CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services

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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA Serial Number:	NDA 204-958 (SN 0063)
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
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Biometrics Division:	Biometrics I, HFD-710
Statistical Reviewer:	Jialu Zhang, Ph.D.
Concurring Reviewers:	James Hung, Ph.D.
Medical Division:	Division of Cardiovascular and Renal Products, HFD-110
Clinical Team:	Efficacy Reviewer: Fortunato Senatore, MD, PhD Safety Reviewer: Nhi Beasley, PharmD
Project Manager:	Alison Blaus

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1. INTRODUCTION

1.1 Overview

Reference is made to the Agency's Complete Response for the Cangrelor New Drug Application NDA 204958 on April 30, 2014. After subsequent meetings, the sponsor resubmitted the NDA with additional analyses and information to address the issues raised in the Complete Response letter.

The statistical review for this re-submission mainly focuses on several items in CHAMPION PHOENIX trial

1. Landmark analysis
2. Sensitivity analyses on the primary composite endpoint (removing intraprocedural stent thrombosis from the primary composite endpoint, using more conservative definition of MI, et al)
3. Efficacy analyses on site-reported primary endpoint
4. Discrepancies between Sponsor's results and Dr. Marciniak's results

1.2 Data Sources

The analysis datasets of CHAMPION PHOENIX resubmission is located at \\CDSESUB1\evsprod\NDA204958\0063\m5\datasets\tmc-can-10-01-crlresp\analysis\legacy\datasets.

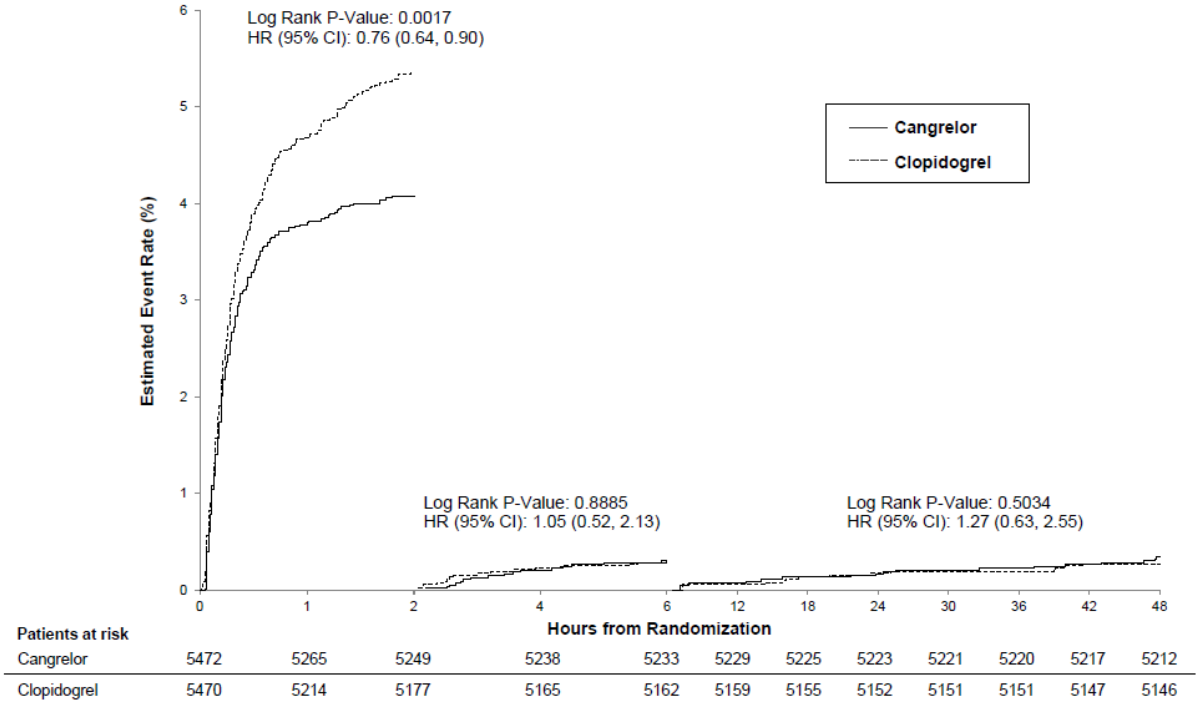
2. STATISTICAL EVALUATION

2.1 Landmark Analysis

The sponsor provided landmark analysis to demonstrate that essentially all of the difference in primary events rates between the randomized groups was in the first 2 hours after randomization. The primary endpoint events were divided into those which occurred within 2 hours after randomization, those which occurred between 2 hours and 6 hours, and those between 6 hours and 48 hours. Figure 1 is the landmark analysis based on the protocol-defined primary endpoint (Death/MI/IDR/ST). To further examine the robustness of the results, the sponsor performed

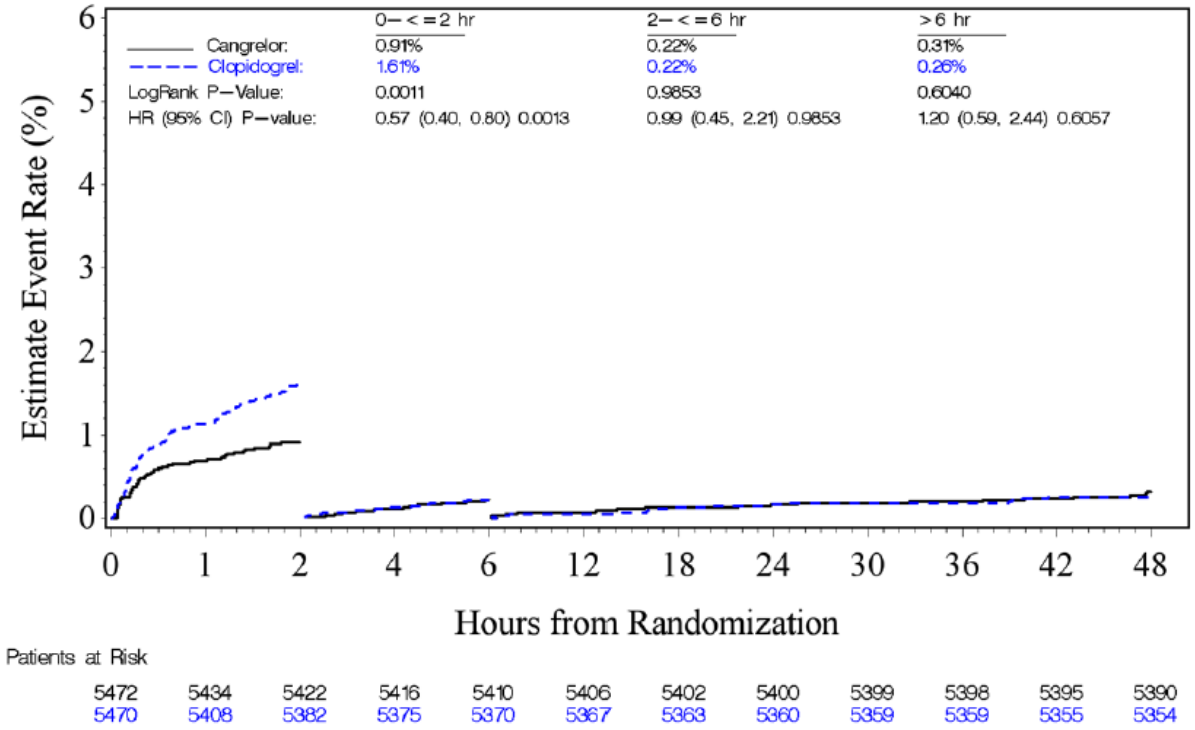
similar landmark analysis using a supplemental primary endpoint that excluded IPST and used a more conservative definition of MI (Death/SCAI MI/IDR/ARC-ST), which was shown in Figure 2. Table 1 listed the total number of events in each treatment group for every time period in the landmark analyses. The reviewer was able to verify all the results.

Figure 1: Landmark analysis on First Occurrence of Death/MI/IDR/ST



[Source: Figure 6 in Sponsor's response document, confirmed by the reviewer]

Figure 2: Landmark Analysis on First Occurrence of Death/SCAI MI/IDR/ARC-ST



[Source: Figure 105.1.1.1.312 in Sponsor's response dated Feb 17, 2015, confirmed by the reviewer]

Table 1: Total Patients and Patients with Events in Landmark Analyses

Endpoint	Period	Treatment Group	Patients with 1st Events	Total Number of Patients
Death, MI, IDR, and ST	0-2 hr	Cangrelor	223	5472
		Clopidogrel	293	5470
	2-6 hr	Cangrelor	16	5249
		Clopidogrel	15	5177
	6-48 hr	Cangrelor	18	5233
		Clopidogrel	14	5162
Death, SCAI MI, IDR, and ARC ST	0-2 hr	Cangrelor	50	5472
		Clopidogrel	88	5470
	2-6 hr	Cangrelor	12	5422
		Clopidogrel	12	5382
	6-48 hr	Cangrelor	17	5410
		Clopidogrel	14	5370

[Source: Table 3 in Sponsor's response dated Feb 23, 2015, confirmed by the reviewer]

It was also noted that among the 138 Death/SCAI MI/IDR/ARC-ST events that occurred within 2 hours, 65 subjects (43 in clopidogrel arm and 22 in cangrelor arm) had a composite event of

Death/SCAI MI/IDR/ARC-ST within 5 minutes from infusion of the study drug (Table **11**). Of these 65 adjudicated events, 24 of them (17 in clopidogrel arm and 7 in cangrelor arm) were also reported at site. The site-reported time of these 24 events was later than the event time determined by CEC (many of them were a few hours or even a few days later). The sponsor stated that CEC determined the event time at the earliest time point according to the specific information for each event type.

The reviewer further examined the 138 Death/SCAI MI/IDR/ARC-ST events included in the first two-hour landmark analysis. Out of the 138 adjudicated events, 76 events (51 events in clopidogrel arm and 25 events in cangrelor arm) were also reported by site. If calculated by the event time recorded at site, 32 events of these 76 events (22 in clopidogrel and 10 in cangrelor) occurred beyond 2 hours after randomization.

The sponsor's landmark analysis was based on the event time determined by CEC. This may explain why the sponsor's landmark analysis only found treatment effect in the first 2 hours but not after 2 hours.

2.2 Sensitivity analyses on the adjudicated primary composite endpoint

To address the issue that some subcomponents of the primary endpoint may not represent clinical benefit, the sponsor performed additional sensitivity analyses. Table 2 and Table 3 showed results by excluding IPST and using several more conservative definitions of MI. The point estimate of all the sensivity analyses were trending to the right direction and showed consistency compared to the protocol-defined primary endpoint. Cangrelor does not appear to affect death rate.

Table 2: Protocol-Defined and Supplemental Primary Endpoints at 48 Hours (mITT)

	Cangrelor (N=5472)	Clopidogrel (N=5470)	OR and 95% CI	p-value
Protocol-Defined Primary Endpoint				
Death/MI/IDR/ST[1]	257/5470 (4.7)	322/5469 (5.9)	0.78 (0.66, 0.93)	0.0049
Death	18/5470 (0.3)	18/5469 (0.3)	1.00 (0.52, 1.92)	0.9996
MI	207/5470 (3.8)	255/5469 (4.7)	0.80 (0.67, 0.97)	0.0224
IDR	28/5470 (0.5)	38/5469 (0.7)	0.74 (0.45, 1.20)	0.2167
ST[1]	46/5470 (0.8)	74/5469 (1.4)	0.62 (0.43, 0.90)	0.0101
Supplemental Primary Endpoints				
Death/MI (SCAI definition)/IDR/ARC-ST	79/5470 (1.4)	114/5469 (2.1)	0.69 (0.52, 0.92)	0.0110
MI by SCAI definition	53/5470 (1.0)	81/5469 (1.5)	0.65 (0.46, 0.92)	0.0149
ARC-ST	12/5470 (0.2)	22/5469 (0.4)	0.54 (0.27, 1.10)	0.0858
Death/MI (CK-MB ≥ 10X ULN)/IDR/ARC-ST	77/5470 (1.4)	111/5469 (2.0)	0.69 (0.51, 0.92)	0.0123
MI (CK-MB ≥ 10X ULN)	50/5470 (0.9)	78/5469 (1.4)	0.64 (0.45, 0.91)	0.0128

[1]Includes ARC-ST and IPST. Adjusted for loading dose and baseline patient status in logistic regression.

[Source: Table 12 in Sponsor's response document, confirmed by the reviewer]

Table 3: Sensitivity Analyses of the Primary Endpoint at 48 Hours (mITT)

	Cangrelor (N=5472)	Clopidogrel (N=5470)	OR and 95% CI	p-value
Protocol-Defined Primary Endpoint				
Death/MI/IDR/ST[1]	257/5470 (4.7)	322/5469 (5.9)	0.78 (0.66, 0.93)	0.0049
Removal of IPST				
Death/MI/IDR/ARC-ST	230/5470 (4.2)	286/5469 (5.2)	0.80 (0.67, 0.95)	0.0115
Removal of IPST and MIs Identified Solely by CK-MB Elevations >3X ULN but < 10X ULN[2]				
Death/MI/IDR/ARC-ST	106/5470 (1.9)	161/5469 (2.9)	0.65 (0.51, 0.83)	0.0007
Removal of IPST and all MIs Identified Solely by CK-MB Elevations[3]				
Death/MI/IDR/ARC-ST	86/5470 (1.6)	130/5469 (2.4)	0.66 (0.50, 0.86)	0.0025
Removal of IPST and all MIs				
Death/IDR/ARC-ST	43/5470 (0.8)	54/5469 (1.0)	0.79 (0.53, 1.19)	0.2615

1Includes ARC-ST and IPST. Adjusted for loading dose and baseline patient status in logistic regression.
2Includes peri-procedural MIs with one of the following: CK-MB ≥10X ULN or MI with either ischemic symptoms or 12-lead ECG changes).
3Includes peri-procedural MIs identified by either ischemic symptoms or 12-lead ECG changes.

[Source: Table 14 in the Sponsor's response document, confirmed by the reviewer]

Table 2 listed the counts of the individual components of the protocol-defined primary endpoint based on all events occurred within 48 hours. To avoid double counting, the reviewer calculated the counts of individual components by assigning each subject only one type of event. For those subjects who had more than one type of event at the same time, the more severe event would be used. For example, if a patient had a MI and ST at the same time, only MI would be counted. The reviewer follow the order of death > MI > IDR > ST. Table 4 showed the individual component counts for a number of composite endpoints.

Table 4: Individual Component Counts for the Composite Endpoints

	protocol-defined primary endpoint				
	Composite	Death	MI	IDR	ST
clopidogrel	322	14	254	11	43
cangrelor	257	12	204	9	32
	Death/SCAI MI/IDR/ARC-ST				
	Composite	Death	SCAI MI	IDR	ARC ST
clopidogrel	114	16	81	13	4
cangrelor	79	15	50	12	2
	removal of IPST and MIs (identified Solely by CKMB>3ULN but <10ULN) from the primary endpoint				
	Composite	Death	MI	IDR	ST
clopidogrel	161	16	130	11	4
cangrelor	106	15	80	9	2

[Source: reviewer's analysis]

The sensitivity analyses of the primary endpoint showed in Table 2 and Table 3 were all based on mITT population. The reviewer also performed similar analyses in the ITT population (Table 5). The conclusion, nevertheless, remains unchanged.

Table 5: Supplemental Primary Endpoint at 48 Hours (ITT population)

Endpoint	cangrelor (N=5581)	clopidogrel (N=5564)	OR and 95% CI
protocol-defined primary endpoint	260	325	0.79 (0.67, 0.93)
Death/SCAI MI/IDR/ARC-ST	82	117	0.70 (0.52, 0.92)
SCAI MI	53	81	0.65 (0.50, 0.92)
ARC-ST	12	22	0.54 (0.27, 1.10)
Death/MI (CKMB>=10ULN)/IDR/ARC-ST	80	114	0.70 (0.52, 0.93)
MI (CKMB>=10ULN)	50	78	0.64 (0.45, 0.91)
removal of IPST	233	289	0.80 (0.67, 0.95)
removal of IPST and MIs (CK-MB elevations >3ULN but < 10ULN)	109	164	0.66 (0.51, 0.84)
removal of IPST and all MIs (CKMB elevations)	89	133	0.66 (0.51, 0.87)
removal of IPST and all Mis	46	57	0.80 (0.54, 1.19)

[Source: reviewer's analysis]

2.3 Site-reported Events

The reviewer verified sponsor's site reported results. The sponsor submitted the SAS program used to derive site reported event from raw data and the reviewer was able to verify sponsor's results.

Table 6: Site-Reported Primary Events at 48 Hours (mITT population)

	Cangrelor (N=5472)	Clopidogrel (N=5470)	OR and 95% CI	p-value
Protocol-Defined Primary Endpoint				
Death/MI/IDR/ST[1]	257/5470 (4.7)	322/5469 (5.9)	0.78 (0.66, 0.93)	0.0049
Site-Reported Events				
Death/MI/IDR/ST[2]	96/5470 (1.8)	121/5469 (2.2)	0.79 (0.60, 1.03)	0.0862
Death/MI/IDR/ST (IDR eCRF)[3]	94/5470 (1.7)	118/5469 (2.2)	0.79 (0.60, 1.04)	0.0957

1. Includes ARC-ST and IPST.
2. Includes MIs recorded by the site on the MI eCRF page, IDR recorded by the site on the Revascularization eCRF page, and ST from death, MI, IDR, Follow-up, and PCI eCRF pages.
3. Includes MIs recorded by the site on the MI eCRF page, unplanned revascularizations recorded by the site on the Revascularization eCRF page, and ST recorded by the site on the IDR eCRF.

[Source: Table 15, confirmed by the reviewer]

2.4 Discrepancies between Sponsor's results and Dr. Marciniak's results

In the Advisory Committee Meeting on February 12, 2014, Dr. Marciniak presented his analysis results based on site-reported events, which showed discrepancies with what the sponsor presented. The reviewer extracted the dataset used by Dr. Marciniak from his reviews and further examined Dr. Marciniak's analyses and sponsor's analyses. Table 7 is sponsor's results based on mITT population, which were presented by the sponsor during the AC meeting. Table 8 is based on ITT population and Table 9 is Dr. Marciniak's results, which is also based on ITT population. The patient types listed in the three tables were based on the investigator's initial assessment of clinical presentation as entered into the IVRS, not the derived patient type.

Table 7: Sponsor's Results on Primary endpoint by Index Events (mITT population)

	adjudicated primary endpoint		site-reported primary endpoint	
	Clopidogrel	Cangrelor	clopidogrel	cangrelor
Angina	217/3172 (6.8%)	182/3186 (5.7%)	65/3172 (2.1%)	52/3186 (1.6%)
UA/NSTEMI	82/1428 (5.7%)	53/1464 (3.6%)	37/1428 (2.6%)	26/1464 (1.8%)
STEMI	23/870 (2.6%)	22/822 (2.7%)	16/870 (1.8%)	16/822 (2.0%)
All	322/5470 (5.9%)	257/5472 (4.7%)	118/5470 (2.2%)	94/5472 (1.7%)

Table 8: Sponsor's Primary endpoint by Index Events (ITT population)

	adjudicated primary endpoint		site-reported primary endpoint	
	Clopidogrel	Cangrelor	Clopidogrel	cangrelor
angina	217/3208 (6.8%)	182/3220 (5.7%)	65/3208 (2.0%)	53/3220 (1.7%)
UA/NSTEMI	82/1435 (5.7%)	53/1479 (3.6%)	37/1435 (2.6%)	27/1479 (1.8%)
STEMI	26/921 (2.8%)	25/882 (2.8%)	20/921 (2.2%)	21/882 (2.4%)
All	325/5564 (5.8%)	260/5581 (4.7%)	122/5564 (2.2%)	101/5581 (1.8%)

Table 9: Tom's Results on Primary endpoint by Index Events (ITT population)

	adjudicated primary endpoint		site-reported primary endpoint	
	Clopidogrel	Cangrelor	clopidogrel	Cangrelor
angina	217/3208 (6.8%)	182/3220 (5.7%)	68/3208 (2.1%)	58/3220 (1.8%)
UA/NSTEMI	82/1435 (5.7%)	53/1479 (3.6%)	37/1435 (2.6%)	32/1479 (2.2%)
STEMI	26/921 (2.8%)	25/882 (2.8%)	21/921 (2.3%)	25/882 (2.8%)
all	325/5564 (5.8%)	260/5581(4.7%)	126/5564 (2.3%)	115/5581 (2.1%)

The ITT population in PHOENIX trial comprised 5581 patients in the cangrelor arm and 5564 patients in the clopidogrel arm. Among those in the ITT population, 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. The major difference on site-reported events between mITT population and ITT population is in STEMI patients. Using mITT population, the site-reported event rates in STEMI patients were 1.8% in clopidogrel arm and 2.0% in cangrelor arm. Using ITT population, the site-reported event rates in STEMI patients were 2.2% in clopidogrel arm and 2.4% in cangrelor arm. In both cases, the cangrelor arm had a slightly higher event rate than clopidogrel arm. However, the results based on subgroups need to be interpreted with caution.

Dr. Marciniak included 18 extra events in his analyses on the site-reported events. As a result, site-reported event rates in his analyses were 2.8% in cangrelor arm and 2.3% in clopidogrel arm. These 18 subjects were listed in Table 10. Of these 18 subjects who were not reported by the investigators at site but were considered having a primary event at 48 hours by Dr. Marciniak, only one subject was adjudicated to have a primary endpoint event at 48 hours. Further details and discussions about these 18 patients can be found in the clinical review by Dr. Senatore and Dr. Beasley.

Table 10: Extra Subjects with Events at 48 Hours by Dr. Marciniak

Subject ID	Index Event	Abnormal	Site	US	Adjudicated Event 48 Hours	Adjudicated Event 30 Days	Treatment
401021013	NSTE-ACS	Yes	401021	Yes	No	No	cangrelor
401030289	Angina	No	401030	Yes	No	No	cangrelor
439001076	NSTE-ACS	Yes	439001	No	No	No	cangrelor
439001085	NSTEMI	Yes	439001	No	No	No	cangrelor
439004181	NSTE-ACS	Yes	439004	No	No	No	cangrelor
443002052	NSTEMI	Yes	443002	No	No	No	cangrelor
443002145	NSTE-ACS	Yes	443002	No	No	No	cangrelor
449001009	NSTEMI	Yes	449001	No	No	No	clopidogrel
449004029	Angina	No	449004	No	No	No	clopidogrel
449005002	NSTEMI	Yes	449005	No	No	No	cangrelor
449005032	Angina	No	449005	No	No	No	cangrelor
449012005	Angina	No	449012	No	No	No	cangrelor
449017033	Angina	No	449017	No	No	No	clopidogrel
449021003	Angina	No	449021	No	Yes	Yes	cangrelor
495002197	NSTE-ACS	Yes	495002	No	No	No	cangrelor
495005197	NSTEMI	Yes	495005	No	No	No	cangrelor
495005476	Angina	No	495005	No	No	No	cangrelor
495005567	Angina	No	495005	No	No	No	clopidogrel

Appendix

Table 11: Comparison of Adjudicated Event Time and Site Reported Event Time

Subject ID	Treatment	Randomization Time	Drug Start Time	Adjudicated Event Time	Site-reported Event Time
401001168	clopidogrel	15DEC11:09:48:00	15DEC2011:10:05:00	15DEC11:10:06:00	
401010028	clopidogrel	21DEC10:11:54:00	21DEC2010:12:18:00	21DEC10:12:20:00	
401010103	clopidogrel	09AUG11:09:42:00	09AUG2011:10:44:00	09AUG11:10:48:00	11AUG11:08:40:00
401011070	clopidogrel	06SEP12:11:53:00	06SEP2012:12:25:00	06SEP12:12:28:00	06SEP12:13:30:00
401025016	clopidogrel	04OCT11:17:55:00	04OCT2011:18:17:00	04OCT11:18:03:00	05OCT11:12:05:00
401027083	clopidogrel	16MAY12:08:38:00	16MAY2012:08:52:00	16MAY12:08:55:00	16MAY12:09:02:00
401028004	clopidogrel	26JAN11:17:23:00	26JAN2011:17:57:00	26JAN11:18:00:00	27JAN11:03:27:00
401030075	clopidogrel	29JUN11:13:26:00	29JUN2011:14:55:00	29JUN11:14:57:00	29JUN11:17:23:00
401030173	clopidogrel	30NOV11:10:50:00	30NOV2011:12:03:00	30NOV11:12:07:00	30NOV11:20:00:00
401030232	clopidogrel	22FEB12:10:27:00	22FEB2012:11:35:00	22FEB12:11:35:00	24FEB12:06:00:00
401055020	clopidogrel	21JAN11:12:53:00	21JAN2011:12:58:00	21JAN11:13:02:00	
401058008	clopidogrel	23MAR11:14:08:00	23MAR2011:14:20:00	23MAR11:14:24:00	31MAR11:09:47:00
401058029	clopidogrel	20JUN12:14:46:00	20JUN2012:15:01:00	20JUN12:14:58:00	20JUN12:15:24:00
401077048	clopidogrel	04OCT11:11:43:00	04OCT2011:12:01:00	04OCT11:12:05:00	
401079035	clopidogrel	10MAR11:11:40:00	10MAR2011:11:46:00	10MAR11:11:47:00	
401079151	clopidogrel	11OCT11:09:47:00	11OCT2011:09:52:00	11OCT11:09:56:00	
401079204	clopidogrel	16JAN12:07:35:00	16JAN2012:07:47:00	16JAN12:07:48:00	19JAN12:18:09:00
401085036	clopidogrel	05OCT11:15:28:00	05OCT2011:15:43:00	05OCT11:15:45:00	
401091101	clopidogrel	02MAR11:11:20:00	02MAR2011:11:35:00	02MAR11:11:36:00	
401091338	clopidogrel	09DEC11:12:25:00	09DEC2011:12:37:00	09DEC11:12:39:00	
401091597	clopidogrel	25MAY12:13:35:00	25MAY2012:13:42:00	25MAY12:13:45:00	
401092073	clopidogrel	02AUG12:12:35:00	02AUG2012:12:43:00	02AUG12:12:45:00	
407012029	clopidogrel	21MAR12:14:57:00	21MAR2012:14:58:00	21MAR12:14:59:00	21MAR12:23:00:00
420003076	clopidogrel	08FEB12:17:33:00	08FEB2012:17:42:00	08FEB12:17:45:00	
420009333	clopidogrel	07DEC11:14:00:00	07DEC2011:14:03:00	07DEC11:14:04:00	
420009375	clopidogrel	19DEC11:13:05:00	19DEC2011:13:08:00	19DEC11:13:09:00	
420009402	clopidogrel	28DEC11:12:05:00	28DEC2011:12:10:00	28DEC11:12:11:00	

420009485	clopidogrel	25JAN12:10:56:00	25JAN2012:11:00:00	25JAN12:11:01:00	
420009670	clopidogrel	23MAR12:16:23:00	23MAR2012:16:26:00	23MAR12:16:27:00	
420009832	clopidogrel	24MAY12:17:29:00	24MAY2012:17:32:00	24MAY12:17:33:00	
420009864	clopidogrel	14JUN12:13:21:00	14JUN2012:13:24:00	14JUN12:13:25:00	
439002038	clopidogrel	05APR12:15:37:00	05APR2012:15:40:00	05APR12:15:44:00	
449004028	clopidogrel	21DEC11:09:43:00	21DEC2011:09:45:00	21DEC11:09:45:00	
449013047	clopidogrel	03FEB12:15:40:00	03FEB2012:15:43:00	03FEB12:15:46:00	04FEB12:00:05:00
449017003	clopidogrel	09AUG11:09:55:00	09AUG2011:10:00:00	09AUG11:10:05:00	09AUG11:18:00:00
459003016	clopidogrel	30JAN12:14:54:00	30JAN2012:15:02:00	30JAN12:15:06:00	30JAN12:15:12:00
459003045	clopidogrel	17MAY12:11:22:00	17MAY2012:11:26:00	17MAY12:11:29:00	17MAY12:11:29:00
459007016	clopidogrel	19AUG11:09:02:00	19AUG2011:09:10:00	19AUG11:09:15:00	19AUG11:10:00:00
495002252	clopidogrel	24JUN12:13:30:00	24JUN2012:13:32:00	24JUN12:13:31:00	
495005346	clopidogrel	22FEB12:18:14:00	22FEB2012:18:23:00	22FEB12:18:25:00	
495005404	clopidogrel	06APR12:12:23:00	06APR2012:12:29:00	06APR12:12:31:00	
495005553	clopidogrel	09AUG12:12:39:00	09AUG2012:12:45:00	09AUG12:12:48:00	
495005587	clopidogrel	07SEP12:16:03:00	07SEP2012:16:05:00	07SEP12:16:06:00	
401007046	cangrelor	04JUN12:10:46:00	04JUN2012:11:00:00	04JUN12:11:02:00	
401029049	cangrelor	11JAN12:09:30:00	11JAN2012:09:40:00	11JAN12:09:43:00	
401053011	cangrelor	20DEC10:12:28:00	20DEC2010:12:43:00	20DEC10:12:45:00	
401079060	cangrelor	26APR11:17:57:00	26APR2011:18:08:00	26APR11:18:09:00	26APR11:18:09:00
401079193	cangrelor	21DEC11:14:12:00	21DEC2011:14:15:00	21DEC11:14:19:00	
401091423	cangrelor	07FEB12:14:25:00	07FEB2012:14:36:00	07FEB12:14:38:00	
420009059	cangrelor	05SEP11:09:57:00	05SEP2011:10:02:00	05SEP11:10:03:00	05SEP11:12:59:00
420009098	cangrelor	20SEP11:18:32:00	20SEP2011:18:35:00	20SEP11:18:36:00	
420009162	cangrelor	13OCT11:13:47:00	13OCT2011:13:50:00	13OCT11:13:51:00	13OCT11:14:00:00
420009655	cangrelor	19MAR12:17:04:00	19MAR2012:17:07:00	19MAR12:17:08:00	
420009695	cangrelor	30MAR12:17:41:00	30MAR2012:17:43:00	30MAR12:17:45:00	
420009798	cangrelor	03MAY12:13:04:00	03MAY2012:13:07:00	03MAY12:13:08:00	
420009836	cangrelor	29MAY12:14:30:00	29MAY2012:14:33:00	29MAY12:14:34:00	29MAY12:17:40:00
443002177	cangrelor	16NOV11:10:00:00	16NOV2011:10:05:00	16NOV11:10:05:00	
449004044	cangrelor	10APR12:10:12:00	10APR2012:10:15:00	10APR12:10:18:00	10APR12:21:57:00
449005048	cangrelor	25APR12:12:43:00	25APR2012:12:53:00	25APR12:12:55:00	

449021003	cangrelor	25MAY12:19:03:00	25MAY2012:19:30:00	25MAY12:19:30:00	25MAY12:19:30:00
466001043	cangrelor	22MAY12:14:24:00	22MAY2012:14:25:00	22MAY12:14:30:00	26MAY12:19:15:00
466002056	cangrelor	27JUN12:14:17:00	27JUN2012:14:18:00	27JUN12:14:23:00	
495005503	cangrelor	27JUN12:16:25:00	27JUN2012:16:35:00	27JUN12:16:39:00	
495005540	cangrelor	01AUG12:15:51:00	01AUG2012:15:54:00	01AUG12:15:55:00	
495005618	cangrelor	25SEP12:13:00:00	25SEP2012:13:04:00	25SEP12:13:05:00	

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/s/

JIALU ZHANG
03/25/2015

PEILING YANG
03/25/2015
Signed on behalf of Dr. HM James Hung.

March 27, 2015

This REV-BIOMETRICS-21 (Primary Review) was replaced by the corrected review dated 3/25/2015.

The changes in the new document include adding page numbering and removing a hyperlink in the Introduction section.

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 0063)
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: December 23, 2014 PDUFA due date: June 23, 2015
Review Priority:	6 month resubmission
Biometrics Division:	Biometrics I, HFD-710
Statistical Reviewer:	Jialu Zhang, Ph.D.
Concurring Reviewers:	James Hung, Ph.D.
Medical Division:	Division of Cardiovascular and Renal Products, HFD-110
Clinical Team:	Efficacy Reviewer: Fortunato Senatore, MD, PhD Safety Reviewer: Nhi Beasley, PharmD
Project Manager:	Alison Blaus

Keywords: landmark analysis, site-reported events

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1. INTRODUCTION

1.1 Overview

Reference is made to the Agency's Complete Response for the Cangrelor New Drug Application NDA 204958 on April 30, 2014. After subsequent meetings, the sponsor resubmitted the NDA with additional analyses and information to address the issues raised in the Complete Response letter.

The statistical review for this re-submission mainly focuses on several items in CHAMPION PHOENIX trial

1. Landmark analysis
2. Sensitivity analyses on the primary composite endpoint (removing intraprocedural stent thrombosis from the primary composite endpoint, using more conservative definition of MI, et al)
3. Efficacy analyses on site-reported primary endpoint
4. Discrepancies between Sponsor's results and Dr. Marciniak's results

1.2 Data Sources

The analysis datasets of CHAMPION PHOENIX resubmission is located at \\CDSESUB1\evsprod\NDA204958\0063\m5\datasets\tmc-can-10-01-crlresp\analysis\legacy\datasets.

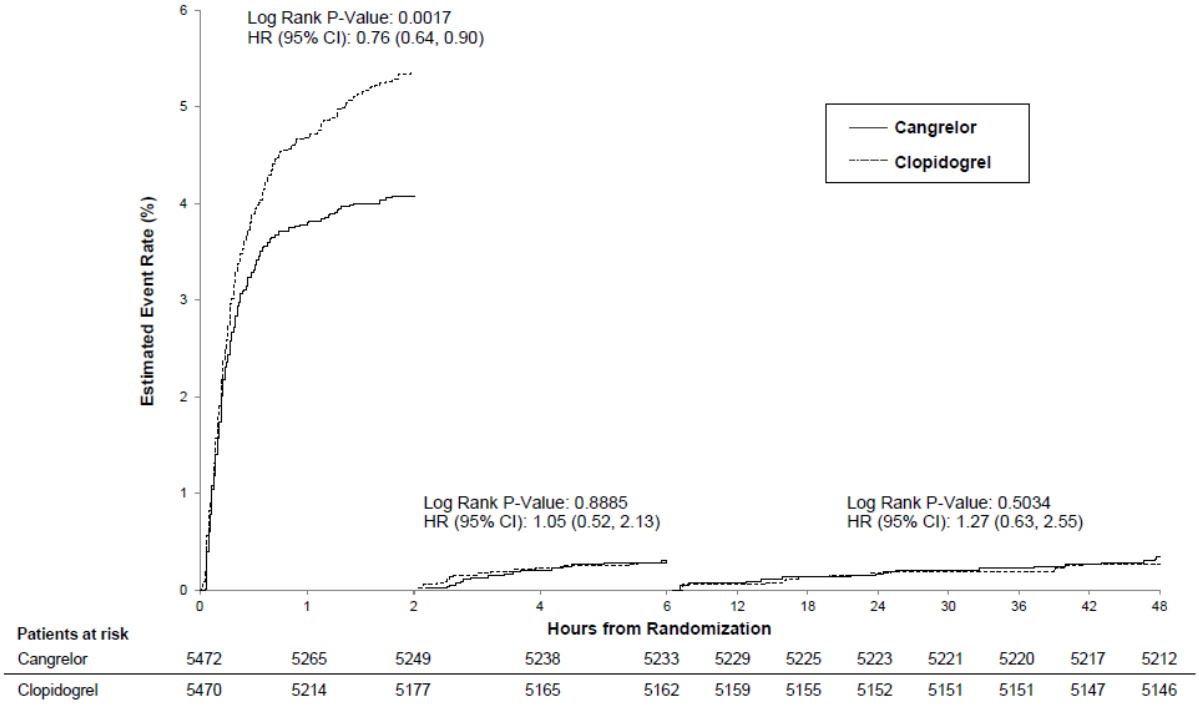
2. STATISTICAL EVALUATION

2.1 Landmark Analysis

The sponsor provided landmark analysis to demonstrate that essentially all of the difference in primary events rates between the randomized groups was in the first 2 hours after randomization. The primary endpoint events were divided into those which occurred within 2 hours after randomization, those which occurred between 2 hours and 6 hours, and those between 6 hours and 48 hours. Figure 1 is the landmark analysis based on the protocol-defined primary endpoint (Death/MI/IDR/ST). To further examine the robustness of the results, the sponsor performed

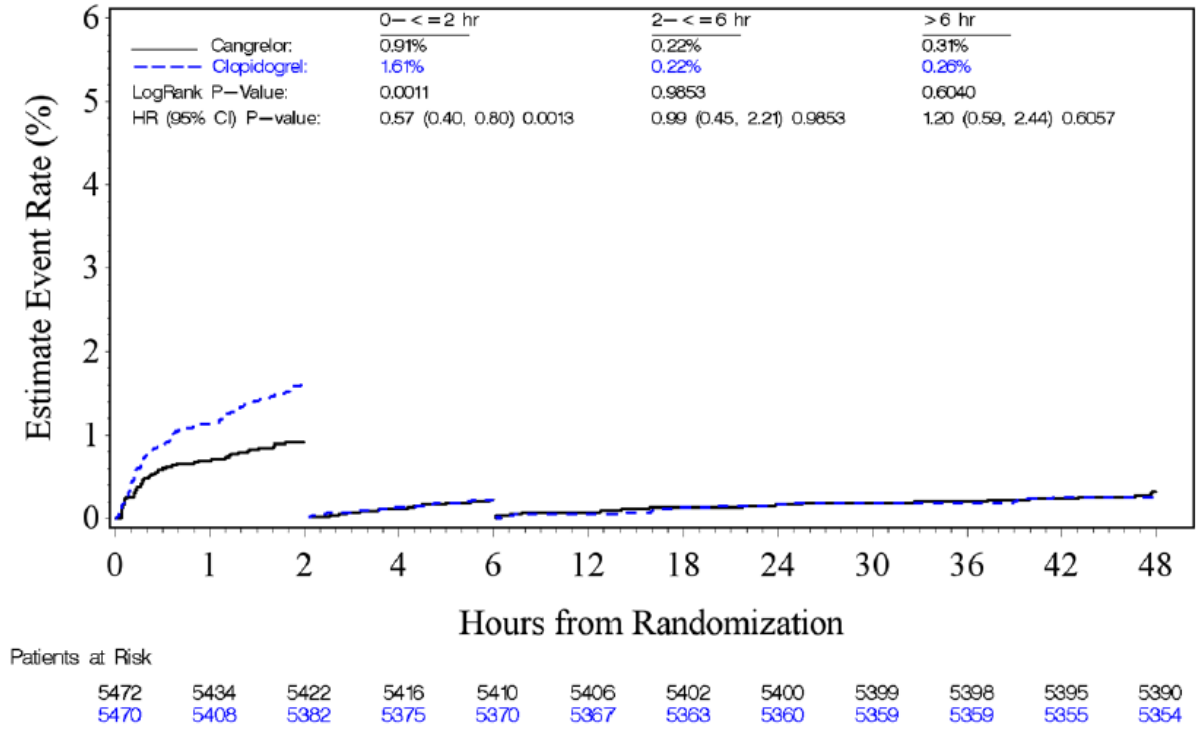
similar landmark analysis using a supplemental primary endpoint that excluded IPST and used a more conservative definition of MI (Death/SCAI MI/IDR/ARC-ST), which was shown in Figure 2. Table 1 listed the total number of events in each treatment group for every time period in the landmark analyses. The reviewer was able to verify all the results.

Figure 1: Landmark analysis on First Occurrence of Death/MI/IDR/ST



[Source: Figure 6 in Sponsor's response document, confirmed by the reviewer]

Figure 2: Landmark Analysis on First Occurrence of Death/SCAI MI/IDR/ARC-ST



[Source: Figure 105.1.1.1.312 in Sponsor's response dated Feb 17, 2015, confirmed by the reviewer]

Table 1: Total Patients and Patients with Events in Landmark Analyses

Endpoint	Period	Treatment Group	Patients with 1st Events	Total Number of Patients
Death, MI, IDR, and ST	0-2 hr	Cangrelor	223	5472
		Clopidogrel	293	5470
	2-6 hr	Cangrelor	16	5249
		Clopidogrel	15	5177
	6-48 hr	Cangrelor	18	5233
		Clopidogrel	14	5162
Death, SCAI MI, IDR, and ARC ST	0-2 hr	Cangrelor	50	5472
		Clopidogrel	88	5470
	2-6 hr	Cangrelor	12	5422
		Clopidogrel	12	5382
	6-48 hr	Cangrelor	17	5410
		Clopidogrel	14	5370

[Source: Table 3 in Sponsor's response dated Feb 23, 2015, confirmed by the reviewer]

It was also noted that among the 138 Death/SCAI MI/IDR/ARC-ST events that occurred within 2 hours, 65 subjects (43 in clopidogrel arm and 22 in cangrelor arm) had a composite event of

Death/SCAI MI/IDR/ARC-ST within 5 minutes from infusion of the study drug (Table **11**). Of these 65 adjudicated events, 24 of them (17 in clopidogrel arm and 7 in cangrelor arm) were also reported at site. The site-reported time of these 24 events was later than the event time determined by CEC (many of them were a few hours or even a few days later). The sponsor stated that CEC determined the event time at the earliest time point according to the specific information for each event type.

The reviewer further examined the 138 Death/SCAI MI/IDR/ARC-ST events included in the first two-hour landmark analysis. Out of the 138 adjudicated events, 76 events (51 events in clopidogrel arm and 25 events in cangrelor arm) were also reported by site. If calculated by the event time recorded at site, 32 events of these 76 events (22 in clopidogrel and 10 in cangrelor) occurred beyond 2 hours after randomization.

The sponsor's landmark analysis was based on the event time determined by CEC. This may explain why the sponsor's landmark analysis only found treatment effect in the first 2 hours but not after 2 hours.

2.2 Sensitivity analyses on the adjudicated primary composite endpoint

To address the issue that some subcomponents of the primary endpoint may not represent clinical benefit, the sponsor performed additional sensitivity analyses. Table 2 and Table 3 showed results by excluding IPST and using several more conservative definitions of MI. The point estimate of all the sensivity analyses were trending to the right direction and showed consistency compared to the protocol-defined primary endpoint. Cangrelor does not appear to affect death rate.

Table 2: Protocol-Defined and Supplemental Primary Endpoints at 48 Hours (mITT)

	Cangrelor (N=5472)	Clopidogrel (N=5470)	OR and 95% CI	p-value
Protocol-Defined Primary Endpoint				
Death/MI/IDR/ST[1]	257/5470 (4.7)	322/5469 (5.9)	0.78 (0.66, 0.93)	0.0049
Death	18/5470 (0.3)	18/5469 (0.3)	1.00 (0.52, 1.92)	0.9996
MI	207/5470 (3.8)	255/5469 (4.7)	0.80 (0.67, 0.97)	0.0224
IDR	28/5470 (0.5)	38/5469 (0.7)	0.74 (0.45, 1.20)	0.2167
ST[1]	46/5470 (0.8)	74/5469 (1.4)	0.62 (0.43, 0.90)	0.0101
Supplemental Primary Endpoints				
Death/MI (SCAI definition)/IDR/ARC-ST	79/5470 (1.4)	114/5469 (2.1)	0.69 (0.52, 0.92)	0.0110
MI by SCAI definition	53/5470 (1.0)	81/5469 (1.5)	0.65 (0.46, 0.92)	0.0149
ARC-ST	12/5470 (0.2)	22/5469 (0.4)	0.54 (0.27, 1.10)	0.0858
Death/MI (CK-MB ≥ 10X ULN)/IDR/ARC-ST	77/5470 (1.4)	111/5469 (2.0)	0.69 (0.51, 0.92)	0.0123
MI (CK-MB ≥ 10X ULN)	50/5470 (0.9)	78/5469 (1.4)	0.64 (0.45, 0.91)	0.0128

[1]Includes ARC-ST and IPST. Adjusted for loading dose and baseline patient status in logistic regression.

[Source: Table 12 in Sponsor's response document, confirmed by the reviewer]

Table 3: Sensitivity Analyses of the Primary Endpoint at 48 Hours (mITT)

	Cangrelor (N=5472)	Clopidogrel (N=5470)	OR and 95% CI	p-value
Protocol-Defined Primary Endpoint				
Death/MI/IDR/ST[1]	257/5470 (4.7)	322/5469 (5.9)	0.78 (0.66, 0.93)	0.0049
Removal of IPST				
Death/MI/IDR/ARC-ST	230/5470 (4.2)	286/5469 (5.2)	0.80 (0.67, 0.95)	0.0115
Removal of IPST and MIs Identified Solely by CK-MB Elevations >3X ULN but < 10X ULN[2]				
Death/MI/IDR/ARC-ST	106/5470 (1.9)	161/5469 (2.9)	0.65 (0.51, 0.83)	0.0007
Removal of IPST and all MIs Identified Solely by CK-MB Elevations[3]				
Death/MI/IDR/ARC-ST	86/5470 (1.6)	130/5469 (2.4)	0.66 (0.50, 0.86)	0.0025
Removal of IPST and all MIs				
Death/IDR/ARC-ST	43/5470 (0.8)	54/5469 (1.0)	0.79 (0.53, 1.19)	0.2615

1Includes ARC-ST and IPST. Adjusted for loading dose and baseline patient status in logistic regression.
2Includes peri-procedural MIs with one of the following: CK-MB ≥10X ULN or MI with either ischemic symptoms or 12-lead ECG changes).
3Includes peri-procedural MIs identified by either ischemic symptoms or 12-lead ECG changes.

[Source: Table 14 in the Sponsor's response document, confirmed by the reviewer]

Table 2 listed the counts of the individual components of the protocol-defined primary endpoint based on all events occurred within 48 hours. To avoid double counting, the reviewer calculated the counts of individual components by assigning each subject only one type of event. For those subjects who had more than one type of event at the same time, the more severe event would be used. For example, if a patient had a MI and ST at the same time, only MI would be counted. The reviewer follow the order of death > MI > IDR > ST. Table 4 showed the individual component counts for a number of composite endpoints.

Table 4: Individual Component Counts for the Composite Endpoints

	protocol-defined primary endpoint				
	Composite	Death	MI	IDR	ST
clopidogrel	322	14	254	11	43
cangrelor	257	12	204	9	32
	Death/SCAI MI/IDR/ARC-ST				
	Composite	Death	SCAI MI	IDR	ARC ST
clopidogrel	114	16	81	13	4
cangrelor	79	15	50	12	2
	removal of IPST and MIs (identified Solely by CKMB>3ULN but <10ULN) from the primary endpoint				
	Composite	Death	MI	IDR	ST
clopidogrel	161	16	130	11	4
cangrelor	106	15	80	9	2

[Source: reviewer's analysis]

The sensitivity analyses of the primary endpoint showed in Table 2 and Table 3 were all based on mITT population. The reviewer also performed similar analyses in the ITT population (Table 5). The conclusion, nevertheless, remains unchanged.

Table 5: Supplemental Primary Endpoint at 48 Hours (ITT population)

Endpoint	cangrelor (N=5581)	clopidogrel (N=5564)	OR and 95% CI
protocol-defined primary endpoint	260	325	0.79 (0.67, 0.93)
Death/SCAI MI/IDR/ARC-ST	82	117	0.70 (0.52, 0.92)
SCAI MI	53	81	0.65 (0.50, 0.92)
ARC-ST	12	22	0.54 (0.27, 1.10)
Death/MI (CKMB>=10ULN)/IDR/ARC-ST	80	114	0.70 (0.52, 0.93)
MI (CKMB>=10ULN)	50	78	0.64 (0.45, 0.91)
removal of IPST	233	289	0.80 (0.67, 0.95)
removal of IPST and MIs (CK-MB elevations >3ULN but < 10ULN)	109	164	0.66 (0.51, 0.84)
removal of IPST and all MIs (CKMB elevations)	89	133	0.66 (0.51, 0.87)
removal of IPST and all Mis	46	57	0.80 (0.54, 1.19)

[Source: reviewer's analysis]

2.3 Site-reported Events

The reviewer verified sponsor's site reported results. The sponsor submitted the SAS program used to derive site reported event from raw data and the reviewer was able to verify sponsor's results.

Table 6: Site-Reported Primary Events at 48 Hours (mITT population)

	Cangrelor (N=5472)	Clopidogrel (N=5470)	OR and 95% CI	p-value
Protocol-Defined Primary Endpoint				
Death/MI/IDR/ST[1]	257/5470 (4.7)	322/5469 (5.9)	0.78 (0.66, 0.93)	0.0049
Site-Reported Events				
Death/MI/IDR/ST[2]	96/5470 (1.8)	121/5469 (2.2)	0.79 (0.60, 1.03)	0.0862
Death/MI/IDR/ST (IDR eCRF)[3]	94/5470 (1.7)	118/5469 (2.2)	0.79 (0.60, 1.04)	0.0957

1. Includes ARC-ST and IPST.
2. Includes MIs recorded by the site on the MI eCRF page, IDR recorded by the site on the Revascularization eCRF page, and ST from death, MI, IDR, Follow-up, and PCI eCRF pages.
3. Includes MIs recorded by the site on the MI eCRF page, unplanned revascularizations recorded by the site on the Revascularization eCRF page, and ST recorded by the site on the IDR eCRF.

[Source: Table 15, confirmed by the reviewer]

2.4 Discrepancies between Sponsor's results and Dr. Marciniak's results

In the Advisory Committee Meeting on February 12, 2014, Dr. Marciniak presented his analysis results based on site-reported events, which showed discrepancies with what the sponsor presented. The reviewer extracted the dataset used by Dr. Marciniak from his reviews and further examined Dr. Marciniak's analyses and sponsor's analyses. Table 7 is sponsor's results based on mITT population, which were presented by the sponsor during the AC meeting. Table 8 is based on ITT population and Table 9 is Dr. Marciniak's results, which is also based on ITT population. The patient types listed in the three tables were based on the investigator's initial assessment of clinical presentation as entered into the IVRS, not the derived patient type.

Table 7: Sponsor's Results on Primary endpoint by Index Events (mITT population)

	adjudicated primary endpoint		site-reported primary endpoint	
	Clopidogrel	Cangrelor	clopidogrel	cangrelor
Angina	217/3172 (6.8%)	182/3186 (5.7%)	65/3172 (2.1%)	52/3186 (1.6%)
UA/NSTEMI	82/1428 (5.7%)	53/1464 (3.6%)	37/1428 (2.6%)	26/1464 (1.8%)
STEMI	23/870 (2.6%)	22/822 (2.7%)	16/870 (1.8%)	16/822 (2.0%)
All	322/5470 (5.9%)	257/5472 (4.7%)	118/5470 (2.2%)	94/5472 (1.7%)

Table 8: Sponsor's Primary endpoint by Index Events (ITT population)

	adjudicated primary endpoint		site-reported primary endpoint	
	Clopidogrel	Cangrelor	Clopidogrel	cangrelor
angina	217/3208 (6.8%)	182/3220 (5.7%)	65/3208 (2.0%)	53/3220 (1.7%)
UA/NSTEMI	82/1435 (5.7%)	53/1479 (3.6%)	37/1435 (2.6%)	27/1479 (1.8%)
STEMI	26/921 (2.8%)	25/882 (2.8%)	20/921 (2.2%)	21/882 (2.4%)
All	325/5564 (5.8%)	260/5581 (4.7%)	122/5564 (2.2%)	101/5581 (1.8%)

Table 9: Tom's Results on Primary endpoint by Index Events (ITT population)

	adjudicated primary endpoint		site-reported primary endpoint	
	Clopidogrel	Cangrelor	clopidogrel	Cangrelor
angina	217/3208 (6.8%)	182/3220 (5.7%)	68/3208 (2.1%)	58/3220 (1.8%)
UA/NSTEMI	82/1435 (5.7%)	53/1479 (3.6%)	37/1435 (2.6%)	32/1479 (2.2%)
STEMI	26/921 (2.8%)	25/882 (2.8%)	21/921 (2.3%)	25/882 (2.8%)
all	325/5564 (5.8%)	260/5581(4.7%)	126/5564 (2.3%)	115/5581 (2.1%)

The ITT population in PHOENIX trial comprised 5581 patients in the cangrelor arm and 5564 patients in the clopidogrel arm. Among those in the ITT population, 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. The major difference on site-reported events between mITT population and ITT population is in STEMI patients. Using mITT population, the site-reported event rates in STEMI patients were 1.8% in clopidogrel arm and 2.0% in cangrelor arm. Using ITT population, the site-reported event rates in STEMI patients were 2.2% in clopidogrel arm and 2.4% in cangrelor arm. In both cases, the cangrelor arm had a slightly higher event rate than clopidogrel arm. However, the results based on subgroups need to be interpreted with caution.

Dr. Marciniak included 18 extra events in his analyses on the site-reported events. As a result, site-reported event rates in his analyses were 2.8% in cangrelor arm and 2.3% in clopidogrel arm. These 18 subjects were listed in Table 10. Of these 18 subjects who were not reported by the investigators at site but were considered having a primary event at 48 hours by Dr. Marciniak, only one subject was adjudicated to have a primary endpoint event at 48 hours. Further details and discussions about these 18 patients can be found in the clinical review by Dr. Senatore and Dr. Beasley.

Table 10: Extra Subjects with Events at 48 Hours by Dr. Marciniak

Subject ID	Index Event	Abnormal	Site	US	Adjudicated Event 48 Hours	Adjudicated Event 30 Days	Treatment
401021013	NSTE-ACS	Yes	401021	Yes	No	No	cangrelor
401030289	Angina	No	401030	Yes	No	No	cangrelor
439001076	NSTE-ACS	Yes	439001	No	No	No	cangrelor
439001085	NSTEMI	Yes	439001	No	No	No	cangrelor
439004181	NSTE-ACS	Yes	439004	No	No	No	cangrelor
443002052	NSTEMI	Yes	443002	No	No	No	cangrelor
443002145	NSTE-ACS	Yes	443002	No	No	No	cangrelor
449001009	NSTEMI	Yes	449001	No	No	No	clopidogrel
449004029	Angina	No	449004	No	No	No	clopidogrel
449005002	NSTEMI	Yes	449005	No	No	No	cangrelor
449005032	Angina	No	449005	No	No	No	cangrelor
449012005	Angina	No	449012	No	No	No	cangrelor
449017033	Angina	No	449017	No	No	No	clopidogrel
449021003	Angina	No	449021	No	Yes	Yes	cangrelor
495002197	NSTE-ACS	Yes	495002	No	No	No	cangrelor
495005197	NSTEMI	Yes	495005	No	No	No	cangrelor
495005476	Angina	No	495005	No	No	No	cangrelor
495005567	Angina	No	495005	No	No	No	clopidogrel

Appendix

Table 11: Comparison of Adjudicated Event Time and Site Reported Event Time

Subject ID	Treatment	Randomization Time	Drug Start Time	Adjudicated Event Time	Site-reported Event Time
401001168	clopidogrel	15DEC11:09:48:00	15DEC2011:10:05:00	15DEC11:10:06:00	
401010028	clopidogrel	21DEC10:11:54:00	21DEC2010:12:18:00	21DEC10:12:20:00	
401010103	clopidogrel	09AUG11:09:42:00	09AUG2011:10:44:00	09AUG11:10:48:00	11AUG11:08:40:00
401011070	clopidogrel	06SEP12:11:53:00	06SEP2012:12:25:00	06SEP12:12:28:00	06SEP12:13:30:00
401025016	clopidogrel	04OCT11:17:55:00	04OCT2011:18:17:00	04OCT11:18:03:00	05OCT11:12:05:00
401027083	clopidogrel	16MAY12:08:38:00	16MAY2012:08:52:00	16MAY12:08:55:00	16MAY12:09:02:00
401028004	clopidogrel	26JAN11:17:23:00	26JAN2011:17:57:00	26JAN11:18:00:00	27JAN11:03:27:00
401030075	clopidogrel	29JUN11:13:26:00	29JUN2011:14:55:00	29JUN11:14:57:00	29JUN11:17:23:00
401030173	clopidogrel	30NOV11:10:50:00	30NOV2011:12:03:00	30NOV11:12:07:00	30NOV11:20:00:00
401030232	clopidogrel	22FEB12:10:27:00	22FEB2012:11:35:00	22FEB12:11:35:00	24FEB12:06:00:00
401055020	clopidogrel	21JAN11:12:53:00	21JAN2011:12:58:00	21JAN11:13:02:00	
401058008	clopidogrel	23MAR11:14:08:00	23MAR2011:14:20:00	23MAR11:14:24:00	31MAR11:09:47:00
401058029	clopidogrel	20JUN12:14:46:00	20JUN2012:15:01:00	20JUN12:14:58:00	20JUN12:15:24:00
401077048	clopidogrel	04OCT11:11:43:00	04OCT2011:12:01:00	04OCT11:12:05:00	
401079035	clopidogrel	10MAR11:11:40:00	10MAR2011:11:46:00	10MAR11:11:47:00	
401079151	clopidogrel	11OCT11:09:47:00	11OCT2011:09:52:00	11OCT11:09:56:00	
401079204	clopidogrel	16JAN12:07:35:00	16JAN2012:07:47:00	16JAN12:07:48:00	19JAN12:18:09:00
401085036	clopidogrel	05OCT11:15:28:00	05OCT2011:15:43:00	05OCT11:15:45:00	
401091101	clopidogrel	02MAR11:11:20:00	02MAR2011:11:35:00	02MAR11:11:36:00	
401091338	clopidogrel	09DEC11:12:25:00	09DEC2011:12:37:00	09DEC11:12:39:00	
401091597	clopidogrel	25MAY12:13:35:00	25MAY2012:13:42:00	25MAY12:13:45:00	
401092073	clopidogrel	02AUG12:12:35:00	02AUG2012:12:43:00	02AUG12:12:45:00	
407012029	clopidogrel	21MAR12:14:57:00	21MAR2012:14:58:00	21MAR12:14:59:00	21MAR12:23:00:00
420003076	clopidogrel	08FEB12:17:33:00	08FEB2012:17:42:00	08FEB12:17:45:00	
420009333	clopidogrel	07DEC11:14:00:00	07DEC2011:14:03:00	07DEC11:14:04:00	
420009375	clopidogrel	19DEC11:13:05:00	19DEC2011:13:08:00	19DEC11:13:09:00	
420009402	clopidogrel	28DEC11:12:05:00	28DEC2011:12:10:00	28DEC11:12:11:00	

420009485	clopidogrel	25JAN12:10:56:00	25JAN2012:11:00:00	25JAN12:11:01:00	
420009670	clopidogrel	23MAR12:16:23:00	23MAR2012:16:26:00	23MAR12:16:27:00	
420009832	clopidogrel	24MAY12:17:29:00	24MAY2012:17:32:00	24MAY12:17:33:00	
420009864	clopidogrel	14JUN12:13:21:00	14JUN2012:13:24:00	14JUN12:13:25:00	
439002038	clopidogrel	05APR12:15:37:00	05APR2012:15:40:00	05APR12:15:44:00	
449004028	clopidogrel	21DEC11:09:43:00	21DEC2011:09:45:00	21DEC11:09:45:00	
449013047	clopidogrel	03FEB12:15:40:00	03FEB2012:15:43:00	03FEB12:15:46:00	04FEB12:00:05:00
449017003	clopidogrel	09AUG11:09:55:00	09AUG2011:10:00:00	09AUG11:10:05:00	09AUG11:18:00:00
459003016	clopidogrel	30JAN12:14:54:00	30JAN2012:15:02:00	30JAN12:15:06:00	30JAN12:15:12:00
459003045	clopidogrel	17MAY12:11:22:00	17MAY2012:11:26:00	17MAY12:11:29:00	17MAY12:11:29:00
459007016	clopidogrel	19AUG11:09:02:00	19AUG2011:09:10:00	19AUG11:09:15:00	19AUG11:10:00:00
495002252	clopidogrel	24JUN12:13:30:00	24JUN2012:13:32:00	24JUN12:13:31:00	
495005346	clopidogrel	22FEB12:18:14:00	22FEB2012:18:23:00	22FEB12:18:25:00	
495005404	clopidogrel	06APR12:12:23:00	06APR2012:12:29:00	06APR12:12:31:00	
495005553	clopidogrel	09AUG12:12:39:00	09AUG2012:12:45:00	09AUG12:12:48:00	
495005587	clopidogrel	07SEP12:16:03:00	07SEP2012:16:05:00	07SEP12:16:06:00	
401007046	cangrelor	04JUN12:10:46:00	04JUN2012:11:00:00	04JUN12:11:02:00	
401029049	cangrelor	11JAN12:09:30:00	11JAN2012:09:40:00	11JAN12:09:43:00	
401053011	cangrelor	20DEC10:12:28:00	20DEC2010:12:43:00	20DEC10:12:45:00	
401079060	cangrelor	26APR11:17:57:00	26APR2011:18:08:00	26APR11:18:09:00	26APR11:18:09:00
401079193	cangrelor	21DEC11:14:12:00	21DEC2011:14:15:00	21DEC11:14:19:00	
401091423	cangrelor	07FEB12:14:25:00	07FEB2012:14:36:00	07FEB12:14:38:00	
420009059	cangrelor	05SEP11:09:57:00	05SEP2011:10:02:00	05SEP11:10:03:00	05SEP11:12:59:00
420009098	cangrelor	20SEP11:18:32:00	20SEP2011:18:35:00	20SEP11:18:36:00	
420009162	cangrelor	13OCT11:13:47:00	13OCT2011:13:50:00	13OCT11:13:51:00	13OCT11:14:00:00
420009655	cangrelor	19MAR12:17:04:00	19MAR2012:17:07:00	19MAR12:17:08:00	
420009695	cangrelor	30MAR12:17:41:00	30MAR2012:17:43:00	30MAR12:17:45:00	
420009798	cangrelor	03MAY12:13:04:00	03MAY2012:13:07:00	03MAY12:13:08:00	
420009836	cangrelor	29MAY12:14:30:00	29MAY2012:14:33:00	29MAY12:14:34:00	29MAY12:17:40:00
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449004044	cangrelor	10APR12:10:12:00	10APR2012:10:15:00	10APR12:10:18:00	10APR12:21:57:00
449005048	cangrelor	25APR12:12:43:00	25APR2012:12:53:00	25APR12:12:55:00	

449021003	cangrelor	25MAY12:19:03:00	25MAY2012:19:30:00	25MAY12:19:30:00	25MAY12:19:30:00
466001043	cangrelor	22MAY12:14:24:00	22MAY2012:14:25:00	22MAY12:14:30:00	26MAY12:19:15:00
466002056	cangrelor	27JUN12:14:17:00	27JUN2012:14:18:00	27JUN12:14:23:00	
495005503	cangrelor	27JUN12:16:25:00	27JUN2012:16:35:00	27JUN12:16:39:00	
495005540	cangrelor	01AUG12:15:51:00	01AUG2012:15:54:00	01AUG12:15:55:00	
495005618	cangrelor	25SEP12:13:00:00	25SEP2012:13:04:00	25SEP12:13:05:00	

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/s/

JIALU ZHANG
03/11/2015

HSIEN MING J HUNG
03/11/2015

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

ADDENDUM

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
Statistical Reviewer:	Jialu Zhang, Ph.D.
Concurring Reviewers:	James Hung, Ph.D.
Medical Division:	Division of Cardiovascular and Renal Products, HFD-110
Clinical Team:	Efficacy Reviewer: Fortunato Senatore, MD, PhD Safety Reviewer: Nhi Beasley, PharmD
Project Manager:	Alison Blaus

Keywords: patient type, loading dose

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This addendum includes additional analyses performed by the reviewer after the Advisory Committee Meeting on February 13, 2014.

1. Intended Loading Dose Versus Actual Loading Dose

In the statistical review dated January 11 2014, the reviewer pointed out there was an imbalance on the actual loading dose between two treatment groups. Specifically, almost all cangrelor patients had 600 mg clopidogrel loading dose but over 25% clopidogrel patients received 300 mg loading dose. The reviewer compared cangrelor with clopidogrel by actual loading dose. As the review also pointed out, the comparisons are not randomized comparisons.

The reviewer further examined the relationship between actual loading dose and intended loading dose. All clopidogrel patients except two received the same loading dose as intended. Since almost all cangrelor patients received 600 mg clopidogrel loading dose and the patients were stratified by intended loading dose at randomization, a valid comparison can be made by comparing cangrelor with clopidogrel using the intended loading dose (Table 1). This is a better comparison than the non-randomized comparison using the actual loading dose.

Table 1 Comparison of Cangrelor versus Clopidogrel by Intended Loading Dose

intended loading dose	Cangrelor		clopidogrel		OR	95% CI
	Events (%)	N	Events (%)	N		
300 mg	81 (5.8%)	1405	95 (6.8%)	1401	0.84	(0.62, 1.14)
600 mg	176 (4.3%)	4065	227 (5.6%)	4068	0.77	(0.63, 0.94)

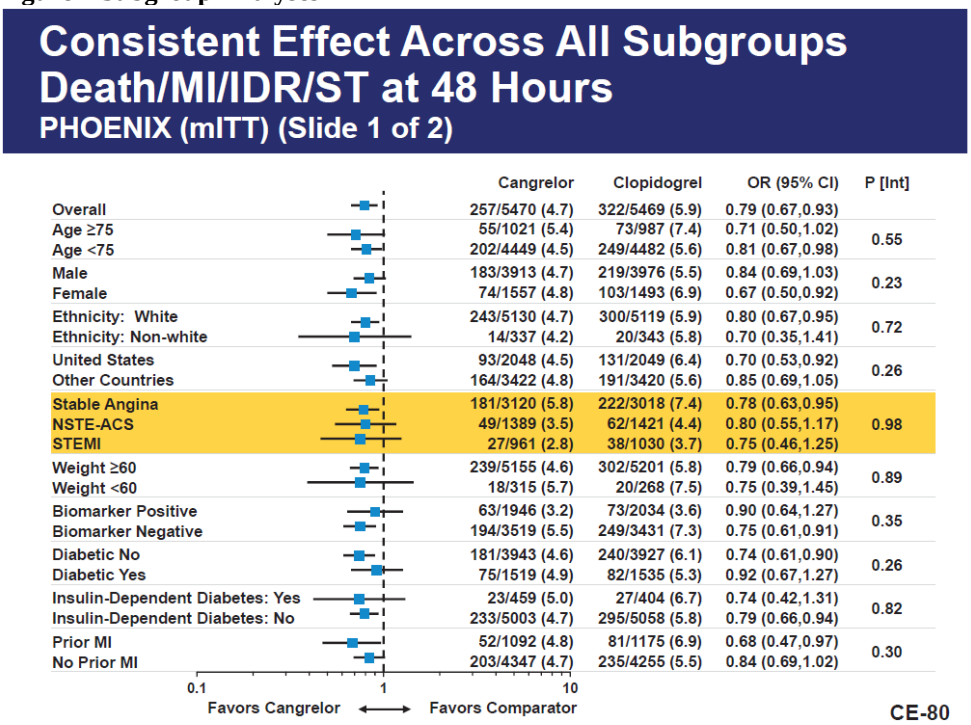
Source: reviewer's analysis

The overall event rate is lower in patients with intended loading dose of 600 mg, regardless of the treatment group.

2. Derived Patient Type

The sponsor examined the treatment effect across different subgroups. One subgroup analysis involved different patient types (STEMI, NSTE-ACS, stable angina) and was highlighted in Figure 1 below. However, the derived patient type was used instead of the site-reported patient type.

Figure 1 Subgroup Analyses



[Source: Sponsor's slide presented at the Advisory Committee Meeting on Feb 13, 2014]

According to the clinical study report, "patient type was reported as determined by the site investigators at the time of randomization, and as programmatically derived from patient data collected in the CRF. Data provided by the site investigators at the time of randomization via the IV/WRS was limited by the amount of clinical information available at the time and could not be updated within the IV/WRS by system design, even when more data became available. For this reason, programmatic assessment of patient type using the data in the eCRF was used in all efficacy and safety analyses. " (Clinical Study Report Section 9.7.1.8.1). However, neither the statistical analysis plan nor the study protocol had pre-specified the algorithm.

Table 2 and Table 3 compared cangrelor with clopidogrel by derived patient type and site-reported patient type, respectively.

Table 2 Comparison of Cangrelor with Clopidogrel by Derived Patient Type

	cangrelor			Clopidogrel				
	N	event	%	N	event	%	OR	95% CI
stable angina	3120	181	5.8	3018	222	7.4	0.78	(0.63, 0.95)
UA/NSTEMI	1389	49	3.5	1421	62	4.4	0.8	(0.55, 1.18)
STEMI	961	27	2.8	1030	38	3.7	0.76	(0.46, 1.25)

Source: reviewer's analysis

Table 3 Comparison of Cangrelor with Clopidogrel by Site-reported Patient Type

	cangrelor			Clopidogrel				
	N	event	%	N	event	%	OR	95% CI
stable angina	3185	182	5.7	3171	217	6.8	0.83	(0.67, 1.01)
UA/NSTEMI	1464	53	3.6	1428	82	5.7	0.62	(0.43,0.88)
STEMI	821	22	2.7	870	23	2.6	1.01	(0.56,1.83)

Source: reviewer's analysis

Upon further examination, there were a total of 2204 patients who had different derived patient type from the site-reported type.

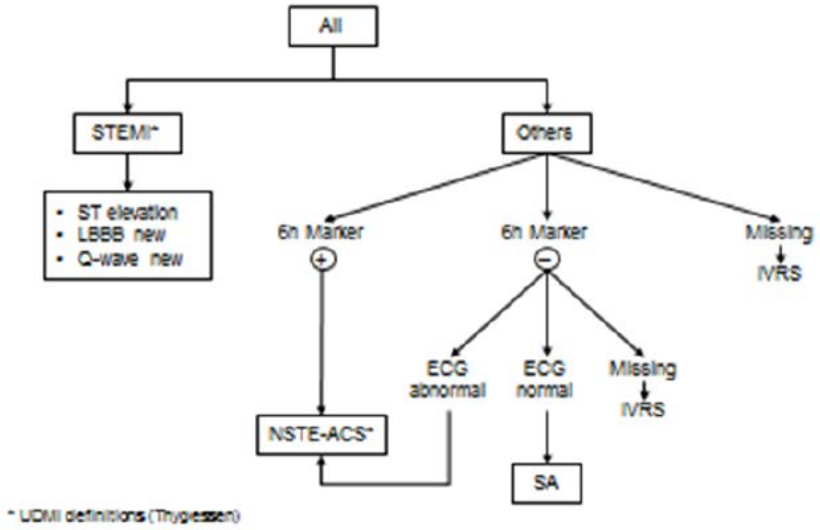
Table 4 Discrepancy between Site-reported Patient Type and Derived Patient Type

		site-reported patient type		
		Stable Angina	NSTE-ACS	STEMI
Derived patient type	Stable Angina	5347	864	6
	NSTE-ACS	980	1821	24
	STEMI	101	229	1773

Source: reviewer's analysis

The sponsor provided a schematic (Figure 2) in the response to FDA information request to show the logic used for deriving the patient type.

Figure 2 Derived Patient Type



[Source: Sponsor's response to FDA information request, March 19, 2014]

The logic shown in Figure 2 was mostly consistent with the sponsor's SAS program that was used to derive the patient type except that the schematic did not include patients without ECG before

randomization/start of study drug. The following is the summary of algorithm based on the sponsor's SAS program to derive patient type.

1. If no ECG performed before randomization or before the start of study drug
    a. If site reported patient type is STEMI, then derived patient type is STEMI
    b. If site reported patient type is not STEMI, then go to step 3
2. If there was ECG performed before randomization or before the start of study drug
    a. the derived patient type is STEMI if one of the follows
        i. ST segment elevation > 0.1 mV (>1mm) in at least two contiguous leads
        ii. New Left Bundle Branch Block
        iii. New Q-wave (> 0.03 seconds)
    b. If patient had none of the above 3 criteria, then go to step 3
3. The derived patient type is NSTE-ACS if the patient had the one of the following
    a. Other presumed new abnormality indicating myocardial infarction
    b. ST segment depression > 0.1 mV (>1mm) in at least two contiguous leads
    c. Abnormal biomarker (defined later)
4. If patient had ECG before randomization or before the start of study drug and patient was not STEMI or NSTE-ACS and had normal biomarker, then derived patient type is stable angina
5. If patient type still undetermined, use site-reported patient type

In order to determine the biomarker status, the lab time needs to be within 6 hour window prior to randomization and before the start of study drug (or before randomization if the time of taking first study drug is not available). The last qualified lab value was used to determine whether biomarker is normal or abnormal.

1. The biomarker is abnormal if
    a. If troponin collected is greater than the high range; or
    b. If troponin is missing and CKMB collected is greater than the high range
2. The biomarker is normal if
    a. If troponin collected is less than the high range; or
    b. If troponin is missing and CKMB collected is less than the high range

It is unclear why the derived patient type had such big discrepancy (20%) when compared with the initial assessment of the patient type by investigators. The sponsor needs to provide further explanation in their future submission.

3. GPIIb/IIIa Usage in PCI, PLATFORM and PHOENIX

The reviewer also examined the use of GPIIb/IIIa inhibitors (GPI) in all three CHAMPION trials. The sponsor amended the protocols for CHAMPION PCI and CHAMPION PLATFORM on 08 May 2007 to discourage the use of GPIIb/IIIa inhibitors (GPI). As shown in Table 5 and Table 6, the rate of GPI usage declined after the amendment.

Table 5 GPI Usage in CHAMPION PCI

	Cangrelor		clopidogrel	
	N	GPI use (%)	N	GPI use (%)
Before May 8, 2007	1746	583 (33.3)	1720	589 (34.2)
After May 8, 2007	2600	565 (21.7)	2599	571 (22.0)

Source: reviewer's analysis

Table 6 GPI Usage in CHAMPION PLATFORM

	cangrelor		clopidogrel	
	N	GPI use (%)	N	GPI use (%)
Before May 8, 2007	418	67 (16.0)	425	73 (17.1)
After May 8, 2007	2235	174 (7.8)	2217	171 (7.7)

Source: reviewer's analysis

The reviewer further examined the primary events in each trial by GPI usage. (Table 7, Table 8 and Table 9). The use of GPI did not appear to affect the treatment effect of cangrelor. Although CHAMPION PCI and CHAMPION PLATFORM had a higher rate of GPI usage, the use of GPI is not likely the reason to explain the negative results in the two trials.

Table 7 Comparison of Cangrelor with Clopidogrel by GPI Usage in CHAMPION PCI

GPI use	TRT	N	# events (%)	OR (95% CI)
Yes	cangrelor	1141	97 (8.5)	
	clopidogrel	1155	100 (8.7)	
	total	2296	197 (8.6)	0.98 (0.73, 1.31)
No	cangrelor	3193	211 (6.6)	
	clopidogrel	3156	193 (6.1)	
	total	6349	404 (6.4)	1.09 (0.89, 1.33)

Source: reviewer's analysis

Table 8 Comparison of Cangrelor with Clopidogrel by GPI Usage in CHAMPION PLATFORM

GPI use	TRT	N	# events (%)	OR (95% CI)
Yes	cangrelor	240	28 (11.7)	
	clopidogrel	243	33 (13.6)	
	total	483	61 (12.6)	0.84 (0.49, 1.44)
No	cangrelor	2411	156 (6.5)	
	clopidogrel	2395	177 (7.4)	
	total	4806	333 (6.9)	0.87 (0.69, 1.08)

Source: reviewer's analysis

Table 9 Comparison of Cangrelor with Clopidogrel by GPI Usage in CHAMPION PHOENIX

GPI use	TRT	N	# events (%)	OR (95% CI)
Yes	cangrelor	153	27 (17.7)	
	clopidogrel	227	46 (20.3)	
	total	380	73 (19.2)	0.82 (0.68, 0.97)
No	cangrelor	5317	230 (4.3)	
	clopidogrel	5242	276 (5.3)	
	total	10559	506 (4.8)	0.84 (0.50, 1.43)

Source: reviewer's analysis

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/s/

JIALU ZHANG
04/23/2014

KOOROS MAHJOOB
04/23/2014
I concur with the review and sign it on behalf of DR. James Hung.

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
Statistical Reviewer:	Jialu Zhang, Ph.D.
Concurring Reviewers:	James Hung, Ph.D.
Medical Division:	Division of Cardiovascular and Renal Products, HFD-110
Clinical Team:	Efficacy Reviewer: Fortunato Senatore, MD, PhD 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 $P2Y_{12}$ 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 $P2Y_{12}$ 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 $P2Y_{12}$ 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.

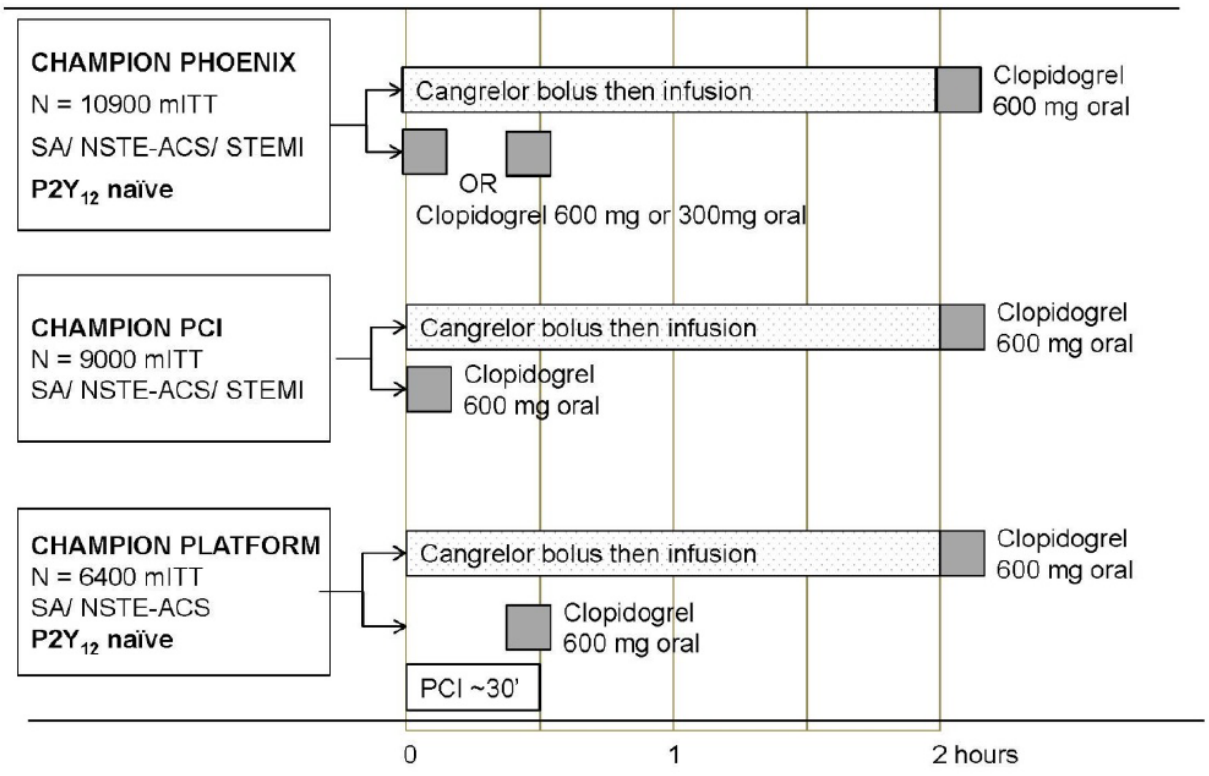
2. INTRODUCTION

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 $P2Y_{12}$ platelet inhibition with IV cangrelor reduces thrombotic events and improves clinical outcomes compared with oral $P2Y_{12}$ 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, NSTE-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 \\Cdsesub1\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 \\Cdsesub1\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 \\Cdsesub1\evsprod\NDA204958\0000\m5\datasets\tmc-can-05-03\analysis\legacy\datasets and \\Cdsesub1\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

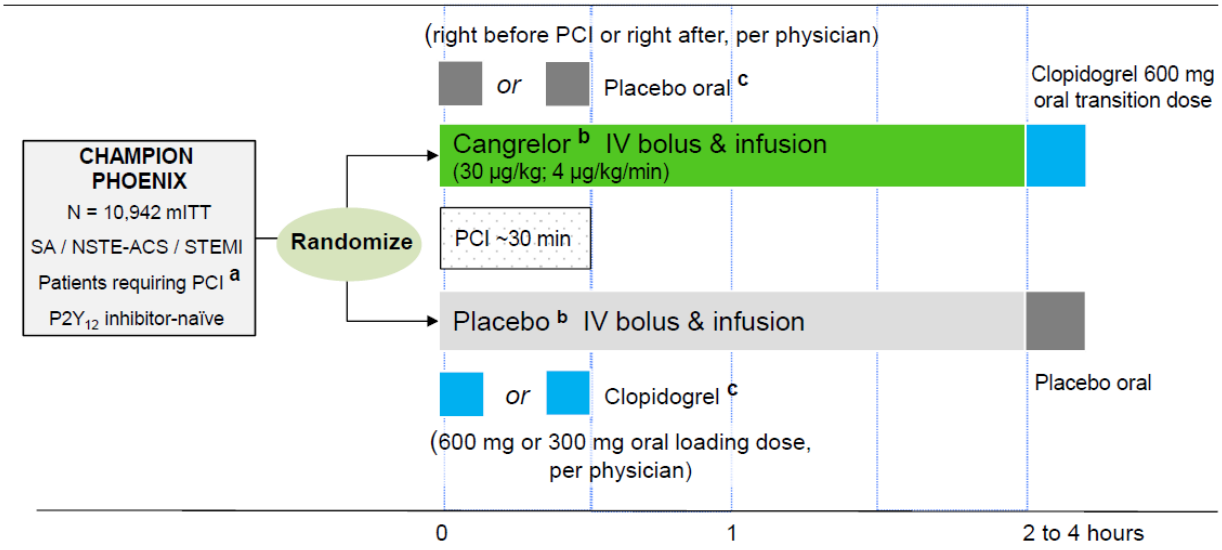
3.2.1.1 Study Design and Endpoints

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 $P2Y_{12}$ inhibitor. Enrolled patients had stable angina (SA), non-ST-segment elevation acute coronary syndrome (NSTE-ACS), 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 NSTE-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 endpint 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 NSTE-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 >= 80%, the trial will continue as planned. If not, the sample size will be re-estimated and if the power >= 80 % and the re-estimated sample size <= 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,

$$\emptyset\left(\frac{\hat{\theta}(t_k - t_{k-1}) - \left[c_k\sqrt{t_k} - z_{k-1}\sqrt{t_{k-1}}\right]}{\sqrt{t_k - t_{k-1}}}\right)$$

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 $n_{new} \approx \frac{\tau_k}{t_k} n_{planned}$, where $\tau_k = \frac{1}{\hat{\theta}^2}\left(\frac{1}{\sqrt{t_k - t_{k-1}}}\left(c_k\sqrt{t_k} - z_{k-1}\sqrt{t_{k-1}}\right) + Z_\beta\right)^2 + t_{k-1}$

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:

$$c'_k = \frac{1}{\sqrt{\tau_k}}\left(\frac{\sqrt{\tau_k - t_{k-1}}}{\sqrt{t_k - t_{k-1}}}\left(c_k\sqrt{t_k} - \sqrt{t_{k-1}}Z(t_{k-1})\right) + \sqrt{t_{k-1}}Z(t_{k-1})\right)$$

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			
	Cangrelor (N=5472)	Clopidogrel (N=5470)	OR and 95% CI	P value
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				
	Cangrelor (N=5472)	Clopidogrel (N=5470)	RR and 95% CI	OR and 95% CI	P-value
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				
	Cangrelor (N=5472)	Clopidogrel (N=5470)	RR and 95% CI	OR and 95% CI	P-value
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.

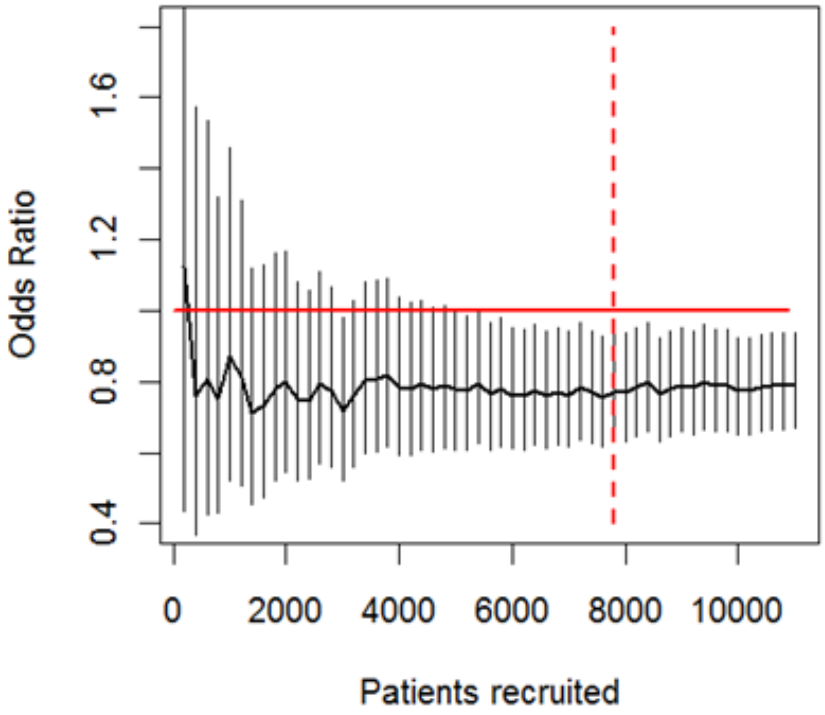
Table 11. Analyses on Secondary Endpoints

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

	n/N (%) of patients		Treatment Comparison		
Population	**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

	Number (%) of patients		Treatment Comparison		
Variable	**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]

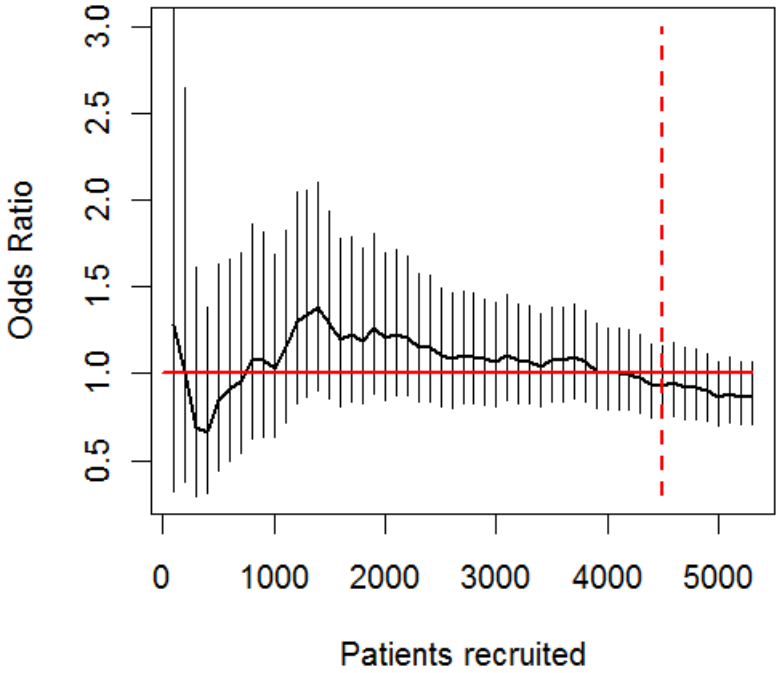
The first patient enrolled in CHAMPION PLATFORM on Oct 3, 2006. 50% interim analysis was based on data received by October 30, 2008. IARC had a closed session meeting to discuss 70% interim analysis results on May 1, 2009. The 70% interim analysis was based on 2260 patients in cangrelor and 2256 patients 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

	n/N (%) of patients		Treatment Comparison		
Population	**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	n/N (%) of patients		Treatment Comparison		
Variable	**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

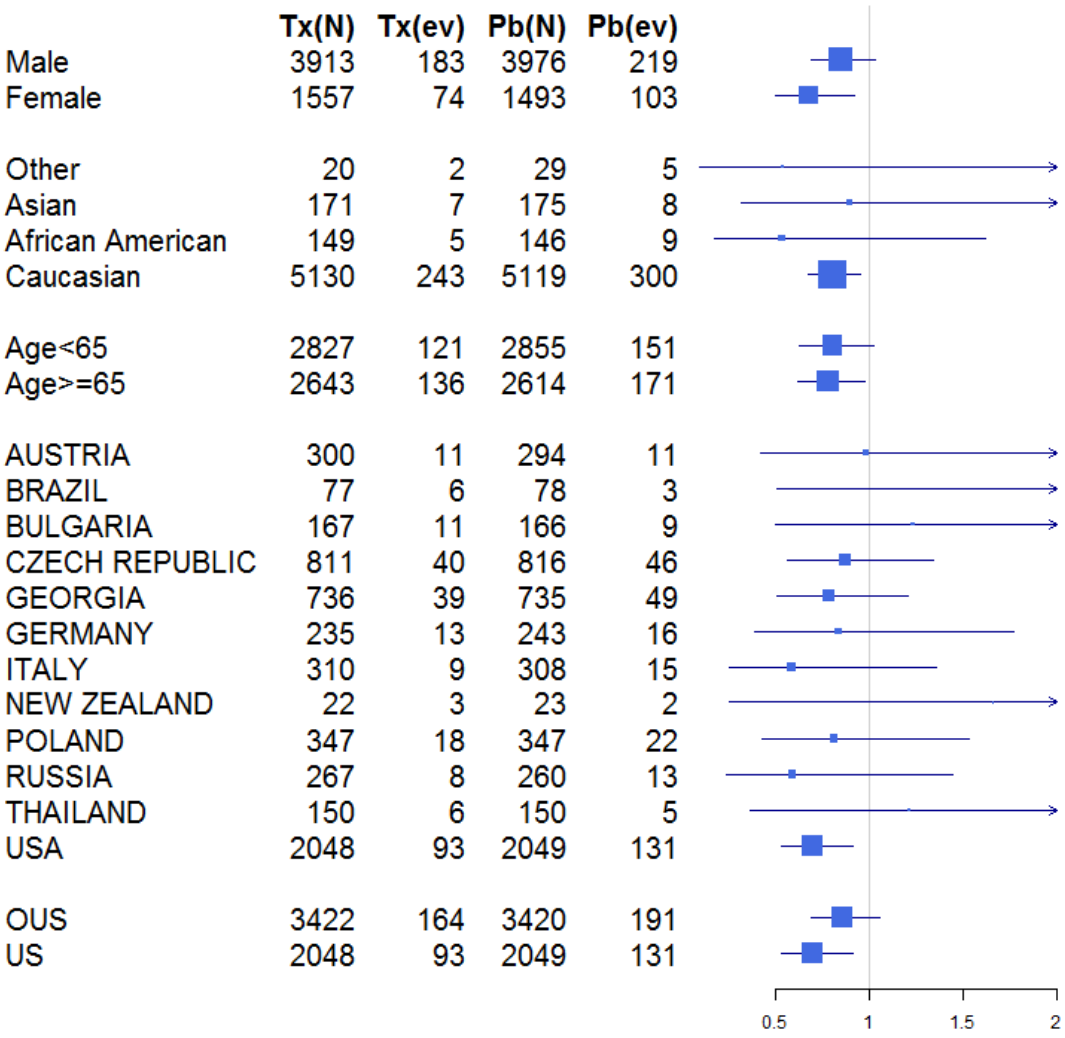
4.1 Gender, Race, Age, and Geographic Region

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

		Cangrelor			Clopidogrel				
Subgroups	Value	N	Event	Event rate	N	Event	Event rate	Odds Ratio	95% CI
	Male	3913	183	0.05	3976	219	0.06	0.84	(0.69, 1.03)
Gender	Female	1557	74	0.05	1493	103	0.07	0.67	(0.5, 0.92)
	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)
Race	Caucasian	5130	243	0.05	5119	300	0.06	0.8	(0.67, 0.95)
	Age<65	2827	121	0.04	2855	151	0.05	0.8	(0.63, 1.02)
Age	Age>=65	2643	136	0.05	2614	171	0.07	0.78	(0.61, 0.98)
	Non US	3422	164	0.05	3420	191	0.06	0.85	(0.69, 1.05)
US	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

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 204-958 **Applicant: Medicines Company** **Stamp Date: 04/30/2013**

Drug Name: Cangrelor **NDA/BLA Type: standard**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	x			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	x			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	x			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	x			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? __Yes_____

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	x			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	x			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.		x		The sponsor proposed an interim analysis at 70% information time that can lead to sample size re-estimation in the SAP dated October 25, 2012. The interim analysis was conducted in June, 2012.

File name: 5_Statistics Filing Checklist for a New NDA_BLA110207

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Appropriate references for novel statistical methodology (if present) are included.	x			
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	x			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.			x	Dropout rate is low

Reviewing Statistician Date

Supervisor/Team Leader Date

File name: 5_Statistics Filing Checklist for a New NDA_BLA110207

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