Ihr Prufarzt Sie dabei unterstützt, den Versicherer zu verständigen, erhalten Sie eine Kopie der Meldung. Wenn Sie Ihre Anzeige direkt an den Versicherer richten, informieren Sie bitte Zusätzlich den Prufarzt.

Sie sind verpflichtet, sämtliche geeigneten Schritte zu unternehmen, um die Ursachen und das Ausmass dieses Schadens zu ermitteln und die Folgen zu verhindern oder so gering wie möglich zu halten.

Während der Dauer der klinischen Studie dürfen Sie sich—ausser in Notfällen—nur nach vorheriger Rücksprache mit dem Prufarzt einer anderen medizinischen Behandlung unterziehen. Der Prufarzt ist von einer Notfallbehandlung unverzüglich zu unterrichten.

Sie erhalten ein Exemplar der Versicherungsbedingungen. Bitte beachten Sie insbesondere die Punkte 1.4 (ausschlüsse), 3 (Versicherungsleistungen) und 4 (Pflichten des Versicherungsnehmers).

Bitte beachten Sie auch, dass Sie auf dem Weg vom und zum Prufzentrum nicht unfallversichert sind.

Datenschutz und Vertraulichkeit

Informationen zum Datenschutz entnehmen Sie bitte dem separaten Dokument „Patienteninformation und Einwilligungserklärung zum Datenschutz“.

FRAGEN ZUR STUDIE

Wenn Sie Fragen zur Studie haben, wenden Sie sich bitte an Ihren Prufarzt (siehe Seite 1).. Außerhalb

agreed, is clear from the insurance documents, which you get.

If you suspect that by participating in the study your health was injured or an existing disease reinforced, you need to report this immediately to the insurer directly (possibly with the assistance of your investigator), so not to jeopardize your insurance coverage.

(Name, address, phone number, fax, insurance number)

If your investigator supported your communication to the insurer, you will receive a copy of the message. If you target your report directly to the insurer, please inform additionally the investigator.

You are obliged to take all appropriate steps to determine the causes and extent of the damage and to prevent or keep the consequences as low as possible.

During the duration of the clinical study—except in emergencies—you may undergo another medical treatment. only after prior consultation with the investigator. The investigator shall be notified immediately of any emergency treatment.

You will receive a copy of the insurance conditions. Please note in particular points 1.4 (exclusions), 3 (insurance) and 4 (obligations of the insured).

Please also note that you are not insured against accidents on the way to and from the test center.

Privacy and confidentiality

For privacy information, please refer to the separate document "Patient information and consent form for data protection."

QUESTIONS ABOUT THE STUDY

If you have questions about the study, please contact your investigator (see page 1). Outside of

der Sprechzeiten können Sie Herrn Prof. Dr. Med. Peter Radke unter 0451-5000-6000 erreichen.

Nach dem Deutschen Arzneimittelgesetz können Sie weitere Informationen über die Durchführung der klinischen Studie beim Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) anfordern: Telefonnummer des BfArM: 0228/207-4318; Fax: 0228/207-4355; E-Mail: klinpruefung@bfarm.de
Sie erhalten ein Exemplar dieser Patienteninformation und Einwilligungserklärung.

Prof. Dr. med. Peter Radke
Universitätsklinikum Schleswig-Holstein
Medizinische Klinik 2
Ratzeburger Allee 160, 23538 Luebeck Germany

Titel des Prüfplans:
CHAMPION Phoenix: Eine klinische Studie zum Vergleich von Cangrelor mit Clopidogrel als Standardbehandlung bei Patienten, die eine perkutane Koronarintervention benötigen

Prüfplannummer: TMC-CAN-10-01

In klinischen Studien werden personenbezogene Daten, insbesondere medizinische Befunde, erfasst, gespeichert und verarbeitet. Die Verwendung der Angaben über Ihre Gesundheit erfolgt nach gesetzlichen Bestimmungen und setzt vor der Teilnahme an der klinischen Studie folgende freiwillig abgegebene Einwilligungserklärung voraus, d. h. ohne Unterzeichnung der folgenden Einwilligungserklärung können Sie nicht an der klinischen Studie teilnehmen.

PATIENTENINFORMATION UND EINWILLIGUNGSERKLÄRUNG ZUM DATENSCHUTZ

1) Mir ist bekannt, dass im Rahmen dieser klinischen Studie Informationen, insbesondere Angaben über meine Gesundheit, erhoben und in Papierform und auf elektronischen Datenträgern vom Prüfarzt (Adresse siehe oben) aufgezeichnet werden. Soweit erforderlich, werden die erhobenen Informationen pseudonymisiert (d. h. verschlüsselt mit einem Zahlencode) weitergegeben:

a) an The Medicines Company (den Studienauftraggeber) 8 Sylvan Way, Parsippany, NJ 07054, USA – in der Europäischen Union (EU) vertreten durch The Medicines Company UK Ltd., 11 Milton Park, Abingdon, Oxfordshire, OX 144RS,

office hours you can reach Professor Dr. Peter Radke reached 0451-5000-6000.

According to the German Drug Law you can request more information about the carrying out of the clinical trial at the Federal Institute for Drugs and Medical Devices (BfArM): Phone number of the BfArM: 0228/207-4318, Fax: 0228/207-4355; Email: klinpruefung@BfArM.de
You will receive a copy of the patient information and consent form.

Prof. Dr. med. Peter Radke
Universitätsklinikum Schleswig-Holstein
Medizinische Klinik 2
Ratzeburger Allee 160, 23538 Luebeck Germany

Study title:
CHAMPION Phoenix: A clinical trial comparing cangrelor with clopidogrel as a standard treatment in patients requiring percutaneous coronary intervention

Protocol number: TMC-CAN-10-01

In clinical studies, personal data, in particular medical findings, are collected, stored and processed. Use of the information about your health is in accordance with legal provisions and participating in the clinical study depends upon voluntarily giving consent in advance, i.e. without the signing of the consent form, you are not allowed to participate in the clinical trial.

PATIENT INFORMATION AND CONSENT TO PRIVACY

1) I am aware that in the context of this clinical trial information, in particular information about my health, can be collected and recorded on paper and on electronic media by the investigator (see address above). Where necessary, the information collected is anonymized (i.e., encrypted with a numerical code):

a) at The Medicines Company (the study principal) 8 Sylvan Way, Parsippany, NJ 07054, USA - represented by The Medicines Company UK Ltd, in European Union (EU), 11 Milton Park, Abingdon, Oxfordshire, OX 144RS, UK - or a person

UK – oder eine von diesem beauftragte Stelle zur wissenschaftlichen Auswertung.

b) im Falle eines Antrags auf Zulassung oder Erneuerung der Zulassung: an den Antragsteller und die für die Zulassung zuständige Behörde (innerhalb und ausserhalb der EU)

c) im Falle unerwünschter Ereignisse: an den Studienauftraggeber, The Medicines Company, an die zuständige Ethikkommission und die zuständige Bundesoberbehörde; letztere kann die Daten ihrerseits an die Europäische Datenbank, ausländische Behörden (innerhalb und ausserhalb der EU) sowie an die beteiligten Prufärzte weitergeben.

Mir ist bekannt, dass meine Daten mittels einer Patientenidentifikationsnummer pseudonymisiert werden. Demographische Daten, darunter auch mein Alter und mein Geschlecht, werden ebenfalls erhoben. Die Daten werden ausschliesslich verwendet, um die Richtigkeit meiner medizinischen Informationen zu bestätigen und eine Verwechslung mit anderen Studienteilnehmern zu verhindern. Es kann nicht vollkommen ausgeschlossen werden, dass ich durch die Verwendung dieser zusätzlichen Informationen identifiziert werde.

2) Mir ist auch bekannt, dass autorisierte und zur Verschwiegenheit verpflichtete Beauftragte des Studienauftraggebers sowie Mitarbeiter nationaler Behörden (der zuständigen nationalen Aufsichtsbehörden, d. h. Landes- oder Bezirksbehörden) oder der Bundesbehörden und/oder Vertreter vergleichbarer Behörden in anderen Ländern (innerhalb und ausserhalb der EU, z. B. die US-amerikanische Food and Drug Administration [FDA]) in meine beim Prufarzt vorhandenen personenbezogenen Daten, insbesondere meine Gesundheitsdaten, Einsicht nehmen können, soweit dies für die Überprüfung der ordnungsgemässen Durchführung der Studie notwendig ist. Für diese Massnahme entbinde ich den Prufarzt hiermit von der ärztlichen Schweigepflicht.

3) Die Einwilligung zur Erhebung und Verarbeitung meiner personenbezogenen Daten, insbesondere der Angaben über meine Gesundheit, ist unwiderruflich. Ich bin bereits darüber aufgeklärt worden, dass ich jederzeit die Teilnahme an dieser klinischen Studie beenden kann. Sollte ich meine Einwilligung in die Verarbeitung meiner Daten schriftlich widerrufen, werden für die Zwecke der oben genannten

appointed by this body for scientific evaluation.

b) in the case of an application for approval or renewal of approval: the applicant and the authority competent for the appropriate authorization authority (within and outside the EU)

c) in the case of undesired events: to the study sponsor, The Medicines Company, to the appropriate Ethics Committee and the appropriate government authority; the latter can pass on the data to the European database, foreign authorities (within and outside the EU) and to the participating investigators.

I am aware that my data using a patient identification number are pseudonyms. Demographic data, including my age and my gender will also be collected. The data will be used exclusively to confirm the accuracy of my medical information and prevent confusion with other study participants. It can not be completely excluded that I will be identified through the use of this ancillary information.

2) I am also aware that the authorized and committed to secrecy representative of the study sponsor and the staff of national authorities (the appropriate national oversight authorities, i.e. state or district authorities) or federal authorities and/or representatives of comparable authorities in other countries (within and outside the EU, such as the U.S. Food and Drug Administration [FDA]) can access my personal data, especially my health information, available from the investigator, as far as the review for the carrying out proper study is necessary. For this measure, I hereby absolve the investigator of the physician confidentiality.

3) The consent to the collection and processing of my personal data, particularly the information about my health, is irrevocable. I'm already been informed that I can stop participating in this clinical trial anytime. Should I withdraw my consent to the processing of my personal data in writing, for the purposes of the clinical trial mentioned no further personal data will be collected and recorded. In the

klinischen Studie keine weiteren personenbezogenen Daten erfasst und aufgezeichnet. Im Fall eines solchen Widerrufs meiner Einwilligung, an der klinischen Studie teilzunehmen, erkläre ich mich damit einverstanden, dass die bis zu diesem Zeitpunkt gespeicherten Daten ohne Angabe meines Namens weiterhin verwendet werden dürfen, soweit dies erforderlich ist, um

- a) Wirkungen des zu prüfenden Medikaments festzustellen,
- b) sicherzustellen, dass meine schutzwürdigen Rechte nicht beeinträchtigt werden,
- c) der Pflicht zur Vorlage umfassender und vollständiger Zulassungsunterlagen zu genügen.

4) Mir ist bekannt, dass meine Daten und der Identifikationsschlüssel, der erforderlich ist, um die Studiendaten mit mir in Verbindung zu bringen, bis zu 15 Jahre nach Beendigung oder Abbruch der klinischen Studie aufbewahrt werden, wie es die Vorschriften über die klinische Prüfung von Arzneimitteln bestimmen. Danach werden meine personenbezogenen Informationen gelöscht, soweit nicht gesetzliche Aufbewahrungsfristen entgegenstehen. Ich weiss, dass nur der Prüfarzt und seine Kollegen Zugriff auf den Schlüssel haben, der benötigt wird, um meine Studiendaten mit mir in Verbindung zu bringen.

5) Ich bin über folgende gesetzliche Regelung informiert: Falls ich meine Einwilligung, an der Studie teilzunehmen, widerrufe, müssen alle Stellen, die meine personenbezogenen Daten, insbesondere Gesundheitsdaten, gespeichert haben, unverzüglich prüfen, inwieweit die gespeicherten Daten für die in Nr. 3 a) bis c) genannten Zwecke noch erforderlich sind. Nicht mehr benötigte Daten sind unverzüglich zu löschen.

6) Ich habe das Recht, alle über mich erhobenen Informationen sowie die Ergebnisse meiner Untersuchungen oder der Behandlung einzusehen, es sei denn, dies ist aus technischen Gründen nicht länger möglich (d. h. wenn die Daten bereits pseudonymisiert wurden und eine Verbindung zwischen Ihren Informationen und Ihrer Person nicht länger hergestellt werden kann). Bei fehlerhafter Erfassung personenbezogener Daten habe ich das Recht, eine Korrektur zu verlangen.

7) Informationen, die Rückschlüsse auf meine Person zulassen, werden spätestens im Studienbericht pseudonymisiert (d. h., es kann keine

case of such a withdrawal of my consent to participate in the clinical trial, I declare my agreement that the stored data up to this point can still be used without giving my name, to the extent necessary to

- a) determine the effects of the study drug,
- b) ensure that my legitimate rights are not impaired,
- c) satisfy the obligation to provide comprehensive and full registration documents.

4) I am aware that my data and identification key, required to associate the study data with me, are kept up to 15 years after completion or termination of the clinical trial as the requirements concerning the clinical trial of drugs specify. Then will my personal information be erased, unless there are statutory retention periods. I know that only the investigators and his colleagues have access to the key, needed to associate my study data with me.

5) I am informed about the following regulation: If I revoke my consent to participate in the study, all places that have my personal data, particularly health data, stored must, and without undue delay, be deleted immediately except the extent to which the stored data are still required for the purposes referred to in No. 3 a) to c).

6) I have the right to view the information collected about me and the results of my investigations or treatment, unless this is no longer possible for technical reasons (i.e., if the data were already anonymized and a connection between your information and your person can no longer be produced. I have the right to require correction of faulty collection of personal data.

7) Information, that allows conclusions about my person, will be anonymized (i.e., no connection can be made to you) no later than in the study report.

Verbindung mehr zu Ihnen hergestellt werden). Der Abschlussbericht über die Ergebnisse dieser klinischen Studie darf veröffentlicht, an die zuständigen Gesundheitsbehörden in verschiedenen Bundesländern weitergeleitet und einer oder mehreren Zulassungsbehörden vorgelegt werden.

8) Mir ist bekannt, dass der Prufarzt meinen Hausarzt über meine Teilnahme an dieser klinischen Studie informieren und gegebenenfalls personenbezogene Gesundheitsdaten über mich einholen wird.

Ja Nein

(patient signature lines)

Prof. Dr. med. Peter Radke
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EINWILLIGUNGSERKLÄRUNG FÜR DIE TEILNAHME AN EINER KLINISCHEN STUDIE

Titel des Prüfplans: CHAMPION Phoenix: Eine klinische Studie zum Vergleich von Cangrelor mit Clopidogrel als Standardbehandlung bei Patienten, die eine perkutane Koronarintervention benötigen

Prüfplannummer: TMC-CAN-1 0-01

- Ich habe diese Patienteninformation und Einwilligungserklärung aufmerksam durchgelesen und alles verstanden.
- Ich wurde über Wesen, Bedeutung, Risiken und Tragweite dieser klinischen Studie aufgeklärt.
- Ich hatte Gelegenheit, Fragen zu stellen und alle meine Fragen wurden zu meiner Zufriedenheit beantwortet.
- Ich habe das Recht, die Teilnahme an der klinischen Studie jederzeit ohne Angabe von Gründen zu beenden. In diesem Fall habe ich keine Nachteile zu befürchten.
- Ich werde die medizinischen Anweisungen für die Durchführung der klinischen Studie befolgen und meinem Prufarzt auf Anfrage sämtliche Informationen mitteilen, die für die klinische Studie erforderlich sind. Ich werde den

The final published report about the results of this clinical study may be forwarded to the appropriate health authorities in different countries and submitted to one or more regulatory authorities.

8) I understand that the investigator will inform my personal physician about my participation in this clinical trial and possibly will seek personal health data on me.

Yes No

(patient signature lines)

Prof. Dr. med. Peter Radke
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Medizinische Klinik 2
Ratzeburger Allee 160, 23538 Luebeck Germany

CONSENT FORM FOR PARTICIPATION IN A CLINICAL STUDY

Study title:
CHAMPION Phoenix: A clinical trial comparing cangrelor with clopidogrel as a standard treatment in patients requiring percutaneous coronary intervention

Protocol number: TMC-CAN-10-01

- I have read this patient information and consent form carefully and understood everything.
 - I was enlightened about the nature, significance, implications, and risks of this clinical trial.
 - I had the opportunity to ask questions and all my questions were answered to my satisfaction.
 - I have the right to quit participation in the clinical trial at any time without giving reasons. In this case I have no disadvantages to fear.
- I will follow the medical instructions for carrying out the clinical trial and report to my investigator on request complete information that is required for the clinical study. I will inform my investigator immediately about every possible side effect. I am

Prufarzt unverzüglich über jede mögliche Nebenwirkung informieren. Mir ist bewusst, dass ich meine Gesundheit gefährde, wenn ich unvollständige oder fehlerhafte Angaben mache.

- Ich habe ein unterzeichnetes und datiertes Exemplar der Patienteninformation und Einwilligungserklärung für meine Unterlagen erhalten. Die Versicherungsbedingungen wurden mir ausgehändigt.

- Ich bestätige hiermit, dass ich in keinem Abhängigkeitsverhältnis zum Prufarzt und/oder dem Auftraggeber der klinischen Studie stehe.

- Ich nehme an dieser klinischen Studie aus freiem Willen teil. Ich kann die Teilnahme auch verweigern.

- Der Prufarzt wird mich über neue Erkenntnisse informieren, die sich im Verlauf der Studie ergeben und die Einfluss auf meine Bereitschaft zur Fortsetzung meiner Studienteilnahme haben können.

(patient signature lines)

Ich bestätige hiermit, dass ich dem oben genannten Patienten persönlich den Zweck, die Dauer und die vorhersehbaren Risiken der klinischen Studie erläutert und sämtliche Fragen vollständig beantwortet habe. Ich bestätige, dass kein Abhängigkeitsverhältnis zwischen dem oben genannten Patienten und mir und/oder dem Auftraggeber der klinischen Studie besteht. Weiterhin erkläre ich, dass ich die Datenschutzbestimmungen entsprechend § 7 (2) und (3) Nr. 15 der GCP-Verordnung beachten und einhalten werde.

(investigator signature lines)

aware that I endanger my health if I provide incomplete or erroneous information.

- I have received a signed and dated copy of the patient information and consent form for my records. The insurance conditions were delivered to me.

- I confirm herewith that I am in no dependent relationship with the investigator and/or the sponsor of the clinical trial.

- I will participate in this clinical trial voluntarily. I can also refuse participation.

- The investigator will inform me about new findings that in the course of the study arise and that can have an impact on my willingness to continue my study participation.

(patient signature lines)

I confirm herewith that I personally explained to the patient mentioned above the purpose, duration and the foreseeable risks of the clinical trial and I have answered all questions completely. I confirm that no dependent relationship exists between the above referenced patient and myself and/or the sponsor of the clinical trial. Furthermore, I declare that I will observe and comply with the data protection regulations § 7 (2) and (3) No. 15 of GCP-regulation.

(investigator signature lines)

Attachment 8

From: Bigby, Barbara [Bigby.Barbara@scrippshealth.org]
Sent: Thursday, April 04, 2013 3:48 PM
To: Marciniak, Thomas
Cc: Robert Bjork Jr MD ; Price, Matthew J. MD
Subject: RE: CHAMPION PHOENIX Study

1. CANGRELOR FOR INJECTION INVESTIGATOR'S BROCHURE

Edition No. 5,	Replaces Edition No. 4
Release Date: 4 May 2010	Dated: 19 August 2008
Data Cutoff Date: 3 September 2009	Data Cutoff Date: 23 May 2008

2. Investigational New Drug

CANGRELOR

A clinical trial comparing cangrelor to clopidogrel standard of care therapy in subjects who require percutaneous coronary intervention:

CHAMPION PHOENIX

Cangrelor versus standard therapy to achieve optimal management of platelet inhibition

Protocol No. TMC-CAN-10-01

U.S. IND No. 56,812

PROTOCOL VERSION: Amendment 1

Amendment to Original Protocol Dated 15 June, 2010

3. ICF dated 1-25-11, Quest Diagnostics CKMB Manual 08 Sept 2010, Pharmacy Manual 7-Sep-2010, 1572
4. No other information was provided.
5. The Scripps IRB was aware of the closing of the CHAMPION-PCI trial for lack of efficacy, not safety concerns, because Paul Teirstein, MD had participated in that trial at our site. There was a belief at the time that suboptimal study design might have been responsible for cangrelor's apparently poor performance. These discussions took place in 2009 and were not captured in the minutes for the PHOENIX study review.

From: Marciniak, Thomas [mailto:Thomas.Marciniak@fda.hhs.gov]
Sent: Thursday, April 04, 2013 9:24 AM
To: Bigby, Barbara
Cc: Robert Bjork Jr MD ; Price, Matthew J. MD
Subject: RE: CHAMPION PHOENIX Study

Thanks. I would like to know the following:

1. The version of the Investigator's Brochure used for the initial IRB approval.
2. The version of the protocol used for the initial IRB approval.
3. What other materials The Medicines Company provided regarding cangrelor for IRB review.
4. Whether The Medicines Company communicated any aspects of the FDA review of the protocol.
5. Any discussion regarding study design or the CHAMPION PCI and PLATFORM results at the IRB meeting, e.g., IRB minutes.

Tom Marciniak

From: Bigby, Barbara [<mailto:Bigby.Barbara@scrippshealth.org>]

Sent: Thursday, April 04, 2013 11:51 AM

To: Marciniak, Thomas

Cc: Robert Bjork Jr MD ; Price, Matthew J. MD

Subject: CHAMPION PHOENIX Study

Dear Mr. Marciniak,

I've attached the original, IRB-approved informed consent form for this study.
Please let us know if you need more information.

*Barbara G Bigby, ALM, CIP
Director, Regulatory Services
Scripps Clinical Research
11025 North Torrey Pines Road, Suite 200
La Jolla CA 92037
Tel: 858 652-5410; Fax: 858 652-5554*

From: Marciniak, Thomas [Thomas.Marciniak@fda.hhs.gov]

Sent: Wednesday, April 03, 2013 12:55 PM

To: Bjork, Robert L. MD

Subject: IND 56,812 CHAMPION PHOENIX Protocol # TMC-CAN-10-01 informed consent document

I am doing some preliminary checking in preparation for a review of this study. It is possible to get a copy of the informed consent document used at Scripps for this study for comparison to what The Medicines Company has submitted?

Thomas A. Marciniak, M.D.
Medical Team Leader, Cardiovascular & Renal Products
Food and Drug Administration
10903 New Hampshire Avenue
Building 22, Room 4166
Silver Spring, MD 20903-0002
301-796-1118 (voice)
301-796-9841 (fax)

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/s/

THOMAS A MARCINIAK
01/10/2014