THE MEDICINES COMPANY®

NDA 204958

Cangrelor for injection

Cardiovascular and Renal Drugs

Advisory Committee Briefing Document

Advisory Committee Meeting

12th February 2014

EXECUTIVE SUMMARY

The Medicines Company is seeking approval of cangrelor in the following two indications:

1. **In the PCI setting:** for the reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI).
2. **In the Bridging setting:** to maintain $P2Y_{12}$ inhibition in patients with acute coronary syndromes (ACS) or patients with stents who are at increased risk for thrombotic events (such as stent thrombosis) when oral $P2Y_{12}$ therapy is interrupted due to surgery.

Cangrelor is a novel, intravenous (IV), direct-acting, $P2Y_{12}$ receptor antagonist that blocks adenosine diphosphate (ADP)-induced platelet activation and aggregation. Cangrelor provides fast-onset, potent, and consistent $P2Y_{12}$ inhibition, with reversible binding and a half-life of 3 to 6 minutes.

Cangrelor was specifically designed for use in an acute setting as an immediately bioavailable, direct-acting, reversible antagonist of the $P2Y_{12}$ receptor. These properties clearly differentiate cangrelor from oral $P2Y_{12}$ inhibitors designed and studied for use in a chronic setting, including the thienopyridine class of $P2Y_{12}$ inhibitors, exemplified by clopidogrel and prasugrel, or the cyclopentyltriazolopyrimidine ticagrelor, which require intestinal absorption and have a prolonged duration of effect.

Oral platelet $P2Y_{12}$ inhibitors have been shown to reduce ST and/or ischemic events including death in patients with ACS and in patients undergoing PCI in a series of randomized controlled trials [CAPRIE Steering Committee, 1996; Steinhubl et al, 2002; Fox et al, 2004; Wiviott et al, 2007; Wallentin et al, 2009]. However, they have several limitations in the acute treatment phase of patients with cardiovascular disease who require PCI or surgery, including delayed onset of action, an unpredictable platelet inhibitory response, and inability to reverse their antiplatelet effects resulting in a prolonged duration of effect. These characteristics are not ideal in an acute setting.

There are currently no treatment strategies available that provide consistent and effective platelet $P2Y_{12}$ inhibition that can be turned on when needed (such as in patients undergoing PCI) and that can be turned off when it is not, thus avoiding an increased bleeding risk, which is particularly important in patients with ACS or stents who require surgery.

In the acute setting, the ideal solution would: (1) reduce thrombotic risk by providing consistent and effective $P2Y_{12}$ inhibition, (2) be well tolerated with no increase in bleeding risk, (3) work well across all subgroups in a variety of clinical settings, and (4) provide controlled $P2Y_{12}$ inhibition that is turned on when needed and turned off when not.

Cangrelor's profile allows the established clinical benefit of $P2Y_{12}$ inhibition to be available to patients requiring antithrombotic protection either during interventional procedures or during interruption of oral $P2Y_{12}$ inhibitor therapy, without undue compromise of normal hemostasis. In

these settings, control and rapid reversibility of effect are key attributes, providing flexibility and addressing the needs of both interventional and surgical teams. Cangrelor is the only intravenous $P2Y_{12}$ inhibitor whose pharmacokinetics (PK) provides platelet inhibition within minutes and recovery of platelet function within 60 minutes following cessation of infusion.

PIVOTAL TRIALS

CHAMPION PHOENIX [TMC-CAN-10-01] is the pivotal study supporting the efficacy of cangrelor in the PCI setting and BRIDGE [TMC-CAN-08-02] is the pivotal study in the Bridging setting.

Data from three randomized controlled trials (CHAMPION PHOENIX, CHAMPION PLATFORM [TMC-CAN-05-03] and CHAMPION PCI [TMC-CAN-05-02]) conducted in 25,107 patients with CAD provide supportive evidence of the safety of cangrelor in patients who require $P2Y_{12}$ inhibition in an acute setting.

The CHAMPION PLATFORM (PLATFORM) and CHAMPION PCI (PCI) trials were terminated early due to a low likelihood of reaching the primary efficacy endpoint per pre-specified stopping rules and based on the recommendation by the Interim Analysis Review Committee (IARC). At the time of stopping, the studies had enrolled, respectively 98% and 83% of the planned enrollment – a total population of 13,942 patients including 6,989 treated with cangrelor. Neither of the Phase III studies met its primary objective. However, the non-discriminating ascertainment of biomarker MIs obscured the evidence of drug effect on death, Q-wave MI and acute stent thrombosis which led to the design and implementation of the PHOENIX trial.

CHAMPION PHOENIX

The CHAMPION PHOENIX (PHOENIX) trial was a randomized (1:1), multicenter, double-blind, double-dummy trial designed to test whether a $P2Y_{12}$ treatment strategy of IV cangrelor (30 µg/kg bolus, 4 µg/kg/min infusion for 2 to 4 hours) at the time of PCI followed by transition to 600mg oral clopidogrel is superior to high (loading) dose clopidogrel (600 mg or 300 mg) oral therapy at reducing thrombotic events during and immediately after PCI.

The PHOENIX trial was completed with a total enrollment of 11,145 patients with SA, non-ST-elevation acute coronary syndrome (NSTE-ACS), or STEMI undergoing PCI. PHOENIX was designed to demonstrate that cangrelor provides superior efficacy to clopidogrel standard of care, as measured by the primary endpoint – a composite of all-cause mortality, myocardial infarction, ischemia-driven revascularization (IDR) and stent thrombosis (ST) at 48 hours.

PHOENIX was designed based on the observations from PCI and PLATFORM. Specifically, a contemporary definition of peri-procedural MI and ST were applied to assure that only the events that occurred after randomization were measured as endpoints in the PCI and PLATFORM trials [Cutlip et al, 2007; Thygesen et al, 2007; Leonardi et al, 2012; McEntegart et al, 2012]. Myocardial infarction was defined according to the Universal Definition of MI published in 2007

[Thygesen et al, 2007], which relies on clinical features including electrocardiogram (ECG) findings, elevated biomarkers and imaging to recognize and discriminate peri-procedural MI with greater specificity. The key secondary endpoint, ST measured events that occurred during and after PCI, when an IV $P2Y_{12}$ inhibitor could have the greatest effect and was defined according to the Academic Research Consortium (ARC) consensus criteria for post-procedural ST [Cutlip et al, 2007], with a pre-specified expansion to include intra-procedural ST (IPST) to measure events that have been demonstrated to be clinically important and associated with subsequent out-of-lab ST and mortality [Généreux et al, 2013; Brener et al, 2013; Harrison et al, 2013; Pride et al, 2012].

The use of an angiographic core lab for review of all patient index procedure and revascularization angiography films allowed objective determination of intra-procedural complications, including ST. Clinical Events Committee (CEC) adjudication of cardiovascular mortality, MI, IDR, and ST also provided objectivity as part of the study design.

At 48 hours, the PHOENIX study demonstrated that, compared to clopidogrel cangrelor provided:

- A significant reduction in the primary efficacy endpoint of all-cause mortality, MI, IDR, and ST (4.7% vs 5.9%, respectively; OR, 0.79 [95% CI 0.66-0.93], p=0.005), which was maintained at 30 days (6.0% vs 7.0%, respectively; OR, 0.85 [95% CI 0.73-0.99], p=0.035)
- A significant reduction in ST (0.8% vs 1.4%, respectively; OR, 0.62 [95% CI 0.43-0.90], p=0.010)
- A significant reduction in MI (3.8% vs 4.7%, respectively; OR, 0.80 [95% CI 0.67-0.97], p=0.022)
- No difference in all-cause mortality (0.3% vs 0.3%, respectively; OR, 1.00 [95% CI 0.52,1.92], p>0.999)

In the PHOENIX trial the primary safety endpoint was the incidence of 48-hour non-CABG bleeding, as measured by the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries Trial (GUSTO) scale. The GUSTO bleeding definition was selected as the primary safety bleeding analysis variable due to its widespread clinical acceptability and established predictive correlation with adverse clinical outcomes [The GUSTO Investigators, 1993; Rao et al, 2006]. Other bleeding scales were derived based on the data reported by investigators, including TIMI (Thrombolysis in Myocardial Infarction), BARC (Bleeding Academic Research Consortium), and ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy).

At 48 hours, the PHOENIX study demonstrated that, compared to clopidogrel cangrelor provided:

- No statistical difference in non-CABG GUSTO severe/life-threatening bleeding (0.2% vs 0.1%, respectively; OR, 1.50 [95% CI 0.53-4.22], p=0.439) or GUSTO moderate bleeding (0.4% vs 0.2%, respectively; OR, 1.69 [95% CI 0.85-3.37], p=0.128)
- No statistical difference in transfusion (0.5% vs 0.3%, respectively; OR 1.56 [0.83-2.93], p=0.169)
- A significant increase in non-CABG ACUITY major bleeding (4.3% vs 2.5%, respectively; OR, 1.72 [95% CI 1.39-2.13], p=<0.001), driven by hematoma ≥5 cm
- A significant increase in non-CABG GUSTO mild (2.7% vs 1.6%, respectively; OR, 1.72 [95% CI 1.32-2.25], p=<0.001) and ACUITY minor bleeding (11.8% vs 8.6%, respectively; OR, 1.42 [95% CI 1.26-1.61], p=<0.001), driven by ecchymosis, puncture site oozing, and hematoma <5 cm

In PHOENIX, there were (2 vs. 4) bleeding related deaths with cangrelor compared to clopidogrel and there were numerically more clinically important bleeding events of intracranial hemorrhage (3 vs. 2), cardiac tamponade (9 vs. 1), retroperitoneal bleeds (7 vs. 3) and gastrointestinal bleeds (16 vs. 10) among cangrelor-treated patients.

Safety Results from all CHAMPION trials

In the pooled CHAMPION program, consisting of PHOENIX, PLATFORM and PCI, in which 12,565 patients were treated with cangrelor in the setting of PCI, at a dose of 30 µg/kg followed by 4 µg/kg/min for 2 to 4 hours, the bleeding outcomes were similar to those observed in PHOENIX with no increase in the primary safety outcome of GUSTO severe/life-threatening bleeding (0.2% vs. 0.2%) at 48 hours. There was no difference in fatal bleeding (8 vs. 9) but there was a numerical increase in clinically important bleeding events including more intracranial hemorrhages (9 vs. 3), cardiac tamponade (15 vs. 3), retroperitoneal bleeds (24 vs. 15) and gastrointestinal bleeds (20 vs. 15) among cangrelor-treated patients.

The number of adverse events (AEs) between cangrelor- and control-treated patients in the pooled safety population was similar. There was a similar pattern of patients with AEs, and serious adverse events (SAEs) between cangrelor- and control-treated patients in the PHOENIX trial (AEs: 20.2% vs. 19.1%, respectively; SAEs: 2.1% vs. 1.7%, respectively) and in the pooled CHAMPION trials (AEs: 23.3% vs. 22.1%, respectively; SAEs: 2.3% vs. 2.3%, respectively).

In the pooled CHAMPION trials, dyspnea was reported more frequently with cangrelor (1.2%) than control (0.4%). However, most cases were mild (64.9%) or moderate (34.5%) in intensity. Renal AEs of special interest including acute renal failure (16/12,565; 0.1% vs 12/12,542; 0.1%), renal failure (12/12,565; 0.1% vs 6/12,542; 0.0%) and increased serum creatinine (23/12,565; 0.2% vs 14/12,542; 0.1%) and hypersensitivity AEs of special interest, including angioedema (2/12,565; 0.0% vs 0/12,542; 0.0%), anaphylactic reaction (2/12,565; 0.0% vs 1/12,542; 0.0%) and anaphylactic shock (1/12,565; 0.0% vs 0/12,542; 0.0%), were reported after administration of cangrelor in the CHAMPION trials.

In the CHAMPION trials, study drug discontinuation occurred more frequently with cangrelor (0.6% vs. 0.4%) with coronary artery dissection, coronary artery perforation, and dyspnea being the most frequent events leading to discontinuation.

BRIDGE

Patients who require $P2Y_{12}$ inhibitor therapy and must undergo surgery represent a treatment challenge. Product labels for the oral $P2Y_{12}$ inhibitors recommend discontinuation 5 to 7 days prior to surgery to limit the risk of excess surgical bleeding. However, the risk of ischemic events increases when $P2Y_{12}$ inhibition is stopped prematurely [Dutch Stent Thrombosis CSR].

To asses if cangrelor can provide an alternative platelet management option in this setting, a pharmacodynamic study, BRIDGE was designed as a double-blind, randomized, placebo-controlled, multicenter trial, involving 210 patients with an ACS or treated with a coronary stent receiving treatment with an oral $P2Y_{12}$ inhibitor, and who were awaiting coronary artery bypass graft (CABG) surgery.

The primary objective was to demonstrate that cangrelor at an infusion dose of 0.75 μg/kg/min maintains low levels of platelet reactivity as if an oral $P2Y_{12}$ inhibitor had not been discontinued up until the time of surgery, without increasing surgical bleeding.

In BRIDGE, the results demonstrated that:

- Cangrelor at an infusion dose of 0.75 μg/kg/min IV provides consistent inhibition of platelet reactivity during infusion. The primary efficacy endpoint was met with 98.8% of cangrelor-treated patients maintaining target levels of platelet inhibition (<240 Verify*Now*® P2Y12 Reaction Units (PRU)) for all time points measured over the bridging period compared to 19.0% of placebo patients (relative risk [RR], 5.2 [95% CI, 3.3-8.1] p <0.001).
- After discontinuation of the cangrelor infusion (1 to 6 hours before surgery), platelet function prior to surgery was similar for cangrelor and placebo groups (p=0.212).

In BRIDGE, the main safety endpoint of excessive CABG-related bleeding was not different for cangrelor- and placebo- treated patients (12/102, 11.8% vs. 10/96, 10.4%, respectively). Similarly, the incidence of any transfusion was not increased with cangrelor (25.5% vs. 32.3% with placebo). Cangrelor was associated with a numerical increase in non–CABG-related bleeding occurring during the 5 to 7-day bridging period while the infusion was still being administered. There was a numerical increase in GUSTO mild and TIMI/ACUITY minor bleeding, driven primarily by ecchymosis, oozing at the puncture site, and hematoma <5 cm at the puncture site. These events are not known to be correlated with long term adverse clinical outcomes and the overall incidence of minor bleeding may have been increased in part by repeat venipuncture associated with the trial conduct.

The number of AEs and SAEs were similar between cangrelor- and control-treated patients in the BRIDGE trial (AEs: 54.7% vs. 55.4%, respectively; SAEs: 10.4% vs. 8.9%, respectively).

The pharmacodynamic (PD) effects observed in BRIDGE confirmed the presence of $P2Y_{12}$ inhibition. BRIDGE provides information on the use of cangrelor in settings such as bridging where $P2Y_{12}$ inhibition can be continued until shortly before surgery to lower the risk of thrombotic events, with rapid return of platelet function to lower the risk of surgical bleeding.

Net Clinical Benefit of Cangrelor Compared with Clopidogrel

In the contemporary management of patients who require fast, reliable and flexible $P2Y_{12}$ inhibition in the acute setting cangrelor is a potential solution due to its immediate bioavailability, rapid onset of effect and fast offset. The results of the CHAMPION program demonstrated that cangrelor compared to control is effective with an acceptable safety profile when administered to patients with CAD undergoing PCI.

The CHAMPION PHOENIX trial demonstrated that cangrelor confers a significant 22% relative risk reduction (RRR) in the primary composite efficacy endpoint of Death/MI/IDR or ST superior to clopidogrel in patients who require PCI with a number needed to treat (NNT) of 84. Supportive evidence of efficacy, including reductions in stent thrombosis, were observed in the CHAMPION PLATFORM and PCI trials.

The significant reductions in the incidence of MI and ST are objective, clinically meaningful, and important. For every 114 patients undergoing PCI with cangrelor compared to conventional therapy, one MI might be avoided (NNT = 114 in CHAMPION PHOENIX) and for every 195 patients undergoing PCI with cangrelor compared to conventional therapy, one ST might be avoided (NNT = 195 in CHAMPION PHOENIX). Stent thrombosis is a catastrophic complication of PCI and can occur at any time [Holmes et al, 2010]. Stent thrombosis presents as STEMI or cardiogenic shock, with case fatality reaching as high as 45% in some studies. The implications of cangrelor therapy as a novel strategy to manage patients in an acute setting undergoing PCI is important and may resolve the management dilemmas now faced by these patients and their caregivers.

Cangrelor does not significantly increase clinically meaningful bleeding risk in patients undergoing PCI as evaluated in 12,565 cangrelor-treated patients from the three CHAMPION studies. For every 1844 patients undergoing PCI with cangrelor compared to conventional therapy, one GUSTO severe/life-threatening bleed might occur resulting in a number needed to harm (NNH) of 1844 in CHAMPION PHOENIX. An increase in non-CABG minor bleeding was the major driver of increased bleeding observed with cangrelor. Most of the non-bleeding adverse reactions such as dyspnea and hypersensitivity were mild to moderate in intensity.

For each 1000 patients who were given cangrelor instead of clopidogrel, 9 myocardial infarctions, 6 stent thrombosis, and 2 ischemia driven revascularization end-point events were prevented. The cost was 1 excess severe or life threatening bleed, 2 moderate bleeds and 11

minor bleeding events. There was no difference in fatal bleeding and there was no difference in overall mortality. The modest increase in bleeding risk does not compromise the use of cangrelor for patients undergoing PCI. The Sponsor proposes contraindicating the use of cangrelor in patients who have a history of intracranial hemorrhage (ICH) to reduce the risk of such events. The sponsor is also proposing to include a warning concerning the concomitant use of other anti-platelets (warfarin and glycoprotein IIb/IIIa inhibitors) due to increased risk of bleeding. Should a major bleeding event occur, the effect of cangrelor can be rapidly reversed by discontinuing the infusion, with rapid clearance of drug and a return to normal platelet function within 60 minutes.

Conclusion

In conclusion, the acceptable benefit-risk profile of cangrelor makes it a clinically important option for patients who require fast, reliable and flexible $P2Y_{12}$ inhibition in the acute setting for the contemporary management of patients undergoing PCI or requiring bridging off oral $P2Y_{12}$ inhibitors to surgery.

LIST OF ABBREVIATIONS

Abbreviation or Specialist Term	Explanation
[^{3}H]	Tritiated
8-SPT	8-(*p*-sulfophenyl) theophylline
ACC	American College of Cardiology
ACS	acute coronary syndrome(s)
ACUITY	Acute Catheterization and Urgent Intervention Triage Strategy
ADP	adenosine diphosphate
AE	adverse event(s)
AESI	AE(s) of special interest
AHA	American Heart Association
A/H/N	aspirin, heparin, and nitroglycerin
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ARC	Academic Research Consortium
ASA	acetylsalicylic acid (aspirin)
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under curve
AUC_{inf}	area under the concentration time curve extrapolated to infinity
AUC_{last}	area under the concentration time curve up to last measurable concentration
BARC	Bleeding Academic Research Consortium
C_{1hour}	end of infusion concentration
CABG	coronary artery bypass grafting (surgery)
CAD	coronary artery disease
CEC	Clinical Events Committee
CHF	congestive heart failure
CI	confidence interval
CK-MB	creatine kinase-myocardial band isoenzyme
CL	plasma clearance
C_{max}	maximum plasma concentration

Abbreviation or Specialist Term	Explanation
CrCL	creatinine clearance
CSR	Clinical Study Report
C_{ss}	steady state concentration
CV%	coefficient of variation
DAPT	dual antiplatelet therapy
DES	drug eluting stent(s)
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
FDA	Food and Drug Administration (USA)
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GP IIb/IIIa inhibitor(s)	glycoprotein IIb/IIIa inhibitor(s)
GTN	nitroglycerin
GUSTO	Global Use of Strategies To Open coronary arteries
h	hour(s)
HPLC	high performance liquid chromatography
HR	hazard ratio
IC_{50}	concentration required to give 50% inhibition of the measured response
ICH	intracranial hemorrhage(s)
IDR	ischemia-driven revascularization
IMS	International Medical Statistics
IND	Investigational New Drug Application (USA)
IPST	Intra-procedural ST
IQ	interquartile
ITT	intent to treat
IV	intravenous
IVRS	interactive voice-response system
kg	kilogram(s)
L	liter(s)
LC-NMR	liquid chromatography-nuclear magnetic resonance
LMWH	low molecular weight heparin
LTA	light transmission aggregometry

Abbreviation or Specialist Term	Explanation
LVEF	left ventricular ejection fraction
MACE	major adverse cardiac events
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
mL	milliliter(s)
mITT	modified intent to treat
min	minute(s)
NC	not calculable
NDA	New Drug Application (USA)
ng	nanogram(s)
nM	nanomolar
NNH	number needed to harm
NNT	number needed to treat
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
non-Q-MI, non-QMI	non-Q-wave myocardial infarction
NSTE-ACS	non-ST-elevation acute coronary syndrome
NSTEMI	non-ST-segment elevation myocardial infarction
OECD	Office of Economic Cooperation and Development
OR	odds ratio
PAD	peripheral artery disease
PCI	percutaneous coronary intervention
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PRU	Verify*Now*® P2Y12 Reaction Unit
PTCA	percutaneous transluminal coronary angioplasty
Q1	first quartile
Q3	third quartile
QT_c	QT interval corrected for heart rate
Q-MI, QMI	Q-wave myocardial infarction
ROC	receiver-operating characteristic
RR	relative risk

Abbreviation or Specialist Term	Explanation
RRR	relative risk reduction
SAE	serious adverse event(s)
SD	standard deviation
SDS-PAGE	sodium dodecyl sulfate polyacrylamide gel electrophoresis
SE	standard error
SMQ	standardized MedDRA query
ST	stent thrombosis
STEMI	ST-segment elevation myocardial infarction
$t_{1/2}$	half-life
T_{max}	time to maximal concentration
TIA	transient ischemic attack(s)
TIMI	Thrombolysis in Myocardial Infarction
Tn	troponin
UA	unstable angina
ULN	upper limit of normal
UDMI	Universal definition of MI
UFH	unfractionated heparin
US	United States
VASP-P	vasodilator-stimulated phosphoprotein phosphorylation
Vz	volume of distribution
WBIA	whole blood impedance aggregometry
µg	microgram(s)
µL	microliter(s)
µM	micromolar(s)

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1. INTRODUCTION

The Medicines Company has submitted a New Drug Application (NDA) for the use of cangrelor in patients undergoing PCI and in patients bridging to surgery. The Division of Cardiovascular and Renal Products (DCRP) of the US Food and Drug Administration (FDA) have scheduled an Advisory Committee meeting for 12 February 2014 to discuss regulatory considerations surrounding the application.

This briefing book summarizes key aspects of the cangrelor development program and NDA, including:

PCI Indication – addressed in Sections 1 through 10 in this Briefing Book

- Pharmacokinetic (PK) and pharmacodynamic (PD) properties of cangrelor, an intravenous (IV), rapid onset, reversible, platelet $P2Y_{12}$ inhibitor
- Relevant medical background information for PCI
- Efficacy data from the Phase 3 CHAMPION PHOENIX study
- Safety data from the CHAMPION PHOENIX, PLATFORM and PCI studies
- Risk/benefit analysis

Bridge Indication – addressed in Section 11 in this Briefing Book

- Pharmacodynamic and safety data from the BRIDGE study

1.1. Pharmacologic class and mode of action

Cangrelor is a novel, intravenous (IV), direct-acting, $P2Y_{12}$ receptor antagonist that blocks adenosine diphosphate (ADP)-induced platelet activation and aggregation.

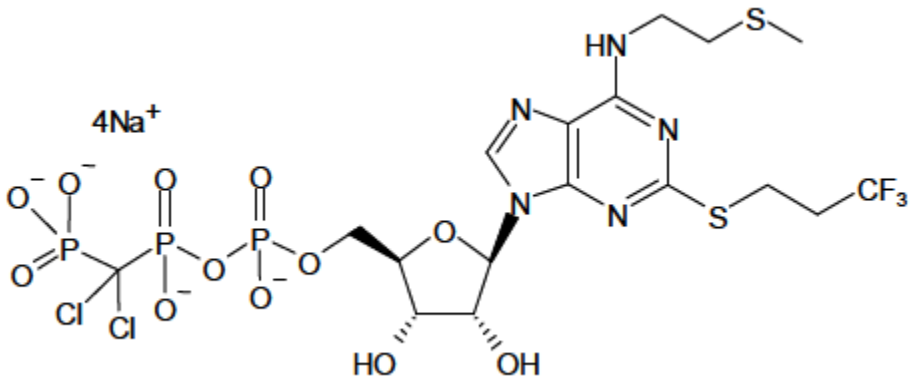
Cangrelor provides direct, rapid, potent, and consistent platelet $P2Y_{12}$ inhibition during IV infusion, with reversible binding and a half-life in man of 3 to 6 minutes.

- Rapid onset of effect: IV with immediate bioavailability, direct acting (not a prodrug), providing the flexibility to transition to or from oral $P2Y_{12}$ inhibition at any point.
- Potent: substantial $P2Y_{12}$ inhibition at 30 µg/kg IV bolus then 4 µg/kg/min IV infusion for 2 to 4 hours in the PCI setting.
- Consistent: the maximum plasma concentration (C_{max}), area under curve (AUC), and steady state concentrations (C_{ss}) for cangrelor increase linearly with doses up to the maximum infusion rate tested. The PK/PD response for cangrelor is consistent regardless of sex, renal status, age, or presentation status.
- Rapid offset of effect: cangrelor is a substituted nucleotide that is rapidly inactivated in the circulation by dephosphorylation to a nucleoside metabolite. Therefore, clearance is independent of organ function. Platelet function returns to normal within 60 minutes of stopping the infusion.

This profile allows the established clinical benefit of $P2Y_{12}$ inhibition to be available to patients requiring antithrombotic protection either during interventional procedures or after interruption of oral $P2Y_{12}$ inhibitor therapy, without undue compromise of normal hemostasis. In these settings, control and rapid reversibility of effect are key attributes, providing flexibility and address the needs of both the interventional and the surgical teams.

The chemical structure of cangrelor is similar to adenosine triphosphate (ATP). The chemical name of cangrelor is tetrasodium salt of N6-[2-(methylthio)ethyl]-2-[(3,3,3 trifluoropropyl)thio]-5´-adenylic acid, monoanhydride with (dichloromethylene) bisphosphonic acid. The chemical structure is shown below:

Figure 1: Chemical structure of cangrelor



1.2. Proposed indication and dose

The proposed indications for cangrelor are:

1. Cangrelor is a $P2Y_{12}$ platelet inhibitor indicated for the reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI).
2. Cangrelor is indicated to maintain $P2Y_{12}$ inhibition in patients with acute coronary syndromes (ACS) or patients with stents who are at increased risk for thrombotic events (such as stent thrombosis) when oral $P2Y_{12}$ therapy is interrupted due to surgery.

The recommended dose regimens for cangrelor are a 30 µg/kg bolus injection followed by a 4 µg/kg/min infusion for 2 hours in the PCI setting and 0.75 µg/kg/min continuous IV infusion for up to seven days in the BRIDGE setting. Further information supporting the Bridge indication can be found in this briefing book in Section 11.

1.3. Regulatory history for the PCI indication

The Medicines Company (and previously Astra-Zeneca who was the Sponsor until 2003) has been in regular communication with FDA regarding the development of cangrelor throughout its development. Notably with respect to the Phase 3 CHAMPION PCI, PLATFORM and PHOENIX trials, The Medicines Company received the following key advice that guided the design of the Phase 3 trials:

- At the July 2005 End of Phase 2 meeting the Agency noted that it is likely that any effect of cangrelor due to it's pharmacodynamic properties will most likely be on clinical outcomes such as acute MI and revascularization, not survival. The Agency agreed to the primary endpoint and definitions of all-cause mortality, non-fatal MI, and IDR at 48 hours as well as the use of the GUSTO scale to capture bleeding.
- At the November 2009 meeting, where the results of PCI and PLAFTORM were reviewed, the Division agreed that one clinical trial similar to the PCI and PLATFORM trials (as noted above) demonstrating a decrease in the composite clinical endpoint of death/non-fatal MI/ST is likely sufficient for an NDA submission.
- In September 2010, in comments received on the PHOENIX protocol, the Agency requested MDCO to revise the protocol to allow the investigator to determine the timing of clopidogrel administration. The Agency also noted that it would be prudent to control overall error rate for PHOENIX at the two-sided 0.01 level as the single pivotal trial.

2. RATIONALE FOR PRODUCT DEVELOPMENT

2.1. Platelet $P2Y_{12}$ inhibitors are effective and reduce thrombotic complications including stent thrombosis in patients undergoing PCI

Treatment of atherosclerotic disease and ACS with PCI and stent implantation can involve significant localized injury to the vascular endothelium [Thomas et al, 2009], even in stable patients [Babu et al, 2011]. This vascular trauma is prothrombotic, inflammatory, and can result in ischemic events [Bonello et al, 2006]. Specifically, exposure of the subintimal layer of the vessel to platelets activates the coagulation system, is a potent stimulus for thrombin formation, and agonists released in this process increase platelet reactivity. In turn, increased platelet reactivity is central to the propagation of the thrombotic process.

Platelets are the "first responders" to vascular tissue injury or the presence of a foreign surface such as procedural instrumentation or a stent, and as a result platelets adhere to the site of injury and can become activated by numerous agonists during the thrombotic response to injury. Platelet activation leads to a range of responses that play a critical role in arterial thrombosis and the associated inflammatory responses, including platelet aggregation, dense and α-granule secretion and further pro-coagulant activity. ADP is an important agonist released from dense granules of platelets activated in the thrombotic process. Each activation agonist, such as thrombin or ADP, has one or more receptors on the platelet surface. One of the receptors for ADP on the platelet—the $P2Y_{12}$ receptor—plays an important role in the amplifying and sustaining platelet activation initiated by other pathways, leading to stable platelet-rich thrombus generation [Dorsam and Kunapuli, 2004; Gurbel et al, 2004]. Activation of the $P2Y_{12}$ receptor by ADP and subsequent amplification of the thrombotic response implies that blocking the $P2Y_{12}$ receptor would have important inhibitory effects on overall platelet function regardless of the initial activating stimuli [Storey, 2006]. This phenomenon, coupled with the restricted distribution of the $P2Y_{12}$ receptor in humans, makes the receptor an ideal target for pharmaceutical therapy. Inhibition of the $P2Y_{12}$ receptor is an accepted component of an antithrombotic regimen.

Antiplatelet therapies, in particular the $P2Y_{12}$ receptor inhibitors, reduce ischemic events, including MI and ST [Yousuf and Bhatt, 2011; Wiviott et al, 2007; Wallentin et al, 2009]. Reductions in the rate of ST have been observed with more effective $P2Y_{12}$ inhibition: 29% for clopidogrel 600 mg vs 300 mg, 25% for prasugrel vs clopidogrel 300 mg, and 52% for ticagrelor vs clopidogrel 300 mg [Wiviott et al, 2007; Wallentin et al, 2009; CURRENT OASIS-7 Investigators, 2010]. A meta-analysis of 42,198 patients from five randomized, placebo-controlled trials that compared new $P2Y_{12}$ antagonists (prasugrel, ticagrelor, cangrelor) with clopidogrel in PCI confirmed that new $P2Y_{12}$ platelet inhibitors significantly reduce the risk of ST (by 40%, p=0.001) and death (by 15%, p=0.008) following PCI [Bellemain-Appaix et al, 2010].

Long-term treatment with an oral $P2Y_{12}$ inhibitor has emerged as a standard of care to prevent secondary thrombotic events including MI and ST in patients with ACS and patients with

coronary artery disease (CAD) who have undergone PCI. $P2Y_{12}$ inhibition is recommended in treatment guidelines with Class-I recommendations [Anderson et al, 2011; Levine et al, 2011; Hillis et al, 2011; Hamm et al, 2011; Van de Werf et al, 2008; Wijns et al, 2010] to initiate and prolong without interruption dual antiplatelet therapy (DAPT) to 12 months or even longer in those undergoing PCI with stents, especially after ACS [Farb and Boam, 2007; Levine et al, 2011].

2.2. Periprocedural thrombotic complications remain a major concern in patients with coronary artery disease undergoing PCI

PCI with stent implantation is widely used to decrease death or myocardial infarction (MI) in patients with ACS and to reduce angina and improve quality of life in patients with stable angina [Mehta et al, 2005; De Bruyne et al, 2012; Bavry et al, 2006; Bhatt et al, 2004]. Despite advances in adjunctive pharmacotherapy, thrombotic complications such as ST and MI during and immediately after PCI remain a major concern [Desai and Bhatt, 2010].

While older IV antiplatelet agents with different platelet targets such as glycoprotein (GP) IIb/IIIa inhibitors are able to reduce periprocedural MI successfully, their use has not been associated with a lower risk of ST, but rather a later onset of ST [Rinaldi et al, 2008; Assali et al, 2000]. Additionally, their effect cannot be quickly reversed and they can cause an increase in bleeding complications [Bhatt and Topol, 2000].

Stent thrombosis occurring after PCI is an infrequent but serious complication [Holmes et al, 2010]. Stent thrombosis can present as STEMI or cardiogenic shock, with case fatality reaching as high as 45% in some studies [Airoldi et al, 2007; Schulz et al, 2009; Iakovou et al, 2005; Urban et al, 2011]. The incidence of ST is known to be increased in patients undergoing PCI in the setting of an ACS and in those who discontinue dual antiplatelet therapy [Airoldi et al, 2007; Schulz et al, 2009; Iakovou et al, 2005; Urban et al, 2011].

The Academic Research Consortium (ARC) has standardized the definitions of ST by categorizing the specificity of the adjudicated event (definite, probable, or possible) and its timing relative to PCI (acute, subacute, late, and very late) [Cutlip et al, 2007]. However, these categories only refer to events occurring after the patient has left the cardiac catheterization laboratory. Intra-procedural complications including intra-procedural stent thrombosis (IPST) (ie, the development of occlusive or non-occlusive new thrombus in or adjacent to a recently implanted stent before the PCI procedure is completed) are also clinically important and associated with subsequent out-of-lab ST and mortality [Brener et al, 2013; Harrison et al, 2013; Pride et al, 2012]. Although IPST has been reported from the time of early investigations of drug-eluting stents [Chieffo et al, 2004], recent reports have used systematic ascertainment within large clinical databases to determine the impact of IPST. Although not frequent, IPST occurs with similar incidence to out of lab ST <30 days and because it occurs at the time of coronary intervention in the catheter laboratory there may be means to modify its impact [Brener et al, 2013].

In an independent core laboratory analysis, [Brener et al, 2013] performed a frame-by-frame review of angiograms from the combined HORIZONS-AMI and ACUITY databases. They reported that IPST occurred in 47 (0.7%) of 6,591 patients. Among patients with IPST compared with those without IPST, major adverse ischemic events were "markedly" higher, including mortality at 30 days (12.9% vs. 1.4%, p <0.0001) and 1 year (12.9% vs. 3.1%, p <0.0001), and out-of-lab ARC definite or probable ST at 30 days (17.4% vs. 1.8%, p<0.0001) and 1 year (19.9% vs. 2.7%, p <0.0001). IPST was a significant independent predictor of 1-year mortality (hazard ratio [HR]: 3.86; 95% confidence interval [CI]: 1.66 to 9.00, p= 0.002).

A second study [Xu et al, 2013] using similar methods and definition of IPST as Brener et al, found 23 cases of IPST among 1901 consecutive patients, (1.2%) with ACS who were undergoing PCI. Those with, versus without IPST, had significantly more MACE at 30 days (26.1% vs. 8.7%, p=0.01) and 1-year (30.4% vs. 14.4%, p=0.02), as well as increased ARC-defined ST at 30 days (17.4% vs. 2.0%, p=0.0013) and 1 year (21.7% versus 3.0%, p=0.0007). Death at 30 days was numerically increased in patients with IPST versus without (4.3% vs. 0.7%).

2.3. An unmet need exists in the PCI setting

Oral platelet $P2Y_{12}$ inhibitors have several limitations in the acute treatment phase of patients with ischemic cardiovascular disease who require revascularization by PCI or surgery, including delayed onset of action, an unpredictable response, and poor reversibility of effect.

Patients in the acute phase of cardiovascular illness may have several bioavailability issues due to nausea, use of opiates, or impaired perfusion resulting in reduced absorption and may not derive sufficient antiplatelet effect from an oral platelet $P2Y_{12}$ inhibitor [Heestermans et al, 2008; Biscaglia et al, 2013; Součková et al, 2013]. Additionally, multiple sources of variation in clopidogrel pharmacokinetics (PK) and pharmacodynamics (PD) have been described resulting in an unpredictable patient response to oral loading doses especially in an acute setting [Frelinger et al, 2013] and increased risk of ischemic events. Clopidogrel is a prodrug that after oral ingestion is absorbed in the intestine. About 85% of the drug is hydrolyzed by esterases to an inactive carboxylic acid derivative and a small fraction is converted by hepatic cytochrome P450 (CYP) 3A4 mono oxygenase to the active thiol metabolite. The active metabolite irreversibly binds to the ADP $P2Y_{12}$ receptor, resulting in a partial inhibition of platelet aggregation. However, a considerable inter-individual variability in platelet response to clopidogrel has been reported [Gurbel et al, 2003; Angiolillo et al, 2004; Gurbel et al, 2005; Serebruany et al, 2005]. An increase in ST has also been observed in patients with platelet loss of function CYP2C19 polymorphism who are unable to effectively metabolize clopidogrel to its active metabolite [Sibbing et al, 2009]. Lastly, in patients in whom an antiplatelet effect is no longer desirable, such as in patients with bleeding complications after PCI or those requiring surgery, the pharmacodynamic effect is only very slowly reversible, requiring generation of new platelets not exposed to the active metabolite.

More potent oral agents such as prasugrel and ticagrelor are also subject to similar limitations [Bonello et al, 2011; Alexopoulos et al, 2012; Agrawal and Bhatt, 2013; Parodi et al, 2013; Steg et al, 2013].

To overcome some of these limitations, clopidogrel pretreatment (ie, treatment given in sufficient time before catheterization to be effective) is often administered. While pretreatment with clopidogrel has been shown in some, though not all, studies to reduce ischemic events, it does necessitate treatment prior to delineation of the coronary anatomy, which might then be problematic if emergent cardiac surgery is required or intra-procedural complications such as coronary artery perforation occur [Bellemain-Appaix et al, 2012]. The largest randomized clinical trial of pretreatment did not find a statistically significant benefit of pretreatment with 300 mg of clopidogrel [Steinhubl et al, 2002] and extrapolations regarding the 600 mg clopidogrel dose are assumptions made on the basis of PK and PD alone and have not been proven clinically [CURRENT OASIS-7 Investigators, 2010]. The PRAGUE-8 trial also showed no improvement between pre-treatment >6 hours before and on-table clopidogrel administration, but did find an increased risk of bleeding [Widimský et al, 2008]. Furthermore, pretreatment can either delay coronary artery bypass graft (CABG) surgery or increase unnecessarily the risk of bleeding in patients who in the end do not need revascularization or who go to the operating room immediately after undergoing coronary angiography. As a result of this treatment dilemma, a number of physicians choose to administer oral $P2Y_{12}$ inhibitors after the PCI is completed and surgery has been confirmed as not required.

There are currently no treatment strategies available that provide consistent and effective platelet $P2Y_{12}$ inhibition that can be turned on when needed (such as in an acute PCI setting) and that can be turned off when not, thus avoiding increased bleeding risk in patients who require subsequent surgery.

3. OVERVIEW OF CANGRELOR NONCLINICAL DEVELOPMENT

3.1. The Nonclinical Program

The nonclinical testing program for cangrelor was consistent with existing regulatory guidance for an intravenously administered therapeutic intended for short-term administration. All pivotal studies were conducted in compliance with the principles of Good Laboratory Practice (GLP) as detailed in the Department of Health United Kingdom Good Laboratory Practice Programme and in accordance with standards of the Office of Economic Cooperation and Development (OECD) that were in place at time of conduct.

Doses selected in the pharmacodynamic studies evaluated a full range of dose-response activity. The dose ranges varied based on the model system and endpoints evaluated. The animal pharmacology studies demonstrated the potency, selectivity, and specificity of cangrelor as an inhibitor of ADP-induced platelet aggregation in vitro. In addition, the relationships between anti-aggregatory, anti-thrombotic, and anti-hemostatic activities as well as interactions with thrombolytic drugs were examined in vivo. Furthermore, the contribution of the major metabolites of cangrelor to pharmacodynamic and toxic effects was determined.

The doses for each of the safety pharmacology and toxicity studies were chosen to provide substantial challenge to the test animals and expected to cause systemic toxic effects. Low doses were in ranges expected to provide no-observed-effect and/or no-observed-adverse-effect levels (NOEL and NOAEL, respectively).

3.2. Key conclusions of the Nonclinical Program

- In vitro studies established cangrelor as a potent inhibitor of ADP-induced platelet aggregation including when administered in combination with other antithrombotic agents including t-PA and aspirin. Importantly, no metabolite exhibited activity at physiologically relevant concentrations.
- In a series of studies in rats and dogs, IV cangrelor exhibited dose-related reversible inhibition of ADP-induced platelet aggregation and associated thrombus formation at doses at least 10-fold lower than the NOAEL doses identified in pivotal toxicity studies.
- The effects of cangrelor on platelet activation were short-lived upon cessation of infusion, with substantial recovery occurring within a range of 15 to 60 minutes post-infusion. Offset of effect of cangrelor activity was rapid and dose independent, with full restoration of hemostasis, as assessed by bleeding time, seen within 10 minutes of cessation of infusion.
- Safety pharmacology studies indicated administration of cangrelor induced transient hypothermia in mice, which is a class effect associated with administration of adenosine and adenosine analogs (metabolites of cangrelor are adenosine analogs). There were no treatment-related effects of cangrelor on cardiovascular or respiratory systems in anesthetized rats or cats and the autonomic nervous system in anaesthetized cats. Furthermore, telemetry

studies demonstrate that cangrelor does not have any adverse effects on hemodynamic and cardiovascular parameters including QRS and QT intervals in anesthetized dogs.

- The plasma pharmacokinetic properties of cangrelor and the major metabolite, AR-C69712XX, are similar between rats, dogs, and humans, and are linear and dose proportional.
- Upon cessation of infusion, plasma cangrelor levels decline with an initial plasma elimination half-life ($t_{1/2}$) of 1 minute in the dog, and 1 to 2 minutes in the rat.
- The primary route of elimination of cangrelor metabolites in the rat and dog is fecal. No unchanged cangrelor is excreted.
- In the animal studies conducted with cangrelor there were no findings that indicate a substantive safety risk for the proposed use of the drug. The primary adverse effects of cangrelor in the pivotal toxicity studies in rats and dogs were localized to the renal pelvis and upper ureter. The primary insult appeared to be to the transitional epithelium, manifested by epithelial ulceration and necrosis, associated reactive epithelial hyperplasia and inflammation. These effects occurred after a minimum of 7 days of dosing, and showed signs of reversibility, and were not associated with the primary metabolite observed in human urine. There are measurable levels of urinary metabolites in rats and dogs that are present in only trace amounts in humans indicating a potential species specific effect for the renal system pathology restricting it to animals and not humans. In addition, based on the clinical safety database the nonclinical findings do not translate to a clinical safety concern.
- The pivotal toxicity studies in rats and dogs also showed an increase in levels of the liver function enzymes aspartate aminotransferase (AST) and alanine aminotransferase (ALT). However, there was no associated histopathological evidence of liver toxicity that could be attributed to cangrelor. In addition, there were no treatment effects on alkaline phosphatase (ALP) activity.
- Cangrelor and its metabolites are not genotoxic.
- Development and reproductive toxicity studies indicate cangrelor affects male and female fertility at high doses, but these are reversible following cessation of dosing. Cangrelor is not a teratogen, but there were effects on fetal growth in rats and rabbits at high doses. Cangrelor did not exhibit any selective effects on pre- and post-natal development.

4. CANGRELOR CLINICAL DEVELOPMENT PROGRAM

The goal of the cangrelor development program was to demonstrate the safety and effectiveness of cangrelor in patients with CAD who require $P2Y_{12}$ inhibition in the setting of PCI. The PCI population included patients with coronary artery disease, from stable angina to STEMI, who required percutaneous intervention.

The clinical development program includes 18 clinical studies and 13,325 cangrelor-treated subjects. These studies were conducted in compliance with Good Clinical Practice (GCP).

Phase 1 – Clinical Pharmacology

Seven clinical pharmacology studies in both healthy volunteers and volunteers with renal impairment (196 subjects exposed) provide PK/PD and safety/tolerability data, and established the dosing regimen for Phase 2 and Phase 3 studies.

Six Phase 1 healthy volunteer studies [SC-931-5014, SC-931-5036, SC-931-9017, SC 931-5037, and SC-931-5109, TMC-CAN-04-02] demonstrated that cangrelor is a potent, direct $P2Y_{12}$ antagonist with a rapid onset and offset, and has a linear dose-response relationship that produces a consistent pharmacodynamic effect. Phase 1 studies also investigated cangrelor's metabolism and distribution, and clinical drug-drug interaction potential.

The transition between IV (cangrelor) and oral $P2Y_{12}$ (600 mg clopidogrel) inhibition was also evaluated [TMC-CAN-04-02] to establish the transition dosing regimen for the cangrelor arm in Phase 3 studies.

8 Phase 2 Studies

The Phase 2 program was conducted in patients with CAD. Four studies, either open label, placebo- or active-controlled [SC-931-5058, SC-931-5060, SC-931-5129 Part 1, and SC-931-5129 Part 2], were completed in patients experiencing ACS as well as those requiring PCI (423 patients exposed). These studies evaluated the potential dose range and duration of infusion for cangrelor, interactions with commonly-used cardiovascular drugs, as well as PD and PK aspects of cangrelor action. An additional Phase 2 study [SC-931-5135] conducted in STEMI patients was terminated prematurely by the previous sponsor due to reprioritization of drug development plans.

The BRIDGE trial (Stage I, n=11; Stage II, n=210) tested cangrelor for bridging patients with ACS or patients with stents at increased risk of thrombotic events due to discontinuation of an oral platelet $P2Y_{12}$ inhibitor prior to cardiac surgery (Section 11.1).

Two TRANSITION trials [MDCO-CAN-12-03; MDCO-CAN-13-01] (N=24) were implemented to study the transition between IV (cangrelor) and oral (ticagrelor and prasugrel, respectively) $P2Y_{12}$ inhibition in patients with cardiovascular disease.

3 CHAMPION Phase 3 Studies - PHOENIX, PLATFORM, and PCI

CHAMPION PHOENIX is the pivotal study of the efficacy of cangrelor in the PCI setting and provides evidence of the efficacy and safety of cangrelor as a clinically important therapeutic option for the contemporary management of patients who require $P2Y_{12}$ inhibition in an acute setting.

The Phase 3 Program encompassed 25,107 patients with CAD in three clinical trials, (CHAMPION PHOENIX (n=11,145), CHAMPION PLATFORM (n=5364) and CHAMPION PCI (n=8884)) and when pooled provides supportive evidence of the safety of cangrelor.

References for key publications pertaining to the clinical development program are provided in Appendix 1.

5. CANGRELOR CLINICAL PHARMACOLOGY PROGRAM

5.1. Overview and objectives of the Cangrelor Clinical Pharmacology Program

The Clinical Pharmacology program for cangrelor was designed to:

- Determine whether the observed preclinical PK/PD profile of cangrelor translated to healthy volunteers and to the clinical setting in relevant patient groups
- Determine the dosing regimen in different populations
- Provide information for transition to/from oral $P2Y_{12}$ inhibitor therapy

Summary characteristics of the PK/PD profile of cangrelor determined from in this program are summarized in this overview, and key studies are discussed in more detail in this section.

Cangrelor provides direct, rapid, potent, and consistent platelet $P2Y_{12}$ inhibition during IV infusion, with reversible binding and a half-life in man of 3 to 6 minutes.

- *Rapid onset of effect:* IV with immediate bioavailability, direct acting, providing the flexibility to transition to or from oral $P2Y_{12}$ inhibition at any point.
- *Potent*: substantial $P2Y_{12}$ inhibition at doses determined to be required within a particular clinical setting: 30 µg/kg IV bolus then 4 µg/kg/min IV infusion for 2 h in the PCI setting; 0.75 µg/kg/min IV infusion for up to 7 days in the Bridge setting.
- *Consistent*: the maximum plasma concentration (C_{max}), area under curve (AUC), and steady state concentrations (C_{ss}) for cangrelor increase linearly with doses up to the maximum infusion rate tested. Phase 1 and 2 studies including male, female, elderly, and renally impaired patients and subjects found that the PK/PD profile of cangrelor is maintained in these subpopulations.
- *Rapid offset of effect:* cangrelor is a substituted nucleotide that is rapidly inactivated in the circulation by dephosphorylation to a nucleoside metabolite. Platelet function returns to normal within 60 min of stopping the infusion.

The attributes of rapid clearance and short half-life are consistent and independent of dose across the 10 clinical studies in which PK measurements were made. In addition, the mechanism for plasma clearance of cangrelor makes its metabolism largely independent of organ (e.g., hepatic/renal) function, with a low potential for drug-drug interactions. The PK studies includes healthy male and female volunteers, ACS patients managed both medically and with PCI, renally-impaired patients and an interaction study with aspirin, heparin, and nitroglycerin (A/H/N). A consistent and predictable PK profile was observed, and confirmed with a population PK/PD model, across all populations studied. Within study, inter-subject variability in clearance was low (14-22% in studies where formally assessed).

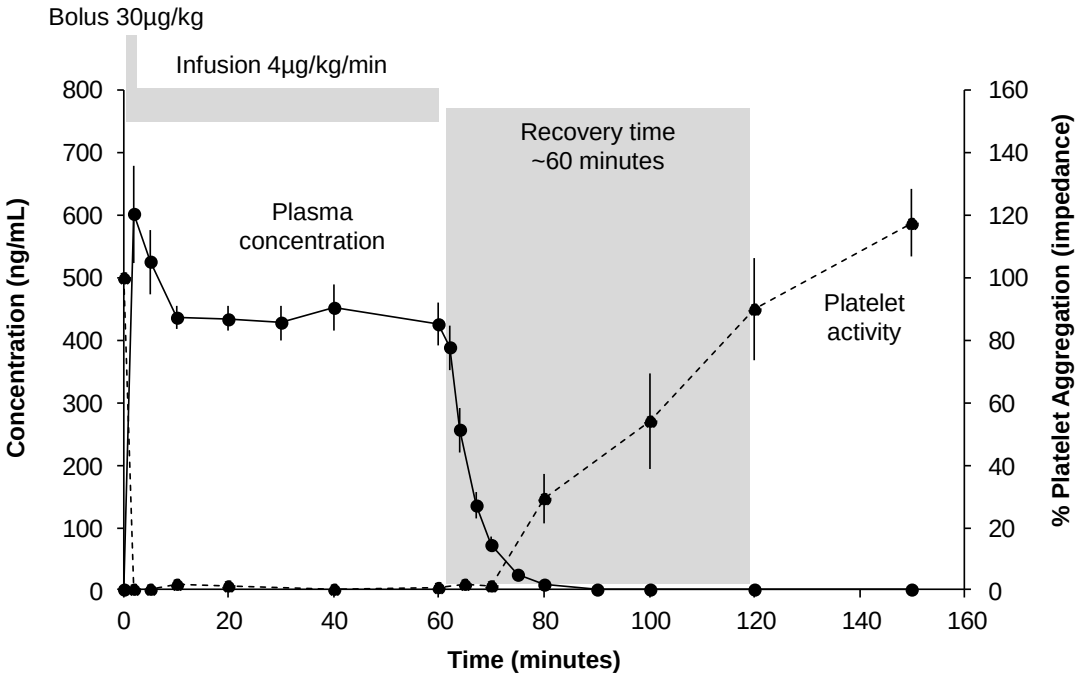
The PD profile of cangrelor is consistent with its PK profile, with immediate effects on platelet function following administration of a bolus plus infusion. Platelet function returns to normal

within 60 minutes of cessation of the cangrelor infusion. Patients receiving cangrelor can be easily transitioned to clopidogrel, ticagrelor or prasugrel.

The cangrelor dosing regimen (bolus and infusion) tested in the PCI setting in Phase 3 clinical trials was established in a Phase I study TMC-CAN-04-02. After administration of the bolus in healthy volunteers, cangrelor demonstrated immediate onset of $P2Y_{12}$ inhibition, which was maintained by the infusion. The PD effect of either drug was not attenuated by transition between the two drugs. Platelet function recovered within 60 minutes following discontinuation of cangrelor infusion.

The PK and $P2Y_{12}$ inhibition profile resulting from the pharmacological and molecular properties is illustrated in the PK/PD summary (Figure 2) for the 30 µg/kg IV bolus plus 4 µg/kg/min IV infusion dose from Study TMC-CAN-04-02.

Figure 2: PK/PD profile of cangrelor (30 µg/kg IV bolus plus 4 µg/kg/min IV infusion) in study TMC-CAN-04-02



Inhibition of response to 20 µM ADP as measured by whole blood impedance aggregometry
Source: TMC-CAN-04-02 data on file, Table 14.3.1; Akers 2010
kg = kilogram; IV = intravenous; min = minute; mL = milliliter; ng = nanogram; µg = microgram; µM = micromolar; PD = pharmacodynamics; PK = pharmacokinetics.

A thorough QT-interval study [TMC-CAN-08-01] was also performed to establish the ECG safety of cangrelor. No QT prolongation was noted.

5.2. Pharmacokinetic (PK) properties in Humans

The PK properties of cangrelor can be summarized as follows:

Cangrelor has immediate bioavailability, with a linear dose response. The maximum plasma concentration (Cmax), area under the curve (AUC), and steady state concentrations (Css) for cangrelor increase linearly with doses up to the maximum infusion rate tested [SC-931-5014, SC-931-5036, SC-931-5129, Part 1]

- The PK behavior is similar among patient populations, with low inter-individual variability. Clinical studies indicate no important covariate effects including age, race, gender, renal function, or study patient type on PK [SC-931-5014, SC-931-5036, SC-931-5109]
- There is no evidence of any changing response to cangrelor at any dose or over time during infusions lasting from 24 hours up to 7 days [SC-931-5014, SC-931-5036, SC-931-5058, SC-931-5060, SC-931-5129 Part 1, BRIDGE]
- Cangrelor is a substituted nucleotide that is rapidly converted to a nucleoside (inactive) [Study SC-100199, a sub-study to SC-931-9017] by ectonucleotidases in the blood vessel wall. The nucleoside is oxidized to the nucleoside sulfoxide, which is then excreted via the urine. There are no active metabolites.
- Clearance is rapid (43.9 L/h) with a half-life of 3 to 6 minutes [TMC-CAN-04-02] and is independent of dose or organ function. The volume of distribution is small at 3.9L and is consistent with distribution being largely limited to the plasma compartment
- Although clearance varied with weight (higher clearance in heavier patients) the impact of weight on drug exposure is minimal with the predicted shift in exposure (C_{ss} or AUC) of less than 10% for higher or lower weight patients, with no observed clinical impact [Population PK/PD Model].

5.3. Pharmacodynamic (PD) properties in Humans

The PD properties of cangrelor can be summarized as follows:

- Cangrelor provides potent, direct-acting $P2Y_{12}$ antagonism. The PD profile is consistent with the underlying PK profile, with dose-related $P2Y_{12}$ inhibition achieved within minutes of starting the infusion, maintained at plateau during infusion and declining rapidly upon cessation of infusion at all dose levels [SC-931-5014, SC-931-5036,TMC-CAN-04-02, SC-931-5058, SC-931-5129 Part 1].
- At doses used for specific clinical settings (for example, PCI or BRIDGE), platelet reactivity, measured ex vivo using a range of techniques, is maintained below levels that provide evidence of effective $P2Y_{12}$ inhibition and are associated with reduced risk of thrombotic events.

- Cangrelor has a rapid offset of action, with platelet function restored within 60 minutes of cessation of infusion, as assessed by recovery of platelet responses measured ex vivo [TMC-CAN-04-02].
- The PD profile is consistent among various platelet function assays. The extent of $P2Y_{12}$ inhibition and the onset, on-infusion (maintenance, consistency) and offset characteristics of cangrelor are demonstrated by a range of PD assessments including aggregometry (light transmittance and whole blood impedance), the Verify*Now*® P2Y12 assay, and flow cytometry [for example, TMC-CAN-04-02, TMC-CAN-05-02-S1/TMC-CAN-05-03-S1, Transition I and II].
- There was no evidence for increased (rebound) platelet reactivity following cessation of cangrelor infusion at tested doses (up to 4 µg/kg/min) [SC-931-5014, SC-931-5036, SC-931-5109, SC-931-5129 Part 2, TMC-CAN-04-02].

5.4. Studies establishing and confirming the dose regimen for PCI

As a competitive, reversible $P2Y_{12}$ antagonist, the clinically effective concentration (dose) of cangrelor is partly a function of patient factors, thrombotic stimulus and associated ADP concentration present in a particular environment.

Patients with ACS (with or without ST-segment elevation) undergoing PCI may have an active thrombotic process before the procedure. However, vessel injury as a result of the PCI itself can induce thrombosis even in stable patients. In the PCI setting the priority is to achieve an immediate high level of $P2Y_{12}$ inhibition and reduced platelet reactivity that is maintained during the peri-procedural period, in all patients regardless of demographic factors, co-morbid conditions, or presentation.

Consistent with this objective, the dosing regimen selected for PCI is a 30 µg/kg IV bolus followed by a 4 µg/kg/min IV infusion for 2 hours to 4 hours. The key study leading to this selection was a Phase I study, TMC-CAN-04-02 (Groups A and B), supported by results from the earlier Phase II studies in ACS [SC-931-5058, SC-931-5060)] and PCI [SC-931-5129 Part 1, SC-931-5129 Part 2]. Collectively, these studies established that this dose regimen could achieve the immediate, substantial and maintained $P2Y_{12}$ inhibition required in the PCI setting (Table 1).

Table 1: Summary of studies establishing and confirming the dose regimen for cangrelor in the PCI indication

Study	Population; N Total (N cangrelor)	Objective	Design (*Platelet Function Test*)	Cangrelor Dose Regimen; Duration	Key PK/PD Findings
Infusion only dosing					
SC-931-5058	Patients with UA/non-Q-MI; 39 (39)	To investigate safety, tolerability, PD and PK for infusion up to 72h, identify dose that resulted in 100% inhibition in 90% of patients	5 center, 3 part open-label study using a stepped dose titration followed by a plateau infusion (*WBIA*)	Parts 1,2: 0.05, 0.2, 0.5, 2 µg/kg/min IV infusion; Part 3: 0.2, 1, 2, 4 µg /kg /min IV; 24-72 h	ADP-induced aggregation effectively abolished by 2 and 4 µg/kg/min doses Inhibition was rapidly reversible, with platelet function restored in most patients <1 h after stopping the infusion, Rapid decline in cangrelor plasma levels after stopping infusion, evident within 20 min. The PK profile was unaffected by changes in either infusion rate or duration (up to 72 h): Clearance is high: CL 44.3 L/h (inter-individual variability 14.4%);with a low initial volume of distribution (5.1 L)
SC-931-5060	Patients with UA/non-Q-MI; 91 (45)	To investigate safety, tolerability and PK, for infusion up to 72h	8-center, double-blind, placebo-controlled study (*None*)	4 µg/kg/min IV infusion; 72 h	Consistent plasma concentrations of cangrelor maintained on-infusion and were not affected by the longer duration of infusion (72 h). Population mean CL 41.0 ± 1.6 (SE) L/h (inter-individual variability 22.1%)
SC-931-5129 Part 1	Patients undergoing PCI; 200 (149)	To investigate safety, tolerability, PK, platelet aggregation, outcomes, and bleeding with 3 doses of cangrelor	25- center, double-blind, placebo-controlled pilot study (*WBIA*)	1, 2, and 4 µg/kg/min IV infusion; 18-24 h	Platelet inhibition was maximal within 15 min of infusion start, maintained during infusion and returned to baseline <15 min of stop in all groups, except for those receiving 4 µg/kg/min, (recovered by the next time point assessed at 24 h). Mean inhibition of aggregation before end of infusion was 13%, 94%, 87%, and 99% for placebo, 1, 2, and 4 µg/kg/min groups
SC-931-5129 Part 2	Patients undergoing PCI with ≥1 lesion with >60% stenosis; 199 (105)	To investigate safety, platelet aggregation and bleeding (no PK assessment)	17-center, open-label, abciximab controlled pilot study (*WBIA*)	4 µg/kg/min IV infusion; 18-24h	Mean platelet inhibition was 100% before the end of infusion for both cangrelor and abciximab groups for 95% and 100% of patients, respectively. At 12-24 h post infusion, platelet responses returned to baseline in patients who received cangrelor, whereas there was persistent inhibition in those who had received abciximab.

Study	Population; N Total (N cangrelor)	Objective	Design (*Platelet Function Test*)	Cangrelor Dose Regimen; Duration	Key PK/PD Findings
Bolus plus Infusion Dosing					
TMC-CAN-04-02 (Groups A & B)	Healthy volunteers; 22 (22)	To investigate safety, tolerability, PD and PK of two bolus plus infusion dosing regimens (A & B)	Single-center, randomized, four-arm, open-label study (*WBIA, Flow Cytometry*)	A: 15 µg/kg bolus + 2 µg/kg/min IV infusion; 1h B: 30 µg/kg bolus +4 µg/kg/min IV infusion; 1h	Immediate onset (~2 min) of maximal platelet inhibitory effect Steady state plasma level attained in ~10 min after IV bolus+ infusion. Cangrelor PK was linear between the two doses tested. Inhibition was complete (100%) and sustained during the infusion. Cangrelor eliminated with a $T_{1/2}$ of ~3 min: CL 42.5 (A) and 43.9 (B) L/h; initial volume of distribution 3.6 (A) and 3.9 (B) L Antiplatelet activity disappeared rapidly after discontinuation of infusion with almost complete reversal of platelet activity in ~1 h after the end of infusion.

CL = plasma clearance; h = hour; IV = intravenous; L = liter; min = minutes;
non-Q-MI = non-Q-wave myocardial infarction; PCI = percutaneous transluminal intervention;
PD = pharmacodynamic; PK = pharmacokinetic; SE = standard error; $T_{1/2}$ = half-life; UA = unstable angina;
µg = microgram; WBIA = whole blood impedance aggregometry.

The key points from the Phase 1 and 2 studies related to dose selection were as follows:

- Phase 1 studies with volunteers established that there was a consistent response to cangrelor across gender, age and renally impaired subjects
- Phase 2 studies conducted with a range of infusion doses in patients with ACS with or without PCI found the highest levels of inhibition of platelet aggregation (assessed by whole blood impedance aggregometry, WBIA) with the 2 and 4 µg/kg/min infusion doses
- The 4 µg/kg/min dose produced the maximal level of inhibition of platelet aggregation
- In studies that included clinical outcome measures for ischemic events, cardiac biomarkers, and bleeding, all doses were generally well tolerated, with no statistical differences (although with very small numbers) among dose groups

In keeping with the objective of attaining an immediate PK/PD effect, a Phase I study was then conducted to evaluate a matched bolus with each of the 2 and 4 µg/kg/min infusion doses.

5.4.1. Study [TMC-CAN-04-02] Groups A and B

This study demonstrated immediate onset of PD effect with both the IV bolus of 15 µg/kg + 2 µg/kg/min infusion combination (n=12) or with the IV 30 µg/kg bolus + 4 µg/kg/min infusion

combination (n=10), a linear dose response, and maintenance of consistent platelet inhibition during IV infusion with rapid offset of effect following cessation of the 1h infusion.

Consistent and complete inhibition of platelet responsiveness to ADP, as measured by whole blood impedance aggregometry (WBIA), was achieved immediately (within 2 minutes) after bolus administration for both doses.

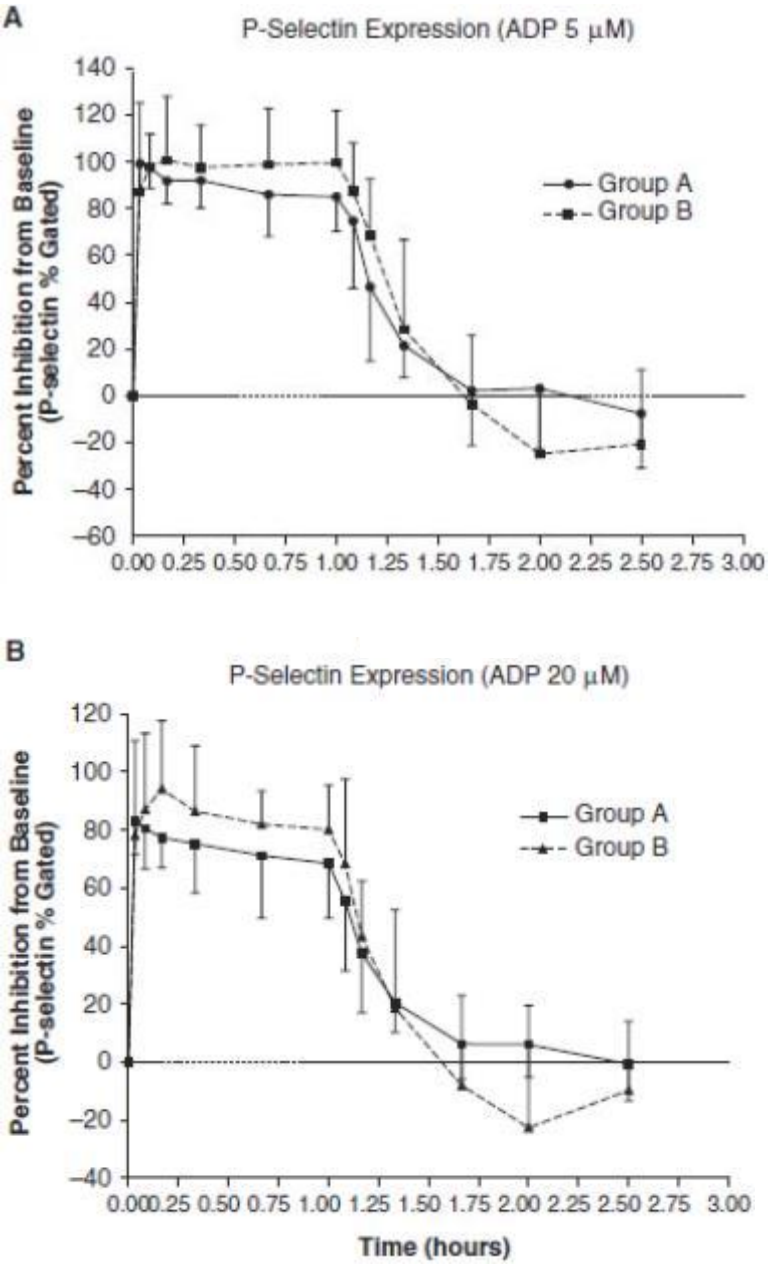
Cangrelor plasma concentration reached steady state at 10 minutes. The PK profile was linear and dose-proportional. Steady state was maintained for the duration of the infusion and dropped off rapidly when the infusion was discontinued. Platelet responsiveness recovered by 50% within 10 to 30 minutes of stopping the infusion, with full recovery in most subjects approximately 60 minutes after infusion cessation. The PK data from this study were consistent with data from the other Phase I studies [SC-931-5014, SC-931-5036] and confirm that rapid functional recovery of platelet function following cessation of cangrelor infusion reflects the rapid decline in circulating concentrations.

Both doses produced near maximal platelet inhibition as determined by WBIA. However, flow cytometric assessment of P-selectin expression with flow cytometry, which reflects the earlier step of platelet activation allowed better discrimination between the pharmacodynamic effect of the two doses.

Accordingly, cangrelor inhibited 5 μM ADP-induced P-selectin expression by 85% ± 15% and 100% ± 22% in the low- and high-dose cangrelor arms, respectively, following a 1-hour infusion ($P < .05$) (Figure 3, Panel A). Using a higher ADP concentration (20 μM), cangrelor inhibited P-selectin expression by 68% ± 19% and 80% ± 15% in the low- and high-dose treatment (Figure 3, Panel B).

Therefore, with no safety concerns raised in the Phase 2 studies, with infusion durations of up to 72 hours, the higher dose of 30-μg/kg bolus + 4-μg/kg/ min infusion that resulted in the maximal extent of inhibition with lowest variability among patients was selected for study in Phase 3. To provide IV $P2Y_{12}$ inhibition for the average duration of PCI plus some additional post-procedural coverage before transition to oral $P2Y_{12}$ inhibition, the duration of infusion was specified as a minimum of 2 hours, up to 4 hours for the PCI setting.

Figure 3: Effect of cangrelor on agonist-induced platelet activation by flow cytometry. Inhibition of P-selectin expression in response to ADP

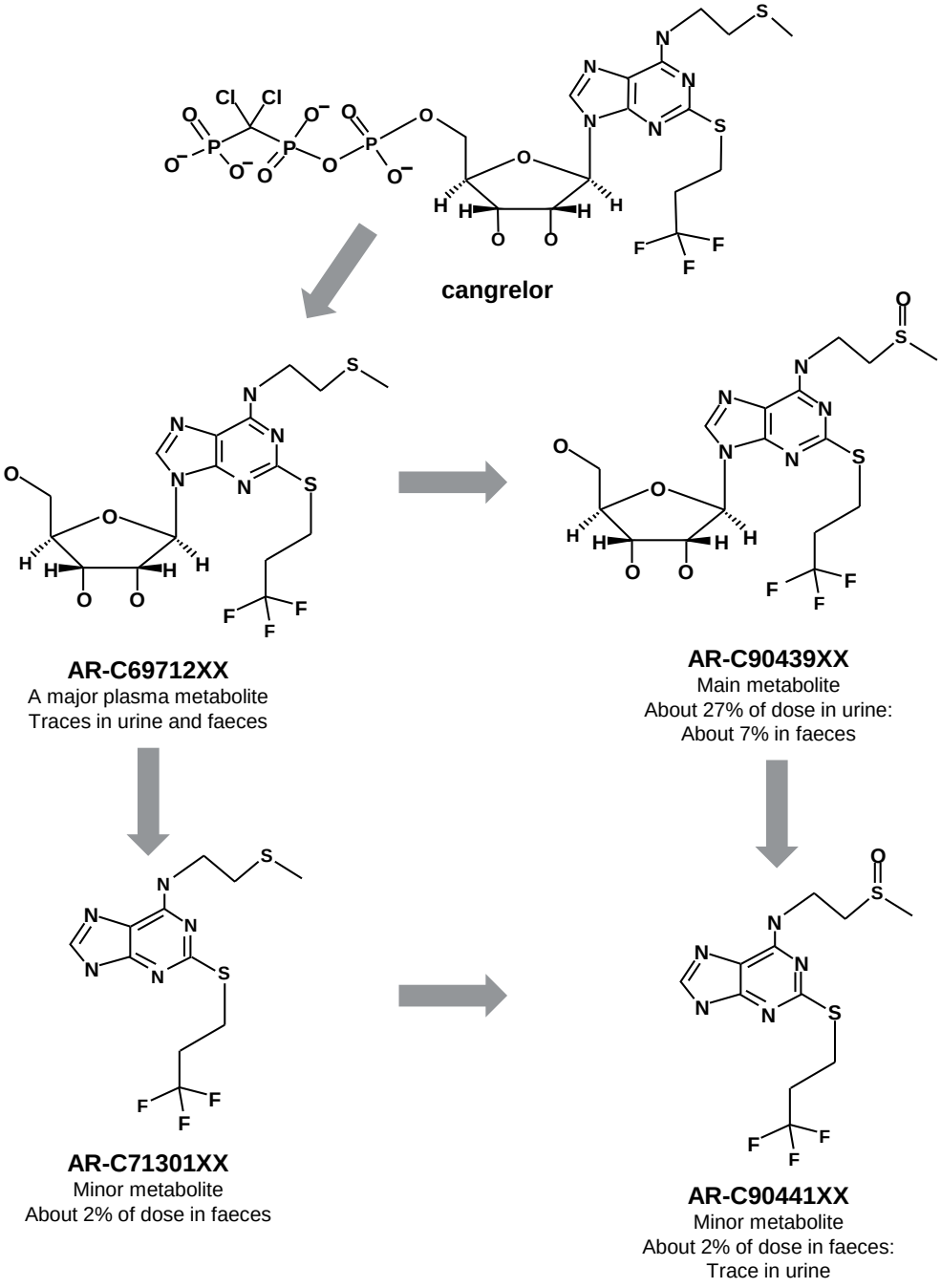


5.4.2. Studies supporting and explaining the observed clinical PK/PD profile of cangrelor

Collectively, these studies [SC-931-9017, SC-100199, SC-102050] demonstrated that the short half-life of cangrelor is explained by rapid inactivation in the circulation (by a dephosphorylation step) to a nucleoside metabolite, AR-C69712XX, which is over 70,000-fold less potent than cangrelor at the human $P2Y_{12}$ receptor. This explains cangrelor's highly predictable pharmacodynamic behavior across all populations (healthy volunteers and patients) studied.

The primary metabolite (AR-C69712XX) reached a maximum concentration (C_{max}) of 65 ng eq AR-C69931XX/mL (26% of AR-C69931XX C_{max}), and remained below the concentration achieved by the parent compound until after the end of infusion. A diagram presenting the postulated routes of metabolism of cangrelor is given in Figure 4.

Figure 4: Postulated major routes of metabolism of AR-C69931MX



Source: SC-931-9017 data on file, Figure 10.

5.4.3. Studies evaluating transition strategies from cangrelor to oral $P2Y_{12}$ inhibitors

These studies were designed to determine how to transition from $P2Y_{12}$ inhibition with cangrelor during the acute peri-procedural period to post procedural maintenance $P2Y_{12}$ inhibition with clopidogrel, ticagrelor or prasugrel. In each case, a strategy was identified that enabled patients to transition from cangrelor to the oral $P2Y_{12}$ inhibitor with continuation of the antiplatelet effect. The results of these studies indicate transition dosing strategies as summarized below:

- *Transition from cangrelor to clopidogrel:* Administer a 600 mg loading dose of clopidogrel immediately following discontinuation of the cangrelor infusion (TMC-CAN-04-02).
- *Transition from cangrelor to ticagrelor*: Administer a 180 mg loading dose of ticagrelor during or immediately following discontinuation of the cangrelor infusion (TRANSITION I).
- *Transition from cangrelor to prasugrel*: Administer a 60 mg loading dose at the end of the cangrelor infusion, or optimally, 30 minutes before the end of the cangrelor infusion (TRANSITION II).

5.5. Studies exploring potential for drug-drug interactions and PK/PD variability in specific subpopulations

As described previously, cangrelor is rapidly inactivated in the circulation by dephosphorylation to a nucleoside metabolite, AR-C69712XX. The rapidity of loss of circulating parent drug and the metabolite profile is highly consistent with the initial dephosphorylation step being through ectonucleotidase activity in the blood vessel wall [Robson et al, 2006], and so independent of organ (eg, hepatic/renal) function. Based on the highly specific initial metabolic step for cangrelor, there was a low expectation of significant interaction with "typical" metabolic processes. Nevertheless, standard assessments of potential for inhibition or induction of cytochrome P450 isoenzyme systems by cangrelor or its metabolites were conducted.

The overall conclusion from these in vitro and clinical studies [SC-102858, 300739180, 300736967, SC-931-5037, SC-931-5109, SE 10009], is that cangrelor does not have significant clinical drug-drug interaction potential and that its PK/PD profile is maintained in specific subpopulations.

5.6. Effect of cangrelor at the therapeutic and supratherapeutic dose levels on the QT/QTc interval in healthy volunteers

The TMC-CAN-08-01 study demonstrated that cangrelor does not affect cardiac repolarization, even at a supratherapeutic dose.

An initial phase established the safety of a supratherapeutic dose of cangrelor (60 µg/kg IV bolus plus 8 µg/kg/min IV infusion for 3 hours) in 6 healthy volunteers. In the main phase, 71 subjects were treated in a 4-way crossover design: all receiving cangrelor at therapeutic (30 µg/kg IV

bolus plus 4 µg/kg/min of IV infusion for 3 hours plus) and supratherapeutic (60 µg/kg IV bolus plus 8 µg/kg/min IV infusion for 3 hours) doses.

Based on assessment of individual corrected QT, individual corrected QT interval of the electrocardiogram (QTcI), Fridericia corrected QT, Fridericia corrected QT interval of the electrocardiogram (QTcF), and ECG morphology analysis, it was concluded that neither therapeutic nor supratherapeutic doses of cangrelor affected cardiac repolarization or ECG morphology.

5.7. Conclusions

The Clinical Pharmacology program supports the use of cangrelor in the proposed indications. Cangrelor was specifically designed as a direct-acting, reversible antagonist of the $P2Y_{12}$ receptor.

In the PCI setting, the priority is to achieve an immediate high level of $P2Y_{12}$ inhibition and reduced platelet reactivity that is maintained during the periprocedural period in an environment of vessel injury with prothrombotic stimulus and resultant ADP production, and this is achieved using the IV bolus (30 µg/kg) + IV infusion (4 µg/kg/min) regimen.

Finally, with regard to treatment pathways and continuum of patient care, individual study data and PK/PD modeling indicate that patients can be transitioned from oral $P2Y_{12}$ inhibition to IV cangrelor and vice versa without interruption of $P2Y_{12}$ inhibition.

6. PIVOTAL TRIALS

6.1. Trials establishing efficacy and safety

CHAMPION PHOENIX is the pivotal study of the efficacy of cangrelor in the PCI setting and provides evidence of the efficacy and safety of cangrelor as a clinically important therapeutic option for the contemporary management of patients who require $P2Y_{12}$ inhibition in an acute setting.

The Phase 3 Program encompassed 25,107 patients with CAD in three clinical trials, (CHAMPION PHOENIX (n=11,145), CHAMPION PLATFORM (n=5364) and CHAMPION PCI (n=8884)) and when pooled provides supportive evidence of the safety of cangrelor. The design characteristics of the three studies are described below.

Table 2: Three randomized controlled trials provide evidence of efficacy and safety

Study	Patient Population	N (mITT)	Cangrelor Dose	Dose duration	Comparator	Efficacy Endpoint
CHAMPION PHOENIX	ACS/CAD undergoing PCI	10942	30 µg/kg bolus 4 µg/kg/min	2-4 h	Clopidogrel 600 mg or 300 mg[a]	48 h Death/MI/IDR/ ST
CHAMPION PLATFORM	ACS/CAD undergoing PCI	5301	30 µg/kg bolus 4 µg/kg/min	2-4 h	Clopidogrel 600 mg[b]	48 h Death/MI/IDR
CHAMPION PCI	ACS/CAD undergoing PCI	8667	30 µg/kg bolus 4 µg/kg/min	2-4 h	Clopidogrel 600 mg[c]	48 h Death/MI/IDR

Source: Data on file PLATFORM: Table 1.1 and Table 3.1.2.3; Data on file PCI Table.1.1 and Table 3.1.2.1; Data on file PHOENIX: Table.1.1 and Table 3.1.2.1

ACS = acute coronary syndrome. CAD = coronary artery disease. ITT = intent-to-treat. kg = kilograms. PCI = percutaneous coronary intervention. min = minutes. µg = micrograms.

[a]Clopidogrel loading dose (or matching placebo) was administered as directed by the investigator. At the time of patient randomisation, a clopidogrel loading dose of 600 mg or 300 mg was specified by the investigator.

[b]All patients randomised to the comparator arm received clopidogrel 600 mg following PCI.

[c]All patients randomized to the comparator arm received clopidogrel 600 mg at the time of PCI.

6.1.1. Design of pivotal clinical studies

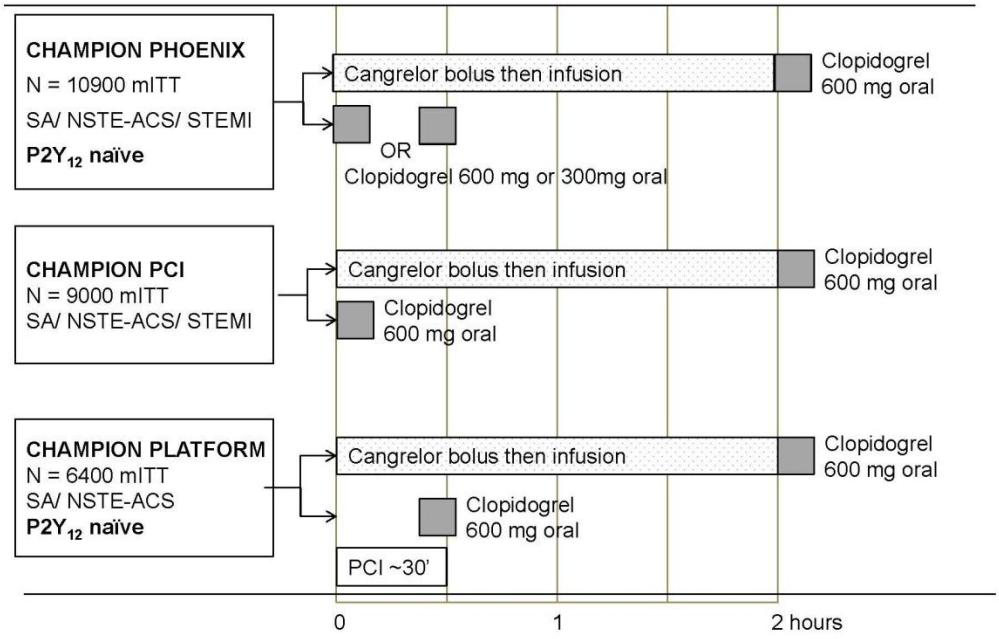
6.1.1.1. CHAMPION program

The CHAMPION trials were designed to demonstrate that IV $P2Y_{12}$ inhibition with cangrelor at the time of PCI reduces thrombotic events, including stent thrombosis.

The CHAMPION trials were three randomized (1:1), double-blind, double-dummy trials designed to test whether cangrelor (30 µg/kg bolus, 4 µg/kg/min infusion for 2 to 4 hours) at the time of PCI followed by transition to oral clopidogrel is superior to oral clopidogrel (300 or 600 mg) at reducing thrombotic events during and immediately after PCI. The CHAMPION trial

designs are presented in Figure 5. The three Phase 3 CHAMPION trials were very similar in design, and they form the basis of the safety and efficacy claims for cangrelor. All three trials were double-blind, double-dummy, and randomized. Therefore, all patients received an IV and an oral study drug. In all trials, IV study drug was administered as a bolus (30 μg/kg of cangrelor or matching placebo), followed by an infusion (4 μg/kg per minute of cangrelor or matching placebo). The bolus and infusion were to be administered as soon as possible following randomization after confirmation of suitable anatomy in patients with stable angina or NSTE-ACS. In patients with STEMI, IV study drugs could be administered before the coronary anatomy was known. The infusion was to be continued for ≥2 hours or until the conclusion of the index PCI, whichever was longer. At the end of the infusion, patients in the cangrelor arm received 600 mg of clopidogrel. A comparison of the design features among the three CHAMPION trials is provided in Table 3. The comparator arm differed in the three studies. In CHAMPION-PCI clopidogrel was given at the time of PCI; in CHAMPION-PLATFORM clopidogrel 600 mg was given at the end of PCI; and in CHAMPION-PHOENIX clopidogrel 300 mg or 600 mg, as by site standard of care, was to be administered either before or immediately after PCI.

Figure 5: CHAMPION: study designs



SA = stable angina. NSTE-ACS = non-ST segment elevation acute coronary syndrome. STEMI = ST-segment elevation myocardial infarction. PCI = percutaneous coronary intervention. mITT = modified intent-to-treat.

After 98.7% of patients were enrolled in CHAMPION PCI and 84% of patients in CHAMPION PLATFORM, the trials were terminated early following the PLATFORM 70% interim analysis,

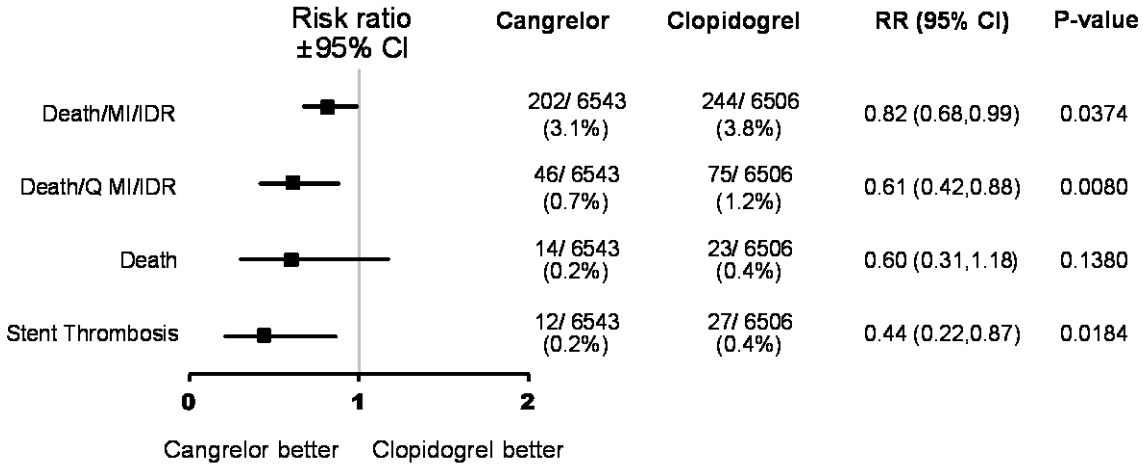
due to a low likelihood of reaching the primary efficacy endpoint per pre-specified stopping rules. No safety issues were identified that contributed to the decision of study discontinuation.

The primary objective of these two trials was not met. Incidence of the protocol-defined primary efficacy endpoint, defined as the composite of Death/MI/IDR, was not significantly reduced in cangrelor treated patients (CHAMPION PLATFORM: 7.0% cangrelor vs. 8.0% clopidogrel mITT patients; OR: 0.87, 95% CI: 0.71, 1.07; p=0.1746; CHAMPION PCI: 7.5% vs. 7.1%; OR: 1.05, 95% CI: 0.88, 1.24; p=0.5929).

An analysis of the efficacy components within the 14,000 patient dataset studied in these two double-blind, randomized trials suggested signs of cangrelor efficacy, including reductions in the incidence of thrombotic events such as ST, Q-wave MI (QMI) and IDR. (CHAMPION PLATFORM: 69% reduction in ST, 50% reduction in QMI, 21% reduction in IDR; CHAMPION PCI: 37% reduction in ST, 60% reduction in QMI, 44% reduction in IDR). However similar sized reductions with cangrelor were not observed on the endpoint of peri-procedural MI (8% reduction in CHAMPION PLATFORM and 9% increase in CHAMPION PCI).

These findings led to the hypothesis of methodological failure in measurement of peri-procedural MI. The protocol definition of MI was not sufficiently specific to differentiate between evolving pre-procedural biomarker MIs (especially as only one baseline biomarker sample was collected) and MI events that developed during PCI, when the study drug could have an effect. A post hoc analysis using the universal definition of MI (UDMI), published in 2007, to ascertain the occurrence of PCI-MI in the composite efficacy endpoints allowed exploration of study data without the potentially confounding influence of evolving pre-procedural biomarker MIs. Results using the UDMI definition presented in Figure 6 demonstrate that cangrelor reduced (18% significant reduction) the composite of death, UDMI, and IDR at 48 hours compared to clopidogrel 600 mg in a pooled analysis of both trials [White et al, 2012].

Figure 6: Post-hoc analysis of cangrelor efficacy from CHAMPION PCI & CHAMPION PLATFORM using UDMI



Systematic application of the same post hoc analysis to each trial demonstrated similar findings (CHAMPION PLATFORM: 28% statistically significant reduction in death/UDMI/IDR; CHAMPION PCI: 11% statistically non-significant reduction). These findings led to the hypothesis that the definition of peri-procedural MI used in CHAMPION PCI and CHAMPION PLATFORM was not specific enough, especially in patients with evolving MI at baseline, to differentiate between MI events that occurred prior to study randomization and MI events that developed after randomization, when the study drug could have had an effect.

6.1.1.2. Pivotal Clinical Trial for Efficacy

CHAMPION PHOENIX (implemented from 2010 to 2013) was designed to address the methodological issues identified in the prior CHAMPION trials. CHAMPION PHOENIX applied contemporary endpoint definitions for MI and stent thrombosis that had not been published at the time of CHAMPION PCI and CHAMPION PLATFORM study design [Cutlip et al, 2007; Thygesen et al, 2007; Leonardi et al, 2012].

The definition of MI used in the CHAMPION PHOENIX trial followed the universal definition published in 2007, which provides additional rigor to the assessment of PCI-MI due to a reliance on clinical features including ECG findings, elevated biomarkers, and imaging to recognize MI, as determined by clinical events committee (CEC) adjudication [Leonardi et al, 2012]. Compared to the earlier CHAMPION trials, PHOENIX used more restrictive criteria to define peri-procedural MI in patients for whom baseline MI could not be excluded. The CHAMPION PHOENIX trial was designed with these criteria to avoid confounding peri-procedural MIs with evolving pre-procedural MIs in patients with elevated biomarkers. The definition of peri-procedural MI in the CHAMPION PHOENIX trial required assessment of patients' baseline biomarker status. In patients with elevated biomarkers at presentation, only MIs that could clearly be discerned as a complication of the PCI and occurred post-randomization, according to the UDMI, were included as PCI-related MI endpoints.

Stent thrombosis was a key secondary endpoint in the CHAMPION PHOENIX trial and was defined to measure events that occurred during and after procedure. Post-procedure stent thrombosis was defined according to the ARC consensus criteria intended for standardized use and interpretability across clinical trials [Cutlip et al, 2007]. Intra-procedural ST (IPST) was defined as any procedural new or worsened thrombus related to the stent, and was included as an expansion of the ARC stent thrombosis definition in order to measure events that occur during the procedure when an IV $P2Y_{12}$ inhibitor could have greatest effect [Brener et al, 2013].

The use of an angiographic core lab for review of all patient index procedure and revascularization angiography films allowed objective determination of intra-procedural complications. CEC adjudication of cardiovascular mortality, MI, IDR, and stent thrombosis also provided objectivity as part of the study design.

All clinical events in the CHAMPION PHOENIX trial were adjudicated by the Clinical Events Classification (CEC) committee at DCRI according to the CEC Charter for the study.

The CHAMPION PHOENIX trial was completed with a total enrollment of 11,145 patients with SA, NSTE-ACS, or STEMI undergoing PCI.

Table 3: Comparison of design features of the CHAMPION studies

	CHAMPION PCI/PLATFORM	CHAMPION PHOENIX
Patient population	• 70% Tn elevated at baseline • Prior Clopidogrel maintenance (PCI only) • PCI required w/ following: STEMI: safety only (PCI) NSTEMI: Tn elevated UA: ECG changes & pain & age/diabetes Stable angina: capped (15%)	• Assume 35% Tn elevated at baseline • P2Y12 inhibitor naive • PCI required w/ following: STEMI NSTE-ACS: defined as UA and NSTEMI Stable angina
Comparator	600 mg clopidogrel • PCI: Load before PCI start • PLATFORM: Load after PCI start	300 mg or 600 mg (per hospital practice) • PHOENIX: Load before or after PCI start per physician
Efficacy endpoint	Primary: Death/MI/IDR at 48 hours	Primary: Death/MI/IDR/ST at 48 hours Key Secondary: ST at 48 h
Safety endpoint	Bleeding Events at 48 hours AEs and SAEs at 48 hours Death at 30 days and 1 year	Bleeding Events at 48 hours AEs and SAEs at 48 hours Death at 30 days
MI definition	• Not UDMI: reliance on cardiac markers alone to define PCI MI ○ 1 baseline sample ○ Biomarker normal at baseline: MI defined as CK-MB ≥3x ULN post PCI ○ Biomarker elevated at baseline: elevation in CK-MB ≥3x ULN & 50% increase from baseline sample or ECG changes	• UDMI implemented: reliance on cardiac markers & other evidence of ischemia to define PCI MI ○ 2 baseline samples at least 6 hours apart required in NSTE-ACS patients to confirm resolving MI at baseline ○ Baseline normal patients: MI defined as CK-MB ≥3x ULN post PCI ○ Baseline abnormal patients were classified as MI increasing or decreasing: ○ Increasing: re-elevation in CK-MB post PCI (≥3xULN & 50% increase from baseline) + additional evidence of ischemia (2 of 2): ECG changes AND angiographic evidence ○ Decreasing: re-elevation in CK-MB post PCI (≥3xULN & 50% increase from baseline) + additional evidence of ischemia (1 of 3): ischemic symptoms,

	CHAMPION PCI/PLATFORM	CHAMPION PHOENIX
		ECG changes or angiographic evidence
Stent thrombosis definition	Non-standard definition in IDR patients but confirmed by CEC using angiographic source data.	ARC definition in patients IPST = any *procedural* new or worsened thrombus related to the stent based on angiographic evidence
Statistics	Event rate placebo: 7.7%; Effect size: 23-25%	*Assumed* Event rate placebo: 5.1%; *Assumed* Effect size: 24.5%
Status	Terminated early due to low likelihood of meeting primary efficacy endpoint; CHAMPION PCI: 98% complete (N=8882); CHAMPION PLATFORM: 84% complete (N=5364)	Conducted and completed as planned (N=11145)

Sources: Bhatt 2009; Harrington 2009; White 2012; Bhatt 2013; Leonardi 2012

Tn=Troponin. PCI = percutaneous coronary intervention. STEMI = ST segment elevation myocardial infarction. NSTEMI = non-ST-segment elevation myocardial infarction. UA = unstable angina. ECG = electrocardiogram. NSTE-ACS = non ST- elevation acute coronary syndrome. MI = myocardial infarction. IDR = ischemia-driven revascularization. ST = stent thrombosis. UDMI = universal definition of myocardial infarction. CK-MB = creatine phosphokinase - myocardial band. ULN = upper limit of normal. ARC = Academic Research Consortium. IPST = intra-procedural stent thrombosis. CEC = Clinical Events Committee. AE=adverse event. SAE= serious adverse event.

6.1.2. Control groups

6.1.2.1. Active comparator dose

High (loading) dose clopidogrel (600 mg or 300 mg) was the control therapy in the CHAMPION program that incorporated a double-blind, double-dummy design. At the time of the PHOENIX study start (September 2010); only clopidogrel and prasugrel had marketing authorizations in the USA. In addition, prasugrel, as well as ticagrelor are only approved for use in ACS patients. International Medical Statistics (IMS) data on the usage of oral $P2Y_{12}$ inhibitors for 2012 and 2013 are presented in Table 4, demonstrating that clopidogrel remains the most commonly used oral $P2Y_{12}$ inhibitor in US practice.

Table 4: Use of oral $P2Y_{12}$ inhibitors

	Full year 2012 * (% share of all tablets)	YTD Sep 2013 * (% share of all tablets)
Clopidogrel	92.1%	90.0%
Prasugrel	6.1%	6.3%
Ticagrelor	1.7%	3.7%

* IMS data.

In CHAMPION PHOENIX, oral clopidogrel was to be administered immediately before or immediately after PCI as a 600-mg or 300-mg loading dose after patient randomization into the trial, per investigator discretion. In the CHAMPION PCI and CHAMPION PLATFORM trials, cangrelor was compared to a clopidogrel loading dose of 600 mg administered either immediately before (CHAMPION PCI) or after (CHAMPION PLATFORM) PCI.

Placebo in IV and oral form and double-dummy techniques were employed to ensure study blinding. The administration of placebo in both treatment arms was ethically acceptable and not considered a burden for the patient that would outweigh the advantage of a double-blind study. IV placebo was reconstituted and administered as bolus and infusion in the same way as IV cangrelor study drug.

Oral clopidogrel represents the current standard of care and the most commonly used agent worldwide for patients with ACS undergoing PCI. The approved loading dose of clopidogrel was 300 mg through the course of the CHAMPION program and remains 300 mg [Plavix US Package Insert, 2011; Plavix SmPC, 2013]. However, multiple guidelines for PCI recommend a 600 mg loading dose for clopidogrel [Bassand et al, 2007; Kushner et al, 2009; Van de Werf et al, 2008]. The CHAMPION PCI and CHAMPION PLATFORM studies were designed to compare cangrelor to a clopidogrel loading dose of 600 mg.

Following the implementation of the CHAMPION PCI and PLATFORM trials, evidence from a large randomized trial did not establish the optimal loading dose for clopidogrel [CURRENT-OASIS 7 Investigators, 2010]. For this reason, the CHAMPION PHOENIX trial was designed to allow administration of either 600 mg or 300 mg as a loading dose for clopidogrel at the investigator's discretion. Based on a widespread preference for 600 mg among interventional cardiologists and medical centers as standard practice during the course of the trial, it was anticipated that most patients would receive 600 mg.

6.1.2.2. Active comparator timing of administration

In the CHAMPION program, the timing of treatment with $P2Y_{12}$ inhibition was dependent on first delineating coronary anatomy through diagnostic angiography and confirming suitability for PCI. An initial diagnostic angiogram was required for all except STEMI patients in the trial population. The purpose of this step was to ensure the study subject did not have coronary anatomy requiring CABG surgery, which is reported to occur in approximately 10% of patients with ACS [Stone et al, 2004]. This is a reality of practice at many centers, where the concern is not to administer oral clopidogrel to patients who might proceed to CABG due to the high risk of surgical bleeding known to be associated with oral $P2Y_{12}$ inhibitors when taken at the time of surgery. Pre-loading with clopidogrel, or other oral $P2Y_{12}$ inhibitors prior to angiography creates a dilemma in patients who require surgery: stop treatment for the recommended 5 to 7 days and risk thrombosis, or continue treatment and risk bleeding.

The CHAMPION trials were aligned with US and EU guidelines in place at the time of trial design. The CHAMPION trial population included all patients undergoing PCI, including SA,

NSTE-ACS and STEMI. Guidelines specify different approaches that are appropriate in different patient populations. At the time of the CHAMPION PHOENIX trial design the following guidelines were in effect:

- ACC (American College of Cardiology) /AHA (American Heart Association) – Focused Updates for STEMI and PCI [Kushner et al, 2009]:
  - Clopidogrel or prasugrel after the patient is selected for invasive management, before or at the time of PCI; 600 mg clopidogrel preferred, prasugrel included; this does not apply to SA patients
- ESC – NSTE- ACS [Bassand et al, 2007]
  - For all patients, an immediate 300 mg loading dose of clopidogrel is recommended, followed by 75 mg clopidogrel daily (I-A).
  - In patients considered for an invasive procedure/PCI, a loading dose of 600 mg of clopidogrel may be used to achieve more rapid inhibition of platelet function (IIa-B).

Furthermore, the trial designs were aligned with clinical practice at institutions who want to wait until the anatomy is known before treating with $P2Y_{12}$ inhibitors. In the USA, the contemporary National Cardiovascular Data Registry (NCDR) reporting in 2013 showed that only approximately 24% of NSTEMI patients who presented in the Emergency Department between June 2007 and June 2010 received a pre-treatment with thienopyridine in the Emergency Department within 24 hours prior to intervention [Diercks et al, 2013].

The likely reasons for $P2Y_{12}$ administration after the anatomy is known may include that recent and emerging clinical data suggest that pretreatment confers an increased risk of bleeding with little benefit (PRAGUE-8; ARMYDA 5; ACCOAST) [Widimský et al, 2008; Di Sciascio et al, 2010; Montalescot et al, 2013], practicality in management of ACS patients with fast times to the catheter laboratory, reduced bioavailability of oral $P2Y_{12}$ inhibitors in ACS patients [Parodi et al, 2013; Alexopoulos et al, 2012], and potential for delays to CABG in ~10% of patients with ACS if loaded before the anatomy is known [Ebrahimi et al, 2009].

6.1.2.3. Cangrelor

Cangrelor was administered as an IV bolus and infusion (30 µg/kg bolus, 4 µg/kg/min infusion) for a minimum of 2 hours and up to 4 hours. All cangrelor patients in the PCI setting were transitioned to chronic $P2Y_{12}$ inhibition with oral clopidogrel 600mg immediately following discontinuation of cangrelor infusion followed by daily maintenance with oral clopidogrel 75 mg.

Any patient who received either a bolus or infusion was categorized as receiving the IV study drug. The exposure data are summarized by treatment group for the following variables (Table 43, Appendix 4):

- Number of patients who received cangrelor
- Bolus dose (µg) and weight-adjusted bolus dose (µg/kg)
- Infusion dose (µg) and weight-adjusted infusion dose rate (µg/kg/min)

- Overall infusion duration (time between start of initial infusion and permanent stop)
- Total cangrelor dose (mg)

6.1.3. Efficacy endpoints

6.1.3.1. Thrombotic events as a measure of efficacy

Thrombotic events including mortality, MI, IDR, and ST are objective and clinically meaningful measures of efficacy that are relevant in the PCI setting.

In CHAMPION PHOENIX, mortality, ST, IDR, and MI were adjudicated by an independent CEC through 30 days after randomization.

All-cause mortality

Mortality was adjudicated for cardiovascular cause of death by the CEC in CHAMPION PHOENIX. Mortality data through 1 year were collected for the CHAMPION PCI and CHAMPION PLATFORM trials only. Mortality as reported by the site within each study is included in this Briefing Book.

Myocardial infarction

Myocardial infarction in CHAMPION PHOENIX was defined according to the Universal Definition of MI published in 2007, which relies on clinical features including ECG findings, elevated biomarkers and imaging to recognize MI. To assess PCI-related MI (Type 4a), this definition requires assessment of patients' baseline status that was determined based on a combination of troponin samples as well as ischemic symptoms and electrocardiogram (ECG) changes to be baseline normal, abnormal, or unknown. For patients with normal baseline status, MI after PCI is easy to measure (defined as a creatine phosphokinase - myocardial band [CK-MB] mass ≥3x upper limit of normal [ULN]). For patients determined to be baseline abnormal (ie, baseline MI confirmed or cannot be excluded), more restrictive criteria to define MI after PCI are required (defined by a combination of CKMB re-elevation with supportive evidence of ischemia including ECG changes, angiographic evidence, and ischemic symptoms). These criteria are more restrictive than those published in Standardized Definitions for End Point Events in Cardiovascular Trials DRAFT October 20, 2010.

48-hour PCI-MI was not assessed in STEMI patients. Only MI as defined per protocol in CHAMPION PHOENIX and as ascertained retrospectively based on adjudicated results from CHAMPION PLATFORM and CHAMPION PCI using the UDMI definition was included in the integrated efficacy analysis. Specifically, in CHAMPION PLATFORM and CHAMPION PCI, new or recurrent MIs as adjudicated by the CEC were considered to meet the Universal Definition of MI when the patient had normal baseline or unknown baseline troponin levels. If baseline troponin levels were abnormal, only Q-wave MIs were considered as UDMI.

Ischemia-driven revascularization

IDR was collected at *48 hours and 30 days* in all three CHAMPION trials. IDR was adjudicated by the CEC using pre-specified, detailed criteria for determining the presence of ischemia and the types of procedures qualifying as revascularizations due to ischemia. The incidence of IDR was reviewed and adjudicated by the CEC through 48 hours and 30 days.

Stent thrombosis

Stent thrombosis at 48 hours was a key secondary endpoint in the CHAMPION PHOENIX trial and was defined to measure events that occurred during and after procedure, when an IV $P2Y_{12}$ inhibitor could have the greatest effect. Post-procedure stent thrombosis was defined according to the Academic Research Consortium (ARC) consensus criteria intended for standardized use and interpretability across clinical trials [Cutlip et al, 2007]. Intra-procedural ST (IPST) was defined as any procedural new or worsened thrombus related to the stent, and was included as an expansion of the ARC ST definition in order to measure intra-procedural events that have been demonstrated to be clinically important and associated with subsequent out-of-lab ST and mortality [Généreux et al, 2013; Brener et al, 2013; Harrison et al, 2013; Pride et al, 2012]. The use of a blinded angiographic core lab for review of all patient index procedure and revascularization angiography films allowed consistent and objective determination of procedural complications related to ST.

In the CHAMPION PLATFORM and PCI studies, ST was only assessed in patients with IDR. Data for ST as adjudicated at 48 hours and 30 days within each study are included in this Briefing Book.

6.1.4. Safety endpoints

6.1.4.1. Hemorrhagic events as a measure of safety

Bleeding events were reported as endpoints in the CHAMPION PHOENIX trial. The GUSTO bleeding scale was selected as the primary safety bleeding analysis scale due to its widespread clinical acceptability and established predictive correlation with adverse clinical outcomes [The GUSTO Investigators 1993; Rao 2006]. Other bleeding scales were derived based on data reported by investigators, including TIMI, BARC, and ACUITY. Bleeding events were reported as endpoints in CHAMPION PHOENIX according to different bleeding scales as described in Appendix 2.

To enable a thorough and systematic evaluation of bleeding all bleeding events, data was collected and reported on a dedicated bleeding page in the CRF as shown in Appendix 3. This included documentation of clinical overtness, the site of the bleeding event as well as transfusion and supporting laboratory data including hemoglobin and hematocrit. The specifically designed bleeding CRF page allowed identification of individual bleed terms that could be readily used to derive common bleeding scales.

Hemoglobin and hematocrit levels were reported on the bleeding CRF page and categorized according to their maximum drop. We relied on the sites to enter relevant hematology data pertinent to a given bleed using the bleeding CRF page. Prospectively defined in the Statistical Analysis Plan, these data were used in the determination of bleeding events according to different bleeding scales. Additional laboratory data including hemoglobin and hematocrit were also reported by sites but were not pre-specified to be used for bleeding analysis. For group level summary across sites, laboratory data were standardized to the conventional units and normalized to a reference normal range. For individual patient laboratory value changes over time, non-normalized laboratory data was to be used as a change from baseline for a given patient and does not need to be modified by a normalization factor.

Transfusion data were also collected for each blood product and this information was used to adjust the hemoglobin and hematocrit drop values as described in Appendix 2. Thus, common bleeding scales were derived based on data reported on the bleeding page on the CRF by investigators. Any bleeding events that in the opinion of the investigator met the criteria for "requiring intervention" or "clinically overt" were also reported on the bleeding page and applied to ascertain bleeding event rates according to specific scales as documented in Appendix 2.

7. PATIENT POPULATION

The CHAMPION studies included patients with CAD who required $P2Y_{12}$ inhibition in an acute setting.

The study populations evaluated in the three CHAMPION studies included patients with CAD, from SA to ACS who required $P2Y_{12}$ inhibition in the PCI setting.

Patients exposed to cangrelor were representative of patients with CAD. The population exhibited commonly expected risk characteristics in relation to acuity of presentation and comorbidities such as diabetes mellitus, history of hypertension, history of previous PCI, and advanced age.

7.1. Demographic and baseline characteristics

A comparison of patient demographic characteristics, baseline medical history, and prior oral $P2Y_{12}$ therapy for CHAMPION PHOENIX and the three pooled CHAMPION study populations are provided in Table 5.

The PCI population (ITT) studied in the CHAMPION trials covered the spectrum of CAD including SA (31%), NSTE-ACS (57%), and STEMI (12%). At baseline, 50% of the CHAMPION Pooled patient population had at least one troponin sample >ULN suggesting an MI was ongoing or resolving before the PCI. The mean age was 63 years: 45% of patients were ≥65 years old, most were male (72%) and white (86%). Comorbidities common among patients with CAD, at frequencies typical of a general PCI population, were observed. Overall, 30% of patients presented with diabetes mellitus, 76% had a history of hypertension, and 65% of hyperlipidemia, and 23% had a history of previous MI. Twenty-three percent (23%) of patients had a history of previous PCI/stent and 12% were being treated with oral $P2Y_{12}$ inhibitor therapy prior to PCI.

Demographic and baseline characteristics were generally similar in all 3 CHAMPION trials. However, the proportion of SA patients (56%) was higher in the CHAMPION PHOENIX trial. The proportion of SA patients (56%) was higher in the CHAMPION PHOENIX trial compared to the CHAMPION Pooled population. This was a result of the trial design that included patients in whom endpoints such as procedural MI can be more accurately measured. CHAMPION PCI was the only one of the CHAMPION trials that allowed enrollment of patients receiving long term oral $P2Y_{12}$ therapy for ST prevention following stent placement, which comprised 37% of the population. Detailed baseline and demographic characteristics for patients in the CHAMPION PHOENIX and CHAMPION Pooled datasets are presented as follows in Table 5, Table 6 and Table 7.

Table 5: Summary of selected baseline characteristics for pivotal efficacy and safety datasets

	PCI setting			
	CHAMPION PHOENIX[a]		CHAMPION Pooled [a]	
Variable Statistic/ Category	**Cangrelor (N=5581)**	**Clopidogrel (N=5564)**	**Cangrelor (N=12707)**	**Clopidogrel (N=12677)**
Male sex, n (%)	3982 (71.3)	4042 (72.6)	9195 (72.4)	9128 (72.0)
Median age (years)	64.0	64.0	63.0	63.0
≥65 years, n (%)	2689 (48.2)	2662 (47.8)	5800 (45.6)	5743 (45.3)
Race, n (%)				
White	5231 (93.8)	5206 (93.7)	10,928 (86.0)	10,856 (85.6)
Asian	173 (3.1)	177 (3.2)	966 (7.6)	966 (7.6)
Black/African American	156 (2.8)	152 (2.7)	451 (3.5)	464 (3.7)
Other	18 (0.3)	22 (0.3)	345 (2.7)	372 (2.9)
Unknown (missing data)	3 (0.1)	7 (0.1)	17 (0.1)	19 (0.1)
Patient types, n (%) [b]				
SA	3158 (56.6)	3059 (55.0)	3971 (31.3)	3866 (30.5)
NSTE-ACS	1401 (25.1)	1424 (25.6)	7227 (56.9)	7221 (57.0)
STEMI	1022 (18.3)	1081 (19.4)	1509 (11.9)	1590 (12.5)
Troponin I/T >ULN	1885/5534 (34.1)	1947/5520 (35.3)	5895/11809 (49.9)	5987/11759 (50.9)

Sources: CHAMPION PHOENIX data on file, Table 2.1.2.1, Table 2.2.2.1 and Table 1.1; CHAMPION pooled data on file, Table 16.2.1.2.1, Table 16.2.2.2.1 and Table 16.2.3.2.1.

[a] ITT population.

[b] As determined by statistical analysis, taking into account clinical study data available after time of randomization.

SA= stable angina; NSTE-ACS = non-ST-elevation acute coronary syndrome; STEMI = ST-segment elevation myocardial infarction; ULN = upper limit of normal; PCI = percutaneous coronary intervention; ITT = intent-to-treat.

Table 6: Summary of selected medical history for pivotal efficacy and safety datasets

	PCI setting			
	CHAMPION PHOENIX[a]		CHAMPION Pooled[a]	
	Cangrelor (N=5581)	Clopidogrel (N=5564)	Cangrelor (N=12707)	Clopidogrel (N=12677)
Diabetes mellitus	1546/5571 (27.8)	1559/5555 (28.1)	3724/12694 (29.3)	3779/12661 (29.8)
Current smoker	1533/5444 (28.2)	1573/5428 (29.0)	3630/12502 (29.0)	3662/12487 (29.3)
Hypertension	4460/5566 (80.1)	4406/5546 (79.4)	9635/12663 (76.1)	9524/12623 (75.4)
Hyperlipidemia	3412/4942 (69.0)	3380/4908 (68.9)	7579/11694 (64.8)	7504/11641 (64.5)
Cerebrovascular event	276/5559 (5.0)	252/5543 (4.5)	661/12655 (5.2)	639/12625 (5.1)
Family history of CAD	2121/5214 (40.7)	2108/5195 (40.6)	4882/11757 (41.5)	4882/11722 (41.6)
Previous MI	1111/5547 (20.0)	1191/5517 (21.6)	2831/12589 (22.5)	2963/12561 (23.6)
Previous PTCA/PCI	1281/5569 (23.0)	1344/5550 (24.2)	2928/12670 (23.1)	3016/12637 (23.9)
Previous CABG	581/5574 (10.4)	509/5553 (9.2)	1341/12694 (10.6)	1284/12661 (10.1)
Congestive heart failure	565/5567 (10.1)	592/5546 (10.7)	1108/12640 (8.8)	1122/12613 (8.9)
Peripheral artery disease	449/5513 (8.1)	390/5509 (7.1)	898/12498 (7.2)	848/12479 (6.8)

Sources: CHAMPION PHOENIX data on file, Table 2.3.2.1; CHAMPION pooled data on file, Table 16.2.3.2.1;
[a] ITT population.
CAD = coronary artery disease; CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention; PTCA = percutaneous transluminal coronary angioplasty; MI = myocardial infarction; ITT = intent-to-treat.

Table 7: Summary of prior oral $P2Y_{12}$ therapy for pivotal efficacy and safety datasets

Variable Statistic/ Category	PCI setting			
	CHAMPION PHOENIX[a]		CHAMPION Pooled[a]	
	Cangrelor (N=5581)	Clopidogrel (N=5564)	Cangrelor (N=12565)	Clopidogrel (N=12542)
Oral $P2Y_{12}$ therapy received, n/N (%)	NA	NA	1501 (11.9)	1495 (11.9)
Clopidogrel	NA	NA	1495 (11.9)	1487 (11.9)
Prasugrel	NA	NA	NA	NA
Ticlopidine	NA	NA	6 (0.0)	8 (0.1)
Clopidogrel last dose, mg; n/N (%)				
75	NA	NA	1489/1495 (99.6)	1472/1487 (99.0)
>75	NA	NA	5/1495 (0.3)	12/1487 (0.8)

Sources: CHAMPION PHOENIX data on file, Table 3.4.2.1; CHAMPION pooled data on file, Table 16.3.4.2.1
[a] ITT population.
PCI = percutaneous coronary intervention; ITT = intent-to-treat; NA = not applicable.

7.2. Disposition of study participation

In the CHAMPION studies, the primary efficacy population was the mITT population, defined as all patients randomized into the trial who underwent the index PCI and received at least one dose of study drug. Treatment classification for the primary efficacy analyses was based on the randomized treatment.

The majority of patients randomized completed study participation. In CHAMPION PHOENIX, 1.5% of cangrelor-treated patients discontinued study participation at 30 days (Table 8). The incidence was the same in the clopidogrel group. In the CHAMPION PCI and CHAMPION PLATFORM trials patients were followed for 1 year to assess mortality. For this reason, the rate of study discontinuation is greater in the CHAMPION Pooled population. Across all CHAMPION trials, the number of 48-hour completers was 99.8% (Data on file, pooled analysis Table 16.1.2).

The most common reasons for discontinuing study participation were death, lost-to-follow-up, and patient withdrawal of consent.

Table 8: Patient disposition by treatment group

	PCI setting			
	CHAMPION PHOENIX		CHAMPION Pooled	
	Cangrelor (N=5581)	Clopidogrel (N=5564)	Cangrelor (N=12711)	Clopidogrel (N=12680)
Number of patients randomized	5581 (100.0)	5564 (100.0)	12711 (100.0)	12680 (100.0)
ITT population	5581 (100.0)	5564 (100.0)	12707 (100.0)	12677 (100.0)
mITT population	5472 (98.0)	5470 (98.3)	12475 (98.1)	12435 (98.1)
Safety population	5529 (99.1)	5527 (99.3)	12565 (98.9)	12542 (98.9)
Number of subjects completing study, n (%)	5498/5581 (98.5)	5482/5564 (98.5)	12289 (96.7)	12223 (96.4)
Number of subjects discontinued from study	83/5581 (1.5)	82/5564 (1.5)	422/12711 (3.3)	457/12680 (3.6)
Withdrew Consent	5/5581 (0.1)	7/5564 (0.1)	23/12711 (0.2	15/12680 (0.1)
Physician Discretion	1/5581 (0.0)	4/5564 (0.1)	4/12711 (0.0)	11/12680 (0.1)
Lost-to-Follow-up	10/5581 (0.2)	12/5564 (0.2)	73/12711 (0.6)	85/12680 (0.7)
Adverse Event	1/5581 (0.0)	0/5564 (0.0)	1/12711 (0.0)	0/12680 (0.0)
Death	64/5581 (1.1)	57/5564 (1.0)	304/12711 (2.4)	330/12680 (2.6)
Other	2/5581 (0.0)	2/5564 (0.0)	17/12711 (0.1)	16/12680 (0.1)

Sources: CHAMPION PHOENIX data on file, Table 1.0; CHAMPION Pooled data on file, Table 16.1.0; ITT = intent-to-treat. mITT = modified intent-to-treat. NA = not applicable. PCI = percutaneous coronary intervention.

7.3. Extent of study drug exposure

In the CHAMPION program, patients were randomized to $P2Y_{12}$ inhibition with IV cangrelor or oral clopidogrel at the time of PCI. After the anatomy was known, cangrelor (30 µg/kg bolus and 4 µg/kg/min infusion) was administered for a minimum of 2 hours and up to 4 hours per physician discretion. Patients in the cangrelor arm received a transition dose of clopidogrel 600mg immediately following cangrelor infusion. Patients in the comparator arm received a loading dose of clopidogrel (600 mg or 300 mg) and a placebo infusion to maintain the blind.

The extent of IV study drug administration for the CHAMPION PHOENIX and the CHAMPION pooled ITT populations are presented in Table 43, Appendix 4 and demonstrate good compliance with 99% of patients in both treatment groups receiving IV study drug per protocol (30µg/kg IV bolus followed by 4µg/kg/min IV infusion).

Similarly, the median duration of cangrelor infusion was in line with protocol requirements with most patients receiving an infusion for 2 to 4 hours. The median infusion duration administered in the CHAMPION pooled population was 125 minutes (2.1 hours). There was no difference in the median infusion duration tested in CHAMPION PHOENIX.

Cangrelor patients received a median total dose of 47.09 mg (CHAMPION PHOENIX) or 46.43 mg (CHAMPION pooled) over the infusion duration.

The extent of oral study drug administration for the CHAMPION PHOENIX and the CHAMPION pooled ITT populations are presented in Table 44, Appendix 5.

In the cangrelor group, the majority (greater than 99.8%) of patients received a transition dose of 600 mg clopidogrel at the end of the cangrelor infusion. For the majority of patients who did not receive the transition dose, the study medication was administered but was reported as not digested by the patient.

The CHAMPION PHOENIX trial was designed to allow administration of either 600 mg or 300 mg clopidogrel loading dose as active comparator. This was a change from the prior CHAMPION trials for which the active comparator was clopidogrel 600mg. The design change was based on the evidence from a large randomized trial that did not establish the optimal loading dose for clopidogrel [CURRENT-OASIS 7 Investigators, 2010]. Due to widespread preference for 600 mg among interventional cardiologists and medical centers as standard practice during the course of the trial, it was anticipated however that most patients would receive 600 mg.

In CHAMPION PHOENIX, 74% of patients in the clopidogrel group received a loading dose of clopidogrel 600 mg. Clopidogrel 300 mg was administered as loading dose to 26%. Within the CHAMPION PHOENIX patient population, 63% of clopidogrel patients received their loading dose before the start of PCI, defined as time of the guide wire insertion.

Overall in the CHAMPION pooled dataset, 88% of patients in the clopidogrel group received a loading dose of clopidogrel 600 mg which was received in 56% of patients before the start of PCI.

7.4. Procedural concomitant medications during cangrelor administration

Cangrelor has been co-administered with other anticoagulant and antiplatelet medications routinely administered to patients with CAD requiring PCI.

In the CHAMPION program, the medications administered during PCI were representative of common practice and balanced between treatment groups. Procedural anticoagulation is presented for the CHAMPION PHOENIX and the CHAMPION pooled ITT populations in Table 9, and GPIIb/IIIa inhibitor administration in Table 10.

For the CHAMPION pooled population, nearly all patients were reported to be treated with aspirin (94% cangrelor-treated patients, 93% clopidogrel-treated patients). Unfractionated heparin was the next most common concomitant anticoagulant medication administered (74% of patients for both treatment groups) followed by bivalirudin (25% for both treatment groups). Similar results were found for the CHAMPION PHOENIX trial population only.

GPIIb/IIIa inhibitors were co-administered in 13% of the PCI population (CHAMPION pooled), with eptifibatide being the most frequently administered in 9% of cases. Administration as bailout therapy, for new or persistent thrombus formation, slow or no reflow, side branch compromise, dissection, or distal embolization was significantly reduced in patients treated with cangrelor (2.6% vs 3.4% in clopidogrel patients, $p<0.001$; Table 10). The numerical increase in GPIIb/IIIa inhibitor bailout for clopidogrel-treated patients was based on more eptifibatide use, and suggests numerically fewer procedural complications leading to GPIIb/IIIa inhibitor bailout occurred in the cangrelor treatment group. Summarized CHAMPION PHOENIX results are also shown in Table 10, as a comparison.

Table 9: Prior or procedural anticoagulant medications for CHAMPION PHOENIX and CHAMPION Pooled (ITT population)

	CHAMPION PHOENIX		CHAMPION Pooled	
Parameter [a]	**Cangrelor (N=5581) n/N (%)**	**Clopidogrel (N=5564) n/N (%)**	**Cangrelor (N=12707) n/N (%)**	**Clopidogrel (N=12677) n/N (%)**
Aspirin	5267/5576 (94.5)	5234/5557 (94.2)	11913/12679 (94.0)	11810/12653 (93.3)
Unfractionated heparin	4346/5580 (77.9)	4336/5560 (78.0)	9368/12700 (73.8)	9346/12661 (73.8)
Bivalirudin	1278/5580 (22.9)	1291/5559 (23.2)	3182/12699 (25.1)	3226/12667 (25.5)
Low-molecular-weight heparin	744/5580 (13.3)	766/5559 (13.8)	2909/12693 (22.9)	2956/12658 (23.4)
Fondaparinux	158/5579 (2.8)	135/5561 (2.4)	283/12692 (2.2)	258/12660 (2.0)

Source: CHAMPION pooled data on file, Table 16.3.7.2.1; CHAMPION PHOENIX data on file, Table 3.7.2.1.
[a] Prior or procedural medications taken post-baseline and before or during the index procedure for the purpose of procedural anticoagulation.
ITT = intent-to-treat.

Table 10: Procedural GPIIb/IIIa inhibitor administration for CHAMPION PHOENIX and CHAMPION Pooled (ITT population)

	CHAMPION PHOENIX		CHAMPION Pooled	
Parameter	**Cangrelor (N=5581) n/N (%)**	**Clopidogrel (N=5564) n/N (%)**	**Cangrelor (N=12707) n/N (%)**	**Clopidogrel (N=12677) n/N (%)**
GPIIb/IIIa inhibitor Used	158/5580 (2.8)	230/5562 (4.1)	1566/12699 (12.3)	1660/12664 (13.1)
Eptifibatide	69/5580 (1.2)	125/5562 (2.2)	1079/12699 (8.5)	1166/12664 (9.2)
Abciximab	77/5580 (1.4)	78/5562 (1.4)	312/12699 (2.5)	310/12664 (2.4)
Tirofiban	10/5580 (0.2)	23/5562 (0.4)	171/12699 (1.3)	177/12664 (1.4)
GPIIb/IIIa inhibitor as bailout	129/5580 (2.3)	194/5562 (3.5)	329/12699 (2.6)	428/12664 (3.4)
Eptifibatide	57/5580 (1.0)	112/5562 (2.0)	139/12699 (1.1)	211/12664 (1.7)
Abciximab	63/5580 (1.1)	62/5562 (1.1)	119/12699 (0.9)	131/12664 (1.0)
Tirofiban	8/5580 (0.1)	18/5562 (0.3)	70/12699 (0.6)	83/12664 (0.7)

Source: CHAMPION pooled data on file, Table 16.3.6.2.1; CHAMPION PHOENIX data on file, Table 3.4.2.1.

ITT = intent-to-treat. GP = glycoprotein.

8. CLINICAL EFFICACY

The results of CHAMPION PHOENIX demonstrated that cangrelor compared to clopidogrel is effective when administered to patients undergoing PCI. At 48 hours, the CHAMPION PHOENIX trial demonstrated that, compared to clopidogrel, cangrelor provided:

- A significant reduction in the primary efficacy endpoint of all-cause mortality, MI, IDR and ST (4.7% vs 5.9%, respectively; OR, 0.79 [95% CI 0.66-0.93], p=0.005) which was maintained at 30 days (6.0% vs 7.0%, respectively; OR, 0.85 [95% CI 0.73-0.99], p=0.035)
- A significant reduction in ST (0.8% vs 1.4%, respectively; OR, 0.62 [95% CI 0.43-0.90], p=0.010)
- A significant reduction in MI (3.8% vs 4.7%, respectively; OR, 0.80 [95% CI 0.67-0.97], p=0.022)
- No difference in all-cause mortality (0.3% vs 0.3%, respectively; OR, 1.00 [95% CI 0.52,1.92], p>0.999)

8.1. PCI setting

In patients with CAD who require $P2Y_{12}$ inhibition in the PCI setting, cangrelor significantly reduced thrombotic events by providing effective and consistent $P2Y_{12}$ inhibition during infusion. In CHAMPION PHOENIX, a significant 22% reduction in the primary endpoint (death/MI/IDR/ST at 48 hours) was demonstrated in patients treated with cangrelor compared to clopidogrel (p=0.005). The efficacy results are presented in Table 11.

Table 11: Thrombotic events at 48 hours in CHAMPION PHOENIX (mITT population)

	Cangrelor N=5470 n (%)	Clopidogrel N=5469 n (%)	Cangrelor vs Clopidogrel	
			OR and 95% CI	p value [a] for OR
All-cause mortality/MI/IDR/ST [b]	257 (4.7)	322 (5.9)	0.78 (0.66, 0.93)	0.005
Stent thrombosis	46 (0.8)	74 (1.4)	0.62 (0.43, 0.90)	0.010
IPST	35 (0.6)	54 (1.0)	0.65 (0.42, 0.99)	0.043
All-cause mortality	18 (0.3)	18 (0.3)	1.00 (0.52, 1.92)	>0.999
MI	207 (3.8)	255 (4.7)	0.80 (0.67, 0.97)	0.02
IDR	28 (0.5)	38 (0.7)	0.74 (0.45, 1.20)	0.22
All-cause mortality/MI/ST	249 (4.6)	312 (5.7)	0.79 (0.66, 0.94)	0.006
All-cause mortality/MI	220 (4.0)	272 (5.0)	0.80 (0.67, 0.96)	0.016
All-cause mortality/MI/IDR	230 (4.2)	286 (5.2)	0.80 (0.67, 0.95)	0.012

Source: CHAMPION PHOENIX data on file, Tables 5.1.1.1 and 5.0.1.1.

[a] p values based on Chi-squared test.

[b] Adjusted analysis.

CI = confidence interval. IDR = ischemic-driven revascularization. MI = myocardial infarction. mITT = modified intent-to-treat. CEC = Clinical Events Committee. ST = stent thrombosis. OR = odds ratio.

8.1.1. Cangrelor reduced the risk of thrombotic events including stent thrombosis in CAD patients

The key secondary endpoint of ST at 48 hours, consisting of ARC definite ST or IPST as adjudicated by a blinded angiographic core laboratory, was also significantly reduced (38% RRR) in cangrelor treated patients. As shown in CHAMPION PHOENIX, cangrelor reduced both ARC ST and IPST components of the protocol definition of ST independently (Table 12). Importantly, when excluding IPST and using only ARC ST, the primary composite efficacy endpoint remains significant in favor of cangrelor-treated patients (4.2% vs. 5.2%; OR, 0.80 [95% CI 0.67-0.95] p=0.0115).

Table 12: Stent thrombosis events at 48 hours in CHAMPION PHOENIX (mITT population)

			Cangrelor vs Clopidogrel	
	Cangrelor N=5470 n (%)	Clopidogrel N=5469 n (%)	OR and 95% CI	p value [a] for OR
Protocol-defined ST [b]	46 (0.8)	74 (1.4)	0.62 (0.43, 0.90)	0.010
ARC ST only	12 (0.2)	22 (0.4)	0.54 (0.27, 1.10)	0.086
IPST only	35 (0.6)	54 (1.0)	0.65 (0.42, 0.99)	0.043

Source: CHAMPION PHOENIX data on file, Table 5.1.1.1

[a] p values based on Chi-squared test.

[b] One patient in the cangrelor arm and two in the clopidogrel arm had both ARC ST and IPST

CI = confidence interval. mITT = modified intent-to-treat. ST = stent thrombosis. OR = odds ratio.

The PHOENIX results confirm the findings demonstrated in published data that significant associations exist between IPST and clinical outcome. In CHAMPION PHOENIX, patients who experienced IPST at the time of index PCI had significantly increased incidence of thrombotic events at 48 hours. The significantly increased incidence of thrombotic events in patients with IPST was maintained at 30 days.

The 48-hour efficacy outcomes in patients with and without IPST are presented in Table 13. The risk of MACE events are significantly increased in patients with IPST during index PCI. The risk of death is increased 20-fold, the risk of ARC-ST 12-fold. Similar efficacy results were demonstrated at 30 days (Table 14). These data provide strong evidence of a significant association between IPST and clinical outcome and support the clinical relevance of the inclusion of IPST as a component of ST.

Table 13: 48-hour efficacy and safety outcomes in patients with and without IPST during index PCI

48 hour endpoint	IPST	Not IPST	RR (95% CI)	p value
Efficacy (mITT population)	(N=89)	(N=10,850 [a])		
Death/MI/IDR/ARC-ST	26 (29.2)	490 (4.5)	6.47 (4.63,9.04)	<0.0001
Death	5 (5.6)	31 (0.3)	19.66 (7.83,49.40)	<0.0001
ARC ST	3 (3.4)	31 (0.3)	11.80 (3.67,37.88)	<0.0001
IDR	4 (4.5)	62 (0.6)	7.87 (2.92,21.15)	<0.0001
MI	23 (25.8)	439 (4.0)	6.39 (4.44,9.19)	<0.0001

Source: Data on file PHOENIX, Tables 91.5.1.1.1, 91.6.1.4.1

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

Table 14: 30-day efficacy outcomes in patients with and without IPST during index PCI

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

Source: Data on file PHOENIX, Table 91.5.2.1.1

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

The PHOENIX data demonstrate that the significance of IPST as a predictor of clinical outcomes is statistically strong with robust clinical impact. Among patients experiencing definite ST by 48 hours and 30 days, 3/34 (8.8%) and 4/65 (6.2%), respectively, had an earlier IPST. Similarly, 84 of 89 patients with IPST did not experience ARC ST at 30 days, and 86 of 91 ARC ST did not have IPST, indicating little overlap between both outcomes [Généreux et al, 2013].

8.1.2. Cangrelor reduces the risk of thrombotic events including myocardial infarction in CAD patients

An analysis of the individual incidence of the components of the primary efficacy endpoint demonstrated a significant 20% reduction in the incidence of MI in cangrelor-treated patients compared to clopidogrel-treated patients (p=0.022), in addition to the significant reduction in stent thrombosis observed (38% RRR). Numerical reductions in IDR were consistent with these results but not statistically significant. The incidence of all-cause mortality (all of which were adjudicated as cardiovascular in cause) was the same (0.3%) between treatment groups.

Myocardial infarction in CHAMPION PHOENIX was defined according to the Universal Definition of MI published in 2007, which relies on clinical features including ECG findings, elevated biomarkers and imaging to recognize MI. The definition of MI in CHAMPION PHOENIX was an objective and appropriate definition predictive of adverse outcomes including

death at 48 hours [MI>3xULN, RR=4.5; MI>5xULN, RR=12.8; MI >10xULN, RR=22.1] and at 30-days [MI >3xULN, RR=3.9; MI >5xULN, RR= 8.1, MI>10xULN, RR=11.7]. A post-hoc analysis (Table 15) substituting the UDMI published in 2012 (which requires CK-MB re-elevation ≥ 5xULN in addition to clinical features in all patients) into the primary endpoint, demonstrated a significant 26% reduction in the incidence of these events in patients treated with cangrelor. A significant 30% reduction was observed when a re-elevation ≥ 10xULN in addition to clinical features was required.

Table 15: Post-hoc analysis of primary endpoint for large MI (mITT population)

			Cangrelor vs Clopidogrel	
	Cangrelor N=5470 n (%)	**Clopidogrel N=5469 n (%)**	**OR and 95% CI**	**p value [a] for OR**
PHOENIX primary endpoint[b]	257 (4.7)	322 (5.9)	0.78 (0.66, 0.93)	0.005
All-cause mortality/5xMI/IDR/ST	126 (2.3)	169 (3.1)	0.74 (0.59, 0.93)	0.011
All-cause mortality/10xMI/IDR/ST	96 (1.8)	136 (2.5)	0.70 (0.54, 0.91)	0.008

Source: CHAMPION PHOENIX data on file, Tables 5.1.1.1 and 5.0.1.1; Data on file.

[a] p values based on Chi-squared test.

[b] Adjusted analysis.

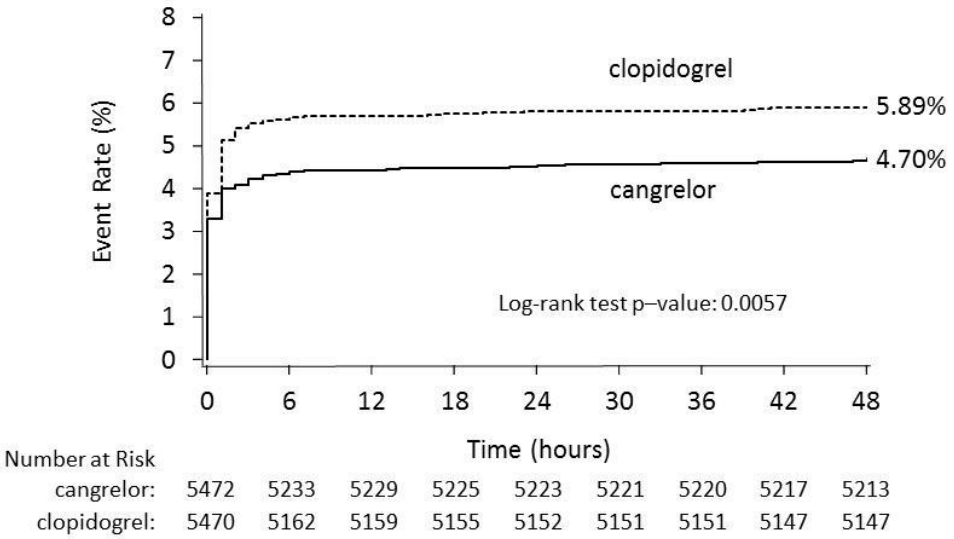
CI = confidence interval. IDR = ischemic-driven revascularization. MI = myocardial infarction. mITT = modified intent-to-treat. CEC = Clinical Events Committee. ST = stent thrombosis. OR = odds ratio.

8.1.3. The reduction in thrombotic events was observed early with cangrelor and was maintained through transition to oral $P2Y_{12}$ therapy

Cangrelor demonstrated early efficacy that is maintained through 48 hours.

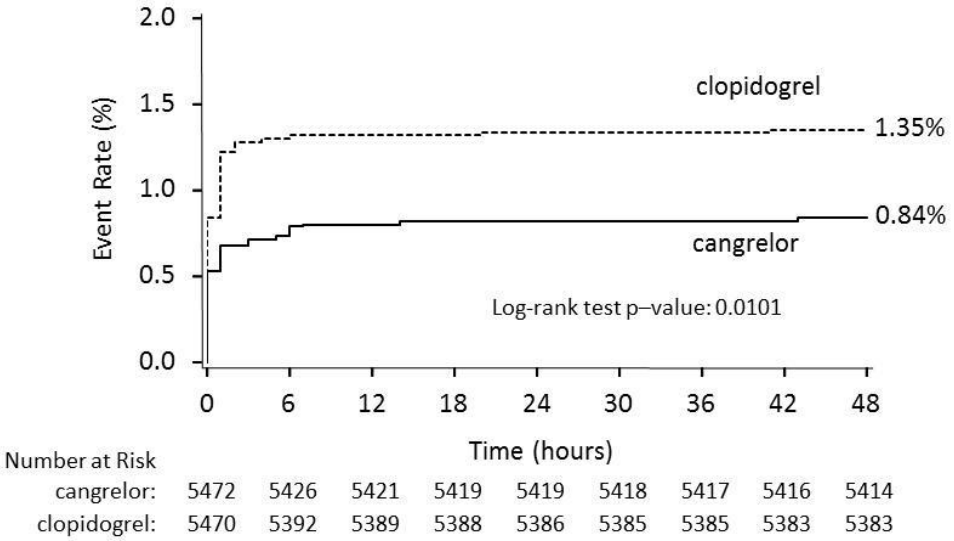
Kaplan-Meier curves for time to first occurrence of death/MI/IDR/ST (Figure 7) and ST (Figure 8) within 48 hours are displayed as follows for CHAMPION PHOENIX. Early separation of the curves within the initial hours after randomization demonstrated an early protective effect of cangrelor for both the composite efficacy endpoint (death/MI/IDR/ST) and ST.

Figure 7: Kaplan-Meier plot of time to first occurrence of death/MI/IDR/ST within 48 hours in the CHAMPION PHOENIX study (mITT population)



Source: CHAMPION PHOENIX data on file, Figure 5.11.1.1.
mITT = modified intent-to-treat. MI = myocardial infarction. IDR = ischemia-driven revascularization. ST = stent thrombosis.

Figure 8: Kaplan-Meier plot of time to first occurrence of ST within 48 hours in the CHAMPION PHOENIX study (mITT population)

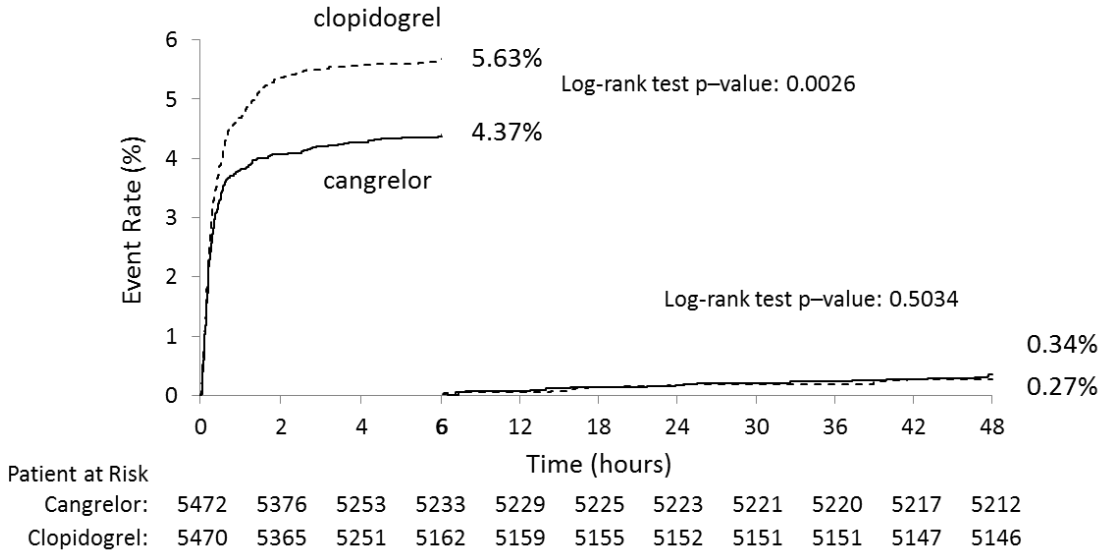


Source: CHAMPION PHOENIX data on file, Figure 5.51.1.1.
mITT = modified intent-to-treat.

Landmark analysis of CHAMPION PHOENIX was also performed for time to first occurrence of death/MI/IDR/ST (Figure 9) at six hours from randomization and the results are displayed below. The early protective effect of cangrelor increased over time and persisted for the first six

hours. The landmark analysis after six hours was to display incremental changes that may occur as patients are transitioned from IV to oral $P2Y_{12}$ therapy. As can be seen, there is no difference in risk between cangrelor and clopidogrel from 6 hours to 48 hours from randomization. This analysis confirms that there is no clinically meaningful gap in $P2Y_{12}$ inhibition with a transition from IV cangrelor to oral $P2Y_{12}$ inhibition.

Figure 9: Landmark analysis on first occurrence of death/MI/IDR/ST within 48 hours in CHAMPION PHOENIX (mITT population)



Source: Data on file, Figure 5.26.1.1.
MI = myocardial infarction. IDR = ischemia-driven revascularization. ST = stent thrombosis.

8.1.4. The reduction in thrombotic events in CHAMPION PHOENIX occurs irrespective of dose or timing of clopidogrel administration

Analysis of the primary endpoint by patient type and clopidogrel loading dose demonstrates that the primary endpoint is reduced in cangrelor-treated patients, irrespective of clopidogrel dose or timing of administration.

At the time of randomization in CHAMPION PHOENIX, on a patient-by-patient basis, a loading dose of 600 mg or 300 mg was specified by the investigator. Per protocol, administration of the double-blind oral medications occurred as soon as possible following randomization, either immediately before or immediately after PCI, per investigator discretion. Overall, the majority (74.4%) of modified intent-to-treat (mITT) patients were stratified to receive a loading dose of clopidogrel 600 mg. Of the 25.6% of patients specified to receive clopidogrel 300 mg, the majority were patients with SA [CHAMPION PHOENIX, data on file]. The majority of patients received clopidogrel 600 mg administered before PCI (38.6%). When administered, clopidogrel 300 mg was primarily given at the start of PCI (24.9%) vs. (0.9%) immediately after PCI [CHAMPION PHOENIX, data on file].

In the sub-group of patients who were assigned 600 mg clopidogrel, the composite incidence of death/MI/IDR/ST was significantly reduced in patients who received cangrelor compared with patients receiving clopidogrel 600 mg loading dose (4.3% vs 5.6%, respectively; OR, 0.77; CI: 0.63, 0.94; p=0.009). In addition, an exploratory analysis of the primary endpoint by patient type and clopidogrel loading dose demonstrated that the primary endpoint is reduced in all types of cangrelor-treated patients, irrespective of clopidogrel dose (Table 16) or timing of administration (Table 17).

Table 16: 48-hour composite efficacy endpoint based on CEC-adjudicated results, by clopidogrel loading dose and patient type (mITT)

	n (%) of patients			
Death/MI/IDR/ST	**Cangrelor**	**Clopidogrel**	**OR and 95% CI**	**p value [a]**
Stable angina patients	*(Placebo capsules)*			
600 mg	133/2473 (5.4)	166/2379 (7.0)	0.76 (0.60,0.96)	0.021
300 mg	48/647 (7.4)	56/639 (8.8)	0.83 (0.56,1.25)	0.377
NSTE-ACS patients	*(Placebo capsules)*			
600 mg	28/992 (2.8)	39/1033 (3.8)	0.74 (0.45,1.21)	0.231
300 mg	21/397 (5.3)	23/388 (5.9)	0.89 (0.48,1.63)	0.698
STEMI patients	*(Placebo capsules)*			
600 mg	15/600 (2.5)	22/656 (3.4)	0.74 (0.38, 1.44)	0.372
300 mg	12/361 (3.3)	16/374 (4.3)	0.77 (0.36,1.65)	0.499

Source: CHAMPION PHOENIX data on file, Table 9.101.1.1, Table 9.102.1.1, and Table 9.103.1.1.

Note: patients in the cangrelor treatment arm received placebo oral capsules *(Placebo capsules)* matching the clopidogrel 600 mg or 300 mg oral loading dose (given as pink capsules for both treatment arms).

CI = confidence interval. RR = relative risk. OR = odds ratio. mITT = modified intent-to-treat.
MI = myocardial infarction. ST = stent thrombosis. IDR = ischemia-driven revascularization.

Table 17: 48-hour composite efficacy endpoint based on CEC-adjudicated results, by clopidogrel loading dose and before or after PCI start (mITT)

	n (%) of patients			
Death/MI/IDR/ST	**Cangrelor**	**Clopidogrel**	**OR and 95% CI**	**p value [a]**
Patients receiving dose before PCI start	*(Placebo capsules)*			
600 mg	90/2105 (4.3)	113/2090 (5.4)	0.78 (0.59, 1.04)	0.088
300 mg	76/1355 (5.6)	92/1352 (6.8)	0.81 (0.59, 1.11)	0.197
Patients receiving dose after PCI start	*(Placebo capsules)*			
600 mg	81/1931 (4.2)	105/1947 (5.4)	0.77 (0.57, 1.03)	0.081
300 mg	5/49 (10.2)	3/49 (6.1)	1.74 (0.39, 7.73)	0.461

Source: CHAMPION PHOENIX data on file, Table 9.106.1.1 and Table 9.107.1.1.

a p value for the odds ratio comparing cangrelor versus clopidogrel.

Note: patients in the cangrelor treatment arm received placebo oral capsules *(Placebo capsules)* matching the clopidogrel 600 mg or 300 mg oral loading dose (given as pink capsules for both treatment arms).

CI = confidence interval. RR = relative risk. OR = odds ratio. mITT = modified intent-to-treat.
MI = myocardial infarction. ST = stent thrombosis. IDR = ischemia-driven revascularization.

8.1.5. Early reduction in thrombotic events is maintained at 30 days with cangrelor

Significant reductions in death/MI/IDR/ST and ST observed in the cangrelor group at 48 hours were maintained at 30 days. The results from the CHAMPION PHOENIX trial demonstrated similar efficacy at 30 days and are presented in Table 18.

In the CHAMPION PHOENIX study at 30 days, the incidence of death/MI/IDR/ST and ST remained significantly lower among cangrelor-treated patients than clopidogrel-treated patients (death/MI/IDR/ST: 15% significant reduction; ST: 32% significant reduction).

Other 30-day composite endpoints defined through different combinations of individual components were numerically consistent with 48-hour analysis, and/or showed no trends contrary to 48-hour efficacy findings.

Table 18: Incidence of thrombotic events at 30 days in CHAMPION PHOENIX (CEC-adjudicated results – mITT Population)

	n (%) of Patients		Cangrelor vs Clopidogrel	
Endpoint	**Cangrelor**	**Clopidogrel**	**OR (95% CI)**	**p value [a] for OR**
CHAMPION PHOENIX, N	5462	5457		
Death/MI/IDR/ST	326 (6.0)	380 (7.0)	0.85 (0.73, 0.99)	0.035
ST	71 (1.3)	104 (1.9)	0.68 (0.50, 0.92)	0.012
Death	60 (1.1)	55 (1.0)	1.09 (0.76, 1.58)	0.643
MI	225 (4.1)	272 (5.0)	0.82 (0.68, 0.98)	0.030
IDR	56 (1.0)	66 (1.2)	0.85 (0.59, 1.21)	0.360
Death/MI/IDR	300 (5.5)	342 (6.3)	0.87 (0.74, 1.02)	0.085
Death/MI/ST	303 (5.5)	359 (6.6)	0.83 (0.71, 0.98)	0.024
Death/MI	274 (5.0)	316 (5.8)	0.86 (0.73, 1.01)	0.074
Death/ST	110 (2.0)	134 (2.5)	0.82 (0.63, 1.05)	0.119

Sources: CHAMPION PHOENIX data on file, Table 5.2.1.1.

[a] p values based on Chi-squared test.

CI = confidence interval; IDR = ischemic-driven revascularization; MI = myocardial infarction; mITT = modified intent-to-treat; CEC = Clinical Events Committee; ST = stent thrombosis; OR = odds ratio; IDR = ischemia-driven revascularization.

8.1.6. Long-term effect on mortality

All-cause mortality data at one year were collected for the CHAMPION PCI and CHAMPION PLATFORM trials only. As summarized in Table 19, no statistically significant difference was noted.

Table 19: All-cause mortality at 1 year – CEC-adjudicated results in the CHAMPION pooled population (mITT population)

	n/N (%) of Patients		Cangrelor vs Clopidogrel	
Endpoint	**Cangrelor (N=12475)**	**Clopidogrel (N=12435)**	**OR (95% CI)**	**p value [a] for OR**
Death [b]	231/6925 (3.3)	256/6880 (3.7)	0.89 (0.75 -1.07)	0.220

Source: Data on file, Table 16.5.2.1.1.

[a] p values based on Chi-squared test.

[b] One-year mortality data from CHAMPION PCI and CHAMPION PLATFORM trials only.

Note: A patient who did not complete the scheduled follow-up and had no event was not counted in denominator.
CI = confidence interval. mITT = modified intent-to-treat. CEC = Clinical Events Committee. OR = odds ratio.

8.2. Comparison of results in subpopulations

Subgroup comparisons for all efficacy analyses were in general consistent with the outcomes for overall trial results.

8.2.1. Comparison of reductions on thrombotic events by subgroup

In subgroup analyses of the CHAMPION PHOENIX, cangrelor reduced the incidence of thrombotic events at 48 hours consistent with overall efficacy results in a variety of pre-defined subgroups.

Subgroup analysis of death/MI/IDR/ST at 48 hours was performed by pre-defined patient subgroups. Odds ratios and associated p values were calculated. Each factor used to define a subgroup was also statistically evaluated for interaction with the primary endpoint. Interaction p values were calculated using the Breslow-Day test. Subgroup analyses from CHAMPION PHOENIX are presented in Figure 10.

In the CHAMPION PHOENIX subgroup analysis, odds ratios for important subgroups consistently favored cangrelor efficacy, with many comparisons at the subgroup category level reaching significance (without adjustment for multiple comparisons). For subgroups based on sex (male or female), age (<75 or ≥75 years), and race (white or non-white), cangrelor efficacy was demonstrated. Cangrelor efficacy was also demonstrated consistently among patients presenting with SA, NSTE-ACS, and STEMI, and among patients with either 600 mg or 300 mg clopidogrel loading dose, or clopidogrel loading before or after PCI start. In patients presenting with SA; those loaded with 600 mg; and those receiving loading dose before PCI, cangrelor efficacy reached significance at the subgroup category level. The subgroups of patients within the US or in other countries showed similar benefit from cangrelor treatment effect (Figure 10).

Based on a p value of <0.05, no statistically significant interactions with baseline patient characteristics were observed for the patient factors analyzed, except for medical history of PAD (p=0.003) (Data on file, Table 9.73.1.1). However, subgroup analysis of a clinically related factor, medical history of smoking, showed no significance for interaction, p=0.992 (Data on file, Table 9.75.1.1).

Figure 10: Subgroup analysis of death/MI/IDR/ST at 48 hours (CHAMPION PHOENIX; mITT Population)

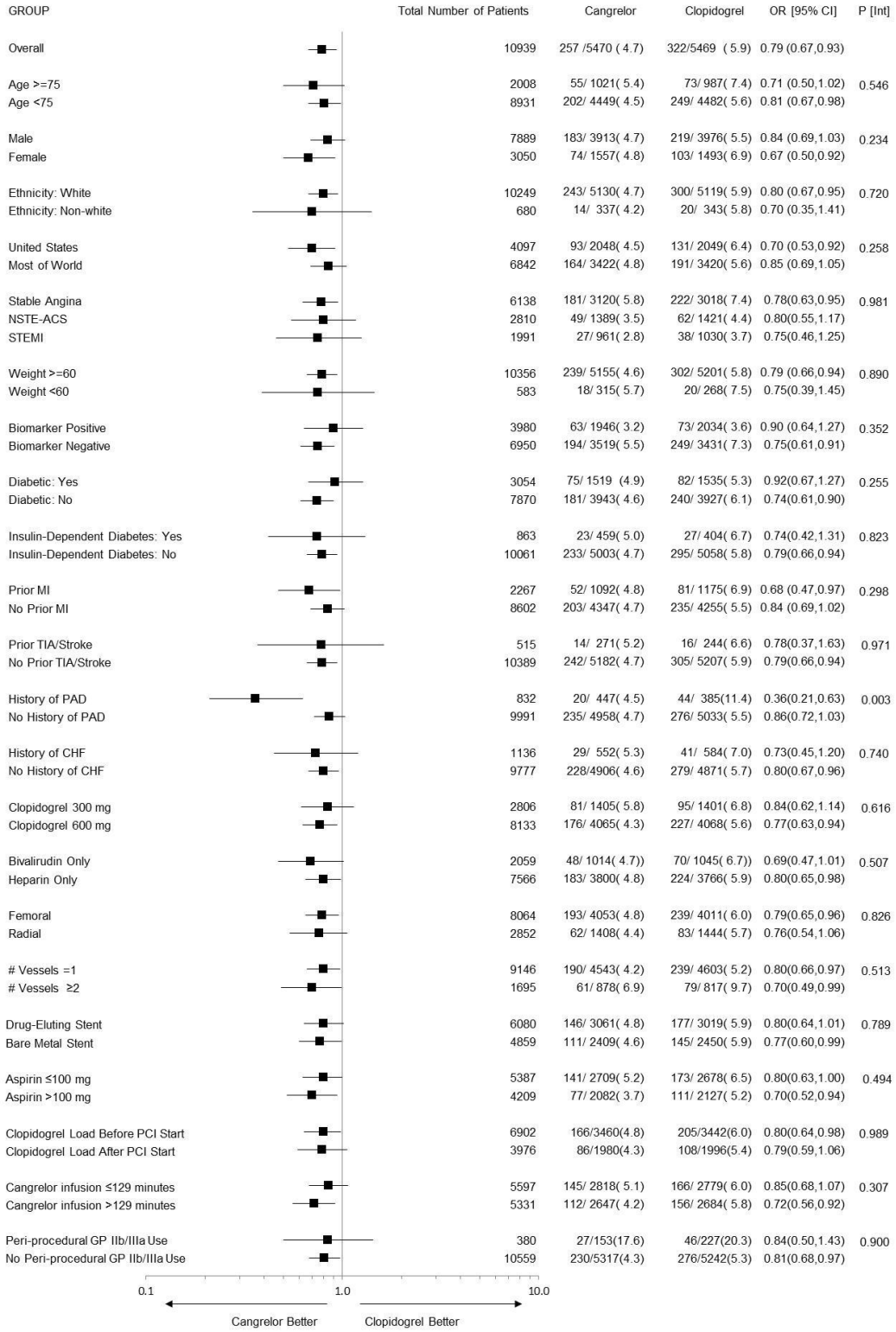


Figure 10 footnotes appear on the following page.

Figure 10 sources: Data on file, Table 5.1.1.1, Table 9.3.1.1, Table 9.5.1.1, Table 9.33.1.1, Table 9.7.1.1, Table 5.1.1.4, Table 5.1.1.5, Table 5.1.1.2, Table 9.39.1.1, Table 9.9.1.1, Table 9.17.1.1, Table 9.19.1.1, Table 9.27.1.1, Table 9.61.1.1, Table 9.73.1.1, Table 9.21.1.1, Table 5.0.1.1, Table 9.15.1.1, Table 9.71.1.1, Table 9.63.1.1, Table 9.25.1.1, Table 9.57.1.1, Table 9.51.1.1, Table 9.65.1.1, Table 9.55.1.1.

Figure 10 abbreviations: mITT = modified intent-to-treat; OR = odds ratio; CI = confidence interval; P[Int] = p value of interaction; ROW = rest of world; SA = stable angina; NSTE-ACS = non-ST elevation acute coronary syndrome; STEMI = ST segment elevation myocardial infarction; MI = myocardial infarction; IDR = ischemia driven revascularization; ST = stent thrombosis; TIA = transient ischemic attack; PAD = peripheral artery disease; CHF = congestive heart failure; GPIIb/IIIa = glycoprotein IIb/IIIa inhibitor; PCI = percutaneous coronary intervention.

9. CLINICAL SAFETY

In the CHAMPION PHOENIX study and in a large pooled dataset of 12,565 cangrelor-treated patients comprised of the three CHAMPION trials, cangrelor exhibited a favorable safety profile for the reduction of cardiovascular thrombotic events, including ST in patients with coronary artery disease, who require $P2Y_{12}$ inhibition in an acute setting.

As defined in the protocol, at 48 hours the CHAMPION PHOENIX study demonstrated that compared to clopidogrel, cangrelor provided:

- No statistical difference in non-CABG GUSTO severe/life-threatening bleeding (0.2% vs 0.1%, respectively; OR, 1.50 [95% CI 0.53-4.22], p=0.439) or GUSTO moderate bleeding (0.4% vs 0.2%, respectively; OR, 1.69 [95% CI 0.85-3.37], p=0.128)
- No statistical difference in transfusion (0.5% vs 0.3%, respectively; OR 1.56 [0.83-2.93], p=0.169)
- A significant increase in non-CABG ACUITY major bleeding (4.3% vs 2.5%, respectively; OR, 1.72 [95% CI 1.39-2.13], p=<0.001), driven by hematoma ≥5 cm
- A significant increase in non-CABG GUSTO mild (2.7% vs 1.6%, respectively; OR, 1.72 [95% CI 1.32-2.25], p=<0.001) and ACUITY minor bleeding (11.8% vs 8.6%, respectively; OR, 1.42 [95% CI 1.26-1.61], p=<0.001), driven by ecchymosis, puncture site oozing, and hematoma <5 cm

In CHAMPION PHOENIX, there were (2 vs. 4) bleeding related deaths within 30 days with cangrelor compared to clopidogrel and there were numerically more clinically important bleeding events of intracranial hemorrhage (3 vs. 2), cardiac tamponade (9 vs. 1), retroperitoneal bleeds (7 vs. 3) and gastrointestinal bleeds (16 vs. 10) among cangrelor-treated patients.

The CHAMPION pooled dataset, at 48 hours, demonstrated for cangrelor vs. clopidogrel respectively:

- No statistical difference in non-CABG GUSTO severe/life-threatening bleeding (0.2% vs 0.2%, respectively; OR, 1.22 [95% CI 0.70-2.11], p=0.488)
- No statistical difference in transfusion (0.7% vs 0.6%, respectively; OR 1.29 [0.94-1.76], p=0.115)
- A significant increase in non-CABG ACUITY major bleeding (4.2% vs. 2.8%, respectively; OR, 1.53 [95% CI 1.34-1.76], p=<0.001), driven by hematoma ≥5 cm
- A significant increase in non-CABG GUSTO mild (16.8% vs. 13.0%, respectively; OR, 1.35 [95% CI 1.26-1.45], p=0.0762) and ACUITY minor bleeding (13.8% vs. 11.0%, respectively; OR, 1.30 [95% CI 1.20-1.40], p=<0.001), driven by ecchymosis, puncture site oozing, and hematoma <5 cm
- Comparable although numerically higher rates of investigator-reported AEs (26.1% vs 23.3%) and SAEs (2.7% vs 2.3%)

In the pooled CHAMPION dataset, there were (8 vs. 9) bleeding related deaths within 30 days with cangrelor compared to clopidogrel and there were numerically more clinically important bleeding events of intracranial hemorrhage (9 vs. 3), cardiac tamponade (15 vs. 3), retroperitoneal bleeds (24 vs. 15) and gastrointestinal bleeds (20 vs. 15) among cangrelor-treated patients.

In the total pooled dataset of all studies, cangrelor demonstrated:

- Comparable although numerically higher rates of investigator-reported AEs (26.1% vs. 23.3%) and SAEs (2.7% vs. 2.3%)

9.1. Bleeding complications associated with the use of cangrelor

The GUSTO bleeding definition was selected as the primary safety bleeding analysis variable due to its widespread clinical acceptability and established predictive correlation with adverse clinical outcomes [The GUSTO Investigators 1993; Rao 2006]. Other bleeding scales were derived based on the data reported by investigators, including TIMI, BARC, and ACUITY. Bleeding events were reported as endpoints in CHAMPION PHOENIX according to different bleeding scales as described in Appendix 2. To enable a thorough and systematic evaluation of bleeding all bleeding events were reported on a dedicated bleeding page in the CRF as shown in Appendix 3. This included documentation of clinical overtness, the site of the bleeding event as well as supporting laboratory data including hemoglobin and hematocrit.

In CHAMPION PHOENIX there was no significant increase in the primary safety outcome of GUSTO severe/life-threatening bleeding or GUSTO moderate bleeding (Table 20). There was an increase in GUSTO mild bleeding, driven primarily by ecchymosis, oozing, and <5 cm hematoma. There was no difference in TIMI major or minor bleeding. There was an increase in ACUITY major bleeding that was primarily driven by an increase in ≥5 cm hematoma at the puncture site, which is not known to be clinically correlated with adverse outcomes [White et al, 2010; Mehran et al, 2011].

Table 20: Analysis of non–CABG-related bleeding complications from CHAMPION PHOENIX (safety population)

	Cangrelor N=5529	Clopidogrel N=5527	OR (95% CI)	p value
GUSTO, n (%)				
Severe/Life Threatening	9 (0.2)	6 (0.1)	1.50 (0.53, 4.22)	0.4387
Moderate	22 (0.4)	13 (0.2)	1.69 (0.85, 3.37)	0.1279
Mild	150 (2.7)	88 (1.6)	1.72 (1.32, 2.25)	<0.001
Mild w/o ecchymosis or puncture site oozing and hematoma <5 cm	98 (1.8)	51 (0.9)	1.94 (1.38, 2.72)	0.0001

	Cangrelor N=5529	Clopidogrel N=5527	OR (95% CI)	p value
TIMI, n (%)				
Major	5 (0.1)	5 (0.1)	1.00 (0.29, 3.45)	>0.999
Minor	9 (0.2)	3 (0.1)	3.00 (0.81, 11.10)	0.0832
Minor w/o ecchymosis or puncture site oozing and hematoma <5 cm	9 (0.2)	3 (0.1)	3.00 (0.81, 11.10)	0.0832
ACUITY, n (%)				
Major	235 (4.3)	139 (2.5)	1.72 (1.39, 2.13)	<0.001
Major w/o hematoma ≥5 cm	42 (0.8)	26 (0.5)	1.62 (0.99, 2.64)	0.0518
Minor	653 (11.8)	475 (8.6)	1.42 (1.26, 1.61)	<0.001
Minor w/o ecchymosis or puncture site oozing and hematoma <5 cm	106 (1.9)	81 (1.5)	1.31 (0.98, 1.76)	0.0656
Blood and blood product utilization, n (%)				
Patients with any transfusion	25 (0.5)	16 (0.3)	1.56 (0.83, 2.93)	0.1594

Source: CHAMPION PHOENIX data on file, Table 6.1.4.1.

CABG = coronary artery bypass graft. BARC = Bleeding Academic Research Consortium. ACUITY = Acute Catheterization and Urgent Intervention Triage Strategy. GUSTO = Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries Trial. TIMI = thrombolysis in myocardial infarction.

In CHAMPION PHOENIX, there was an increase in GUSTO severe/life-threatening bleeding, GUSTO moderate bleeding and GUSTO mild bleeding (Table 21) in patients administered a glycoprotein IIb/IIIa antagonist. Because GPIIb/IIIa inhibitors have been shown to increase the risk of bleeding and thrombocytopenia [EPIC Investigators, 1994; Aster and Bougie, 2007; Huxtable et al, 2006; Greinacher et al, 2009; Kastrati et al, 2011], the CHAMPION program only allowed non-routine, peri-procedural use of GP IIb/IIIa inhibitors. At 48 hours, the CHAMPION PHOENIX study demonstrated that compared to clopidogrel, cangrelor resulted in no increase in thrombocytopenia (2/5529 (0.0%) vs 5/5527 (0.1%), respectively; OR=0.40 [95% CI: 0.08–2.16], p=0.2565).

Table 21: The effect of peri-procedural GPIIb/IIIa use with cangrelor compared to clopidogrel from CHAMPION PHOENIX

	With peri-procedural GPIIb/IIIa		Without peri-procedural GPIIb/IIIa	
	Cangrelor N=153	Clopidogrel N=227	Cangrelor N=5319	Clopidogrel N=5243
GUSTO Severe/Life threatening	1 (0.7%)	1 (0.4%)	8 (0.2%)	5 (0.1%)
GUSTO Moderate	4 (2.6%)	4 (1.8%)	18 (0.3%)	9 (0.2%)
GUSTO Mild	5 (3.3%)	5 (2.2%)	144 (2.7%)	82 (1.6%)

Source: Data on file, Table 9.110.1.1

In the pooled CHAMPION program, the bleeding outcomes were consistent with those observed in CHAMPION PHOENIX with no significant increase in the primary safety outcome of GUSTO severe/life-threatening (Table 22).

Table 22: Analysis of non–CABG-related bleeding complications from the pooled CHAMPION program (safety population)

	Cangrelor N=12,565	Control N=12,542	OR (95% CI)	p value
GUSTO (n, %)				
Severe/Life Threatening	28 (0.2)	23 (0.2)	1.22 (0.70, 2.11)	0.4875
Moderate	76 (0.6)	56 (0.4)	1.36 (0.96, 1.92)	0.0828
Mild	2109 (16.8)	1627 (13.0)	1.35 (1.26, 1.45)	<0.001
Mild w/o ecchymosis or puncture site oozing and hematoma <5 cm	707 (5.6)	515 (4.1)	1.39 (1.24, 1.56)	<0.001
TIMI (n, %)				
Major	32 (0.3)	28 (0.2)	1.14 (0.69, 1.90)	0.6101
Minor	77 (0.6)	51 (0.4)	1.51 (1.06, 2.15)	0.0218
Minor w/o ecchymosis or puncture site oozing and hematoma <5 cm	77 (0.6)	51 (0.4)	1.51 (1.06, 2.15)	0.0218
ACUITY (n, %)				
Major	534 (4.2)	353 (2.8)	1.53 (1.34, 1.76)	<0.001
Major w/o hematoma ≥5 cm	169 (1.3)	123 (1.0)	1.38 (1.09, 1.74)	0.0071
Minor	1738 (13.8)	1381 (11.0)	1.30 (1.20, 1.40)	<0.001
Minor w/o ecchymosis or puncture site oozing and hematoma <5 cm	293 (2.3)	255 (2.0)	1.15 (0.97, 1.36)	0.1053
Blood and blood product utilization (n, %)				
Patients with any transfusion	90 (0.7)	70 (0.6)	1.29 (0.94, 1.76)	0.1154

Source: Data on file, Table 16.6.1.4.1.

CABG = coronary artery bypass graft. BARC = Bleeding Academic Research Consortium. ACUITY = Acute Catheterization and Urgent Intervention Triage Strategy. GUSTO = Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries Trial. TIMI = thrombolysis in myocardial infarction.

9.2. Adverse events

A brief summary of AEs is presented in Table 23 for the pooled CHAMPION safety population. The number of AEs between cangrelor- and control-treated patients in the pooled safety population was similar.

Table 23: Overview of adverse events in CHAMPION pooled safety population

	CHAMPION pooled Safety Population [a]	
	Cangrelor N=12,565 n (%)	**Control N=12,542 n (%)**
Patients who Died [b]	298 (2.4)	323 (2.6)
Patients with Any AEs	2933 (23.3)	2778 (22.1)
Patients with Any SAEs	295 (2.3)	287 (2.3)
Patients Discontinuing Due to AE	75 (0.6)	52 (0.4)

Source: Data on file, Table 16.6.10.4.1 and 16.6.17.4.1

[a] Includes the CHAMPION PHOENIX, PLATFORM and PCI Studies, integrated data

[b] Includes patients who die within 30 days of enrolment; other subsets are patients dying within 3 days, and patients dying within 1 year.

9.2.1. Patients who died

The overall incidence of adverse events leading to death was low and was numerically lower in the cangrelor group than the comparator group in the pooled CHAMPION dataset (Table 24).

Table 24: Summary of deaths by SOC and preferred term occurring in ≥0.1% of patients in the CHAMPION studies (safety population)

System Organ Class/Preferred Term	Cangrelor N=12565 n (%)	Clopidogrel N=12542 n (%)
Patients who died	**298 (2.4)**	**323 (2.6)**
Cardiac disorders	132 (1.1)	150 (1.2)
Myocardial infarction	21 (0.2)	20 (0.2)
Cardiac arrest	20 (0.2)	28 (0.2)
Cardiogenic shock	19 (0.2)	28 (0.2)
Cardiac failure	18 (0.1)	21 (0.2)
Acute myocardial infarction	11 (0.1)	10 (0.1)
Cardiac failure congestive	8 (0.1)	10 (0.1)
Ventricular fibrillation	1 (0.0)	7 (0.1)
General disorders and administration site conditions	79 (0.6)	82 (0.7)
Death	43 (0.3)	49 (0.4)
Sudden cardiac death	16 (0.1)	17 (0.1)
Multi-organ failure	7 (0.1)	4 (0.0)
Sudden death	6 (0.0)	8 (0.1)
Infections and infestations	10 (0.1)	12 (0.1)

System Organ Class/Preferred Term	Cangrelor N=12565 n (%)	Clopidogrel N=12542 n (%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	22 (0.2)	13 (0.1)
Nervous system disorders	15 (0.1)	17 (0.1)
Cerebrovascular accident	6 (0.0)	9 (0.1)
Respiratory, thoracic and mediastinal disorders	14 (0.1)	20 (0.2)
Respiratory failure	6 (0.0)	7 (0.1)
Unknown	3 (0.0)	7 (0.1)
Unknown	3 (0.0)	7 (0.1)

Source: Data on file Table 16.6.17.4.1.
Includes the CHAMPION PHOENIX, PLATFORM and PCI Studies, integrated data

9.2.2. Serious adverse events

The overall incidence of SAEs was low, consistent with the patient population studied and similar in both the cangrelor and control groups (Table 25), suggesting that the risk associated with the use of cangrelor is no greater than that of clopidogrel.

Table 25: Serious adverse events ≥0.1% in the cangrelor-treated patients in CHAMPION studies (safety population)

Preferred terms	Cangrelor (N=12565) n (%)	Clopidogrel (N=12542) n (%)
Patients with at least one SAE	295 (2.3)	287 (2.3)
Cardiogenic shock	24 (0.2)	25 (0.2)
Ventricular fibrillation	22 (0.2)	15 (0.1)
Hypotension	15 (0.1)	15 (0.1)
Chest pain	14 (0.1)	12 (0.1)
Coronary artery dissection	14 (0.1)	11 (0.1)
Renal failure acute	13 (0.1)	7 (0.1)
Cardiac arrest	10 (0.1)	17 (0.1)
Pulmonary edema	10 (0.1)	9 (0.1)
Ventricular tachycardia	10 (0.1)	9 (0.1)
Cardiac failure congestive	10 (0.1)	7 (0.1)
Coronary artery perforation	8 (0.1)	5 (0.0)
Acute pulmonary edema	7 (0.1)	0 (0.0)
Thrombosis in device	4 (0.0)	8 (0.1)

Source: Data on file, Table 16.6.12.4.1.

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

9.2.3. Adverse events leading to discontinuation

In the CHAMPION PHOENIX trial, study drug discontinuation due to an adverse event was numerically more frequent in the cangrelor arm: 0.6% vs. 0.4%. The CHAMPION pooled dataset confirmed similar drug discontinuation rates (0.6% for cangrelor and 0.4% for clopidogrel) and identified coronary artery dissection, coronary artery perforation, and dyspnea as the most frequent events leading to discontinuation patients treated with cangrelor (Table 26).

Table 26: Summary of reported AEs leading to discontinuation of study drug by SOCs in CHAMPION pooled dataset

	CHAMPION studies	
System Organ Class	**Cangrelor (N=12565) n (%)**	**Clopidogrel (N=12542) n (%)**
Patients with at least one AE causing study drug discontinuation	**75 (0.6)**	**52 (0.4)**
Cardiac Disorders	41 (0.3)	28 (0.2)
Respiratory, Thoracic and Mediastinal Disorders	13 (0.1)	2 (0.0)
Vascular Disorders	9 (0.1)	12 (0.1)
Gastrointestinal Disorders	7 (0.1)	5 (0.0)
General Disorders and Administration Site Conditions	3 (0.0)	5 (0.0)
Injury, Poisoning and Procedural Complications	3 (0.0)	1 (0.0)
Immune System Disorders	2 (0.0)	3 (0.0)
Nervous System Disorders	2 (0.0)	3 (0.0)
Skin and Subcutaneous Tissue Disorders	2 (0.0)	0 (0.0)
Eye Disorders	1 (0.0)	0 (0.0)
Renal and Urinary Disorders	1 (0.0)	0 (0.0)
Psychiatric Disorders	1 (0.0)	0 (0.0)
Blood and Lymphatic System Disorders	0 (0.0)	1 (0.0)
Metabolism and Nutrition Disorders	0 (0.0)	0 (0.0)

Source: Data on file, Table 16.6.16.4.1
Note: Zero percentages associated with non-zero patient numbers are due to rounding.
AE = adverse event. SOC = system organ class.

9.2.4. Adverse Events

Non-hemorrhagic adverse events that occurred more frequently in patients treated with cangrelor are reported in Table 27 (at rates of >1.0%).

Table 27: Common Adverse Events

Common adverse events, n (%)		
CHAMPION POOLED	**Cangrelor (N=12565)**	**Clopidogrel (N=12542)**
Hypotension	203 (1.6)	175 (1.4)
Vomiting	177 (1.4)	162 (1.3)
Hypertension	172 (1.4)	149 (1.2)
Dyspnea	145 (1.2)	49 (0.4)

Source: Data on file, Table 16.6.18.4.1
Includes the CHAMPION PHOENIX, PLATFORM and PCI Studies, integrated data

9.3. Adverse events of special interest

Dyspnea, renal function effects, and hypersensitivity were selected as AEs of special interest (AESI) based on knowledge of the pharmacological mechanism of action as well as analysis of preclinical and clinical data.

9.3.1. Dyspnea

In the CHAMPION pooled safety population dyspnea (including exertional dyspnea) was reported in 1.2% (148/12,565) of patients treated with cangrelor and in 0.4% (50/12,542) of patients who received control. Serious adverse events of dyspnea occurred in 3 cangrelor-treated patients vs. 1 clopidogrel-treated patient and 10 cangrelor-treated vs. 3 clopidogrel-treated patients discontinued due to dyspnea. Among the 148 cangrelor-treated patients who had dyspnea, most events were considered mild 96 (64.9%) or moderate 51 (34.5%) and the event in 1 patient was considered severe. The median duration of dyspnea was 1.9 hours in the cangrelor treated group and 3.4 hours in the clopidogrel-treated group. No patient deaths were reported due to dyspnea.

In the CHAMPION PHOENIX trial, dyspnea was reported in 1.2% (65/5529) of patients treated with cangrelor and in 0.3% (18/5527) of patients who received clopidogrel. Serious adverse events occurred in 1 cangrelor vs. 0 clopidogrel treated patients and 4 cangrelor vs. 0 clopidogrel treated patients discontinued due to dyspnea. Most events of dyspnea in cangrelor-treated patients were considered mild 46 (70.59%) or moderate 18 (27.94%) and 1 event was considered severe.

In summary, dyspnea including exertional dyspnea occurred more frequently in the cangrelor-treated patients compared with control-treated patients in all data sets. This observation is consistent with the pharmacological effects of cangrelor.

9.3.2. Renal function effects

The primary adverse effects of cangrelor in rats and dogs occurred in the upper urinary tract, and consisted of injury to renal tubules, renal pelvis, and ureter. Anatomic changes correlated with

increased plasma creatinine and urea, and increased albumin and blood cells in urine. Injury to the urinary tract was reversible following cessation of dosing in an investigative study in rats [Data on file].

Following evidence of renal and urinary tract toxicity from preclinical studies, more intense renal and urinary tract safety monitoring was performed in a Phase II unstable angina (UA)/non–ST-segment elevation MI (NSTEMI), placebo-controlled study [SC-931-5060] using methods such as urinalysis, sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) of urinary proteins, and urine cytology, which have been shown to be highly sensitive for detection of both glomerular and tubular damage [Kolaja et al, 1992]. There was no observed effect on renal function or urinary parameters. Blood urea and creatinine levels were unaffected by infusion of cangrelor. Urine dipstick analysis, urine cytology and SDS-PAGE revealed no clinically relevant, treatment-related findings. Additionally, in a dose-ranging study [SC-931-5109] in patients with renal impairment, the pharmacokinetic, safety and tolerability of cangrelor was studied. Plasma concentration-time profiles for cangrelor were comparable to those observed previously in healthy volunteers and there was no specific relationship between infused dose, concentration and measured safety variables observed.

An analysis using acute renal failure Standardized Medical Dictionary for Regulatory Activities (MedDRA) Query (SMQ) criteria showed a low frequency and similar pattern of AEs between cangrelor and control (Table 28). However, there was a numerical increase in AEs for cangrelor [93/13,301 (0.7%) vs 64/12,861 (0.5%)].

Table 28: Summary of renal AEs of special interest by SOC and preferred term (safety population – all studies)

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

SMQ or System Organ Class	Preferred Term	Cangrelor (N=13301) n (%)	Control (N=12861) n (%)
	Anuria	1 (0.0)	0 (0.0)
	Azotaemia	2 (0.0)	0 (0.0)

Source: Data on file, Table 11.6.24.4.1.

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

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

Most of this numerical difference was derived from the CHAMPION PCI trial, where higher frequencies of these events were observed. Of note, the CHAMPION PCI trial enrolled more patients with a medical history that included hyperlipidemia, family history of CAD, previous PCI, previous CABG and peripheral artery disease (PAD) consistent with more established CAD.

Baseline and post baseline creatinine level data were obtained in the CHAMPION PCI and CHAMPION PLATFORM trials, but were not captured in the CHAMPION PHOENIX trial. An analysis of the incidence of events for the SMQ of acute renal failure based on the baseline renal status was performed in these two trials. The incidence of SMQ of acute renal failure appeared to increase with worsening baseline renal function in the CHAMPION PCI and PLATFORM studies, but the numbers are small (Table 29).

Table 29: Adverse event frequency (Acute Renal Failure SMQ) by baseline renal function in the CHAMPION PCI, PLATFORM and PHOENIX

	CHAMPION Pooled [a]		PCI		PLATFORM		PHOENIX	
	Cangrelor (N=12565) n (%)	Clopidogrel (N=12542) n (%)	Cangrelor (N=4374) n (%)	Clopidogrel (N=4365) n (%)	Cangrelor (N=2662) n (%)	Clopidogrel (N=2650) n (%)	Cangrelor (N=5529) n (%)	Clopidogrel (N=5527) n (%)
Patients with at least one event of SMQ	68 (0.5)	50 (0.4)	35 (0.8)	22 (0.5)	8 (0.3)	8 (0.3)	25 (0.5)	20 (0.4)
Severe (<30 mL/min/ 1.73 m^2)	10/281 (3.5)	5/282 (1.7)	8/165 (4.8)	3/162 (1.9)	2/116 (1.7)	2/120 (1.7)	NA	NA
Moderate (30-60 mL/min/ 1.73 m^2)	25/2197 (1.1)	14/2159 (0.5)	19/1332 (1.4)	10/1302 (0.8)	6/865 (0.7)	4/857 (0.5)	NA	NA
Mild (60-90 mL/min/ 1.73 m^2)	5/2809 (0.2)	11/2790 (0.4)	5/1823 (0.3)	9/1800 (0.5)	0/986 (0.0)	2/990 (0.2)	NA	NA
Normal (>90 mL/min/ 1.73 m^2)	1	0	1/902 (0.1)	0/956 (0.0)	0/650 (0.0)	0/621 (0.0)	NA	NA

Sources: Data on file, Table 16.6.24.4.1, Table 16.6.24.4.8, Table 16.6.24.4.9, Table 16.6.24.4.7, Table 16.6.24.4.10, Table 16.6.24.4.11, Table 16.6.24.4.12, Table 16.6.24.4.13, Table 16.6.24.4.14, Table 16.6.24.4.15, Table 16.6.24.4.16, Table 16.6.24.4.17, Table 16.6.24.4.18, Table 16.6.24.4.19, Table 16.6.24.4.20, and Table 16.6.24.4.21; Table 14.6.24.4.1, Table 14.6.24.4.22, Table 14.6.24.4.23, and Table 14.6.24.4.24.

a CHAMPION PCI/PLATFORM only.

NA = not applicable.

In the combined dataset of placebo-controlled clinical trials, a total of 25/572 (4.4%) patients experienced at least one event in the SMQ of acute renal failure. In these trials, there were numerically fewer patients who experienced events in this SMQ with cangrelor versus placebo. There was no trend observed based on the baseline renal function in either arm.

Further analysis of changes in creatinine clearance (CrCL; <30, 30-50, 50-80, >80, mL/min) by baseline CrCl status in the CHAMPION PCI, CHAMPION PLATFORM, and BRIDGE trial did not demonstrate any pattern of change (improvement or worsening) or any difference based upon treatment allocation.

There were a total of 13 deaths reported in patients within the SMQ of acute renal failure, seven of which were reported in cangrelor-treated patients and six of which were reported in the control group (Table 30).

Table 30: Summary of death caused by events in the SMQ of acute renal failure by SOC and preferred term (safety population – all studies)

SOC/Preferred Term	Cangrelor (N=13301) n (%)	Control (N=12861) n (%)
Renal and urinary disorders	7 (0.1)	6 (0.0)
Acute Renal Failure	3 (0.1)	5 (0.0)
Renal Failure Acute	4 (0.0)	1 (0.0)

Source: Data on file, Table 11.6.17.4.2.

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

SOC = system organ class; SMQ = standardized MedDRA query.

In conclusion, pre-clinical data, early clinical data, and large datasets from late-stage clinical trials indicate no clear safety issues related to renal function, however, small numerical increases in acute renal adverse events, primarily reported in the CHAMPION PCI trial should be noted.

9.3.3. Hypersensitivity

In the CHAMPION pooled safety population the following AEs occurred in cangrelor and clopidogrel groups, respectively, that may have been a manifestation of a hypersensitivity reaction: 2 vs. 2 AEs of bronchospasm, 12 vs. 6 AEs of urticaria and 2 vs. 0 AEs of angioedema. The following SAEs occurred in the cangrelor vs. clopidogrel groups, respectively: 1 vs. 0 SAEs of anaphylactic shock and 2 vs. 0 SAEs of anaphylactic reaction. Both SAEs of anaphylactic reaction lead to discontinuation of cangrelor.

9.4. Safety considerations

9.4.1. Fatal bleeding

In the CHAMPION PHOENIX study there were (2 vs. 4) bleeding related deaths with cangrelor compared to clopidogrel and there were numerically more clinically important bleeding events

including intracranial hemorrhage (3 vs. 2), cardiac tamponade (9 vs. 1), retroperitoneal bleeds (7 vs. 3) and gastrointestinal bleeds (16 vs. 10) among cangrelor-treated patients.

In the CHAMPION pooled safety population, fatal bleeding events within 30 days of dosing were low and generally well-balanced occurring in 8 (0.1%) cangrelor vs. 9 (0.1%) control patients (Table 31). There was a numerical increase in clinically important bleeding events including more intracranial hemorrhages (9 vs. 3), cardiac tamponade (15 vs. 3), retroperitoneal bleeds (24 vs. 15) and gastrointestinal bleeds (20 vs. 15) among cangrelor-treated patients. The pattern of deaths occurring due to bleeding events after 30 days was similar, occurring in 2 cangrelor and 2 control patients.

Table 31: Summary of bleeding-related deaths within 30 days from dosing start

	Hemorrhagic adverse events in CHAMPION pooled safety population [a]		Deaths from hemorrhagic adverse events in CHAMPION pooled safety population [a,b]	
Adverse Event	Cangrelor N=12565	Control N=12542	Cangrelor N=12565	Control N=12542
Total n (%)	2253 (17.9)	1755 (14.0)	8 (0.1)	9 (0.1)
Cardiac n (%)				
Cardiac tamponade	15 (0.1)	3 (0.0)	1 (0.0)	0 (0.0)
Myocardial rupture	3 (0.0)	4 (0.0)	1 (0.0)	4 (0.0)
Ventricle rupture	2 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Gastrointestinal n (%)				
Gastrointestinal hemorrhage	20 (0.1)	15 (0.1)	0 (0.0)	2 (0.0)
Retroperitoneal hemorrhage	24 (0.2)	15 (0.1)	1 (0.0)	0 (0.0)
Neoplasms n (%)				
Tumor hemorrhage	0 (0.0)	1 (0.0)	0 (0.0)	1 (0.0)
Nervous system n (%)				
Cerebral hemorrhage	1 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Cerebrovascular accident	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hemorrhage intracranial	6 (0.0)	3 (0.0)	2 (0.0)	0 (0.0)
Hemorrhagic stroke	1 (0.0)	1 (0.0)	1 (0.0)	1 (0.0)
Primary Hemorrhagic stroke	3 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)
Vascular n (%)				
Shock hemorrhagic	0 (0.0)	2 (0.0)	0 (0.0)	1 (0.0)

Source: Data on file, Tables 16.6.21.4.1, 16.6.23.4.1 and 16.6.21.4.1.5

[a] Includes all CHAMPION studies pooled, integrated data.

[b] Includes patients who died within 30-days from dosing start time.

9.4.2. Intracranial hemorrhage

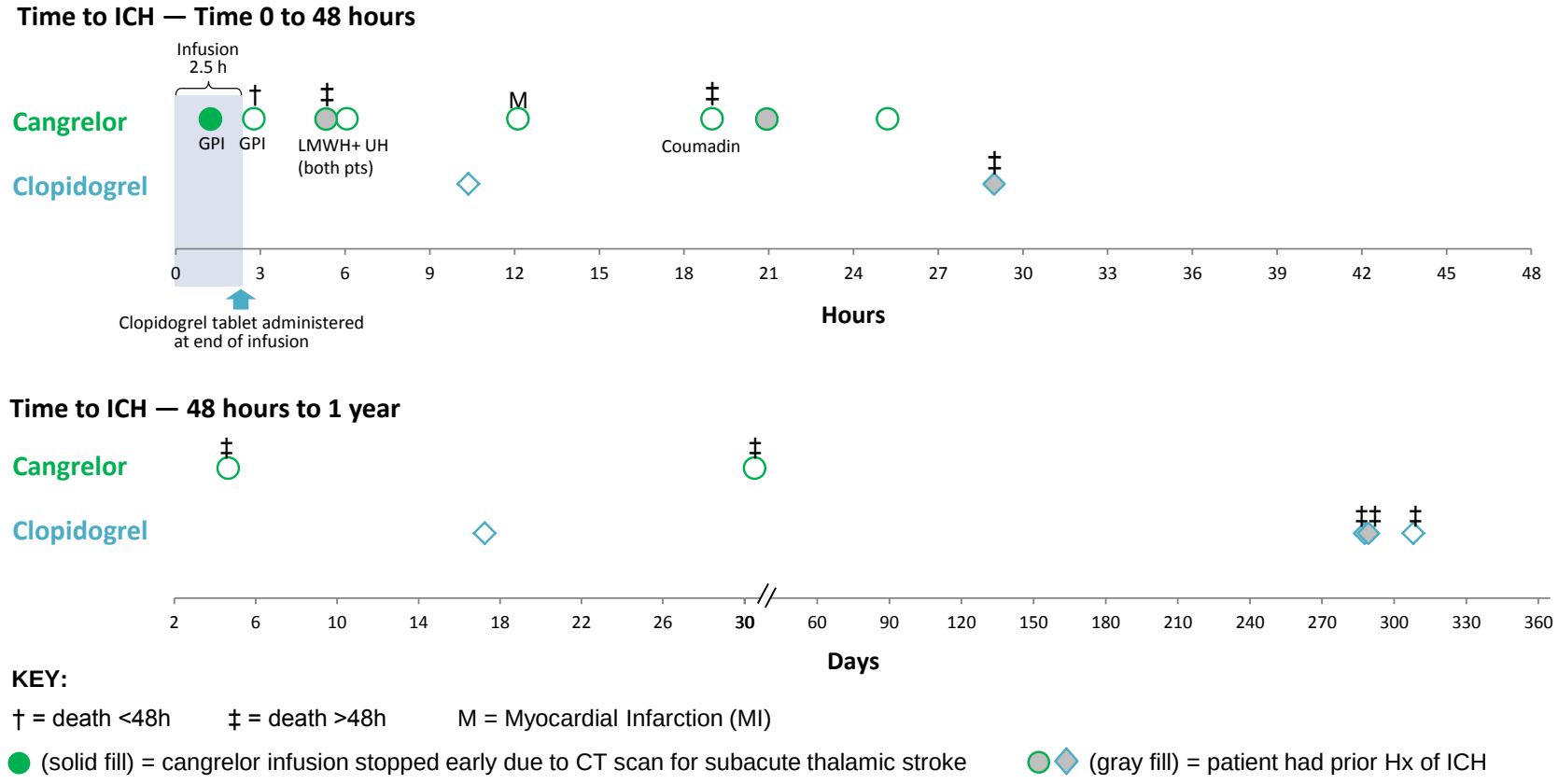
The incidence of ICH in the CHAMPION pooled dataset are presented below (Table 32) and illustrated by time from initial dosing through 1 year (Figure 11). Further analysis of these events demonstrated that four of the events occurred with 6 hours of the cangrelor infusion compared to zero events occurring within the same timeframe for clopidogrel. Review of the patient cases identified that these four patients also received a combination of antithrombotic agents including GP IIb/IIIa inhibitors or multiple heparins which are known to be associated with an increased incidence of hemorrhagic complications including ICH [Blankenship et al, 1999; Vahdat et al, 2000; Ferguson et al, 2004; Drouet et al, 2009]. The Sponsor proposes contraindicating the use of cangrelor in patients who have a history of intracranial hemorrhage (ICH) to reduce the risk of such events. The sponsor is also proposing to include a warning concerning the concomitant use of other anti-platelets (e.g. glycoprotein IIb/IIIa inhibitors) due to an increased risk of bleeding.

Table 32: Incidence of intracranial hemorrhages

	Incidence of ICH		Incidence of ICH leading to Death	
Time from randomization	**Cangrelor N = 12,565**	**Clopidogrel N = 12,542**	**Cangrelor N = 12,565**	**Clopidogrel N = 12,542**
48 hours	8 (0.06)	2 (0.02)	1 (0.01)	0
30 days	9 (0.07)	3 (0.02)	4 (0.03)	1 (0.01)
1 year	10 (0.08)	6 (0.05)	5 (0.04)	4 (0.03)

Source: Data on file CHAMPION Pooled.

Figure 11: Time to intracranial hemorrhage by treatment group

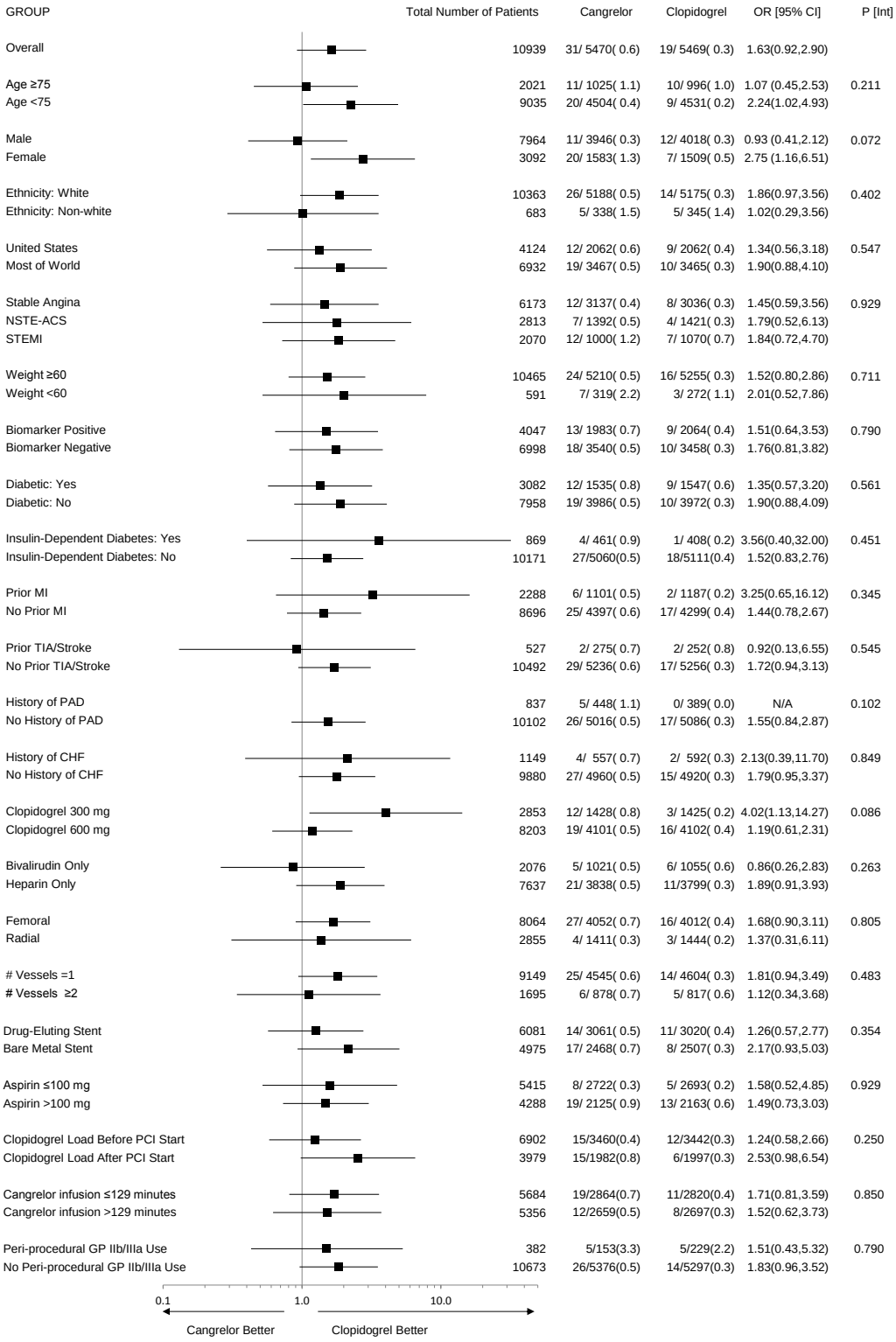


Source: Data on file CHAMPION Pooled.

9.5. Comparison of GUSTO severe/life-threatening and moderate bleeding by subgroup

Predefined subgroups were examined to ensure consistency of effect across subpopulations and the interactions of treatment with subgroups were tested to identify differing treatment effects in subgroups with regard to GUSTO severe/life-threatening and moderate bleeding. The most relevant subgroups from CHAMPION PHOENIX are presented in Figure 12. Subgroup comparisons for all safety analyses were in general consistent with the outcomes for overall trial results.

Figure 12: Subgroup analysis of composite GUSTO severe/life-threatening bleeding and GUSTO moderate bleeding in 48 hours (PHOENIX mITT population)



Source: CHAMPION PHOENIX Data on file, Figure 11.

10. THE CANGRELOR RISK-BENEFIT PROFILE IS WELL ESTABLISHED

The results of the CHAMPION PHOENIX trial demonstrated that cangrelor compared to control is effective with an acceptable safety profile when administered to patients with CAD who require $P2Y_{12}$ inhibition in an acute setting.

At 48 hours, the CHAMPION PHOENIX study demonstrated that, compared to clopidogrel cangrelor provided:

- A significant reduction in the primary efficacy endpoint of all-cause mortality, MI, IDR, and ST (4.7% vs 5.9%, respectively; OR, 0.79 [95% CI 0.66-0.93], p=0.005) which was maintained at 30 days (6.0% vs 7.0%, respectively; OR, 0.85 [95% CI 0.73-0.99], p=0.035)
- A significant reduction in ST (0.8% vs 1.4%, respectively; OR, 0.62 [95% CI 0.43-0.90], p=0.010)
- A significant reduction in MI (3.8% vs 4.7%, respectively; OR, 0.80 [95% CI 0.67-0.97], p=0.022)
- No difference in all-cause mortality (0.3% vs 0.3%, respectively; OR, 1.00 [95% CI 0.52,1.92], p=0.999)

At 48 hours, the CHAMPION PHOENIX study demonstrated that, compared to clopidogrel cangrelor provided:

- No statistical difference in non-CABG GUSTO severe/life-threatening bleeding (0.2% vs 0.1%, respectively; OR, 1.50 [95% CI 0.53-4.22], p=0.439) or GUSTO moderate bleeding (0.4% vs 0.2%, respectively; OR, 1.69 [95% CI 0.85-3.37], p=0.128)
- No statistical difference in transfusion (0.5% vs 0.3%, respectively; OR 1.56 [0.83-2.93], p=0.169)
- A significant increase in non-CABG ACUITY major bleeding (4.3% vs 2.5%, respectively; OR, 1.72 [95% CI 1.39-2.13], p=<0.001), driven by hematoma ≥5 cm
- A significant increase in non-CABG GUSTO mild (2.7% vs 1.6%, respectively; OR, 1.72 [95% CI 1.32-2.25], p=<0.001) and ACUITY minor bleeding (11.8% vs 8.6%, respectively; OR, 1.42 [95% CI 1.26-1.61], p=<0.001), driven by ecchymosis, puncture site oozing, and hematoma <5 cm

The CHAMPION pooled dataset demonstrated that, compared to clopidogrel cangrelor provided:

- No statistical difference in non-CABG GUSTO severe/life-threatening bleeding (0.2% vs 0.2%, respectively; OR, 1.22 [95% CI 0.70-2.11], p=0.488)
- No statistical difference in transfusion (0.7% vs 0.6%, respectively; OR 1.29 [0.94-1.76], p=0.115)

- A significant increase in non-CABG ACUITY major bleeding (4.2% vs. 2.8%, respectively; OR, 1.53 [95% CI 1.34-1.76], p=<0.001), driven by hematoma ≥5 cm
- A significant increase in non-CABG GUSTO mild (16.8% vs. 13.0%, respectively; OR, 1.35 [95% CI 1.26-1.45], p=0.0762) and ACUITY minor bleeding (13.8% vs. 11.0%, respectively; OR, 1.30 [95% CI 1.20-1.40], p=<0.001), driven by ecchymosis, puncture site oozing, and hematoma <5 cm
- Comparable although numerically higher rates of investigator-reported AEs (26.1% vs 23.3%) and SAEs (2.7% vs 2.3%)

Oral $P2Y_{12}$ inhibitors reduce cardiovascular events in patients with ACS and in patients in whom coronary stents are implanted. However, oral $P2Y_{12}$ inhibitors have limitations in the acute setting. Despite advances in adjunctive pharmacotherapy, thrombotic complications during PCI remain a major concern.

The ideal solution in the acute setting would: (1) reduce thrombotic risk by providing consistent and effective $P2Y_{12}$ inhibition, (2) be well tolerated with no increase in bleeding risk, (3) work well regardless of the clinical setting and work across all subgroups, and (4) provide controlled $P2Y_{12}$ inhibition that is turned on when needed and turned off when not.

In the contemporary management of patients who require $P2Y_{12}$ inhibition in the acute setting or require surgery there is now a choice and cangrelor is a potential solution. Clinicians must weigh the benefits of individual therapeutic options with the potential for adverse outcomes. The CHAMPION PHOENIX trial demonstrated that cangrelor confers a significant 21% RRR in the primary composite efficacy endpoint of Death/MI/IDR or ST superior to clopidogrel in patients who require PCI with a number needed to treat (NNT) of 84. Supportive evidence of efficacy, including reductions in stent thrombosis, were observed in the CHAMPION PLATFORM and PCI trials.

The significant reduction in the incidence of MI and ST is objective, clinically meaningful, and important. For every 114 patients undergoing PCI with cangrelor compared to conventional therapy, one MI might be avoided (NNT = 114 in CHAMPION PHOENIX) and for every 195 patients undergoing PCI with cangrelor compared to conventional therapy, one ST might be avoided (NNT = 195 in CHAMPION PHOENIX). Stent thrombosis is a catastrophic complication of PCI and can occur at any time especially after discontinuation of an oral $P2Y_{12}$ inhibitor. Stent thrombosis presents as STEMI or cardiogenic shock, with case fatality reaching as high as 45% in some studies. The implications of cangrelor therapy as a novel strategy to manage patients in an acute setting undergoing PCI is important and may resolve the management dilemmas now faced by these patients and their caregivers.

Cangrelor does not significantly increase clinically meaningful bleeding risk in patients undergoing PCI as evaluated in 12,565 cangrelor-treated patients from the three CHAMPION studies. There was no difference in fatal bleeding (8 vs. 9) but there was a numerical increase in

clinically important bleeding events including more intracranial hemorrhages (9 vs. 3), cardiac tamponade (15 vs. 3), retroperitoneal bleeds (24 vs. 15) and gastrointestinal bleeds (20 vs. 15) among cangrelor-treated patients. For every 1844 patients undergoing PCI with cangrelor compared to conventional therapy, one GUSTO severe/life-threatening bleed might occur resulting in a number needed to harm (NNH) of 1844 in CHAMPION PHOENIX. An increase in non-CABG minor bleeding was the major driver of increased bleeding observed with cangrelor. Most of the non-bleeding adverse reactions such as dyspnea and hypersensitivity were mild to moderate in intensity.

For each 1000 patients who were given cangrelor instead of clopidogrel, 9 myocardial infarctions, 6 stent thrombosis, and 2 ischemia driven revascularization end-point events were prevented. The cost was 1 excess severe or life threatening bleed, 2 moderate bleeds and 11 minor bleeding events. There was no difference in fatal bleeding and there was no difference in overall mortality. The modest increase in bleeding risk does not compromise the use of cangrelor for patients undergoing PCI. The Sponsor proposes contraindicating the use of cangrelor in patients who have a history of intracranial hemorrhage (ICH) to reduce the risk of such events. The sponsor is also proposing to include a warning concerning the concomitant use of other anti-platelets (e.g. glycoprotein IIb/IIIa inhibitors) due to an increased risk of bleeding. Should a major bleeding event occur, the PD effect of cangrelor can be rapidly reversed by discontinuing the infusion with a return to normal platelet function within 60 minutes.

Conclusion

In conclusion, the acceptable benefit-risk profile of cangrelor makes it a clinically important option for patients who require fast, reliable and flexible $P2Y_{12}$ inhibition in the acute setting for the contemporary management of patients undergoing PCI.

11. THE BRIDGE STUDY

11.1. Introduction: Rationale for the study and regulatory history

Patients treated with oral $P2Y_{12}$ inhibitors who must undergo surgery face an increased risk of thrombosis if they stop $P2Y_{12}$ therapy, or an increased risk of surgical bleeding if they continue therapy. There is currently no tested, safe therapeutic option for this treatment challenge.

July 2005 - the concept of the Phase 2 BRIDGE trial was first discussed with the Agency in at the End of Phase 2 meeting.

December 2007 - the BRIDGE study protocol synopsis was provided. The Agency noted that the BRIDGE pharmacodynamic study could potentially support some type of labeling in conjunction with documented evidence of clinical benefit in Phase 3 trials.

August and November 2012 - FDA acknowledged the clinical dilemma and need for an agent that can bridge between the discontinuation of oral platelet $P2Y_{12}$ inhibitors and surgery and requested the provision of additional key information to support an NDA for the proposed indication. This included providing information documenting the absolute risk of adverse clinical outcomes during the bridging period and conversely the risk of bleeding from continued use of clopidogrel close to surgery.

February 2013 – Agreement reached with FDA to submit PCI and Bridge indication

Accordingly, the BRIDGE pharmacodynamic study was performed to demonstrate that consistent inhibition without accumulation of effect can be achieved with cangrelor. Patients with ACS and patients with stents who required $P2Y_{12}$ inhibition to bridge the period from discontinuation of oral $P2Y_{12}$ inhibitors to cardiac surgery were examined in a single randomized, controlled Phase II study. The BRIDGE study was conducted to provide information on how cangrelor might be used in this setting to address the unmet need.

The intent of the BRIDGE study was to approximate $P2Y_{12}$ inhibition as if oral therapy had not been stopped, to confirm the rapid return of platelet function after discontinuation right before surgery, and to assess surgical bleeding. Platelet function testing (assessed by the Verify*Now*® P2Y12 assay) in BRIDGE confirmed $P2Y_{12}$ inhibition.

11.1.1. Medical need: Treatment challenge for patients requiring $P2Y_{12}$ therapy who need surgery

Product labeling and treatment guidelines for all oral $P2Y_{12}$ platelet inhibitors (clopidogrel, prasugrel, and ticagrelor) include the warning that premature discontinuation of oral $P2Y_{12}$ platelet inhibitors confer a high risk for thrombotic cardiac events, such as ST, MI, and death. (Table 33).

Furthermore, labeling and guidelines also recommend discontinuation of these agents at least 5 to 7 days prior to surgery to avoid the increased risk of surgical bleeding known to be associated with oral $P2Y_{12}$ inhibitors when taken at the time of cardiac surgery.

Table 33: Product labeling for oral $P2Y_{12}$ inhibitors

	Plavix (clopidogrel)	Effient (prasugrel)	Brilinta (ticagrelor)
Stop treatment and risk thrombosis	Warnings & Precautions: Premature discontinuation of Plavix may increase the risk of cardiovascular events	Warnings & Precautions: Discontinuation of Effient: premature discontinuation increases the risk of stent thrombosis, MI, and death.	Warnings & Precautions: Discontinuation of Brilinta increases the risk of myocardial infarction, stent thrombosis and death.
Continue treatment and risk bleeding	Warnings and Precautions: Plavix increases risk of bleeding. Discontinue 5 days prior to elective surgery.	Black Box Warning: When possible, discontinue Effient at least 7 days prior to any surgery.	Black Box Warning: When possible, discontinue Brilinta at least 5 days prior to any surgery.

Source: US prescribing information for Plavix, Effient, and Brilinta
MI = myocardial infarction. US = United States.

11.1.2. Increased risk of thrombotic events if oral $P2Y_{12}$ inhibitors are discontinued

The bridging setting requires discontinuation of oral $P2Y_{12}$ therapy for a short period of time—typically for less than 7 days—before surgery. We sought to quantify the risk of stent thrombosis in this time frame to determine the importance of maintaining platelet inhibition.

Pertinent information on the absolute risk of ST in the Bridging setting is available from the Dutch Stent Registry. In that registry, investigators from three large hospitals within the Netherlands collected data on 21,009 PCI patients in order to investigate the overall predictors of ST and predictors of ST in patient types (SA and ACS). Additionally, the data collection in this large Dutch Stent Registry allowed for the analysis of the impact of clopidogrel discontinuation and the timing of the discontinuation on ST [van Werkum et al, 2009]. However, initial published analyses from this database did not specifically calculate the absolute rate of ST, or the relative risk of ST in the immediate time period after the discontinuation of clopidogrel to estimate the risk that a surgical patient might have. The Medicines Company worked with the investigators to utilize data collected in this Registry to conduct additional analyses to determine this information.

The Dutch Stent Thrombosis Registry was queried for cases of stent thrombosis in patients included within the database from January 2004 through February 2007. The sponsor was able to obtain the dataset and in collaboration with Dutch Stent Thrombosis Registry investigators performed additional analysis.

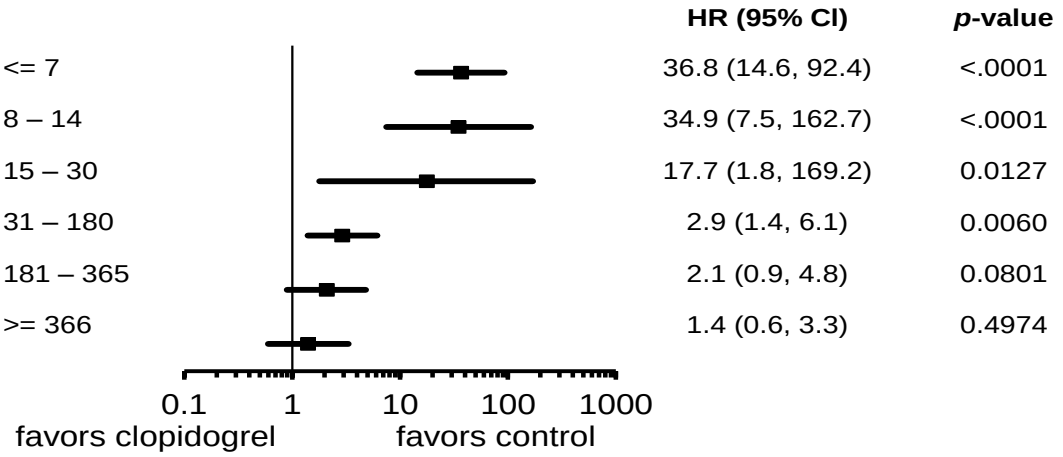
The primary objective of the additional analysis by The Medicines Company (MDCO) was to determine the absolute rate of ST in patients who discontinue clopidogrel after they have undergone PCI with stent implantation based on the large observational registry.

The secondary objectives were to:

- Evaluate the risk of ST as a function of time (within 7 days post discontinuation, between 8 days and 30 days, and between 31 days and 365 days post discontinuation).
- Evaluate the risk of ST as a function of duration of clopidogrel therapy after PCI/stent placement.

A total of 437 patients with ST endpoints were identified. The absolute risk of ST in 21,009 patients from the Dutch Stent Registry who discontinued clopidogrel was calculated to be 4.6% (95% CI: 3.9 to 5.4%) over the study period [Dutch Stent Thrombosis Registry Clinical Study Report]. The risk of ST was shown to be the highest during the first 7 days after discontinuation of clopidogrel (HR 36.8; 95% CI 14.6-92.4). More than one-third of all cases (37.3%) occurred within the first 7 days after discontinuation and more than one-half (53%) occurred within the first 14 days after discontinuation (Figure 13). It is also important to note that this risk of ST following discontinuation was independent of time since stent placement.

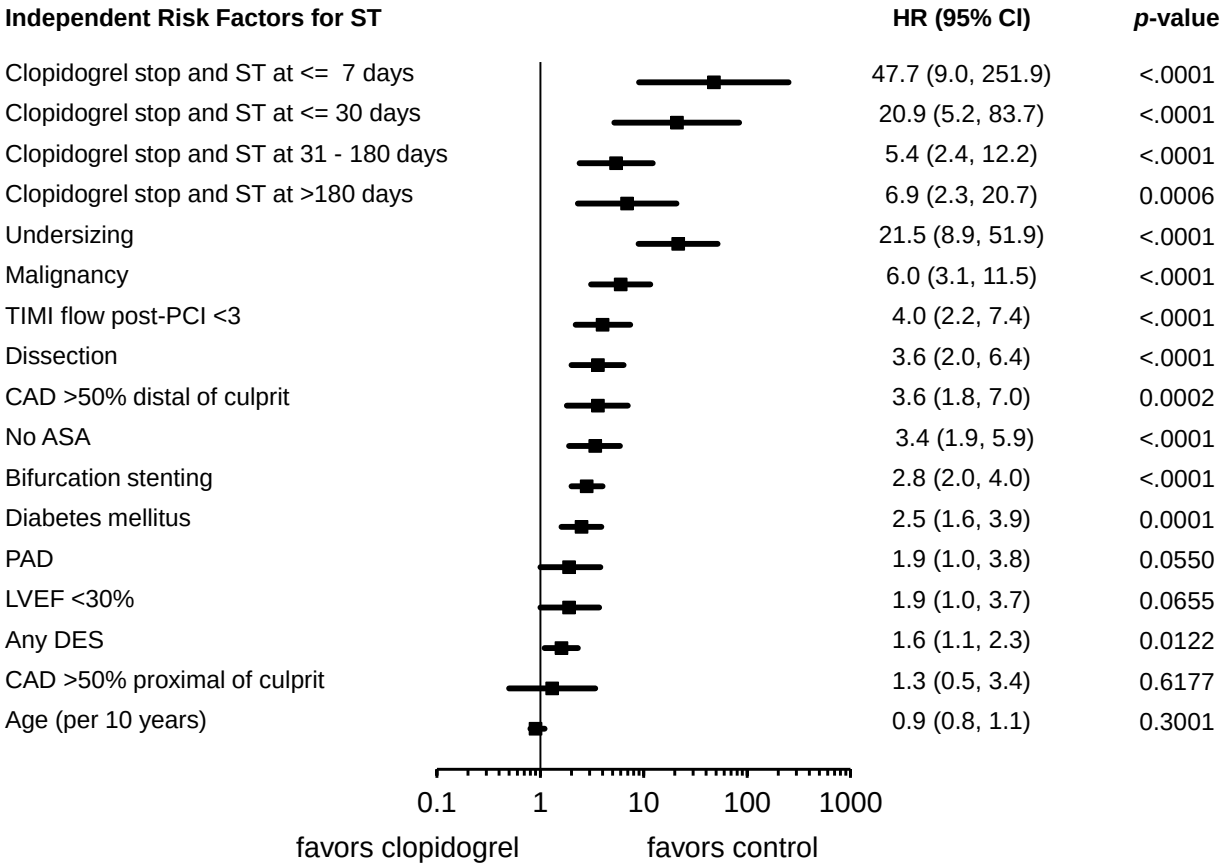
Figure 13: Risk of stent thrombosis at intervals in days from discontinuation



Source: Dutch Stent Registry data on file, Figure 9 and Table 5.2.1.1.
HR = hazard ratio. CI = confidence interval. CSR = clinical study report.

An analysis was also performed to determine independent predictors of ST. The strongest individual predictor of ST was discontinuation of clopidogrel within the last seven days (HR, 47.7; 95% CI: 9.0-251.9; p<0.001) followed by stent under-sizing (HR, 21.5; 95% CI: 8.9-51.9; p<0.001), and discontinuation of clopidogrel within 30 days (HR, 20.9; 95% CI: 5.2-83.7; p<0.001; Figure 14).

Figure 14: Predictors of stent thrombosis



Source: Dutch Stent Registry data on file, Figure 10 and Table 5.9.1.1.

HR = hazard ratio. CI = confidence interval. CSR = clinical study report. CAD = coronary artery disease. ASA = acetylsalicylic acid. PAD = peripheral artery disease. DES = drug-eluting stent. LVEF = left ventricular ejection fraction. ST = stent thrombosis. PCI = percutaneous coronary intervention. TIMI = Thrombolysis in Myocardial Infarction.

Importantly, while stent thrombosis is not a frequent event, it carries a high risk of mortality. In this registry, overall mortality in patients with ST was 13.4%; mortality in patients who discontinued clopidogrel and developed ST was 13.4%. One half of these deaths (9/18) occurred in patients who had ST within 7 days after discontinuation of clopidogrel, and the mortality rate in these patients was 18%. Stent thrombosis can present as ST-elevation myocardial infarction or cardiogenic shock with case fatality reaching as high as 45% to 50% in some studies [Airoldi et al, 2007; Schulz et al, 2009; Iakovou et al, 2005; Urban et al, 2011; Dangas et al, 2012].

11.1.3. Increased risk of bleeding and mortality after surgery when oral $P2Y_{12}$ inhibitors are continued

Surgical bleeding is increased in patients who go to surgery on oral $P2Y_{12}$ inhibition. The prescribing information for clopidogrel, prasugrel and ticagrelor include recommendations to stop these agents 5 to 7 days prior to surgery.

Clopidogrel increases the risk of major hemorrhagic complications in patients undergoing surgery. Continuing oral $P2Y_{12}$ inhibitor therapy during the perioperative period is associated with an increased incidence of major hemorrhagic complications by as much as 50% [Douketis et al, 2012].

A meta-analysis of 3 prospective randomized studies and 17 observational studies up to 2010 showed that recent exposure to clopidogrel before CABG surgery is associated with increased risk of postoperative death (relative risk [RR], 1.30; 95% CI, 1.02–1.67), and re-operations for bleeding (RR, 1.88; 95% CI, 1.37–2.58) [Biancari 2012]. A systematic review of 37 studies comparing postoperative outcomes in patients exposed to clopidogrel in the five days before surgery, versus those who were not exposed showed a higher incidence of reoperation for bleeding (OR, 2.62; 95% CI, 1.96-3.49), and all-cause mortality (OR 1.38; 95% CI, 1.13-1.69) [Au et al, 2012].

A study published in 2002 showed that clopidogrel therapy within seven days of CABG has also been associated with a significant increase in chest tube output at both 8 hours (775 mL vs 516 mL, p=0.005) and 24 hours (1224 mL vs 840 mL, p=0.001) after the procedure. In this study, only 15% of patients in the clopidogrel group remained free of blood product exposure (84.7% vs 61.3%, p=0.001) [Hongo and Ley, 2002].

Clopidogrel is also associated with an increased risk of transfusion post-surgery. A prospective, observational cohort study conducted by Mariscalco et al and published in 2011 showed that in 1947 consecutive patients undergoing coronary surgery clopidogrel administration in the five days preceding coronary surgery was an independent predictor for increased transfusion requirements. Compared to propensity score-matched patients who did not receive clopidogrel, the risk of transfusion was 4-fold higher if clopidogrel was stopped 5 days prior to surgery and increased to 8- to 9-fold higher if the last dose was received within 2 to 3 days of cardiac surgery [Mariscalco et al, 2011].

Numerous studies have identified RBC transfusions as being associated with increased risk of morbidity and mortality [Murphy et al, 2007; Koch et al, 2006; Rao et al, 2004; Surgenor et al, 2006; Reeves and Murphy, 2008; Blumberg, 2005], postoperative infection [Hill et al, 2003; Marik and Corwin, 2008; Taylor et al, 2006; Bernard et al, 2009; Shander et al, 2009], acute respiratory distress syndrome and multi-organ failure [Marik and Corwin, 2008; Chaiwat et al, 2009; Croce et al, 2005], and prolongation of intensive care admission and/or length of hospital stay [Taylor et al, 2006; Corwin et al, 2004; Malone et al, 2003].

Some of the most recent evidence for discontinuing oral $P2Y_{12}$ inhibitors before surgery comes from the data submitted for the prasugrel and ticagrelor New Drug Applications, which further supports and extends the literature. Accordingly, product labeling and guideline recommendations are to delay surgery for at least seven days and ideally longer after discontinuation of prasugrel, and for 5 to 7 days after ticagrelor [Hillis et al, 2011; Hamm et al,

2011; Van de Werf et al, 2008; Wijns et al, 2010; Ferraris et al, 2011; Effient Prescribing Information; Brilinta Prescribing Information].

In the TRITON TIMI-38 trial, prasugrel was associated with a 4-fold increased relative risk (absolute difference, 10.2%; p< 0.001) of CABG-related bleeding compared with clopidogrel in patients with ACS [Wiviott et al, 2007]. While the ticagrelor trial PLATO demonstrated no difference between ticagrelor and clopidogrel major/fatal/life-threatening CABG-related bleeding with respect to time from last intake of study drug before surgery [Held et al, 2011], the data reported do demonstrate a 1.6 to 3- fold increased risk in CABG bleeding for those patients who continued oral $P2Y_{12}$ in the 2 days prior to CABG surgery compared to those patients who waited 5 to 7 days after discontinuation.

The complications associated with increased surgical bleeding are costly as well. Exposure to clopidogrel within seven days before CABG is associated with an increase in major bleeding, hemorrhage-related complications, and transfusion requirements, and leads to greater consumption of healthcare resources [Pickard et al, 2008]. Clopidogrel-exposed patients are more likely to have a prolonged hospitalization compared to those who did not receive clopidogrel as seen in the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) study (12.0 days vs 8.9 days, respectively, p<0.001) [Ebrahimi et al, 2009].

11.2. Overview of the BRIDGE Trial

The BRIDGE trial was designed to

- approximate a level of $P2Y_{12}$ inhibition with IV cangrelor as if oral therapy had not been stopped
- confirm the rapid return of platelet function after discontinuation right before surgery
- assess surgical bleeding with this strategy compared to discontinuation with no replacement therapy

BRIDGE enrolled patients with ACS and/or patients with a stent that were at increased risk of thrombotic events due to discontinuation of an oral $P2Y_{12}$ inhibitor prior to cardiac surgery.

The Accumetrics Verify*Now*® P2Y12 assay was selected to evaluate the pharmacodynamic effects in BRIDGE because of ease of use by surgical teams as a point of care test, and its demonstrated good correlation with the ‘gold standard’ method of LTA.

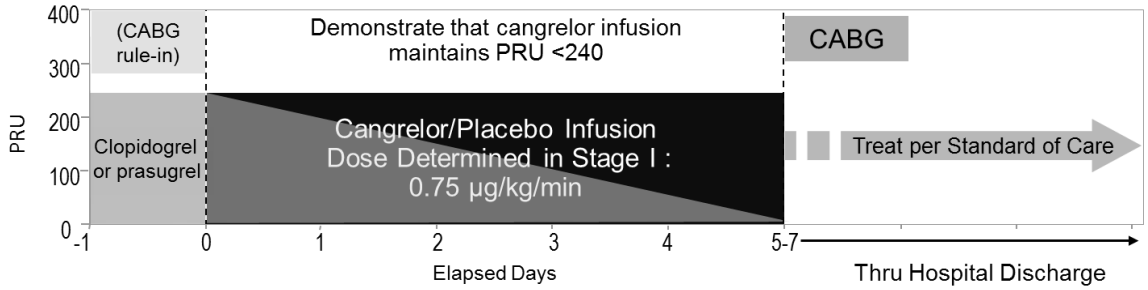
The trial was conducted in two stages:

Stage I was an open-label study designed to identify the dose of cangrelor that would approximate the antiplatelet effect of oral $P2Y_{12}$ inhibitor therapy as if it had not been discontinued. Cangrelor was to be administered as an IV infusion to cohorts of 5 patients in a stepwise fashion at predetermined doses (0.5 µg/kg/min, 0.75 µg/kg/min, 1.0 µg/kg/min, and 1.5 µg/kg/min) until the predetermined endpoint, or a dose of 2.0 µg/kg/min, was reached.

Stage II was a prospective, double-blind, randomized, placebo-controlled, multicenter trial designed to demonstrate that cangrelor (at a dose identified in Stage I) for the duration of the infusion maintained low levels of platelet reactivity as would be expected for oral maintenance $P2Y_{12}$ treatment, assessed by the Accumetrics Verify*Now*® P2Y12 assay, compared to placebo. A total of 210 patients who stopped oral $P2Y_{12}$ therapy because they required cardiac surgery were randomized to cangrelor or placebo in a 1:1 ratio. Study drug infusion was initiated immediately after randomization (within 72 hours of last dose of oral $P2Y_{12}$ inhibitor) throughout the pre-operative period for a minimum of 48 hours. Infusion durations of up to 7 days were allowed, with patients in either arm going to surgery between 48 hours and 7 days as scheduled or individually indicated. Sites were instructed to discontinue the infusion from 1 to 6 hours prior to surgical incision, as convenient for the surgical team in individual patient preparations. Study drug was not administered during or after cardiac surgery.

A schematic of the study design for Stage II is provided in Figure 15.

Figure 15: Stage II study design: Demonstration of effective cangrelor infusion dose



Source: BRIDGE data on file.
CABG = coronary artery bypass graft. PRU = Verify*Now*® P2Y12 Reaction Unit. kg = kilograms. min = minutes. µg = micrograms.

11.2.1. BRIDGE Stage I: Dose selection

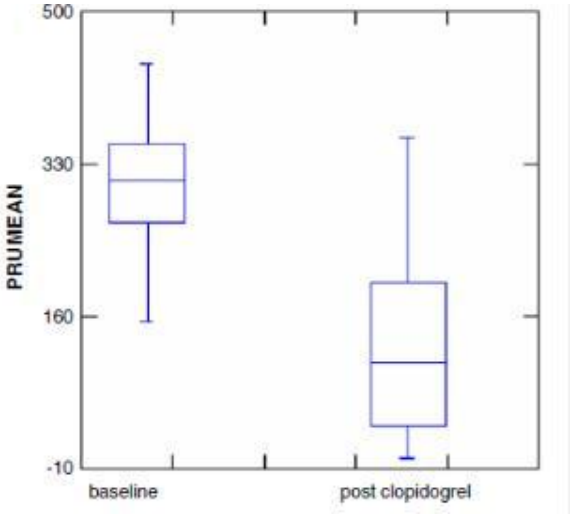
The dose finding Stage I of BRIDGE was designed to find a dose of cangrelor that would approximate the antiplatelet effect of maintenance clopidogrel therapy, rather than provide maximal $P2Y_{12}$ inhibition. While the PCI setting with revascularization and accompanying vessel injury requires a short period of intense antithrombotic therapy, a less intense level of $P2Y_{12}$ receptor inhibition that can be provided without increasing the risk of bleeding is appropriate for the bridging setting. Individual response to clopidogrel is notably variable but platelet inhibition with 75 mg (maintenance dose) clopidogrel is approximately 60% [Malinin et al, 2007] using the Verify*Now*® P2Y12 assay. Similar levels of inhibition have been reported with other assay methodologies. Table 34 shows results from a study with 147 subjects, 110 of whom received a dose of 450 mg clopidogrel, and 37 of whom took 75 mg for 7 days [Malinin et al. 2007].

Table 34: $P2Y_{12}$ inhibition with clopidogrel, assessed by the Verify*Now*® P2Y12 assay

	% inhibition overall	% inhibition 450 mg	% inhibition 75 mg
Subjects	147	110	37
Mean ± SD	64.0±25.3	62.5±25.5	68.7±25.5
Range	16.9-99.8	16.9-99.8	23.2-99.0

Figure 16 as follows from the same study shows the results expressed as Verify*Now*® P2Y12 Reaction Unit (PRU) rather than % inhibition.

Figure 16: Box plot comparison of the baseline and post-clopidogrel administration platelet reactivity using Verify*Now*® P2Y12 assay



Therefore, the pre-specified endpoint for Stage 1 was to find the dose of cangrelor that achieved at least 60% platelet inhibition in 80% of patient samples. A total of 11 patients were enrolled in Stage 1. In Cohort I, a cangrelor dose of 0.5 µg/kg/min prior to surgery maintained platelet inhibition above 60% in only 76.5% (13/17) of patient samples. The primary endpoint was met in Cohort II. Cangrelor at a dose of 0.75 µg/kg/min maintained platelet inhibition above 60% in 94.4% (17/18) of patient samples.

The Accumetrics instrument with the Verify*Now*® P2Y12 assay also provides a pharmacodynamic measure expressed as PRU. During the BRIDGE study, residual platelet reactivity became the preferred measure, [Working Group on Platelet Reactivity Consensus, Bonello et al, 2010], and Stage II of this study used a cutoff level of 240 PRU as a measure of pharmacodynamic efficacy. For comparison to % inhibition levels, 80% of patients in Cohort I and 100% of patients in Cohort II had all on-infusion samples <240 PRU during the cangrelor infusion.

There were no safety-related concerns with cangrelor administration at this dose. The level of inhibition achieved with this dose is somewhat higher than that achieved with clopidogrel, but is

suitable for the bridging setting given that ticagrelor and prasugrel maintain higher levels of inhibition than observed with clopidogrel.

11.2.2. BRIDGE Stage 2

Stage 2 of the study confirmed that cangrelor at 0.75 µg/kg/min provided rapid, potent, and consistent platelet $P2Y_{12}$ inhibition during IV infusion at or below the level that would be expected to be maintained if an oral $P2Y_{12}$ inhibitor had not been discontinued, with rapid offset of effect following cessation of infusion. The primary efficacy endpoint was met, with a significantly higher percentage of cangrelor-treated patients maintaining target levels of $P2Y_{12}$ inhibition throughout the entire infusion of study drug compared with placebo-treated patients [BRIDGE data on file].

11.2.2.1. Choice of endpoint in Stage 2

The primary pharmacodynamic endpoint of the BRIDGE trial (Stage II) was the percentage of patients with all samples during the infusion achieving PRU <240, as determined by Verify*Now*® P2Y12 assay, measured during study drug infusion pre-surgery. This endpoint was selected as it was indicative of low residual platelet reactivity by consensus of the Working Group on Platelet Reactivity [Bonello et al, 2010].

Consistent suppression of platelet activity with effective $P2Y_{12}$ inhibition as achieved with prasugrel, ticagrelor, or cangrelor has demonstrated a substantial reduction in the risk for ST and other thrombotic events in clinical trials. [Wiviott et al, 2007; Wallentin et al, 2009; Bellemain-Appaix et al, 2010]. Clinical studies to date, such as GRAVITAS [Price et al, 2011], ARCTIC [Collet et al, 2012] or TRIGGER-PCI [Trenk et al, 2012] have not demonstrated that qualitative test results can guide individualized platelet inhibition to improve outcomes. However, levels of platelet reactivity associated with increased clinical risk have been recommended for various assays [Bonello et al, 2010; Tantry et al, 2013]. The ADAPT-DES study is the most recent and largest study (n=8583) to provide convincing confirmation of the strong association of high platelet reactivity with increased risk of ST and myocardial infarction (adjusted HR 2.49 [95% CI 1.43–4.31], p=0.001) and myocardial infarction (adjusted HR 1.42 [1.09–1.86], p=0.01), [Stone et al, 2013]. In ADAPT-DES, two levels of high platelet reactivity were defined using the Verify*Now*™ P2Y12 assay: PRU >208, and PRU>230. The results above were for PRU>208, but analogous results were found for PRU>230.

Given the importance of assuring $P2Y_{12}$ inhibition, and the variety of options and still-evolving implications of platelet function testing, the most important information obtained from these assays might be whether the assay can provide evidence of $P2Y_{12}$ inhibition with a high degree of specificity and selectivity. The Verify*Now*™ P2Y12 test at a cutoff of 230 PRU has demonstrated an 87% sensitivity and an 88% specificity for the presence of $P2Y_{12}$ inhibition [Dahlen et al, 2012].

The Verify*Now*™ P2Y12 assay is known to be well correlated with maximal light transmittance aggregometry with oral $P2Y_{12}$ inhibitors clopidogrel, prasugrel and ticagrelor [Jeong et al, 2008;

Malinin et al, 2007; von Beckerath et al, 2006; Jakubowski et al, 2008], and the correlation of PRU with maximal LTA for cangrelor is also good, r=0.94 (p<0.0001) [Data on file].

11.2.2.2. Patient population

Patient demographic characteristics and baseline medical history for the BRIDGE population (safety) are provided in Table 35. Patients were representative of patients with CAD. Overall, approximately 14% of patients had STEMI, and 63% had elevated troponin levels (>ULN) at baseline, consistent with ongoing MI. Patients were mostly elderly (46% of patients were ≥65 years), male (74%), and white (90%). Consistent with the bridging setting in which patients had been receiving oral $P2Y_{12}$ therapy to reduce the risk of thrombotic events, the incidence of prior MI (40%), previous PCI/stent (48%) and treatment with oral $P2Y_{12}$ inhibitors (100%) was higher in this population than in the CHAMPION trials. The incidence of diabetes, CHF, and PAD were also higher and representative of CAD patients requiring treatment with cardiac surgery.

Table 35: Summary of selected baseline characteristics of BRIDGE patients[a]

	Cangrelor (N=106)	Placebo (N=101)
Male sex, n (%)	80 (75.5)	74 (73.3)
Median age (years)	65.0	62.0
≥65 years, n (%)	54 (50.9)	42 (41.6)
Race, n (%)		
White	93 (87.7)	94 (93.1)
Asian	3 (2.8)	0 (0.0)
Black/African American	6 (5.7)	5 (5.0)
Other	4 (3.8)	2 (2.0)
Unknown (missing data)	0	0
Patient types, n (%) [b]		
SA NSTE-ACS	90 (84.9)	89 (88.1)
STEMI	16 (15.1)	12 (11.9)
Troponin I/T >ULN	35/65 (53.8)	46/63 (73.0)
Diabetes mellitus	49/106 (46.2)	47/101 (46.5)
Current smoker	31/106 (29.2)	38/101 (37.6)
Hypertension	87/106 (82.1)	83/101 (82.2)
Hyperlipidemia	76/106 (71.7)	77/101 (76.2)
Cerebrovascular event	9/106 (8.5)	4/101 (4.0)
Family history of CAD	47/106 (44.3)	49/101 (48.5)

	Cangrelor (N=106)	Placebo (N=101)
Previous MI	46/106 (43.4)	36/101 (35.6)
Previous PTCA/PCI	53/106 (50.0)	46/101 (45.5)
Previous CABG	3/106 (2.8)	1/101/ (1.0)
Congestive heart failure	16/106 (15.1)	6/101 (5.9)
Peripheral artery disease	14/106 (13.2)	12/101 (11.9)

BRIDGE data on file, Table 2.1.3, Table 2.3.3 and Table 2.4.3
[a] Safety population.
SA= stable angina; NSTE-ACS = non-ST-elevation acute coronary syndrome; STEMI = ST-segment elevation myocardial infarction; ULN = upper limit of normal; PCI = percutaneous coronary intervention; ITT = intent-to-treat.

Table 36 and Table 37 provide prior medication and patient disposition, respectively.

Table 36: Summary of prior oral $P2Y_{12}$ therapy for BRIDGE patients

Variable Statistic/ Category	Bridging setting BRIDGE[a]	
	Cangrelor (N=106)	Placebo (N=101)
Oral $P2Y_{12}$ therapy received, n/N (%)	106 (100.0)	101 (100.0)
Clopidogrel	105 (99.1)	93 (92.1)
Prasugrel	1 (0.9)	8 (7.9)
Ticlopidine	NA	NA
Clopidogrel last dose, mg; n/N (%)		
75	88/105 (83.8)	65/93 (69.9)
>75	17/105 (16.2)	28/93 (30.1)

Sources: BRIDGE data on file, Table 2.5.3.
[a] Safety population.
PCI = percutaneous coronary intervention; ITT = intent-to-treat; NA = not applicable.

Table 37: Patient disposition by treatment group

	Cangrelor (N=106)	Placebo (N=104)
Number of patients randomized	106 (100.0)	104 (100.0)
ITT population	93 (87.7)	90 (86.5)
mITT population	NA	NA
Safety population	106 (100.0)	101 (97.1)
Subjects completing study, n (%)	101 (95.3)	94 (90.4)

	Cangrelor (N=106)	Placebo (N=104)
Subjects who did not complete the study	5 (4.7)	10 (9.6)
Withdrew Consent	1 (0.9)	2 (1.9)
Physician Discretion	1 (0.9)	0 (0.0)
Lost-to-Follow-up	0 (0.0)	1 (1.0)
Adverse Event	0 (0.0)	0 (0.0)
Death	3 (2.8)	5 (4.8)
Other	0 (0.0)	2 (1.9)

Source: BRIDGE data on file, Table 1.1.

In the BRIDGE trial, patients were randomized to $P2Y_{12}$ inhibition with IV cangrelor or IV placebo during the bridging period. Cangrelor (0.75 µg/kg/min infusion) was initiated immediately after randomization (within 72 hours of last dose of oral $P2Y_{12}$) and maintained throughout the pre-operative period for a minimum of 48 hours.

The median infusion duration for cangrelor was 67 hours, or 2.8 days [BRIDGE data on file, Table 3.1.3]. The maximal infusion duration was 6.7 days. The infusion was discontinued a median of 3 hours prior to surgery, although could be continued until 60 minutes prior to surgery. When administered in the Bridging setting cangrelor patients received a median total dose of 288 mg administered over the infusion duration.

In the BRIDGE trial, concomitant medications administered during the bridging period prior to cardiac surgery were similar between the two arms. Overall, 98% of patients received aspirin, 48% received unfractionated heparin, and 39% received low-molecular weight heparin. Thrombolytics and GPIIb/IIIa inhibitors were not administered during the bridging period as specified in the exclusion criteria.

11.3. Results

11.3.1. Pharmacodynamic efficacy: maintenance of $P2Y_{12}$ inhibition prior to surgery

In patients with CAD who need to discontinue oral $P2Y_{12}$ therapy prior to surgery, cangrelor at an infusion dose of 0.75 µg/kg/min provides evidence of consistent platelet inhibition, maintaining low levels of platelet reactivity as expected if an oral $P2Y_{12}$ inhibitor had not been discontinued.

The primary efficacy endpoint was met, with 98.8% of cangrelor-treated patients maintaining levels of low platelet reactivity for all on-infusion time points measured over the bridging period, compared to 19.0% of placebo-treated patients (RR 5.19 [95% CI, 3.34, 8.07] $p<0.001$) (Table 38). These results were unchanged when analyzed using logistic regression adjusted by

the stratification variable of expected days to surgery (either ≤3 days or >3 days), (RR 5.15 [95% CI, 3.32, 8.00] p=0.001).

Table 38: BRIDGE Primary efficacy analysis (ITT population)

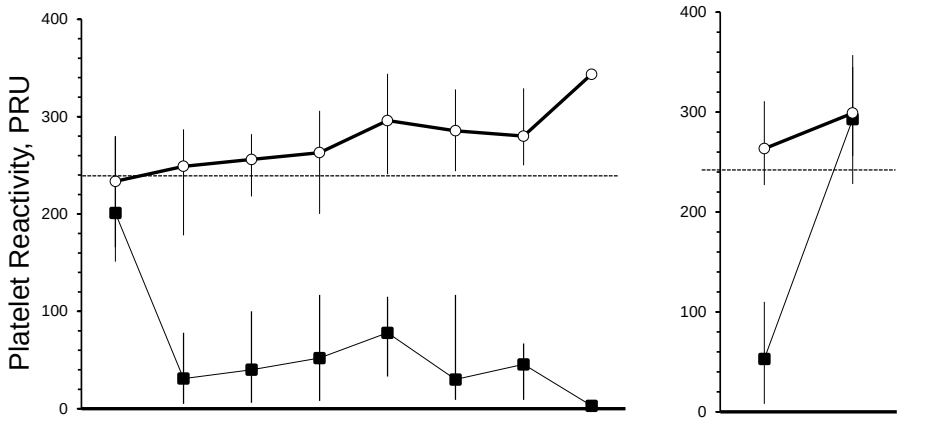
	Stage II			
During Infusion Statistic	**Cangrelor (N=93) n/N (%)**	**Placebo (N=90) n/N (%)**	**p value**	**RR (95% CI)**
Patients with all samples PRU <240 [a]	83/84 (98.8)	16/84 (19.0)	<0.0001 CH <0.0001 LR	5.19 (3.34, 8.07) 5.15 (3.32, 8.00)

Source: BRIDGE data on file, Table 5.1.1.1.
[a] Primary efficacy analysis
CH = Chi-square test. LR = Logistic regression adjusting for stratification factor, expected CABG ≤3 versus >3 days. PRU = Verify*Now*® P2Y12 Reaction Unit. CI = confidence interval. RR = relative risk. ITT = intent-to-treat.

The distribution of platelet reactivity achieved with cangrelor versus placebo during the bridging period is illustrated in Figure 17. In patients receiving cangrelor, platelet reactivity was significantly lower and maintained during the infusion, compared to patients receiving placebo.

The rapid recovery of platelet function after discontinuation of cangrelor infusion, consistent with the reversible binding and short half-life of cangrelor (3 to 6 minutes) is also demonstrated. After discontinuation of cangrelor, platelet reactivity prior to surgery was similar for the cangrelor and placebo groups.

Figure 17: Cangrelor provides effective and consistent $P2Y_{12}$ inhibition during infusion (ITT population)



No. of patients with valid sample in the ITT population

Cangrelor	85	80	70	55	33	7	6	1	84	78
Placebo	86	76	73	57	34	24	14	2	84	75

Source: BRIDGE data on file, Table 5.2.1.1.
Note: Median and interquartile range of PRU values by visit day for Stage II BRIDGE patients treated with cangrelor (black squares) or placebo (white circles). CABG = coronary artery bypass graft. ITT = intent-to-treat. PRU = Verify*Now*® P2Y12 Reaction Unit.

11.3.2. Bleeding

In patients bridging from oral $P2Y_{12}$ inhibitors to surgery, the BRIDGE trial demonstrated for cangrelor vs. control respectively:

- No differences in the rates of protocol-defined excess CABG-related bleeding after discontinuation of the cangrelor infusion (primary safety endpoint) (11.8% vs 10.4%) and transfusion (25.5% vs 32.3%)
- An increase in non–CABG-related GUSTO-moderate bleeding (1.9% vs 1.0%) and ACUITY major bleeding (2.8% vs 1.0%) during the 5 to 7-day bridging period
- An increase in non-CABG related GUSTO mild (17.9% vs. 9.9%) and ACUITY minor bleeding (17.9% vs 9.9%) during the 5 to 7-day bridging period, driven by ecchymosis, puncture site oozing, and hematoma <5 cm

Cangrelor did not increase surgical bleeding risk in the BRIDGE study. There was no statistically or clinically important difference in the primary safety endpoint of protocol-defined excessive surgical bleeding (Table 39). Additionally, other pre-specified markers of surgical bleeding were not increased, including: CABG-related bleeding consistent with the standardized Bleeding Academic Research Consortium (BARC) criteria; chest tube output at 4 and 24 hours

and the number of patients transfused [Mehran et al, 2011]. There were no differences in the number of patients who received transfusions.

Table 39: CABG-related bleeding and transfusion in the BRIDGE trial (Stage II safety population)

	Cangrelor	Placebo
Protocol-defined excessive (n/N: %)	12/102 (11.8)	10/96 (10.4)
Surgical re-exploration	2/102 (2.0)	2/96 (2.1)
24-hour chest tube output of >1.5 liters	8/102 (7.8)	5/96 (5.2)
PRBC transfusions >4 units	6/102 (5.9)	8/96 (8.3)
Consistent with BARC-defined (n/N: %)	10/102 (9.8)	10/96 (10.4)
Fatal bleeding	0/102 (0.0)	0/96 (0.0)
Peri-operative intracranial bleeding within 48 hours	0/102 (0.0)	0/96 (0.0)
Reoperation for the purpose of controlling bleeding	2/102 (2.0)	2/96 (2.1)
Transfusion of ≥5 units of whole blood or PRBC within a 48-hour period	7/102 (6.9)	8/96 (8.3)
Chest tube output ≥2 liters within a 24-hour period	3/102 (2.9)	4/96 (4.2)
Chest tube output (mL) (mean ± SD)		
4 hour	325.4 ± 265.6	297.1 ± 200.2
24 hour	830.4 ± 557.3	805.2 ± 440.4
Blood and blood product utilization		
Patients with any transfusion (n/N: %)	26/102 (25.5)	31/96 (32.3)
Units of whole blood/PRBC (mean ± SD, n)	3.45 ± 2.09 (n=22)	3.73 ± 2.56 (n=30)
Units of platelets (mean ± SD, n)	1.85 ± 0.90 (n=13)	2.62 ± 2.63 (n=13)
Units of FFP (mean ± SD, n)	4.09 ± 2.12 (n=11)	4.67 ± 3.96 (n=15)

Source: BRIDGE data on file, Table 4.2.3, Table 6.1.3.1, Table 6.1.3.2, and Table 6.4.3
BARC = Bleeding Academic Research Consortium. CABG = coronary artery bypass graft. PRBC = packed red blood cell. FFP = fresh frozen plasma. SD = standard deviation.

The median time from the last sample taken during the infusion until the pre-CABG sample in cangrelor treated patients was 4.2 hours. The median time from the termination of the infusion until the start of CABG was 3.1 hours. These times were driven by pre-surgical protocols in the respective institutions.

11.3.3. Non–CABG-related bleeding in patients bridging to surgery

In the cangrelor-treated group there was a numerical increase in non–CABG-related bleeding during the pre-surgery bridging period (Table 40). However, there were no GUSTO Severe/life

threatening or TIMI major events reported in either group. There was a numerical increase in GUSTO mild and TIMI/ACUITY minor bleeding, driven primarily by ecchymosis, oozing at the puncture site, and hematoma <5 cm at the puncture site. These events are not known to be correlated with long term adverse clinical outcomes and the overall incidence of minor bleeding may have been increased in part by repeat venipuncture associated with the trial conduct. There was also a numerical increase in ACUITY major and GUSTO moderate bleeding.

Table 40: Non-CABG-related bleeding in the BRIDGE trial (Stage II safety population)

	Cangrelor N=106	Placebo N=101
GUSTO (n, %)		
Severe/Life Threatening	0 (0.0)	0 (0.0)
Moderate	2 (1.9)	1 (1.0)
Mild	19 (17.9)	10 (9.9)
Mild w/o ecchymosis or puncture site oozing and hematoma <5 cm	6 (5.7)	5 (5.0)
TIMI (n, %)		
Major	0 (0.0)	0 (0.0)
Minor	2 (1.9)	0 (0.0)
Minor w/o ecchymosis or puncture site oozing and hematoma <5 cm	2 (1.9)	0 (0.0)
ACUITY (n, %)		
Major	3 (2.8)*	1 (1.0)
Minor	19 (17.9)	10 (9.9)
Minor w/o ecchymosis or puncture site oozing and hematoma <5 cm	5 (4.7)	5 (5.0)

Source: BRIDGE data on file, Table 6.2.3

*Includes a patient who had a CABG-related bleed prior to CABG.

CABG = coronary artery bypass graft. BARC = Bleeding Academic Research Consortium. PRBC = packed red blood cell. ACUITY = Acute Catheterization and Urgent Intervention Triage Strategy. GUSTO = Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries Trial. TIMI = thrombolysis in myocardial infarction. NA = not applicable.

11.4. Major adverse cardiovascular events in the BRIDGE trial

In Stage II of the BRIDGE trial, ischemic endpoints were low in both treatment groups prior to surgery. The number of deaths in the cangrelor group was numerically lower than in the placebo group during the pre-procedure period. Post-procedure ischemic endpoints were low and similar between the groups (Table 41).

Table 41: Summary of ischemic endpoints (safety population)

Parameter	Cangrelor N=106	Placebo N=101
Incidence of Pre-Procedure Ischemic Endpoints (Randomization to Surgery) (n/N: %)		
Death/MI/IDR/Stroke	3/106 (2.8)	4/101 (4.0)
Death	1/106 (0.9)	3/101 (3.0)
MI	2/106 (1.9)	0/101 (0.0)
IDR	1/106 (0.9)	0/101 (0.0)
Stroke	0/106 (0.0)	1/101 (1.0)
Incidence of Post-Procedure Ischemic Endpoints (Through 30 days) (n/N: %)		
Death/MI/IDR/Stroke	4/102 (3.9)	4/96 (4.2)
Death	1/102 (1.0)	2/96 (2.1)
MI	2/102 (2.0)	1/96 (1.0)
IDR	2/102 (2.0)	0/96 (0.0)
Stroke	1/102 (1.0)	1/96 (1.0)

Source: BRIDGE Data on file: Table 6.5.3.1.
MI = myocardial infarction. IDR = ischemia-driven revascularization.

11.5. Adverse events

There were a similar number of patients with adverse events (AEs) (Table 42) and serious adverse events (SAEs) between cangrelor- and placebo-treated patients: AEs: 58/106 (54.7%) vs 56/101 (55.4%); SAEs: 11/106 (10.4%) vs 9/101(8.9%). Study drug discontinuation due to an AE was numerically more frequent in the cangrelor arm compared to the placebo arm: 6/106 (5.7%) vs 3/101 (3.0%). A total of 20 SAEs (including fatal SAEs) were reported in Stage II of the study; 11 in the cangrelor group and 9 in the placebo group. Overall in Stage II, the number of deaths reported was low. Seven deaths were reported in total, 2 in the cangrelor group and 5 in the placebo group.

Table 42: Adverse events by system organ class sorted by frequency (safety population)

	Stage II	
System Organ Class	Cangrelor (N=106) n/N (%)	Placebo (N=101) n (%)
Subjects with at least one AE	58/106 (54.7)	56/101 (55.4)
Injury, poisoning and procedural complications	21/106 (19.8)	15/101 (14.9)
General disorders and administration site conditions	19/106 (17.9)	12/101 (11.9)
Respiratory, thoracic and mediastinal disorders	19/106 (17.9)	19/101 (18.8)
Cardiac disorders	15/106 (14.2)	16/101 (15.8)

System Organ Class	Stage II	
	Cangrelor (N=106) n/N (%)	Placebo (N=101) n (%)
Gastrointestinal disorders	14/106 (13.2)	9/101 (8.9)
Psychiatric disorders	14/106 (13.2)	4/101 (4.0)
Investigations	10/106 (9.4)	10/101 (9.9)
Musculoskeletal and connective tissue disorders	9/106 (8.5)	5/101 (5.0)
Vascular disorders	9/106 (8.5)	6/101 (5.9)
Nervous system disorders	7/106 (6.6)	6/101 (5.9)
Infections and infestations	6/106 (5.7)	5/101 (5.0)
Metabolism and nutrition disorders	6/106 (5.7)	6/101 (5.9)
Skin and subcutaneous tissue disorders	6/106 (5.7)	0/101 (0.0)
Renal and urinary disorders	5/106 (4.7)	6/101 (5.9)
Blood and lymphatic system disorders	3/106 (2.8)	4/101 (4.0)
Reproductive system and breast disorders	2/106 (1.9)	0/101 (0.0)
Ear and labyrinth disorders	0/106 (0.0)	1/101 (1.0)
Immune system disorders	0/106 (0.0)	1/101 (1.0)

Source: Data on file, Table 8.1.3.3.
AE = adverse event

11.6. Summary

The BRIDGE trial was designed to test whether cangrelor plus standard of care compared to placebo plus standard of care provides consistent $P2Y_{12}$ inhibition, maintaining platelet reactivity following discontinuation of oral $P2Y_{12}$ inhibitors without increasing surgical bleeding.

The primary efficacy endpoint was met with 98.8% of cangrelor-treated patients demonstrating effective levels of platelet inhibition for all on-infusion time points measured over the bridging period, compared to 19.0% of placebo patients (OR, 353 [95% CI, 45.6, 2728] $p<0.001$). Similarly, for all secondary efficacy endpoints measured, cangrelor provided evidence of significantly better $P2Y_{12}$ inhibition during infusion compared to placebo.

Cangrelor provided $P2Y_{12}$ inhibition that could be controlled: after discontinuation of the infusion, platelet function prior to surgery was the same for cangrelor and placebo groups. There is no accumulation of effect and the rapid return of platelet function following discontinuation of the cangrelor infusion is consistent with the short half-life of cangrelor (3 to 6 min).

Cangrelor did not increase surgical bleeding risk in the bridging setting. In the BRIDGE trial there was no difference in the primary safety endpoint of protocol-defined excessive surgical bleeding. Additionally, other pre-specified markers of surgical bleeding were not increased,

including: CABG-related bleeding consistent with the BARC criteria; chest tube output at 4 and 24 hours, and the number of patients transfused.

Cangrelor was associated with a modest increase in non-CABG related bleeding occurring during the 5-day on infusion bridging period (Table 40). There was a numerical increase in GUSTO mild and TIMI/ACUITY minor bleeding driven primarily by ecchymosis, oozing at the puncture site, and hematoma <5 cm located at the puncture site. These events are not known to be correlated with long-term adverse clinical outcomes and the overall incidence of minor bleeding may have been increased in part by repeat venipuncture associated with the trial conduct. There was also a modest increase in ACUITY major and GUSTO moderate bleeding. However, review of the eCRFs for each of the three patients revealed that all of the events were associated with other interventional procedures and were not spontaneous in nature. An analysis of bleeding events demonstrated that cangrelor treatment was not independently associated with increased risk of surgical and non-CABG related bleeding during the bridging period.

The implications of cangrelor therapy as a potential strategy to bridge patients who discontinue oral $P2Y_{12}$ inhibitors prior to surgery is important and may resolve the dilemma now faced by these patients and their caregivers. In conclusion, the acceptable benefit-risk profile of cangrelor makes it a clinically important option for patients who require fast, reliable and flexible $P2Y_{12}$ inhibition in the acute setting for the contemporary management of patients bridging off oral $P2Y_{12}$ inhibitors to surgery.

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5. MDCO-CAN-13-01 (TRANSITION II). A study of the transition from IV cangrelor to oral prasugrel, and prasugrel to cangrelor, in patients with coronary artery disease. 26 August 2013.
6. Population pharmacokinetic/pharmacodynamic evaluation of cangrelor: Report. (Cangrelor Population PK-PD Model.) Protocol Numbers: SC-931-5014, SC-931-5036, TMC-CAN-04-02, TMC-CAN-05-02-S1 and TMC-CAN-08-02. The Medicines Company. 6 April 2013.
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28. TMC-CAN-08-02. Maintenance of platelet inhibition with cangrelor after discontinuation of thienopyridines in patients undergoing surgery: The BRIDGE Trial. 29 March 2013.

29. TMC-CAN-10-01. A clinical trial comparing cangrelor to clopidogrel standard of care therapy in subjects who require percutaneous coronary intervention: CHAMPION PHOENIX. 11 April 2013.

APPENDIX 1

List of key publications and presentations from the cangrelor clinical program to date

Study	Reference
CHAMPION PCI	Harrington RA, Stone GW, McNulty S et al. Platelet inhibition with cangrelor in patients undergoing PCI. *N Engl J Med*. 2009;361:2318-2329.
CHAMPION PLATFORM	Bhatt DL, Lincoff AM, Gibson CM et al. intravenous platelet blockade with cangrelor during PCI. *N Engl J Med*. 2009;361:2330-2341.
CHAMPION PLATFORM	Leonardi S, Truffa AA, Neely LM, et al. A novel approach to systematically implement the universal definition of myocardial infarction: insights from the CHAMPION PLATFORM trial. *Heart.* 2013; 99(17):1282-1287.
CHAMPION (PCI, PLATFORM) trials pooled	White HD, Chew DP, Dauerman HL, et al. Reduced immediate ischemic events with cangrelor in PCI: A pooled analysis of the CHAMPION trials using the universal definition of myocardial infarction. *Am Heart J.* 2012;163:182-190.e4.
BRIDGE	Angiolillo DJ, Firstenberg MS, Price MJ, et al. Bridging antiplatelet therapy with cangrelor in patients undergoing cardiac surgery. *JAMA*. 2012;307(3): 265-274.
BRIDGE	Firstenberg MS, Dyke CM, Angiolillo DJ et al. Safety and efficacy of cangrelor, an intravenous, short-acting platelet inhibitor in patients requiring coronary artery bypass surgery. *Heart Surg Forum.* 2013;16(2):E60-E69.
CHAMPION PHOENIX (design)	Leonardi S, Mahaffey KW, White HD et al. Rationale and design of the cangrelor versus standard therapy to acHieve optimal management of platelet inhibitiON PHOENIX trial. *Am Heart J.* 2012;163:768-776.e2.
CHAMPION PHOENIX	Bhatt DL, Stone GW, Mahaffey KW et al. Effect of platelet inhibition with cangrelor during PCI on ischemic events. *N Engl J Med*. 2013; 368(14):1303-1313.
CHAMPION (PCI, PLATFORM, PHOENIX) trials pooled	Steg PG, Bhatt DL, Hamm CW et al. Effect of cangrelor on periprocedural outcomes in PCI: a pooled analysis of patient-level data. *Lancet*. 2013;382(9909):1981-1992.
CHAMPION PHOENIX IPST	Généreux P, Stone GW, Harrington RA, et al. Impact of Intra-procedural Stent Thrombosis during Percutaneous Coronary Intervention: Insights from the CHAMPION PHOENIX Trial. *J Am Coll Cardiol.* 2013 Oct 24 [Epub ahead of print].

APPENDIX 2

Bleeding Scale Definitions

GUSTO criteria:

Hemorrhage was classified according to severity as GUSTO mild, moderate, or severe/life-threatening, according to the following definitions [The GUSTO Investigators, 1993]:

- Severe/life-threatening: intracranial hemorrhage or if hemodynamic compromise results
- Moderate: transfusion was required
- Mild: bleeding requiring intervention but not requiring blood transfusion or causing hemodynamic compromise

TIMI criteria:

Hemorrhage was classified as TIMI major or minor, according to the following definitions [Antman et al, 2005]:

- **Major:** Any intracranial bleeding or any bleeding associated with clinically overt signs associated with a drop in hemoglobin of >5 g/dL (or, when hemoglobin was not available, an absolute drop in hematocrit >15%)
- **Minor:** Any clinically overt sign of bleeding (including observation by imaging techniques) associated with a fall in hemoglobin of ≥3 g/dL and ≤5 g/dL (or, when hemoglobin was not available, an absolute drop in hematocrit of ≥9% and ≤15%)

To account for transfusion, hemoglobin and hematocrit measurements were adjusted for any packed red blood cells or whole blood given between baseline and post-transfusion measurements. A transfusion of one unit of blood was assumed to result in an increase of 1 g/dL in hemoglobin or of 3% in hematocrit.

Thus, to calculate the true change in hemoglobin or hematocrit if there has been an intervening transfusion between two blood measurements, the following calculations were performed:

Δ hemoglobin = [baseline hemoglobin – post transfusion hemoglobin] + [number of transfused units]

Δ hematocrit = [baseline hematocrit – post transfusion hematocrit] + [number of transfused units x 3]

Bleeding events were classified as instrumented or spontaneous according to the following definitions:

- Instrumented: any hemorrhage that occurred as a result of an invasive procedure

- Spontaneous: any hemorrhage that was not the direct result of an invasive procedure (eg, gingival bleeding, epistaxis, gastrointestinal bleeding).

ACUITY: Bleeding based on the ACUITY scale was defined as follows [Stone et al, 2004].

Major ACUITY bleeding was defined as any one of the following:

- intracranial
- retroperitoneal
- intraocular
- access site hemorrhage requiring radiological or surgical intervention
- ≥5 centimeter (cm) diameter hematoma at puncture site
- reduction in hemoglobin concentration of >4 g/dL without an overt source of bleeding
- reduction in hemoglobin concentration of >3 g/dL with an overt source of bleeding
- re-operation for bleeding
- use of any blood product transfusion

Minor ACUITY bleeding will be defined as all other bleeding not listed above as major.

BARC: Bleeding based on the Bleeding Academic Research Consortium (BARC) scale is defined as [Mehran et al, 2011]:

- Type 0: no evidence of bleeding
- Type 1: bleeding that was not actionable and did not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional
- Type 2: any clinically overt sign of hemorrhage (eg, more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that was actionable but did not meet criteria for Type 3, Type 4 (CABG-related), or Type 5 (fatal bleeding) BARC bleeding.
- Type 3: clinical, laboratory, and/or imaging evidence of bleeding with specific healthcare provider responses, as listed below:
  - Bleeding Academic Research Consortium type 3a bleeding
    - Any transfusion with overt bleeding
    - Overt bleeding plus hemoglobin drop ≥3 to <5 g/dL (provided hemoglobin drop is related to bleeding)
  - Bleeding Academic Research Consortium type 3b bleeding
    - Overt bleeding plus hemoglobin drop ≥5 g/dL (provided hemoglobin drop is related to bleed)

        - Cardiac tamponade
        - Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid)
        - Bleeding requiring intravenous vasoactive drugs
    - Bleeding Academic Research Consortium type 3c bleeding
        - Intracranial hemorrhage (not including microbleeds or hemorrhagic transformation; does include intraspinal); subcategories confirmed by autopsy, imaging, or lumbar puncture
        - Intraocular bleed compromising vision
- Type 4: Coronary Artery Bypass Graft–related bleeding
    - Perioperative intracranial bleeding within 48 hours
    - Reoperation after closure of sternotomy for the purpose of controlling bleeding
    - Transfusion of ≥5 U whole blood or packed red blood cells within a 48-hour period (only allogenic transfusions are considered transfusions for CABG-related bleeds)
    - Chest tube output ≥2 L within a 24-hour period
- Type 5: Fatal bleeding, bleeding that directly caused death with no other explainable cause
    - Probable fatal bleeding (type 5a) is bleeding that was clinically suspicious as the cause of death, but the bleeding was not directly observed and there was no autopsy or confirmatory imaging
    - Definite fatal bleeding (type 5b) is bleeding that was directly observed (by either clinical specimen [blood, emesis, stool, etc.] or imaging) or confirmed on autopsy

For all of the bleeding scale definitions, "clinically overt" or "overt source of" bleeding was defined as follows.

At least one of the following on the eCRF had to be checked:

- Requiring intervention: health care professional-guided medical treatment or percutaneous intervention
- Leading to hospitalization or an increased level of care: prolonged hospitalization or hospital transfer
- Prompting evaluation: an unscheduled visit to healthcare professional resulting in diagnostic testing

AND any of the following on the eCRF had to be checked:

- Clinically overt bleed
- Intracranial hemorrhage
- Intraocular
- Cardiac tamponade

- Retroperitoneal
- Access site bleeding requiring radiologic or surgical intervention
- Reoperation for bleeding
- Hemodynamic compromise
- Epistaxis
- Gross hematuria
- Hematemesis
- Hematoma ≥5 cm at puncture site

APPENDIX 3

PHOENIX CRF Bleeding Event Data Collection Page

Phoenix
Visit '48 Hour Follow Up' Page 'Bleeding Event'
PageObject = PBLD_R | Table = BLD | VisitID = 50 | PanelID = 20 | PanelSequence > 0 (Repeat detail)

Bleeding Event

Date of Bleed: BLDSTDT | Time of Bleed: BLDSTTM 24-hour clock | Type of bleed cbldtype BLDTYPE

Was this bleed associated with CABG? cyesno BLDCABG | Was this bleed associated with PCI? cyesno BLDPCI

Did this bleed involve any of the following? (check all that apply)

- BLDINTER Requiring intervention: health care professional-guided medical treatment or percutaneous intervention
- BLDHOSP Leading to hospitalization or an increased level of care: prolonged hospitalization or hospital transfer
- BLDEVAL Prompting evaluation: an unscheduled visit to healthcare professional resulting in diagnostic testing

Check all that apply:

- CLINOVRT Clinically overt bleed (including bleeding seen on imaging)
- INTRAHEM Intracranial Hemorrhage | Confirmed by cconfirm CONFIRM
- INTRAOC Intraocular | Vision compromised cyesno VISION
- PULMON Pulmonary
- CARDTAMP Cardiac Tamponade
- RETROPER Retroperitoneal
- GASTRO Gastrointestinal
- GENITO Genitourinary
- ACCSITE Access site bleeding requiring radiologic or surgical intervention
- REOP Reoperation for bleeding
- CHEST Chest Tube Output >= 2L within a 24 hour period
- THROMBO Thrombocytopenia | Platelets count cpltcnt PLTCNT
- HHDROP Drop in Hemoglobin and/or Hematocrit
  - Date: HHDROPDT | Time: HHDROPTM 24-hour clock
  - Please indicate the drop in Hemoglobin and/or Hematocrit (check all that apply). Indicate the maximum drop in the parameter.
    - HGBDROP Hemoglobin | Hemoglobin Level chgblevel HGBLEVEL
    - HCTDROP Hematocrit | Hematocrit Level chctlevel HCTLEVEL
- OTHBLD Other Bleeding Event | Specify OTHBLDSP (250)
- HEMCOMP Hemodynamic compromise | Requiring inotropes cyesno INOTROPE
- EPISTAX Epistaxis
- GRHEM Gross Hematuria
- HEMORRH Hemorrhoidal
- HEMATEM Hematemesis
- ECCHYMOS Ecchymosis
- OOZPSITE Oozing at puncture site
- HEMATOMA Hematoma
  - HEM5CM >=5 cm at puncture site
  - HEMOTHER Any other, including bruising
- BLTRAN Blood Transfusion
  - Date: BLTRANDT | Time: BLTRANTM 24-hour clock
  - BLTRANXS Check if multiple transfusions for the bleed episode
  - Enter total number of units for each blood product
    - Whole blood WHOLE (2.0) | Packed RBC PACKED (2.0)
    - Platelets PLATES (2.0) | Fresh Frozen Plasma PLASMA (2.0)

Add New

Narrative text boxes below to be completed for the following Bleeds:
Intracranial Hemorrhage, Intraocular, Reoperation for Bleeding, Retroperitoneal, Hemodynamic Compromise, >5 g/dl drop in Hemoglobin, >15% drop in Hematocrit, or as requested by sponsor.

Clinical Course / Patient Presentation: Patient presentation including any co-morbidities not already on the MedHx panel

CLINICAL (255)

Diagnostics: Labs, procedures used to diagnose the bleed, including date/time and results

DIAGNOSE (255)

Bleed Treatment: Medications, interventions (surgical and non-surgical) to treat the bleed

TREAT (255)

Outcome: Patient outcome including resolution date/time of bleed

OUTCOME (255)

Other Relevant information:

OTHINFO (255)

Add New

Created On: 2012-03-30T13:36:56

APPENDIX 4

Table 43: IV study drug administration for CHAMPION PHOENIX and CHAMPION pooled (ITT population)

	CHAMPION PHOENIX		CHAMPION Pooled	
	Cangrelor (N=5581)	**Clopidogrel (N=5564)**	**Cangrelor (N=12707)**	**Clopidogrel (N=12677)**
Received bolus or infusion, n/N (%)	5527/5581 (99.0)	5524/5564 (99.3)	12557/12707 (98.8)	12528/12677 (98.8)
Weight-adjusted cangrelor bolus (µg/kg)				
N	5527	5523	12557	12523
Mean ± SD	30.2 ± 1.4	NA	30.3 ± 4.4	NA
Median (Q1, Q3)	30.2 (30, 31)	NA	30.2 (30, 31)	NA
Duration of infusion (hours) [a]				
N	5523	5517	12525	12495
Mean ± SD	2.3 ± 0.47	2.3 ± 0.45	2.2 ± 0.5	2.2 ± 0.5
Median (Q1, Q3)	2.2 (2.0, 2.4)	2.2 (2.0, 2.4)	2.1 (2.0, 2.3)	2.1 (2.0, 2.4)
Weight-adjusted cangrelor infusion rate (µg/kg/min)				
N	5523	5516	12525	12,492
Mean (SD)	4.0 ± 0.2	NA	4.0 ± 0.2	NA
Median (Q1, Q3)	4 (4.0, 4.1)	NA	4 (4.0, 4.1)	NA
Total cangrelor dose (bolus and infusion)(mg)				
N	5527	5523	12557	12525
Mean ± SD	49.2 ± 14.3	NA	48.0 ± 14.2	NA
Median (Q1, Q3)	47.1 (40, 56)	NA	46.4 (39, 55)	NA

	CHAMPION PHOENIX		CHAMPION Pooled	
	Cangrelor (N=5581)	**Clopidogrel (N=5564)**	**Cangrelor (N=12707)**	**Clopidogrel (N=12677)**
Received IV infusion, n/N (%)				
N	5523/5581 (99.0)	5517/5564 (99.2)	12525/12707 (98.6)	12495/12677 (98.6)
<90 minutes	93/5523 (1.7)	76/5517 (1.4)	216/12525 (1.7)	162/12495 (1.3)
90 to <120 minutes	70/5523 (1.3)	74/5517 (1.3)	276/12525 (2.2)	285/12495 (2.3)
120 to 240 minutes	5331/5523 (96.5)	5350/5517 (97.0)	11958/12525 (95.5)	11979/12495 (95.9)
>240 to 300 minutes	27/5523 (0.5)	16/5517 (0.3)	70/12525 (0.6)	60/12495 (0.5)
>300 minutes	2/5523 (0.0)	1/5517 (0.0)	5/12525 (0.0)	9/12495 (0.1)

Sources: CHAMPION pooled data on file, Table 16.3.1.2.1 and Table 16.3.3.2.1; CHAMPION PHOENIX data on file, Table 3.1.2.1 and Table 3.3.2.1.
Note: percentages are rounded.
a CHAMPION PHOENIX duration of infusion summary results were converted to hours from minutes for purposes of comparison in this table.
IV = intravenous; ITT = intention to treat; Q1 = first quartile; Q3 = third quartile; SD = standard deviation; NA = not applicable

APPENDIX 5

Table 44: Oral study drug administration for CHAMPION PHOENIX and CHAMPION pooled (ITT population)

Parameter Category	CHAMPION PHOENIX		CHAMPION Pooled	
	Cangrelor (N=5581) n/N (%)	**Clopidogrel (N=5564) n/N (%)**	**Cangrelor (N=12707) n/N (%)**	**Clopidogrel (N=12677) n/N (%)**
Peri-PCI capsules (pink)	*(Placebo)*	*Clopidogrel loading dose (600 mg or 300 mg)*	*(Placebo)*	*Clopidogrel loading dose (600 mg or 300 mg)*
Dosage (mg)				
N	NA	5491	NA	12461
Median (Q1, Q3)	NA	600.00 (300.0, 600.0)	NA	600.00 (600.0, 600.0)
Number of capsules taken [a], n/N (%)				
0 [b]	1/5490 (0.0)	0/5491 (0.0)	4/12470 (0.0)	4/12461 (0.0)
1	0/5490 (0.0)	0/5491 (0.0)	3/12470 (0.0)	3/12461 (0.0)
2	1431/5490 (26.1)	1427/5491 (26.0)	1434/12470 (11.5)	1429/12461 (11.5)
3	0/5490 (0.0)	0/5491 (0.0)	11/12470 (0.1)	5/12461 (0.0)
4	4057/5490 (73.9)	4061/5491 (74.0)	11016/12470 (88.3)	11013/12461 (88.4)
>4	1/5490 (0.0)	3/5491 (0.1)	2/12470 (0.0)	7/12461 (0.1)
Load before start of PCI, n/N (%)	3460/5442 (63.6)	3442/5439 (63.3)	6914/12396 (55.8)	6868/12359 (55.6)
Load after start of PCI, n/N (%)	1982/5442 (36.4)	1997/5439 (36.7)	5482/12396 (44.2)	5491/12359 (44.4)
Post-infusion capsules (blue)	*Clopidogrel transition dose (600 mg)*	*(Placebo)*	*Clopidogrel transition dose (600 mg)*	*(Placebo)*
Number of capsules taken [a], n/N (%)				
0 [b]	2/5447 (0.0)	4/5437 (0.1)	10/12344 (0.1)	9/12318 (0.1)
1	0/5447 (0.0)	1/5437 (0.0)	2/12344 (0.0)	2/12318 (0.0)
2	3/5447 (0.1)	1/5437 (0.0)	5/12344 (0.0)	2/12318 (0.0)
3	0/5447 (0.0)	0/5437 (0.0)	2/12344 (0.0)	5/12318 (0.0)
4	5442/5447 (99.9)	5431/5437 (99.9)	12325/12344 (99.8)	12300/12318 (99.9)
>4	0/5447 (0.0)	0/5437 (0.0)	0/12344 (0.0)	0/12318 (0.0)

Parameter Category	CHAMPION PHOENIX		CHAMPION Pooled	
	Cangrelor (N=5581) n/N (%)	Clopidogrel (N=5564) n/N (%)	Cangrelor (N=12707) n/N (%)	Clopidogrel (N=12677) n/N (%)
Dosage (mg)				
N	5447	NA	12344	NA
Median (Q1, Q3)	600.00 (600.0, 600.0)	NA	600.00 (600.0, 600.0)	NA

Source: CHAMPION pooled data on file, Table 16.3.2.2.1; CHAMPION PHOENIX data on file, Table 3.2.2.1.

[a] For clopidogrel dose, 1 capsule=150 mg. Open-label capsules are excluded from these results.

[b] Study medication was administered to the patient but reported as not digested by the patient.

Note: percentages are rounded.

ITT = intention to treat; PCI = percutaneous coronary intervention; Q1 = first quartile; Q3 = third quartile; SD = standard deviation; NA = not applicable