22 January 2015
EMA/137542/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Kengrexal

International non-proprietary name: cangrelor

Procedure No. EMEA/H/C/003773/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

Table of contents

List of abbreviations

5'NT	5' Nucleotidase
8-SPT	8-psulphophenyl theophyllin
ACS	acute coronary syndrome
ACUITY	Acute Catheterization and Urgent Intervention Triage strategy
ADP	adenosine diphosphate
AE	adverse event(s)
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
API	Active Pharmaceutical Ingredient
AR	Assessment Report
ARC	Academic Research Consortium
ASA	acetylsalicylic acid
ASMF	Active Substance Master File
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the curve
AUC_{0-t}	area under the concentration curve from administration to last observed concentration at t.
$AUC1_{h-t}$	area under the concentration curve from 1 h post-administration to last observed concentration at t.
β-NAG	N-acetyl-β-D-glucosaminidase
BARC	Bleeding Academic Research Consortium
BT	bleeding time
CABG	coronary artery bypass graft
CAD	coronary artery disease
CEC	Clinical Events Committee
CFR	cyclic flow reduction
CFU	Colony Forming Units
CI	confidence interval
Cmax	maximum plasma concentration
CMR	Carcinogenic Mutagenic Reprotoxic

CNS	central nervous system
CoA	Certificate of Analysis
CrCl	creatinine clearance
CSR	clinical study report
Css	concentration at steady state
cTn	Cardiac Troponin
CYP	cytochrome P450
d	Day
D2	dopaminergic
DAPT	dual antiplatelet therapy
DES	drug-eluting stent
DRF	dose range finding
ECG	electrocardiographic / electrocardiogram(s)
EFD	embryo fetal development
F	female
FCA	Freund's complete adjuvant
FFP	fresh frozen plasma
g	gram
GCP	Good Clinical Practice
GGT	gamma glutamyltransferase
GLDH	glutamate dehydrogenase
GLP	Good Laboratory Practice
GP	glycoprotein
GTN	glyceryl trinitrate
GUSTO	Global Use of Strategies to Open Occluded Coronary Arteries
h	hour(s)
H2	Histaminergic
HDPE	High Density Polyethylene
HED	human equivalent dose
h/hr	hour
HPLC	high-performance liquid chromatography
HR	hazard ratio
IDR	ischaemia-driven revascularisation

IC50	half maximal inhibitory concentration
ICH	International Conference on Harmonisation
ID	inner diameter
ID50	half maximal inhibitory dose
IPC	In-Process Control
IPST	intraprocedural stent thrombosis
IR	Infra Red
ITT	intent to treat
IV	intravenous
kg	kilogram(s)
LDPE	Low Density Polyethylene
LOD	Limit of Detection
LOQ	Limit of Quantification
LVEF	left ventricular ejection fraction
M	male
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram(s)
mITT	modified intent to treat
MI	myocardial infarction
min	minutes
mL	milliliter
mm	millimeter
mol	mole
MPS	multiparameter screen
MS	Mass Spectrometry
NA	not applicable
NaCl	sodium chloride
ND	Not detected
NF	national formulary
ng	nanogram

NLT	Not less than
NMR	Nuclear Magnetic Resonance
NMT	Not more than
nM	Nanomolar
NNH	number needed to harm
NNT	number needed to treat
NOAEL	no-observed adverse effect level
NOEC	no-observed adverse effect concerntration
NOEL	no-observed effect level
NSTEMI	non-ST segment elevation myocardial infarction
OECD	Office of Economic Cooperation and Development
OOS	Out of Specification
OR	odds ratio
PAD	peripheral artery disease
PAGE	polyacrylamide gel electrophoresis
pc	post-coitum
PBC	Persistent Bioacumulatic Toxic
PCI	percutaneous coronary intervention
PD	pharmacodynamic(s)
PhEur	European Pharmacopeia
PK	pharmacokinetic(s)
PRBC	packed red blood cell(s)
PRU	P2Y12 Reaction Unit(s)
PSA	passive cutaneous anaphylaxis
PVC	premature ventricular contraction
QOS	Quality Overall Summary
RBC	red blood cell
RH	Relative Humidity
RR	relative risk
RRR	relative risk reduction
SA	stable angina
SAE	serious adverse event(s)
SC	subcutaneous

SD	standard deviation
SDH	succinate dehydrogenase
SDS	sodium dodecyl sulfate
SDS-PAGE	sodium dodecyl sulfate polyacrylamide gel electrophoresis
SmPC	summary of product characteristics
SMQ	standardised MedDRA query
SOC	system organ class
ST	stent thrombosis
STEMI	ST segment elevation myocardial infarction
t1/2	half-life
TEAE	Treatment-emergent adverse event.
TIMI	thrombolysis in myocardial infarction
TK	toxicokinetic
t-PA	tissue plasminogen activator
UA	unstable angina
UDMI	universal definition of myocardial infarction
y	year(s)
µg	microgram(s)
µM	micromolar
USP	United States Pharmacopeia
UV	Ultraviolet
w/v	weight per volume
WFI	Water for Injections

* This is a general list of abbreviations, not all abbreviations will be used.

Key to legacy/alternative descriptors for cangrelor and metabolites

Molecular Species Code	Description of Molecule
Cangrelor FPL 69931MX ARL 69931MX AR-C69931MX	All refer to the Drug Substance synthesized as the tetrasodium (MX) salt and can be regarded as interchangeable. The prefixes "FPL", "ARL" and "AR-C" were codes applied to research compounds by Fisons Pharmaceuticals, Astra and AstraZeneca, respectively
ARL 69931MY	Early research batches were provided as the tri-ammonium (MY) salt
ARL 69931XX AR-C69931XX	The free acid (XX) of cangrelor - the active form in solution and measured by bioanalytical methods
ARL 69712XX AR-C69712XX	The major plasma nucleoside metabolite of cangrelor
ARL 88558KP AR-C88558KP	The putative monophosphate metabolite of cangrelor as the disodium (KP) salt
ARL 71301XX AR-C71301XX	A minor purine base metabolite
ARL 90439XX AR-C90439XX	A sulfoxide metabolite of AR-C69712XX
ARL 90441XX AR-C90441XX	A sulfoxide metabolite of AR-C71301XX

1. Background information on the procedure

1.1. Submission of the dossier

The applicant The Medicines Company UK Ltd submitted on 4 December 2013 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Kengrexal, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 April 2013.

The applicant applied for the following indication.

Percutaneous coronary intervention (PCI)
Kengrexal is a $P2Y_{12}$ platelet inhibitor indicated for the reduction of thrombotic cardiovascular events (including stent thrombosis) in adult patients with coronary artery disease undergoing percutaneous coronary intervention (PCI).
During the pre-operative period when oral $P2Y_{12}$ therapy is interrupted due to surgery ('Bridging')
Kengrexal is also indicated to maintain $P2Y_{12}$ inhibition in adult patients with acute coronary syndromes or in 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 ('Bridging').

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that cangrelor was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0210/2013 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0210/2013 was not yet completed as some measures were deferred.

The PDCO issued an opinion on compliance for the PIP P/0210/2013.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance Cangrelor tetrasodium, The Medicines Company UK Ltd, contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific Advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturers

Manufacturer responsible for batch release

Haelsa Pharma GmbH
Nikolaus-Duerkopp-Str. 4a
33602 Bielefeld
GERMANY

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Pieter de Graeff Co-Rapporteur: Alar Irs

- The application was received by the EMA on 4 December 2013.
- The procedure started on 26 December 2013.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 14 March 2014 (Annex 1).
- The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 13 March 2014 (Annex 2).
- The PRAC RMP Advice and assessment overview was adopted by PRAC on 10 April 2014 (Annex 3)
- During the meeting on 25 April 2014, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 29 April 2014 (Annex 4).
- The applicant submitted the responses to the CHMP consolidated List of Questions on 21 July 2014. The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 02 September 2014 (Annex 5).
- The PRAC RMP Advice and assessment overview was adopted by PRAC on 11 September 2014 (Annex 6)
- During the CHMP meeting on 25 September 2014, the CHMP agreed on a list of outstanding issues to be addressed by the applicant (Annex 7).
- During a meeting of a CV SAG/Expert group on 1 December 2014 Experts were convened to address

questions raised by the CHMP (Annex 8).

- The applicant submitted the responses to the CHMP List of Outstanding Issues on 22 October 2014. The Joint Rapporteur/Co-Rapporteur Assessment Report on the responses provided by the applicant was sent out on 6 January 2015 (Annex 9).
- The PRAC RMP Advice and assessment overview was adopted by PRAC on 9 January 2015 (Annex 10).
- During the meeting on 22 January 2014, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Kengrexal.

2. Scientific discussion

2.1. Problem statement

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

Arterial injury at the site of PCI exposes the thrombogenic subintimal layer to platelets, activates the coagulation system, and serves as a potent stimulus for thrombin formation. The reactivity of platelets to agonists plays a central role in the genesis of thrombosis during and following PCI. PCI and stent implantation can involve significant localised injury to the vascular endothelium [Thomas et al, 2009], even in stable patients [Babu et al, 2011]. This vascular trauma is prothrombotic and inflammatory and can result in ischaemic complications including ST [Bonello et al, 2006]. Stent thrombosis occurring after PCI is an infrequent but serious complication. 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 [Iakovou et al, 2005; Airoldi et al, 2007; Schulz et al 2009; Urban et al, 2011].

Antiplatelet therapies, in particular the $P2Y_{12}$ receptor inhibitors, reduce ischaemic events, including MI and ST [Wiviott et al, 2007; Wallentin et al, 2009; Yousuf and Bhatt, 2011]. To date, only oral $P2Y_{12}$ inhibitors have been available. While older IV antiplatelet agents such as glycoprotein (GP)IIb/IIIa inhibitors are able to reduce MI successfully, their use has not been associated with a lower risk of ST, but rather a later onset of ST [Assali et al, 2000; Rinaldi et al, 2008]. Additionally, their effect cannot be quickly reversed and they can cause an increase in bleeding complications [Bhatt and Topol, 2000].

Oral platelet $P2Y_{12}$ inhibitors have been shown to reduce ischaemic events including death in patients with ACS and in patients undergoing PCI in a series of adequate and well controlled trials [CAPRIE Steering Committee 1996; Steinhubl et al, 2002; Fox et al, 2004; Wiviott et al, 2007; Wallentin et al, 2009].

A meta-analysis of 42,198 patients from five randomised, 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].

Stent thrombosis is a device-induced, arterial thrombosis. Stent thrombosis is a potentially catastrophic complication of PCI [Holmes et al, 2010]. Stent thrombosis can present as ST-segment elevation myocardial infarction (STEMI) or cardiogenic shock, with case fatality reaching as high as 45% in some studies [Iakovou et al, 2005; Airoldi et al, 2007; Schulz et al, 2009; Urban et al, 2011]. These striking data are among the main reasons for recommendations 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].

Limitations of oral $P2Y_{12}$ inhibitors in an acute PCI setting include delayed onset of action, an unpredictable response, and poor reversibility.

Available therapies include clopidogrel and more potent oral agents such as prasugrel and ticagrelor are also subject to 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 catheterisation to be effective) is often administered. The largest randomised 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 et al, 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 [Widimsky et al, 2008]. Furthermore, pre-treatment 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 revascularisation or who go to the operating room immediately after undergoing coronary angiography.

Bridging. A treatment dilemma currently exists in patients receiving oral platelet $P2Y_{12}$ inhibitors for coronary artery disease who require surgery. Product labelling 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 confers a high risk for thrombotic cardiac events, such as ST, MI, and death.

Complicating matters further, product labelling and treatment guidelines also recommend discontinuation of these agents at least five to seven days prior to any surgery to avoid the high risk of surgical bleeding known to be associated with oral $P2Y_{12}$ inhibitors when taken at the time of surgery.

Continuing oral $P2Y_{12}$ inhibitor therapy during the perioperative period is associated with an increased incidence of major haemorrhagic complications by as much as 50% [Douketis et al, 2012]. A meta-analysis of three prospective randomised studies and 17 observational studies showed that recent exposure to clopidogrel before CABG 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 et al, 2012]. A systematic review of 37 studies comparing postoperative outcomes in patients exposed to clopidogrel in the five days before surgery, vs those who were not exposed showed a higher incidence of reoperation for bleeding (odds ratio [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].

Further increased bleeding risk has also been demonstrated with the more potent oral $P2Y_{12}$ inhibitors. In the TRITON thrombolysis in myocardial infarction (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 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 the labeled 5 to 7 days. Accordingly, recommendations are to delay surgery for at least seven days and ideally longer after discontinuation of prasugrel [Van de Werf et al, 2008; Wijns et al, 2010; Ferraris et al, 2011; Hamm et al, 2011; Hillis et al, 2011; Efient SmPC 2013].

There are currently no treatment strategies available that provide consistent and effective platelet P2Y12 inhibition that can be turned on when it is needed (such as in an acute PCI setting) and that can be turned off when it is not, thus avoiding increasing bleeding risk, which is particularly important in patients who require 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. During its development, cangrelor has been identified as FPL-69931MX, ARL 69931MX, and AR-C69931MX for the tetrasodium salt, ARL-69931XX for the free acid, and ARL-69712XX for the major plasma nucleoside metabolite (currently AR-C69712XX). The chemical structure 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..

Proposed Clinical Indications:

Percutaneous coronary intervention (PCI)

Kengrexal is a $P2Y_{12}$ platelet inhibitor indicated for the reduction of thrombotic cardiovascular events (including stent thrombosis) in adult patients with coronary artery disease undergoing percutaneous coronary intervention (PCI).

During the pre-operative period when oral $P2Y_{12}$ therapy is interrupted due to surgery ('Bridging')

Kengrexal is also indicated to maintain $P2Y_{12}$ inhibition in adult patients with acute coronary syndromes or in 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 ('Bridging').

Proposed Dosage Form, Route of Administration, and Dosing Regimen:

Kengrexal 50 mg powder for concentrate for solution for injection or infusion. Kengrexal is intended for intravenous (IV) use, only after reconstitution and dilution.

The proposed posology is as follows:

Percutaneous coronary intervention (PCI)

The recommended dose of Kengrexal for patients undergoing PCI is a 30 µg/kg intravenous bolus followed immediately by 4 µg/kg/min intravenous infusion. The bolus and infusion should be initiated prior to the procedure and continued for at least 2 hours or for the duration of the procedure, whichever is longer. At the discretion of the physician, the infusion may be continued for a total duration of 4 hours.

During the pre-operative period when oral $P2Y_{12}$ therapy is interrupted ('Bridging')

Kengrexal should be administered as a 0.75 µg/kg/min intravenous infusion as soon as possible after the discontinuation of oral $P2Y_{12}$ inhibition and continue the infusion during the bridging period. The infusion can be continued until one hour prior to the administration of anesthesia for surgery when it should be discontinued. Kengrexal at this dose has been studied in clinical trials for bridging periods up to 7 days.

The application is mainly based on the CHAMPION clinical studies, which comprises three phase III studies. Two of these studies (CHAMPION PCI and CHAMPION PLATFORM) have been prematurely terminated due to the low likelihood of reaching their primary endpoint. The only complete phase III study is CHAMPION-PHOENIX. To support the bridging indication, a phase 2 study "BRIDGE" is submitted.

In this application, the point to Consider on the clinical investigation of new medicinal products for the treatment of acute coronary syndrome without persistent ST segment elevation (CPWP/EWP/570/98) is applicable. Compliance with this guidance is discussed later.

No Scientific advice was requested from the EMA. No reference is made to any scientific advice from other regulatory authorities.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a powder for concentrate for solution for injection or infusion containing cangrelor tetrasodium equivalent to 50 mg cangrelor as active substance.

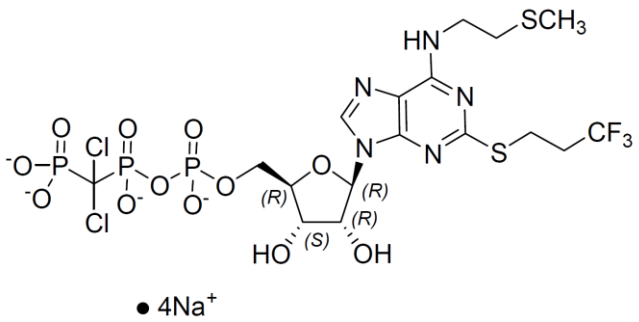
Other ingredients are: mannitol, sorbitol and sodium hydroxide.

The product is available in 10 ml single use Type I glass vials closed with a Flurotec coated butyl rubber stopper and sealed with crimped aluminium seal. The product needs to be reconstituted in 5 ml WFI and further diluted in 500 ml 0.9% sodium chloride or 5% glucose intravenous infusion bags. After reconstitution 1 ml concentrate contains 10 mg cangrelor. After dilution 1 ml of solution contains 200 micrograms cangrelor.

2.2.2. Active Substance

General information

The chemical name of cangrelor tetrasodium is dichloro(((((2R,3R,4S,5R)-3,4-dihydroxy-2-(6-(2-(methylthio)ethylamino)-2-(3,3,3-trifluoropropylthio)-purin-9-yl)tetrahydrofuran-5-yl)methoxy)(hydroxy)phosphoryloxy) (hydroxy)phosphoryl)methylphosphonic acid, tetrasodium salt and it has the following structure:



The structure was confirmed by ^{1}H NMR, ^{13}C NMR, ^{31}P NMR, MS and HR-MS and FT-IR.

Cangrelor tetrasodium is a lyophilised, amorphous, white to off-white powder. Cangrelor tetrasodium is hygroscopic, however, under normal handling conditions associated water levels remain below 10% (the active substance specification limits) and do not impact stability or physical properties of cangrelor tetrasodium. The substance is very soluble in water, practically insoluble in ethanol and acetone and insoluble in methanol.

Cangrelor tetrasodium exhibits stereoisomerism due to the presence of 4 chiral centres. Enantiomeric purity is controlled routinely by specific optical rotation. Polymorphism has not been discussed. Taking into account the finished product pharmaceutical form it was considered justified.

The information on the active substance is provided according to the Active Substance Master File (ASMF) procedure.

Manufacture, characterisation and process controls

Cangrelor tetrasodium is synthesised in seven main steps using commercially available well-defined starting materials with acceptable specifications.

The choice of the two starting materials has been sufficiently justified on the basis of their impact on the final active substance stereochemistry and their impact on its impurities profile. Especially with regard to the latter sufficient information has been provided regarding the origin and fate of potential genotoxic impurities (GTIs) arising from the starting materials. They are adequately controlled in the stage 4 intermediate and in addition it has been shown that any potential GTIs are purged in the downstream process.

Crude cangrelor tetrasodium is purified by column chromatography and lyophilised. The different steps of cangrelor tetrasodium manufacture are performed by two different sites, one for the synthesis and another one for the lyophilisation.

Holding time for intermediates have been established.

The stereochemistry of cangrelor is defined by the stereochemistry of the starting material, which is controlled by appropriate specification. Information has been presented to show that under the manufacturing conditions, epimerization during the process is highly unlikely.

The fate of genotoxic impurities arising from raw material has been discussed and appropriate in-process controls were put in place.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

Specification

The active substance specification includes tests for: appearance, identity (FTIR, HPLC), sodium identification (Ph. Eur.), assay (HPLC), impurities (HPLC, IC), residual solvents (GC), water content (KF), pH (Ph. Eur.), specific rotation (Ph. Eur.) heavy metals (Ph. Eur.), microbial limits test (Ph. Eur.), specific microorganisms (Ph. Eur.) and bacterial endotoxins (Ph. Eur).

Potential genotoxic impurities are adequately controlled in the stage 4 intermediate product ensuring that their levels in final active substance will not exceed the threshold of toxicological concern (TTC) of 1.5 µg/day. Therefore, there is no need to monitor genotoxic impurities in final active substance.

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

The stereochemistry of the active substance is defined by the starting materials and the manufacturing process for the synthesis of cangrelor does not give rise to any isomerization. Therefore, monitoring chiral impurities in final active substance is considered not necessary.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines.

Batch analysis data (three pilot scaled and 6 commercial scale batches) of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on 4 production scale batches and one pilot scale batch of active substance from the proposed manufacturer were provided. One batch was packaged in the intended commercial package. Other batches were packaged in less protective packaging. The batches were stored for 36 months under long term conditions at -20 ± 5 °C and for up to 6 months at 5 ± 3 °C according to the ICH guidelines.

The following parameters were tested: physical description, pH, assay, water content, related substances. In addition, bacterial endotoxins was tested annually on two batches. Microbial enumeration test was conducted on three batches at 24 and 36 months. The analytical methods used were the same as for release and were stability indicating.

All data generated under long-term storage condition (-20 ± 5 °C) met the proposed specification requirements. Satisfactory data were obtained under elevated temperature conditions (2-8 °C) for all batches up to 6 months except for one batch, for which an out of specification result was observed at 6 months. These data support the short term excursion outside the proposed label storage conditions (-20 ± 5°C) during shipping or handling.

A photostability study was conducted as part of the assay and impurity method validation according to ICH QIB. The product was found to be photo sensitive and should be protected from light during storage.

A freeze/thaw study for three cycles was performed on one batch and assay and related impurities were analysed for. No difference in results was observed.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The aim of the pharmaceutical development was to develop a sterile formulation for injection or infusion. Cangrelor is highly soluble in water but degrades primarily by hydrolysis and lacks adequate solution stability. It was therefore developed as a lyophilized dosage form which requires reconstitution with Sterile Water for Injection and further dilution prior to administration.

For finished product development, several dosage strengths, ranging from 10 mg to 300 mg of cangrelor per vial, were developed throughout clinical phase I and II. All the formulations were prepared in the same manner and contained the same qualitative composition as the proposed commercial formulation for Cangrelor for Injection. These formulations were used in different clinical studies. Only the 50 mg per vial dosage strength was further developed for all future Phase III Clinical Trials.

Mannitol is used in the formulation as bulking agent to produce a firm, homogeneous cake. Sorbitol is included in the formulation to avoid formation of crystalline mannitol. Sorbitol also helps to stabilise the formulation and produce an isotonic solution after reconstitution. The amount of sorbitol required to minimise crystallisation of mannitol was determined by using Differential Scanning Calorimetry (DSC). The formulation with 1:1:3 ratio of active substance, sorbitol and mannitol respectively was found to provide optimal characteristics with respect to lyophilised cake while demonstrating acceptable chemical stability. This formulation showed an acceptable tonicity 287-290 mOsM/kg.

A pH of 8.0-9.5 was selected for the formulation to be close to the physiological range as well as to improve stability in aqueous solution. The bulk formulation pH is adjusted with 0.1N sodium hydroxide.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The manufacturing process development has been adequately explained and contained studies on the compatibility with manufacturing parts and filters, light stability, hold time studies and lyophilisation process settings. Considering the active substance instability to heat the choice of the sterilisation method is considered justified.

A 4 % overfill was use to compensate for the displacement volume created by the solid content of the formulation upon reconstitution.

All formulations used during clinical development were prepared in the same manner and contained the same qualitative composition as the proposed commercial formulation for Cangrelor for Injection.

The stability results of the reconstituted and diluted product have been provided and show in-use stability up to 24 hrs at room temperature. However the following statement is included in the SmPC "After opening the vial the powder should be reconstituted immediately prior to dilution and use. Do not refrigerate. From a microbiological point of view, unless the method of reconstitution/dilution precludes the risk of microbiological contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user."

Compatibility with 103 intravenous medicines has been tested and 15 were found to be incompatible with cangrelor for co-administration. However, as results of assay / degradation products of the admixtures have not been provided, it has not been shown that the other 88 products are fully compatible with Cangrelor. This is reflected in the SmPC in section 6.2 "in the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products".

The primary packaging is a 10 ml glass vials (Type 1) closed with a Flurotec coated butyl rubber stopper and sealed with crimped aluminium seal. The material complies with Ph.Eur. requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of seven main steps: thawing of the active substance, preparation of cangrelor bulk solution, bioburden reduction by filtration, sterile filtration and aseptic filling, lyophilisation and stoppering, capping and secondary packaging. Critical steps have been defined and the in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

The process is considered to be a non-standard manufacturing process. The process has been validated and results of three commercial scale validation batches have been provided showing compliance to the requirements. Holding times have been set based on the validation runs and/or media fill results. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form and are the following: appearance (visual), description of constituted solution (visual), reconstitution time (visual), pH (Ph. Eur.), moisture content (KF), identification (HPLC, UV), assay and degradation products (HPLC), particulate matter (Ph. Eur.), sterility (Ph. Eur.), endotoxins (Ph. Eur.) and uniformity of dosage units (Ph. Eur., HPLC). The release and shelf-life limits are identical except for one specified impurity and total degradants.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

The analytical methods have been adequately described and validated.

Batch analysis results are provided for 2 production scale batches and 1 pilot batch manufacture at the proposed manufacturing site confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification. Additional batch analysis results are provided for batches manufactured at other manufacturing sites.

Stability of the product
Stability data of two commercial scale and six pilot scale development batches of finished product stored under long term conditions for 48 months at 25 ºC / 60 % RH and for up to 6 months under accelerated conditions at 40 ºC / 75 % RH according to the ICH guidelines were provided. The batches are representative to those proposed for marketing and were packed in 10 ml type I glass vials with bromobutyl rubber stoppers. Samples were tested according to the shelf life specifications. The analytical procedures used are stability indicating.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The finished product was shown to be stable in the clear glass vial without label and is considered to be not light-sensitive.

Additional stability study on one batch demonstrated that the finished product was stable after freezing (-10°C to -20°C) for up to 14 days. However no data were provided to demonstrate that the reconstituted/diluted solution could be refrigerated therefore "Do not refrigerate" is included in the storage conditions of the SmPC for reconstituted and diluted product.

Based on available stability data, the shelf-life and storage conditions as stated in the SmPC are acceptable.

Adventitious agents
No excipients derived from animal or human origin are used in the product.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics such as sterility, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

None

2.3. Non-clinical aspects

2.3.1. Introduction

The non clinical part of this application is based on studies in animals where pharmacodynamics, pharmacokinetics and toxicology of cangrelor have been characterized. Cangrelor is pharmacologically active in both rats and dogs, and is metabolized similarly in rats, dogs, and humans.

All pivotal toxicity studies were performed in compliance with the principles of Good Laboratory Practice (GLP) that were in place at time of conduct. Some early studies do not claim GLP compliance although they were conducted in a GLP compliant environment. However, the pre-clinical safety program was conducted in the mid 1990s. During this time, ICH safety pharmacology guidelines were not in place. As a result, most of the safety pharmacology studies including CNS evaluation in mice and cardiovascular evaluation in dogs did not contain written assurance of GLP compliance with the exception of a single-dose cardiovascular and respiratory study in rats. The non-GLP status of the safety pharmacology studies was not considered to compromise the scientific integrity or affect the experimental results.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Cangrelor has a highly selective profile for inhibition of the ADP-dependent platelet aggregation; its pharmacology can be characterised as being an inhibitor of platelet aggregation *in vitro*, in various species, rat dog and human, with the rat as a less sensitive animal species. Dose-related pharmacodynamic (PD) platelet inhibitory effects of cangrelor have been characterized too *in vivo*, and these data support cangrelor's therapeutic potential. Cangrelor has shown to be a short-acting, reversible antithrombotic agent in an animal disease model of arterial thrombosis.

In addition, the safety, potency, and efficacy of cangrelor was compared to other IV platelet inhibitors including the GPIIb/IIIa antagonists, Ro 449883 (also known as lamifiban) and GR 144053, in a canine model of thrombosis, and potential PD interactions between cangrelor and other thrombolytic and anticoagulant agents commonly employed in thrombotic-related disorders were studied. Cangrelor is also highly effective in preventing ADP-induced platelet aggregation including when administered in combination with tissue-plasminogen activator.

Secondary pharmacodynamic studies

The nonclinical pharmacology screening of cangrelor indicated no important secondary PD actions such as physiological processes and organ functions unrelated to platelet function including activity on P1 purinergic receptors, adrenergic, dopaminergic (D2), histaminergic, and serotonergic receptor mediated functions, as well as neutrophil activation.

Safety pharmacology programme

The safety pharmacology program consisted of studies in conscious and anesthetized mice, rats, cats, and dogs, which evaluated autonomic, cardiovascular, respiratory, central nervous system (CNS), and behavioral

responses to continuous IV infusions of cangrelor for various durations of dosing ranging from 10 minutes to several days. The main findings are described below:

Cangrelor is associated with some CNS-effects, despite the fact that in a distribution study in rats (at much lower doses: about 1-1.5 mg/kg) almost no distribution to the brain has been observed. The latter fact support the conclusion that a considerable margin of safety is expected for this effect of cangrelor, compared with the therapeutic dose.

Cangrelor does not induce cardiovascular effects in dogs, which might be sufficiently predictive for the human situation. Other data suggest that cangrelor showed an interaction with tissue plasminogen activator, which can interpreted as contributing to the therapeutic effect. Negative pharmacodynamic interactions have not been identified thus far. An hERG-assay, has not been conducted. The lack of this type of data has been justified.

In conclusion, the results of the safety pharmacology studies did not indicate a special safety risk for cangrelor use in humans.

2.3.3. Pharmacokinetics

Methods of analysis

The methods used in the pivotal toxicity studies were not always the validated versions described in the pharmacokinetics section. Moreover, in spite of the fact that stability of the parent compound was only shown for storage periods of 4-8 weeks, and stability of the metabolite in plasma samples could not be established, in the toxicokinetics studies the samples were stored for up to several months. Considering the very variable plasma concentrations of parent compound, and lack of stability data of the metabolite in plasma over the periods of storage of the samples, it must be concluded that overall the reported toxicokinetic data probably are inaccurate and may either under- or overestimate the actual exposure. A satisfactory explanation of the observed variability has not been provided. The possibility that the toxicokinetic data may either under- or overestimate; the actual exposure should be kept in mind when interpreting the data. The applicant indicated that the analytical methods were not technically the same due to the fact the assays have different extraction and detection methods. This has been mentioned in the nonclinical overview.

Absorption

In general, plasma pharmacokinetic properties of cangrelor and its main metabolite AR-C69712XX are similar between rats and dogs, and are linear and dose-proportional. In rats and dogs, steady-state plasma levels of cangrelor were observed at the time the first blood sample was taken and remained stable until the infusion was stopped. After infusion, plasma cangrelor levels declined rapidly with an initial plasma elimination half-life of less than 2 min in the rat and less than 1 min in the dog. Approximately 90% of a total dose of cangrelor was cleared from the plasma during the initial elimination phase. This was followed by a more prolonged terminal elimination phase for the remaining 10% of infused drug. The plasma concentration profile in rabbits declined in a biphasic manner similar to rats and dogs, however, the half-life of the initial phases was significantly longer (~20 minutes). In addition, the exposure (AUC) in rabbits was higher compared to rats and dogs. Plasma clearance differed between the species examined, varying from low in rabbits to moderate in rat and dog. The volume of distribution indicates low distribution into tissues in rabbit, and female dogs, and moderate tissue distribution in rat and male dog. Cangrelor terminal half-life, Vd and AUC values were consistently greater in males compared to females in rats and dogs, however duration of infusions in males was also longer than in the females. The exposure to the main plasma metabolite AR-C69712XX varied between species: 4% of cangrelor in rabbits, 18% of cangrelor in rats, 26% of cangrelor in humans and 52% of cangrelor in dogs. Following repeated infusions, the

exposure to cangrelor increased approximately dose-proportional. Cangrelor or its metabolites are not retained in the body, nor do they accumulate with successive infusions.

Distribution

Cangrelor was highly bound to plasma proteins *in vitro* in rat, dog and human, with a plasma protein binding of ~97-98% in rats, ~92-93% in dogs and ~97-98% in humans, respectively. ARL-69712XX is also highly bound, though less than cangrelor, to plasma proteins, ~88-89% in rats and ~85-86% in dogs. In humans, the plasma protein binding of ARL-69712XX is ~88-89%. The free fraction of cangrelor and ARL-69712XX in dogs at the tested concentrations is therefore a factor 3-4 higher than in rat and human.

Radiolabelled cangrelor in rats quickly distributed to highly vasculated and excretory organs, like liver, kidney, heart, lung and spleen. In addition, high concentrations were found in the pancreas and intestinal tract. Radioactivity in most organs and tissues decreased quickly after infusion, but in the intestinal tract, radioactivity increased further for up to 6 hours, after which it decreased too. The high concentrations in intestinal content can be considered due to biliary excretion. The kidneys also showed high levels for prolonged time. Brain, spinal cord and eyes contained negligible quantities at all time points. There was no evidence of binding to melanine in the eyes. However, it is noted that at very high doses (≥100 mg/kg/day), neurotoxicity was observed. At 6 hours, signs of renal tubular toxicity were seen and radioactivity increased in the order: renal medulla < renal inner cortex < renal pelvis < urine. No specific cellular location of the radioactivity in inner cortex and papilla could be distinguished. Animals predosed with unlabelled cangrelor showed a distinctive pattern of distribution, with radioactivity concentrated in the lumen and adjacent cells of tubules scattered throughout the cortex, this seemed associated with renal tubular degeneration and necrosis. Increased levels of radioactivity in discrete areas of renal pelvis and bladder were consistent with an urothelial distribution and suggest that cangrelor and/or its metabolites were higher at this location than in the surrounding tissue. At 24 hours post dose, most radioactivity had been eliminated from the kidneys.

Only low quantities of radioactivity were detectable in the foetal body. Since the highest concentration in the foetal body was observed 30 minutes after infusion, it was assumed that this radioactivity was due to metabolites more lipophilic than the parent compound crossing the placenta. In the embryo-foetal toxicity studies embryofoetal toxicity was observed at all tested doses. It cannot be excluded that the more prolonged infusion in these studies resulted in higher embryo-foetal exposure than observed in the distribution study.

Metabolism

Cangrelor is rapidly metabolised in the circulation by dephosphorylation to a nucleoside metabolite, AR-C69712XX. The initial inactivation step is followed by metabolism to various products, mainly sulphoxides, which are eliminated. The primary enzyme systems responsible for the metabolism of cangrelor have not been identified. Metabolism of cangrelor was studied in rats and dogs and was similar in both species with no sex differences. The metabolic profile of cangrelor in the examined animals is similar to that in humans.

Excretion

Rats and dogs of both sexes excreted most of the dose within the first 24 hrs and excretion was almost complete after 48 hrs. Overall recovery was >90% for most subgroups. Metabolites are excreted mainly via the feces (male rat 60%, female rat 77%, dog 85%) with a small proportion excreted in the urine (male rat 30%, female rat 18%, dogs of both sexes 11%). This is consistent with a biliary route of excretion as the major pathway of elimination for cangrelor. No unchanged drug could be detected in excreta. The major metabolite in feces was AR-C90441XX, the S-oxide of the purine base of cangrelor. This metabolite was also the major component found

in bile. A major component in urine was AR-C90439XX, the S-oxide derivative of AR-C69712XX, the nucleoside metabolite of cangrelor. No milk excretion studies were performed.

Pharmacokinetic drug interactions

The metabolites AR-C69712XX and AR-C90439XX are inhibitors of CYP2C19. However, AR-C69712XX is not an inhibitor of CYP2C19 at clinically relevant maximal systemic concentrations. For AR-C90439XX no maximal systemic concentration could be calculated; since the Cmax is lower than for AR-C69712XX it can be concluded that the observed inhibition is not clinically relevant. Cangrelor and AR-C69712XX were inducers of CYP2C9 and CYP3A4, but not at clinically relevant systemic concentrations. There was no evidence of CYP inhibition or induction by cangrelor or its metabolites at clinically relevant concentrations, indicating that cangrelor does not interfere with the CYP metabolism of other concomitantly administered drugs.

2.3.4. Toxicology

Single dose toxicity

Single-dose studies were conducted in mice and rats. Cangrelor was administered by bolus IV injection.

In mice, the maximum non-lethal dose ranged from 100-200 mg/kg and in rats from 200-400 mg/kg. Animals that died on study died immediately of within a few minutes after dosing. In surviving animals, overt symptoms were noted directly or developed within 3-30 minutes. These symptoms included neurological effects and transient hypothermia. The latter is a class effect, associated with administration of adenosine and adenosine analogues (metabolites of cangrelor are adenosine analogues).

Recovery was generally within 1-2 hours after dosing. No obvious dose dependence was demonstrated, except for the duration of the effects that was prolonged at higher doses.

At the end of the 2-weeks observation period, necropsy revealed no specific findings in mice. In rats, histopathological findings were noted in the kidneys including basophilic tubules associated with cortical tubular degeneration, interstitial mononuclear cell infiltration, and tubules distended with colloid.

Repeat dose toxicity

Repeated dose toxicity studies were conducted in rats and dogs. Non-GLP 3-day and 1-week dose range-finding studies were conducted to identify appropriate doses for pivotal GLP toxicology studies in which cangrelor was administered by continuous IV infusion for 1 month.

The pivotal studies showed that the kidneys, the urinary tract and the liver were target organs of toxicity. Important for interpretation of the rats studies is the fact that rats are rather insensitive for the pharmacodynamics of cangrelor. In dogs, adverse effects by pharmacodynamics were limited to occasional slight increases APTT times. This effect was toxicologically not relevant.

The adverse effects on the kidneys and the urinary tract consisted of injury to renal tubules, renal pelvis, and ureter. Histopathology changes included tubular dilatation, tubular necrosis, tubular regeneration, basophilic tubules, interstitial nephritis, pelvic inflammation, urothelial hyperplasia and urothelial necrosis. Renal dysfunction was also indicated by elevated plasma creatinine and urea levels and urinary N-acetyl-β-D-glucosaminidase and proteinuria. Injury to the urinary tract exhibited evidence of being reversible following cessation of infusion.

Investigative studies in rats suggested that the cangrelor-related toxicity to the kidneys and urinary tract is essentially of two types, distinguished by absolute exposure and duration of exposure. Single IV bolus dosing studies at high doses (>200 mg/kg) produced damage to proximal tubules in renal cortex. Apparently, at high

doses of cangrelor, metabolites already reach cytotoxic concentrations in the proximal tubules leading to tubular necrosis and interstitial damage. The renal pelvis and ureters were unaffected with this dosing regimen.

Continuous intravenous infusion at lower doses of 25 or 75 µg/kg/min for 7 and 28 days produced a different pathology in which the lesion was localized to the renal pelvis and upper ureter. Apparently, at lower doses, cytotoxic concentrations of metabolites are reached in later parts of nephron. Renal effects were demonstrated within 7 days of treatment. The primary insult appeared to be to the transitional epithelium in the pelvic region, manifested by epithelial ulceration and necrosis, associated reactive epithelial hyperplasia and submucosal inflammation. Depending on the severity of the lesion, necrosis and inflammation extended into the renal parenchyma, connective tissue of the renal hilus and into the peri-ureteral connective tissue. Evidence of reversal of renal pathology was seen after 28 days off-dose.

The mechanism by which cangrelor or metabolites may cause toxic effects on the kidney and urinary tract in rats and dogs is unknown. These effects may be related to the exposure of the urinary tract to AR-C90441XX, a sulphoxide of the purine base. Another possible mechanism may be related to an interaction of the main plasma metabolite AR-C69712XX with the adenosine A1 receptor. With regard to the PCI setting, margins of safety for effects on renal histopathology and function in rats and dogs are high, indicating little clinical relevance. With regard to the BRIDGE setting, however, margins of safety for effects on renal/lower urinary tract histopathology in rats and dogs are moderate (13- and 11-fold for cangrelor and AR-C69712XX, respectively), and for effects on renal function are low (3- and 2-fold for cangrelor and AR-C69712XX, respectively), indicating a potential clinical relevance.

The pivotal toxicity studies in rats and dogs also showed an increase in liver function enzymes. In rats, serum chemistry changes included dose-related increases in AST and ALT as well as increases in urea, and slight reductions in triglyceride and cholesterol levels. Liver weights showed a slight dose-related decrease. Liver necrosis occurred in a few animals of the high dose groups, but no histological changes were found at doses of 3 or 12 µg/kg/min. An investigative study in rats on liver toxicity showed that the increase in AST and ALT in plasma coincided with an increase in ALP and with slight increases in gamma glutamate dehydrogenase and 5'nucleotidase and a rise in bile acids. In addition, there was a slight increase of gamma glutamyltransferase in serum and a remarkable reduction of the mitochondrial enzyme succinate dehydrogenase staining. These data suggest that cangrelor adversely affects the hepato-biliary system by an adverse effect on mitochondrial function. Increased ALP levels in plasma suggest bile duct obstruction. In addition, a publication of Serhan et al (2013) indicates that cangrelor has partial agonistic properties for the $P2Y_{13}$ receptor. The underlying mechanism on cholesterol and lipid metabolism is not entirely clear. Activation of this receptor by cangrelor principally targets HDL metabolism in mice by stimulating hepatic HDL uptake and biliary bile acid excretion, with some differences between intravenous bolus administration versus continuous delivery of cangrelor.

Whereas intravenous bolus administration of cangrelor promotes the secretion of all biliary lipids (cholesterol, bile acids and phospholipids) without any change in plasma lipid levels, continuous delivery of 70 µM cangrelor at a rate of 0.5 µL/h (≈35 µg/kg BW/day) weight for 3 days only increases biliary secretion of bile acids, suggesting metabolic adaptations might occur under continuous activation of $P2Y_{13}$ receptor (Serhan et al, 2013). The absence of effect of cangrelor continuous delivery on biliary secretion of other lipids is intriguing since it is usually reported that biliary secretion of bile acids is coupled to biliary secretion of phospholipid and cholesterol. However, the effect of cangrelor on lipid metabolism reported by Serhan et al in animal studies has not been observed in clinical studies.

Slightly increased weights and/or vacuolation of adrenals in rats and the reduced weights of thymus and the pituitary gland in rats and dogs were observed in the 7-day and 1-month studies in rats. This could mean that cangrelor has some interaction with the hypothalamic-pituitary-adrenocortical axis. This could be a class effect. But it seems not to be clinically relevant, since it was only observed the high-dose groups. For ticagrelor, a

medicinal compound of the same class, inhibition of corticosterone synthesis has been demonstrated at clinical relevant concentrations, but there were no signs of any effects on the adrenal glands in clinical trials.

In dogs, target organs of toxicity were essentially the same as those in rats: the kidney, the urinary tract and the liver.

Additional findings in dogs included gastritis and inflammatory changes in the gut. These effects are most likely the consequence of the fact that cangrelor and its metabolites are primarily eliminated via the bile. Dogs are generally more sensitive for effects on the gastrointestinal tract than rats.

2.3.4.1. Genotoxicity

A battery of genotoxicity tests were performed with cangrelor and two metabolites AR-C69712XX and AR-C71301XX. They gave sufficient indications that Cangrelor has no potential to be mutagenic or clastogenic in the tested situations. Exposure in the *in vivo* mouse study has not been measured, but can be assumed to be sufficient as the high dose of 500 mg/kg is far in excess of the bolus dose for humans of 30 µg/kg. Slight antibacterial property was observed in the Ames test for the major (nucleoside) metabolite AR-C69712XX at a concentration of 400 ug/plate and higher. The minor (base) metabolite AR-C71301XX caused precipitation at a concentration of 250 ug/plate, and therefore higher concentrations could not be tested. It can be concluded that both metabolites do not possess any mutagenic potential up to the tested concentrations of 400 and 250 µg/plate respectively.

2.3.4.2. Carcinogenicity

Carcinogenicity studies were not provided, this is acceptable since cangrelor is intended for short-term administration.

2.3.4.3. Reproduction toxicity

Fertility

Toxic effects of cangrelor on fertility and early embryonic development were assessed in rats. Male rats administered 48 µg/kg/min for a minimum of 8 weeks showed pre-implantation loss, abnormal sperm morphology and several morphologic effects on reproduction organs (epididymis, testes, seminal vesicles). However, all of the males allocated to the treatment-free period in this dose group produced a pregnancy in at least one female and all but one male at this dose showed sperm of normal appearance at the end of the treatment-free period indicating that the functional effects are reversible. At the NOAEL of 12 µg/kg/min steady state plasma concentrations were similar to those in humans.

Female rats administered 48 µg/kg/min showed reduced post-implantation survival of embryos, which could have been secondary to maternal toxicity, although direct embryo-toxicity cannot be ruled out. There were no treatment related effects at 12 µg/kg/min or below. When post-implantation losses are taken into account, exposure at the NOAEL in females is similar to that in humans

Embryonic and Foetal development

Studies on embryo- and foetal development in rats and rabbits showed no teratogenic effects. Rats showed a slight retardation in development of some foetuses at all dose levels (3, 12, and 48 µg/kg/min), indicated by slight reductions in fetal weights and increased incidence of unossified hind limb metatarsals. These effects were in the absence of any overt maternal toxicity. The high-dose group showed also an increased incidence of

incomplete ossification of skull and sternebrae bone. Since no fetal NOAEL was determined in this study, no safety margin for fetal toxicity is determined.

Cangrelor administered to rabbit resulted in foetotoxicity in the presence of maternal toxicity. Rabbits dosed with 4, 12, or 36 µg/kg/min cangrelor showed reversible maternal toxicity (decreased food and water consumption & body weigh) and intrauterine losses /abortion in the low (1 case) mid (4 cases) and high (3 cases) dose groups. Offspring in 36 µg/kg/min dosed group showed growth retardation occurred at decreased foetal weight (female offspring 9%). In all groups a slight reduction in ossification and a slight increase in skeletal variants were observed. A NOAEL could not be determined.

Based on these observations, cangrelor should not be administered to pregnant women.

Pre and postnatal development

Female rats were dosed with (continuously IV) 3, 9 and 30 µg/kg/min cangrelor. Three dams from the 30 µg/kg/min dose group were euthanized (no clear cause of condition) before termination. The increase in the mortality incidence for this group tends to suggest that there was a relationship to the administration of cangrelor. However, pregnancy rates, gestation index, length of gestation, sex ratio, and the live birth index were unaffected by drug treatment at all dose levels. No effects upon cangrelor administration to the F0 Generation dams were seen in F1 Generation pups and adults apart from a very slight non significant but dose dependent reduction in F1 birth weight, consistent with the delay in development seen in the embryo-foetal toxicity study. In F2 Generation pups, viability, clinical condition, litter size, and body weights showed no effects of administration of cangrelor to the F0 generation. NOAEL for maternal toxicity is 9 µg/kg/min and for offspring F1 and F2 generation 30 µg/kg/min. No toxicokinetics were done in this study, but extrapolation from other studies indicate that at the NOAEL for fetal toxicity (highest dose of 30 µg/kg/min), exposure in terms of steady state concentration is sufficiently in excess of clinical exposures.

2.3.4.4. Local tolerance

Separate local tolerance studies were not conducted. However, histopathological findings at the injection sites of rats and dogs administered cangrelor by continuous infusion for 1 month at doses up to 48 and 60 µg/kg/min, respectively, demonstrated that the type, incidence, and severity of injection-site lesions were comparable among cangrelor and vehicle treated groups. Several of the more frequently noted findings in both groups included inflammation, thrombus formation, and vasculitis.

2.3.4.5. Antigenicity

The antigenicity of cangrelor was investigated in Hartley strain guinea pigs by their active systemic anaphylaxis (ASA) and passive cutaneous anaphylaxis (PSA) reactions. The results showed no signs of antigenic potential.

2.3.4.6. Impurities

Seven identified impurities in the drug substance exceed the recommended ICH Q3A (R2) identification threshold of 0.10% in the drug substance. Three of these impurities exceed the qualification threshold of 0.15% for drug substances with a maximum daily dose of ≤2 g. These impurities are: 3312H (AR-C125263XX) at a limit ≤0.3%, 3312P (AR-C88558XX) at a limit ≤0.3%, and 3312.U (AR-C90334XX) at a limit of ≤0.2%. DEREK analyses did not demonstrate any alerts for genotoxicity, mutagenicity, chromosome damage or carcinogenicity. In addition, these impurities were qualified by using a forced degraded drug substance in a male fertility study in rats.

Tributylamine en triethylphosphate are residual solvents in the drug substance limited at ≤1000 ppm and at ≤500 ppm, respectively, in the drug substance. These impurities are not classified by the current ICH guidelines on residual solvents. However, based on available information on toxicology, the proposed limit of 500 ppm for tributylamine and 1000 ppm for triethylphosphate in the drug substance are agreed.

2.3.5. Ecotoxicity/environmental risk assessment

Cangrelor tetrasodium possesses five sites of ionization, four acidic groups and the basic nitrogen of the adenosine ring. The first three ionizations correspond to phosphate groups and are acidic, with the pKa values being ≤2. Therefore these pKa values are not measured using standard techniques. The pKa for the deprotonation of the nitrogen of the adenosine ring was determined by a spectroscopic method and the pKa for the terminal phosphate group was determined.

Based on the log Dow cangrelor tetrasodium is not expected to be PBT, nor vPvB. The applicant has determined distribution coefficients (log D) for cangrelor tetrasodium in octanol/water at low pH values. The results show that above pH 2.2, the compound is highly ionized and therefore extremely hydrophilic, beyond the limits of quantification. The applicant concludes that at physiological pH 7.4, the compound will exist as the tetra-anion and at this pH the log D has been estimated to be <-16.

The PEC surfacewater of cangrelor is 0.008 µg/L, which is below the action limit of 0.01 µg/L. A further assessment is not deemed necessary.

Table: Environmental endpoints

Substance (INN/Invented Name): Cangrelor tetrasodium			
CAS-number (if available): 163706-36-3			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	shake-flask method	Log D_{ow} = -0.43 (pH 0) Log D_{ow} = -0.91 (pH 1) Log D_{ow} = -2.22 (pH 2)	Potential PBT: N
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	Log K_{ow}< 4.5	not B
	BCF	not investigated	
Persistence	DT50 or ready biodegradability	not investigated	potentially P
Toxicity	NOEC or CMR	not investigated	potentially T
PBT-statement :	Cangrelor tetrasodium is not considered PBT, nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default	0.008	µg/L	> 0.01 threshold: N
Other Concerns (e.g. chemical class)	not investigated		

2.3.6. Discussion on non-clinical aspects

Cangrelor pharmacology can be characterized as being an inhibitor of platelet aggregation in vitro, in various species, rat dog and human, with the rat as a less sensitive animal species.

All outstanding issues have been solved.

2.3.7. Conclusion on non-clinical aspects

There are no major objections against the non-clinical part of the dossier, a marketing authorization can be granted from a non-clinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant. The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.4.2. Pharmacokinetics

Introduction

The drug substance cangrelor is chemically similar to adenosine triphosphate (ATP). The empirical formula of cangrelor (as the tetrasodium salt) is $C_{17}H_{21}N_5Cl_2F_3Na_4O_{12}P_3S_2$ and the molecular weight is 864.3 grams (g)/mole. Cangrelor is highly soluble in water. The recommended dose of cangrelor for patients undergoing PCI is a 30 µg/kg intravenous bolus followed immediately by 4 µg/kg/min intravenous infusion. The recommended dose of cangrelor for the bridging indication is 0.75 µg/kg/min intravenous infusion. A total of 9 studies and population pharmacokinetic modelling have been performed.

Methods

Bioanalytical methods were validated HPLC/MS methods, the pharmacokinetic analyses and statistics are acceptable. Several analytical methods were used for the determination of cangrelor and its main circulating metabolite. The Applicant has not submitted any data to support cross-validation, however, it was confirmed that the analytical methods gave comparable results. Population pharmacokinetic modelling was included using data from 8 different studies. In this model cangrelor was described using a two compartment model with an allometric coefficient for body weight.

Absorption

Cangrelor is a solution for intravenous (IV) administration. Therefore, bioavailability, comparative bioavailability, or bioequivalence studies that would be conducted with oral drugs were not relevant for this product. Hence, there are no study reports provided under this heading. The final formulation of cangrelor administered IV throughout the clinical program was a solution diluted in sterile saline. Based on the consistency of key PK parameters within and across studies, there is no evidence that the use of different Drug Product batches resulted in any differences in performance of cangrelor.

Cangrelor is a solution for intravenous (IV) administration. Therefore the influence of food has not been investigated.

Distribution

The volume of distribution (Vz) was investigated in study TMC-Can-04-02, for 2 comparable groups of subjects at different dose levels. The Vz was estimated as the ratio of total administered dose and the product of terminal elimination rate constant and AUCinf.

For the cangrelor 15 µg/kg IV bolus + 2 µg/kg/min (1 hour) group, the Vz was determined to be 5.57 ± 0.549 L and for the cangrelor 30 µg/kg IV bolus + 4 µg/kg/min (1 hour) to be 3.88 ± 1.18 L.

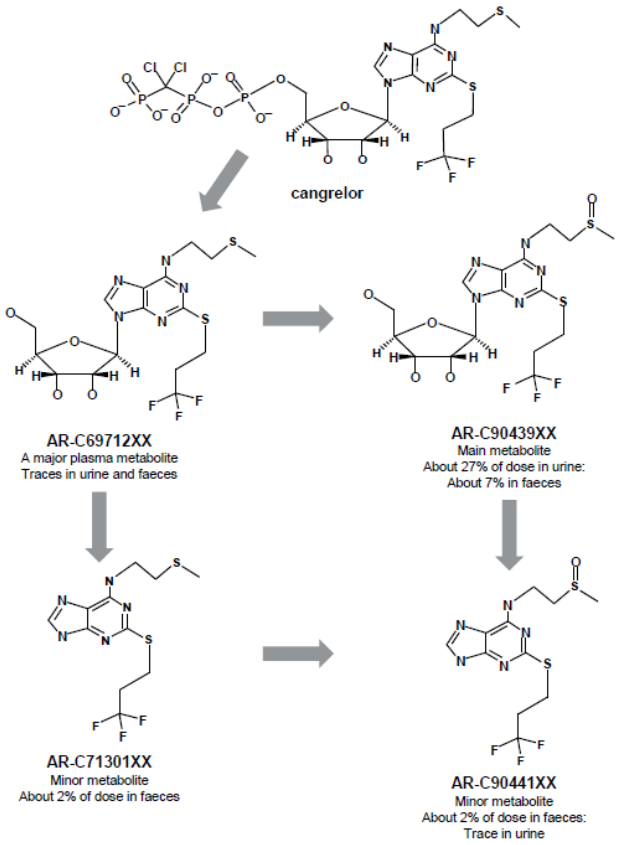
The level of plasma protein binding was determined in study SE 10009. In this in vitro study, the extent of plasma protein binding was investigated for rat, dog and human plasma at target concentrations of 20, 100 and 400 ng/ml. The study demonstrated a high amount of plasma protein binding in human plasma of 97.3-98.1%.

In summary, the volume of distribution is estimated 3.9 L, most likely confined to the blood compartment. Plasma protein binding is high, demonstrated to be 97-98% with no concentration dependency.

Elimination

The elimination of cangrelor has been investigated using a mass balance study, SC-931-9017. Total recovery of the radioactivity was about 93%, primarily recovered in the urine (58%) and a smaller part in the faeces (35%). Cangrelor was not recovered unchanged in urine and faeces. The very rapid initial elimination phase with a half life of 3-6 minutes was followed by a terminal elimination phase starting about 30 hour after the infusion, with a half-life of 51.7 ± 12.7h.

Metabolism



The metabolism of cangrelor is quick and extensive with a very rapid initial elimination phase of the parent. None of the metabolites demonstrate significant activity. The main metabolite is AR-C69712XX formed by rapid de-phosphorylation of the parent. This metabolite demonstrates a Cmax about 26% of that of the parent and is further metabolized to AR-C90439XX, only traces are recovered in faeces and urine. Its sulphoxide metabolite AR-C90439XX demonstrated a Cmax of about 16% of the parent and is the main excreted metabolite, 27% was recovered in urine and 7% in faeces. Minor other metabolites are recovered in faeces and urine such as AR-C90441XX and AR-C71301XX.

Pharmacokinetics of metabolites

The primary metabolite AR-C69712XX demonstrated a Cmax of about 26% of the parent, metabolite AR-C90439XX demonstrated a Cmax of about 16% of the parent as above mentioned. The half-life of both these metabolites was considerably longer than the half-life of the parent, respectively 2.7 ± 0.2 h and 1.0 ± 0.1 h.

Plasma pharmacokinetics parameters for metabolite AR-C90441XX were not determined.

Pharmacokinetics in target population

Only limited pharmacokinetics assessment has been performed in the patient populations. The presented analyses do not indicate a difference in pharmacokinetic profile between patients and healthy volunteers. The presence of such a difference is not expected based on the pharmacokinetic properties of cangrelor. Administration of cangrelor in the target population for the percutaneous coronary intervention (PCI) setting, 30 µg/kg + 4 µg/kg/min has been studied and characterized.

Special populations

Study SC-931-5109 demonstrated that clearance is decreased for both the parent and the metabolites in renally impaired subjects. For this study, renally impaired patients were defined as having a creatinine clearance of 20 - 70 ml/min and healthy volunteers >90 ml/min. The usual creatinine clearance subdivision for renal impairment, as described by the European guidelines is; normal renal function >80 ml/min, mild renal impairment 50-80 ml/min, moderate renal impairment 30-<50 ml/min and severe renal impairment <30 ml/min. Pharmacokinetic data of study SC-931-5109 should have been stratified in accordance with the usual subdivision of renal impairment.

The data available do indicate that renal impairment is not likely to significantly alter the pharmacokinetics.

The clearance of the inactive metabolites was decreased by approximately 2 fold in renally impaired subjects. Also, for the parent compound a small tendency for decreased clearance was observed in patients with decreased renal function.

The influence of an impaired hepatic function has not been investigated by the applicant.

Population pharmacokinetic evaluation did not identify a covariate effect of gender on the pharmacokinetics of cangrelor, nor is it expected based on the specific metabolism of cangrelor.

The population pharmacokinetic modelling approach indicated weight to be a covariate, other factors race, gender, and age did not identify as a covariate effect.

The influence of weight on the pharmacokinetics of cangrelor has been investigated more thoroughly in the pharmacokinetic modelling approach, the effect is estimated to be modest and below 10% at the extremes of the modelled weights.

Interaction

In vitro studies were performed which demonstrate no evidence of CYP inhibition or induction by cangrelor or AR-C69712XX at clinically relevant concentrations, indicating that cangrelor does not interfere with the CYP

metabolism of other concomitantly administered drugs. Transporter interaction studies for both cangrelor and AR-C69712XX at clinically relevant concentrations have been performed. With the exception of BCRP, none of the findings could indicate a potential clinical interaction with transporter proteins.

The in vivo study demonstrates that pharmacokinetics of cangrelor for the parent and AR-C69712XX are unaffected by the concomitant administration of aspirin, heparin or nitroglycerin.

2.4.3. Pharmacodynamics

Mechanism of Action

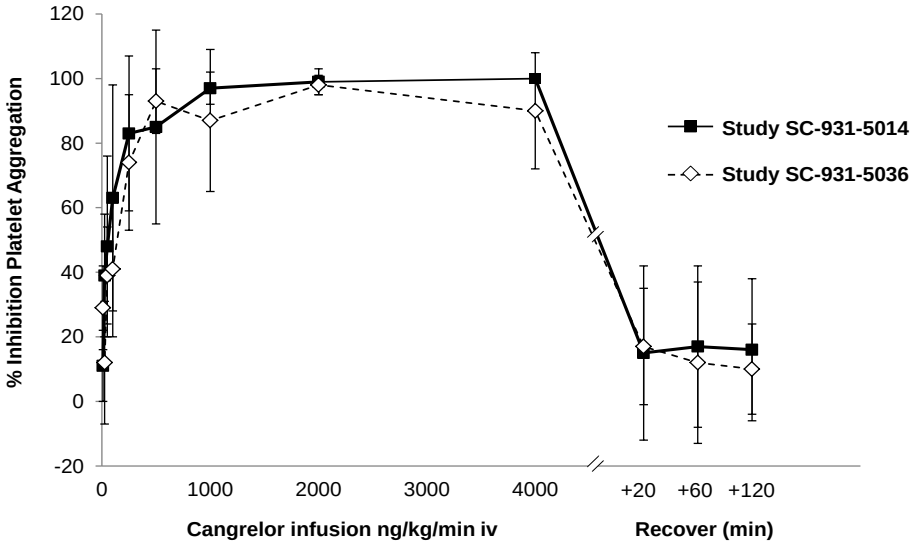
Cangrelor is a novel, intravenous (IV), $P2Y_{12}$ receptor antagonist that blocks adenosine diphosphate (ADP)-induced platelet activation and aggregation. Cangrelor was specifically designed as a direct-acting, competitive, reversible antagonist of the $P2Y_{12}$ receptor. These properties clearly differentiate cangrelor from the thienopyridine class of $P2Y_{12}$ inhibitors, exemplified by clopidogrel and prasugrel, which require metabolic conversion to exhibit $P2Y_{12}$ inhibition and, due to a covalent interaction with the receptor, result in irreversible inhibition that is maintained even when parent drug and active metabolite have been cleared. The requirement for metabolic conversion is also one of the contributory factors to the large inter-individual variability in response seen with the thienopyridine class of $P2Y_{12}$ inhibitors, but not with cangrelor, or the oral, direct acting $P2Y_{12}$ antagonist, ticagrelor. The latter agent, although direct acting and reversible at the receptor level, requires a number of hours to achieve steady state $P2Y_{12}$ inhibition, and a period of hours to days following cessation of treatment for full recovery of platelet responsiveness to ADP.

Primary Pharmacology

Inhibition of Platelet aggregation

In two studies, dose-related reduction of platelet responses to ADP, measured ex vivo, was observed, with over 80% inhibition achieved at doses of 0.5 µg/kg/min and above. Inhibition of ADP-induced aggregation was maintained during the plateau infusion, and generally restored to control values when measured at 20 and 60 minute post-infusion, respectively, for all dose levels.

Figure PD1: Dose-related on-infusion inhibition of platelet function by cangrelor followed by rapid post-infusion recovery in studies SC-931-5014 and SC 931-5036



Inhibition of response to 3 μM ADP as measured by whole blood impedance aggregometry.

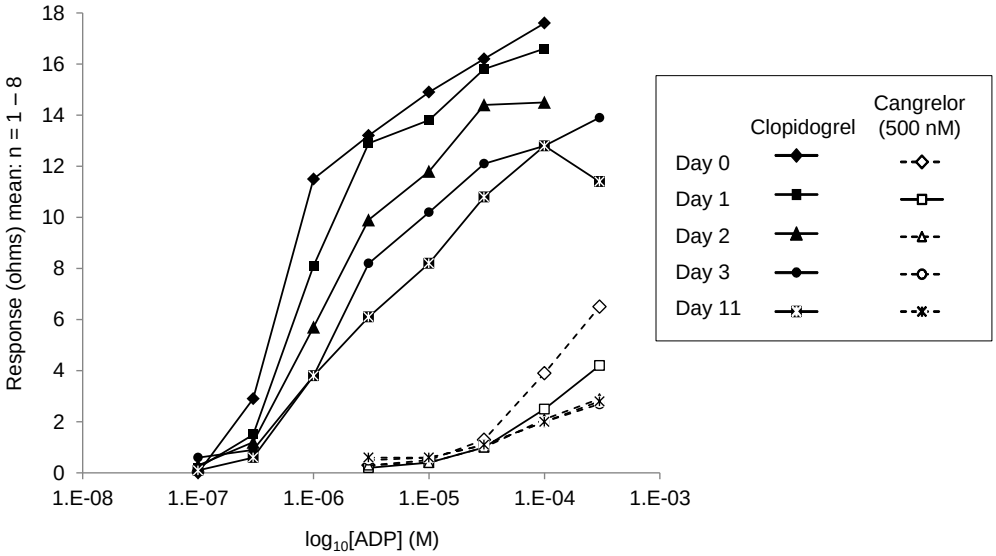
Figure PD1 illustrates the group mean responses at each infusion rate, and post infusion, for percentage inhibition of ADP induced aggregation after 57 minutes into each infusion. Dose-related reduction of platelet responses to ADP, measured ex vivo, was observed, with over 80% inhibition achieved at doses of 0.5 μg/kg/min and above. Inhibition of ADP-induced aggregation was maintained during the plateau infusion, and generally restored to control values when measured at 20 and 60 minute post-infusion, respectively, for all dose levels.

Consistency of effect of cangrelor

In study [SC-931-9064], 8 healthy male volunteers received clopidogrel 75 mg/d for 11 days. Blood samples were taken on Days 0, 1, 2, 3 and 11. Each blood sample was split and ADP-induced platelet aggregation was measured either in the blood sample as taken or after addition in vitro of cangrelor (500 nM, 386 ng/mL).

In the absence of cangrelor, reduction of platelet reactivity to ADP by clopidogrel is dependent upon duration of treatment and, even after 11 days clopidogrel treatment, residual platelet reactivity to 10 μM ADP ranged from 8 to 86%. Addition of cangrelor in vitro resulted in substantial reduction of platelet responses to ADP at concentrations of up to 30 μM, in all cases, at all time-points, regardless of the effect of clopidogrel. However, a response could still be induced by further increases in the ADP challenge (approximately 30% of maximum baseline response at the highest concentration of ADP (300 μM) (Figure PD2).

Figure PD2: ADP-induced platelet aggregation ex vivo in blood samples from healthy volunteers receiving clopidogrel 75 mg/day for up to 11 days. Responses obtained with and without addition of cangrelor in vitro

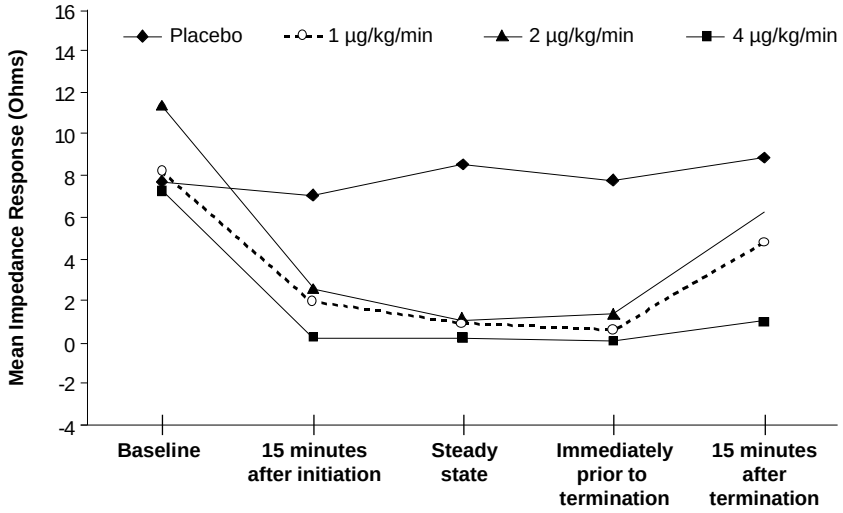


Response to ADP (0.1 – 300 µM) as measured by whole blood impedance aggregometry.

Onset and offset of action of cangrelor in PCI

In study SC-931-5129, cangrelor produced a dose-related reduction in the platelet response to ADP (3 µM) in patients undergoing PCI. Platelet responses returned toward baseline within 15 minutes of discontinuation of infusion in all treatment groups, except for those receiving 4 µg/kg/min of cangrelor where it remained significantly inhibited at 15 minutes (Figure PD3) but had recovered by the next time point assessed (24 hours). This study demonstrated that cangrelor provides potent and consistent platelet $P2Y_{12}$ inhibition during IV infusion, with rapid offset of effect following cessation of infusion in PCI patients.

Figure PD3: Dose-related on-infusion inhibition of platelet function by cangrelor followed by rapid post-infusion recovery in part 1 of study SC-931-5129



Response to 3 μM ADP as measured by whole blood impedance aggregometry.

Secondary Pharmacology

Effect of cangrelor on the QT/QTc interval in healthy volunteers [TMC-CAN-08-01]

An initial phase of the study 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 h plus) and supratherapeutic (60 μg/kg IV bolus plus 8 μg/kg/min IV infusion for 3 h) 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 electrocardiogram (ECG) morphology analysis, it was concluded that neither therapeutic nor supratherapeutic doses of cangrelor affected cardiac repolarization or ECG morphology.

The submitted data from study TMC-CAN-08-01 demonstrate that cangrelor has no relevant effect on QTc even in the supratherapeutic dose of 60 μg/kg IV bolus plus 8 μg/kg/min IV infusion for 3 h.

In a thorough QT study therapeutic and supratherapeutic doses of cangrelor infusion were administered for three hours. Compared to placebo no prolongation of QT, regardless of analysis method, was revealed; the upper bound of each 90% CI did not exceed 5 msec in any of the time points. Oral moxifloxacin was used as a positive control (T_{max} ~2-4h).

Cangrelor did not seem to prolong QT interval. Control treatment with moxifloxacin 400mg slightly prolonged QT interval. At two time points, namely at 2h and 4h post dose, the lower limit of the 90%CI of the prolongation in QT interval was above 5 msec, but remained below 5 msec for all other time points. Tmax of moxifloxacin is 2-4h. No increase in the QT interval was seen for cangrelor supratherapeutic doses. Although the assay sensitivity is not well established, since the lower limit of 90%CI exceeded 5 msec only at two time points, it is agreed with the Applicant that cangrelor does not appear to increase the QT interval.

Pharmacodynamic interactions with other medicinal products or substances

Transition strategy between cangrelor and oral $P2Y_{12}$ inhibitors

Separate set of studies were designed to determine the optimal strategy for transitioning from $P2Y_{12}$ inhibition with cangrelor during the acute peri-procedural period to post procedural maintenance $P2Y_{12}$ inhibition with clopidogrel, ticagrelor, or prasugrel.

- **Clopidogrel**

Study [TMC-CAN-04-02] in healthy volunteers (groups C and D)

Ten healthy volunteers received a 600 mg oral loading dose of clopidogrel and then underwent serial platelet function monitoring for 6 h. Two weeks later these same individuals received a 600 mg clopidogrel loading dose simultaneously with a cangrelor IV bolus (30 μg/kg) and a 2-hour infusion (4 μg/kg/min). A separate group of ten volunteers received a 600 mg clopidogrel loading dose after administration of a cangrelor bolus and a 1-hour infusion.

In this study cangrelor and clopidogrel alone achieved the expected levels of platelet inhibition. However, the sustained platelet inhibition anticipated for clopidogrel treatment did not occur when cangrelor was initiated simultaneously. No such effect was found when clopidogrel was started upon completion of the cangrelor infusion.

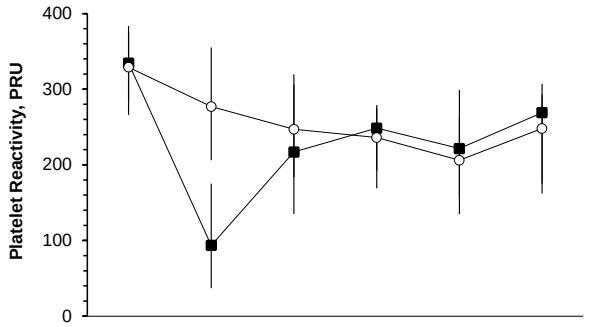
- **CHAMPION Platelet Substudy** [TMC-CAN-05-02-S1/TMC-CAN-05-03-S1] in PCI patients

A total of 234 patients were enrolled into the substudy, of which 167 had valid or evaluable samples for the primary endpoint (% patients in each treatment group who achieved less than a 20% change in PRU (Verify*Now*® P2Y12 assay) from pre-to post-clopidogrel levels at least 10 h after PCI). Platelet function parameters were measured using the Verify*Now*® P2Y12Assay (for the primary endpoint), and at selected sites, using LTA.

The pre-specified primary endpoint was not met, the percentage of patients with <20% change in PRU from baseline at >10 hour after discontinuation of study drug infusion was not statistically different between arms cangrelor ([32/84, 38.1%]; clopidogrel [21/83, 25.3%], difference: 12.79% [95% CI: -1.18%, 26.77%] p=0.076). However, cangrelor provided effective $P2Y_{12}$ inhibition during infusion, with platelet reactivity well below thresholds associated with a risk of thrombotic events in patients undergoing PCI.

Baseline, on-infusion and post-infusion (up to 24 hour) PRU values are shown in figure PD4. This illustrates the significant reduction in PRU during cangrelor infusion, and the similar course followed in the cangrelor and clopidogrel groups post-infusion. No evidence of a rebound "overshoot" in platelet reactivity after cessation of cangrelor infusion.

Figure PD4: TMC-CAN-05-02-S1/TMC-CAN-05-03-S1: Time course for changes in PRU (all patients)



No. of patients with valid sample in the ITT population

Cangrelor+clopidogrel	96	66	47	24	60	27
Placebo/clopidogrel	94	74	52	25	61	25
p-value	0.6926	<.0001	0.4815	0.6347	0.3722	0.7646

Values are expressed as PRU. The circles are the medians (closed circles represent the cangrelor groups, open circles are clopidogrel) and whiskers are the 25th and 75th percentiles. h= hour; PRU = $P2Y_{12}$ reaction units.

- Two phase 2 studies designed to demonstrate that patients treated with cangrelor can be transitioned to oral prasugrel (MDCO-CAN-13-01 (N=12))/ticagrelor (MDCO-CAN-12-03 (N=12)) and that patients treated with prasugrel/ticagrelor can be transitioned to cangrelor without a significant interruption of platelet $P2Y_{12}$ inhibition.

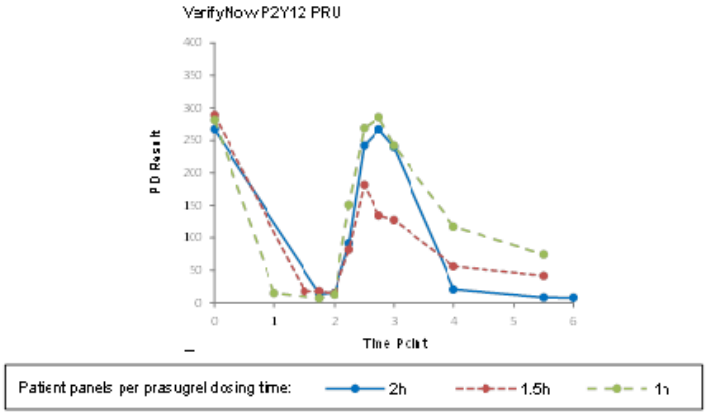
Prasugrel. In study MDCO-CAN-13-01, CAD patients received a bolus plus 2 hour infusion of cangrelor on day 1. Subjects received a 60 mg loading dose of prasugrel during or immediately after infusion of cangrelor. After Day 1, subjects took a maintenance dose of 10 mg of prasugrel every 24 h for either 5 (n=6) or 6 (n=6) doses, thus, discontinuing prasugrel either 48 h or 24 h prior to Day 8 dosing. On study Day 8, subjects received another bolus plus 2 h infusion of cangrelor (figure PD5). Pharmacodynamic effects (platelet aggregation in

response to 20 µM ADP) were assessed. The goal was to determine the time of administration that leads to lowest residual platelet reactivity (greatest inhibition) throughout transition.

During Day 1 cangrelor infusion, extensive platelet inhibition was observed as limited residual platelet reactivity (<4% aggregation) and greater than 95% inhibition for the primary endpoint of final response to 20 µM ADP assessed by LTA. The PD effect of cangrelor was not attenuated by concomitant or previous treatment with prasugrel. In the overall patient population (n=12), no limitation by prasugrel of the inhibitory effect of cangrelor was apparent during the infusion of cangrelor.

On Study Day 1, a loading dose of prasugrel given at 30 minutes before end of cangrelor infusion preserved antiplatelet effects to a greater extent than when prasugrel was given at 1 hour before the end of the cangrelor infusion or at end of cangrelor infusion (2 h). For each prasugrel dosing regimen, recovery of platelet reactivity was temporary, and substantial antiplatelet effects were apparent by 3.5 hours after cangrelor was stopped (Figure PD5).

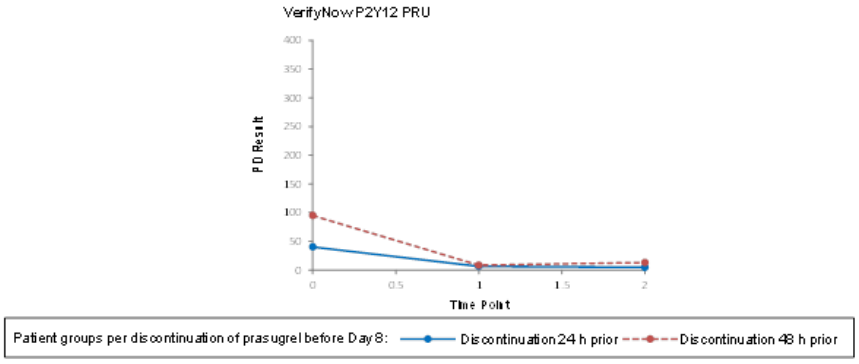
Figure PD5: Pharmacodynamic effects of cangrelor, followed by prasugrel on Study Day 1



PRU= P2Y12 reactivity units; µM = micromolar; h=hours

For the transition between prasugrel and cangrelor on Day 8, there was no apparent interaction between the drugs regardless of whether the prasugrel had been discontinued 24 or 48 hours prior to initiation of the cangrelor infusion.

Figure PD6: Pharmacodynamic effects on Day 8 of cangrelor after discontinuation of prasugrel either 24 or 48 hours prior

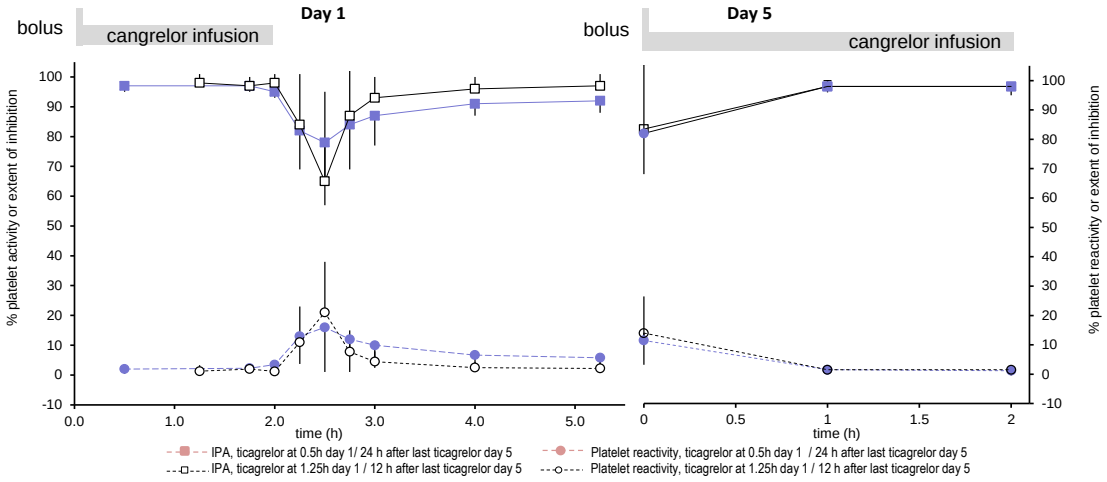


ADP = adenosine diphosphate; PRU= P2Y12 reactivity units; µM = micromolar; h=hours

Ticagrelor. Study MDCO-CAN-12-03 is comparable in design to study MDCO-CAN-13-01, but investigates transition from and to ticagrelor instead. CAD patients received a bolus plus 2 hour infusion of cangrelor. Subjects received a 180 mg dose of ticagrelor either 0.5 hours (n=6) or 1.25 hours (n=6) after initiation of cangrelor. Subjects took 90 mg of ticagrelor twice daily for either 6 (n=6) or 7 (n=6) doses. On study Day 5, subjects received another bolus plus 2 hour infusion of cangrelor. Pharmacodynamic effects (primary endpoint platelet aggregation in response to 20 µM ADP) were assessed.

During the cangrelor infusion, extensive platelet inhibition was observed as reflected by limited residual platelet reactivity (<4% aggregation). No limitation of the inhibitory effect of cangrelor by ticagrelor was apparent. When cangrelor was discontinued on Day 1, the residual platelet reactivity increased during the first 30 minutes and decreased thereafter. When ticagrelor was administered at 0.5 hours (n=6) or 1.25 hours after initiation of cangrelor (n=6), the average final aggregation (primary endpoint) increased to 16% and 21% respectively. This minimal recovery of function is most likely a reflection of the onset of effect with ticagrelor. For the transition between ticagrelor and cangrelor on Day 5, there was no observed interaction between the drugs regardless of whether the ticagrelor had been discontinued 12 or 24 hours prior to initiation of the cangrelor infusion (figure PD7).

Figure PD7: Platelet reactivity (final aggregation) and the extent of inhibition of platelet aggregation as assessed with LTA in response to 20 µM ADP



ADP = adenosine diphosphate; IPA = inhibition of platelet aggregation; LTA= light transmittance aggregometry

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

The key structural attributes of cangrelor allow its rapid inactivation in the circulation by de-phosphorylation to an inactive nucleoside metabolite AR-C69712XX. Pharmacokinetics parameters have only been investigated to a certain limit in special populations. In principle this could be acceptable, as the highly specific metabolism of cangrelor is expected to be independent of such influencing factors.

Dose proportionality for cangrelor has been demonstrated, dose linearity has been confirmed up to an infusion rate of 4 µg/kg/min.

The main metabolite of cangrelor is AR-C69712XX formed by rapid de-phosphorylation of the parent compound. The rapid loss of circulating parent drug by de-phosphorylation is likely mediated through ectonucleotidase activity in the blood vessel wall and so independent of organ function. The pharmacokinetic characteristics of cangrelor and metabolites support the proposed metabolism pathway by endothelial ecto-nucleoside triphosphate di-phosphohydrolase 1. Pharmacokinetics of the main metabolite AR-C69712XX and metabolite AR-C90439XX have been characterized, but not for the metabolite AR-C90441XX. The limited investigation is acceptable as the metabolites demonstrate no relevant activity and have lower plasma levels (exposure) than the parent drug.

The inter-individual variability of cangrelor clearance has been estimated between 14 – 22%.

Limited pharmacokinetic assessment has been performed in the patient populations. However, the presented analyses do not indicate a difference in pharmacokinetic profile between patients and healthy volunteers.

Administration of cangrelor as proposed in the bridge setting initially proposed indication, 0.75 µg/kg/min, has not specifically been studied in patients or healthy volunteers. However, cangrelor demonstrates good dose linearity, and dosing at 0.5 µg/kg/min and 1.0 µg/kg/min has been studied. Population pharmacokinetics estimates the Css of 68.33 µg/ml at the proposed bridge dosing of 0.75 µg/kg/min.

Pharmacokinetics parameters have only been investigated to a certain extent in special populations (see below).

The renal impairment study SC-931-5109 lacked a proper subdivision to the degree of renal impairment and in the therapeutic dose group (4 µg/kg/min) only one subject with severe renal impairment was included. The Applicant presented data from the renal impairment study by severity of renal impairment (mild, moderate and severe), data from two dose levels were combined and dose normalised data (together with eGFR for each renal impairment group) in comparison to healthy volunteers and data from the Phase III studies were included in the population pharmacokinetic analysis. These data showed a moderate effect of renal impairment considered clinically insignificant. However limited information is available in particular in severe renal impairment. (see efficacy and safety sections).

Hepatic impairment studies have not been performed, which can be acceptable as it is not likely to significantly influence pharmacokinetics of the parent or the metabolites and the minimal amount excreted in faeces (approximately 0% unchanged and 35% of total radioactivity).

Regarding other intrinsic factors only weight was found to be a covariate. Other factors like race, gender, and age were not identified as a covariate effect on the pharmacokinetics of cangrelor, nor was that expected based on the specific metabolism of cangrelor.

The influence of weight on the pharmacokinetics of cangrelor has been investigated more thoroughly in the pharmacokinetic modelling approach. The effect is estimated to be modest and below 10% at the extremes of the modelled weights when dosed on weight base. The Applicant submitted data from the population pharmacokinetic analysis which showed that a flat dose regimen does increase the variability considerably.

Due to the highly specific metabolism of cangrelor by de-phosphorylation to an inactive nucleoside metabolite AR-C69712XX, interactions have only been investigated to a certain extent.

In vitro studies demonstrate no evidence of CYP inhibition or induction by cangrelor or AR-C69712XX at clinically relevant concentrations, indicating that cangrelor does not interfere with the CYP metabolism of other concomitantly administered drugs.

No inhibition or induction potential towards CYP2C8 and CYP2B6 were found. Regarding transporter interactions, it is agreed that no further (in vivo) studies are required. However, findings for BCRP inhibition are reflected in the SmPC.

The in vivo study demonstrates that pharmacokinetics of cangrelor for the parent and AR-C69712XX are unaffected by the concomitant administration of aspirin, heparin or nitro glycerine.

All relevant information is included in the SmPC sections 5.2 and 4.2.

Primary Pharmacology

The studies show the rapid onset of action of cangrelor on ADP induced platelet aggregation which offers an advantage in acute settings. The mechanism of action is competitive inhibition at the $P2Y_{12}$ receptor, which can be reversed by high concentrations of ADP. There is a rapid offset of action, with return of platelet function within 60 minutes after discontinuation of the infusion , which implies that cangrelor infusion can be continued until one hour prior to the administration of anaesthesia for surgery when it should be discontinued.

Data on QTc do not indicate that cangrelor is associated with QT prolongation. Some PD data regarding transition of cangrelor from and to other $P2Y_{12}$ receptor antagonists are available, which is currently reflected in the SmPC.

Pharmacodynamic interactions

Clopidogrel.

Regarding switching from cangrelor to clopidogrel, PD data show that the efficacy of clopidogrel is diminished in samples pre-incubated with cangrelor. The presented PD data do not clearly indicate when clopidogrel is fully effective following cangrelor. However, PD results show that platelet reactivity is comparable in patients administered clopidogrel and those administered cangrelor. In addition, clinical trial experience from the main submitted study C-PHOENIX indicate that such transition was successfully implemented, with no relevant difference between clinical events in patients maintained on clopidogrel throughout the study compared to patients administered cangrelor followed by clopidogrel. The advice implemented in the SmPC (section 4.2) is to start clopidogrel loading dose immediately after stopping the cangrelor infusion.

Prasugrel.

Pharmacodynamic results show that transition is best accomplished when prasugrel is administered 30 minutes prior to the end of the cangrelor administration. The differences between the transition to clopidogrel or prasugrel take into consideration their differences in PK/PD properties. Administering prasugrel earlier than 30 min before the end of cangrelor infusion will not offer any advantage because of receptor occupancy. Accordingly the proposed time of 30 min appears optimal.

Regarding transition from prasugrel to cangrelor as during bridging, submitted data are difficult to interpret. As depicted in figure PD7, there are differences in PRU when prasugrel is discontinued 24 or 48 hours prior to cangrelor, though at the measured point of 1 hour, the results are comparable. The rationale of safe transitioning is that which would ensure a continuation of the platelet inhibitory activity achieved by prasugrel when the patient is transitioned to cangrelor (see below under ticagrelor).

Ticagrelor.

The submitted PD data demonstrate minimal effect on the platelet reactivity when ticagrelor is co-administrated with cangrelor. To maintain adequate platelet inhibition during transition from cangrelor to ticagrelor, the most important issue appears to be the onset of action of ticagrelor. With maximal receptor occupancy, as what happens with full doses of cangrelor and ticagrelor, no further PD or safety issues are expected. In line with the

PK/PD data of ticagrelor, platelet inhibition appears to be better maintained when ticagrelor is administered as early as the first half hour of cangrelor infusion.

In conclusion, the SmPC recommendation with regards to transition to oral $P2Y_{12}$ inhibitors is as follows : *For transition, a loading dose of oral $P2Y_{12}$ therapy (clopidogrel, ticagrelor or prasugrel) should be administered immediately following discontinuation of cangrelor infusion. Alternatively, a loading dose of ticagrelor or prasugrel, but not clopidogrel, may be administered up to 30 minutes before the end of the infusion, see section 4.5.*

2.4.5. Conclusions on clinical pharmacology

Pharmacokinetics

Overall, the pharmacokinetic properties have been adequately investigated. Although the investigations regarding the metabolism, special populations and drug interactions are limited, in general the pharmacokinetic results can be accepted. The limited investigation is in general acceptable due the specific metabolism of cangrelor, the rapid inactivation in the circulation by de-phosphorylation.

Pharmacodynamics

The submitted data demonstrate that cangrelor is a competitive inhibitor of the $P2Y_{12}$ receptor, with a rapid onset and offset of action. Data on QTc do not indicate that cangrelor is associated with QT prolongation. Some PD data regarding transition of cangrelor from and to other $P2Y_{12}$ receptor antagonists are available, which is currently reflected in the SmPC.

2.5. Clinical efficacy

The main clinical studies to support the proposed indications of administration of cangrelor during PCI or during bridging are summarised in table E1.

Table E1 : Summary of clinical studies supporting the efficacy of cangrelor.

Study	Protocol Number	Patient Population	N (mITT)	Cangrelor Dose	Dose duration	Comparator	Efficacy Endpoint
CHAMPION PHOENIX	TMC-CAN-10-01	ACS/CAD undergoing PCI	10942	**Table 1.** 30 µg/kg bolus 4 µg/kg/min	2-4 h	Clopidogrel 600 mg or 300 mg	48 h Death/MI/IDR/ ST
CHAMPION PLATFORM	TMC-CAN-05-03	ACS/CAD undergoing PCI	5301	**Table 2.** 30 µg/kg bolus 4 µg/kg/min	2-4 h	Clopidogrel 600 mg	48 h Death/MI/IDR
CHAMPION PCI	TMC-CAN-05-02	ACS/CAD undergoing PCI	8667	**Table 3.** 30 µg/kg bolus 4 µg/kg/min	2-4 h	Clopidogrel 600 mg	48 h Death/MI/IDR
BRIDGE	TMC-CAN-08-02	ACS/stent awaiting cardiac surgery	183	0.75 µg/kg/min	2-7 days	Placebo	PRU <240 during infusion

ACS = acute coronary syndrome; CAD = coronary artery disease; h = hours; kg = kilograms; min = minutes; PCI = percutaneous coronary intervention; mITT = modified intent to treat; MI = myocardial infarction;

IDR = ischaemia-driven revascularization; ST = stent thrombosis; PRU = P2Y12 reaction unit; µg = micrograms.

The three CHAMPION studies (CHAMPION PHOENIX, CHAMPION PLATFORM and CHAMPION PCI) are described and discussed later. The BRIDGE study is described separately reflecting the last CHMP discussion before the withdrawal of the indication by the MAH.

The company initially applied for a PCI and bridge indication as follows :

Percutaneous coronary intervention (PCI)
Kengrexal is a $P2Y_{12}$ platelet inhibitor indicated for the reduction of thrombotic cardiovascular events (including stent thrombosis) in adult patients with coronary artery disease undergoing percutaneous coronary intervention (PCI).

During the pre-operative period when oral $P2Y_{12}$ therapy is interrupted due to surgery ('Bridging')
Kengrexal is also indicated to maintain $P2Y_{12}$ inhibition in adult patients with acute coronary syndromes or in patients with stents who are at increased risk for thrombotic events (such as stent thrombosis) when oral P2Y12 therapy is interrupted due to surgery ('Bridging').

The bridge indication was further withdrawn by the applicant at D180 of the procedure further concerns expressed by the Committee described later in the efficacy and safety parts of this report. Additionally, the initially applied PCI indication was further restricted.

2.5.1. Dose response studies

2.5.1.1. Dose response for PCI indication

The Dose regimen for PCI is a 30µg/kg IV bolus followed by 4 µg/kg/min IV infusion for 2 hours to 4 hours. The key study leading to this selection was the Phase I study, TMC-CAN-04-02 (Groups A and B), supported by results from the Phase II studies in ACS (SC-931-5058, SC 931 5060) and PCI (SC-931-5129 Part 1, and Part 2) (table E2).

Table E2: Summary of dose finding studies for cangrelor in the PCI indication

Study	Population; N Total (N cangrelor)	Objective	Design (*Platelet Function Test*)	Test Product; Dose Regimen; Duration
SC-93 1-5058	Patients with UA/non-Q-MI; 39 (39)	To investigate safety, tolerability, PD and PK	5 center, 3 part open-label study using a stepped dose titration followed by a plateau infusion (*WBIA*)	cangrelor; 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
SC-93 1-5060	Patients with UA/non-Q-MI; 91 (45)	To investigate safety, tolerability and PK	8-center, double-blind, placebo-controlled study (*None*)	cangrelor; 4 µg/kg/min IV infusion; 72 h
SC-93 1-5129 Part 1	Patients undergoing PCI; 200 (149)	To investigate safety, tolerability, PK, platelet aggregation and bleeding	25- center, double-blind, placebo-controlled pilot study (*WBIA*)	cangrelor; 1, 2, and 4 µg/kg/min IV infusion; 18-24 h

Study	Population; N Total (N cangrelor)	Objective	Design (*Platelet Function Test*)	Test Product; Dose Regimen; Duration
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*)	Cangrelor; 4 µg/kg/min IV infusion; 18-24h
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*)	cangrelor; A: 15 µg/kg IV bolus plus 2 µg/kg/min IV infusion; 1h B: 30 µg/kg IV bolus plus 4 µg/kg/min IV infusion; 1h

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.

In studies SC-931-5058 and SC-931-5129, a residual response to ADP (3 µM) was still evident in 76% (16/21), 61% (14/23), and 39% (17/44) of patients receiving cangrelor 0.5, 1, and 2 µg/kg/min, respectively, but only 10% (3/29) at 4 µg/kg/min (table E3). In the PCI setting, the Company decided to take forward as high a dose as possible from a tolerability perspective (4 µg/kg/min IV) to minimize residual platelet reactivity in as high a percentage of the population as possible.

Table E3: Proportion of patients achieving different levels of platelet inhibition in studies SC-931-5058 and SC-931-5129

Cangrelor (µg/kg/min) IV	Study (SC-931-X)	N	Number (%) of Patients Exhibiting Different Levels of Inhibition of Platelet Responsiveness					
			0-20%	>20-40%	>40-60%	>60-80%	>80-100%	=100%
0.5	5058	21[a]	1 (4)	2 (10)	3 (14)	5 (24)	5 (24)	5 (24)
1	5058	14	0 (0)	0 (0)	0 (0)	1 (7)	8 (57)	5 (36)
	5129	9	0 (0)	0 (0)	1 (11)	1 (11)	3 (33)	4 (44)
2	5058	38[b]	0 (0)	0 (0)	0 (0)	0 (0)	13 (34)	25 (66)
	5129	6	0 (0)	0 (0)	1(17)	0 (0)	3 (50)	2 (33)
4	5058	14	0 (0)	0 (0)	0 (0)	0 (0)	2 (14)	12 (86)
	5129 (Part 1)	5	0 (0)	0 (0)	0 (0)	1 (20)	0 (0)	4 (80)
	5129 (Part 2)	10	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	10 (100)

IV = intravenous; kg = kilogram; min = minute; µg = microgram.

The rationale for the 4 µg/kg/min IV infusion in the PCI indication is further supported by the output from the PD model based on P2Y12 Reaction Units (PRU) data from TMC-CAN-05-2-S1 and TMC-CAN-08-02, in which a higher dose of cangrelor appeared to be required in the PCI population compared to the BRIDGE population (Cangrelor Pop PK/PD Model).

Rationale for IV bolus plus IV infusion regimen in PCI

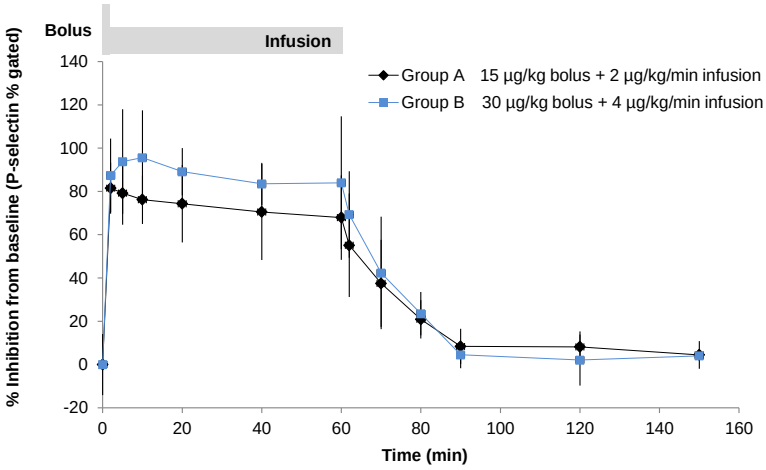
In studies SC-931-5058 and SC-931-5129, cangrelor was administered by IV infusion without an initial bolus loading dose. This resulted in an onset of action at the earliest time-points assessed (30 minutes in SC-931-5058, 15 minutes in SC-931-5129). Consistent with the half-life of cangrelor (3 to 6 minutes), up to 30 minutes of infusion would be required to achieve steady-state without a loading dose and, in a small number of individuals, the half-life was up to 9 minutes. Consequently, for the PCI indication and CHAMPION program, a

bolus plus infusion regimen was introduced, with the aim of achieving immediate and substantial reduction of platelet responsiveness to ADP in the acute interventional setting.

Study [TMC-CAN-04-02] Groups A and B. After bolus administration, a consistent and complete inhibition of platelet responsiveness to ADP, as measured by whole blood impedance aggregometry (WBIA), was achieved immediately (within 2 minutes) The inhibition was more complete and consistent throughout the infusion in the high dose group. 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 profile observed using WBIA in Groups A & B was confirmed using flow cytometry for ADP-induced P-selectin expression (figure E1).

Figure E1: Dose-related on-infusion inhibition of platelet function by cangrelor in study TMC-CAN-04-02 – assessed using P-selectin expression to 20 µM ADP



Inhibition of response to 20 µM ADP as measured by whole blood impedance aggregometry.kg = kilogram; min = minute; µg = microgram.

BRIDGE [TMC-CAN-08-02] was designed to demonstrate that, after discontinuation of oral $P2Y_{12}$ inhibitors and compared to placebo, cangrelor maintains low levels of platelet reactivity as expected when an oral $P2Y_{12}$ inhibitor had not been discontinued up until the time of surgery without increasing surgical bleeding.

In stage 1 of the study, a cangrelor dose infusion of 0.5 µg/kg/min prior to surgery maintained platelet inhibition above 60% in only 76.5% of patient samples and a dose of 0.75 µg/kg/min maintained platelet inhibition above 60% in 94.4% of patient samples (primary endpoint met). When measuring platelet inhibition during infusion according to the Working Group on Platelet Reactivity consensus, 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. A cangrelor dose of 0.75 µg/kg/min was selected for further evaluation in the randomized, double-blind phase (Stage II).

In stage II, the patients were randomized to treatment with either cangrelor or matching IV placebo. Double-dummy techniques were used to maintain the double blind. Study drug infusion was initiated immediately after randomization (within 72 hours of last dose of oral $P2Y_{12}$ inhibitor) and maintained throughout the pre-operative period for a minimum of 48 hours. Infusion durations of up to 7 days were allowed. Sites were instructed to discontinue the infusion 1 to 6 hours prior to surgical incision. Study drug was not administered during or after cardiac surgery (figure E2).

2.5.1.2. Dose response for Bridge indication

The Dose regimen proposed for the BRIDGE indication was an IV infusion of 0.75 µg/kg/min. This was based on the results of the BRIDGE study.

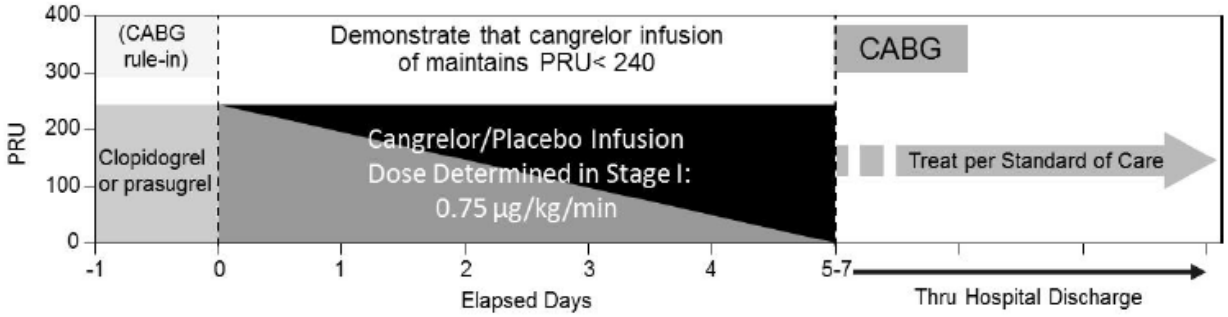
- **Bridge study design**

The BRIDGE [TMC-CAN-08-02] study was designed to demonstrate that, after discontinuation of oral $P2Y_{12}$ inhibitors and compared to placebo, cangrelor maintains low levels of platelet reactivity as expected when an oral $P2Y_{12}$ inhibitor had not been discontinued up until the time of surgery without increasing surgical bleeding.

In stage 1 of the study, a cangrelor dose infusion of 0.5 µg/kg/min prior to surgery maintained platelet inhibition above 60% in only 76.5% of patient samples and a dose of 0.75 µg/kg/min maintained platelet inhibition above 60% in 94.4% of patient samples (primary endpoint met). When measuring platelet inhibition during infusion according to the Working Group on Platelet Reactivity consensus, 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. A cangrelor dose of 0.75 µg/kg/min was selected for further evaluation in the randomized, double-blind phase (Stage II).

In stage II, patients were randomized to treatment with either cangrelor or matching IV placebo in a double blind fashion. Study drug infusion was initiated immediately after randomization (within 72 hours of last dose of oral $P2Y_{12}$ inhibitor) and maintained throughout the pre-operative period for a minimum of 48 hours. Infusion durations of up to 7 days were allowed. Sites were instructed to discontinue the infusion 1 to 6 hours prior to surgical incision. Study drug was not administered during or after cardiac surgery (figure E2).

Figure E2: Stage II study design



CABG = coronary artery bypass graft. PRU = P2Y12 Reaction Unit(s). kg = kilograms. min = minutes. µg = micrograms.

In **Stage II**, 44 of 93 (47.3%) patients in the cangrelor group presented with ACS versus 54 of 90 (60%) patients in the placebo group. In the cangrelor group, 49 of 93 (52.7%) presented with stents while 36 of 90 (40%) in the placebo group had stents. Overall, approximately 13.5% of patients enrolled were STEMI patients.

The ***primary efficacy endpoint*** (Stage II) was the percentage of patients with all samples during the infusion achieving P2Y12 Reaction Unit (PRU) <240, as determined by Verify*Now*™ P2Y12 test, measured during study drug infusion pre-surgery. This endpoint was selected as it is considered by consensus of the Working Group on Platelet Reactivity to be the threshold for the level of platelet inhibition required to maintain a low risk of coronary thrombosis and cardiac ischaemic events [Bonello et al, 2010]. No clinical study has correlated specific values of platelet inhibition by any one assay to thrombotic events and qualitative test results cannot be used to "fine-tune" inhibition. However, cutoff levels for various assays of platelet reactivity associated with increased clinical risk were suggested [Bonello et al, 2010; Tantry et al 2013]. The most important information obtained from assays measuring platelet function 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 test is known to be well correlated with maximal light transmittance aggregometry with oral $P2Y_{12}$ inhibitors clopidogrel, prasugrel and ticagrelor [Jeong 2008; Malinin 2007, von Beckerath 2006, Jakubowski 2008]

- **Bridge study results**

The primary efficacy endpoint was met in 98.8% of cangrelor-treated patients maintaining target levels of platelet inhibition (<240 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) (Table E4).

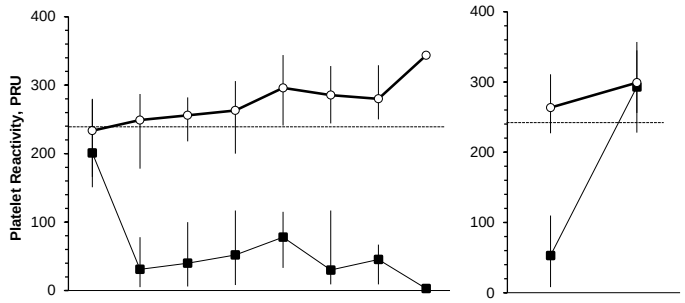
Table E4: BRIDGE: primary endpoint (patients with platelet reactivity <240 PRU throughout entire infusion period) and other outcomes

Endpoint	Cangrelor (N= 93)	Placebo (N= 90)	Relative Risk (95% CI)	p-value
Prior to Study Drug Infusion				
Patients With Platelet Reactivity <240 PRU, % (95% CI, N)	62.4% (52.1-72.7%, 53/85)	52.3% (41.8-62.9%, 45/86)	1.2 (0.9 – 1.5)	0.185
PRU Values, Mean ± SD	210.9 ± 94.0	214.1 ± 85.9	NA	0.817
During Study Drug Infusion				
Patients with Platelet Reactivity <240 PRU Throughout Entire Infusion Period **(Primary Endpoint),** % (95% CI, N)	98.8% (96.5-100%, 83/84)	19.0% (10.7-27.4%, 16/84)	Crude: 5.2 (3.3 – 8.1)	<0.001
			Adjusted: 5.2 (3.3 – 8.0)	<0.001
Patients With Last Sample During Infusion With Platelet Reactivity <240 PRU, % (95% CI, N)	98.8% (96.5-100%, 83/84)	31.0% (21.1-40.8%, 26/84)	3.2 (2.3 – 4.4)	<0.001
PRU Values Last Sample During Infusion, Mean ± SD	68.9 ± 67.8	263.7 ± 68.3	NA	<0.001
Following Discontinuation of Study Drug Infusion				
Patients With Platelet Reactivity <240 PRU, % (95% CI, N)	26.9% (17.1-38.2%, 21/78)	20.0% (11.0-29.1%, 15/75)	1.3 (0.8 – 2.4)	0.313
PRU Values, Mean ± SD	279.7 ± 106.5	297.8 ± 67.3	NA	0.212

Chi-square test was performed for proportions. Logistic regression was performed adjusted for the expected days to surgery (either ≤3 days or >3 days). Analysis of variance was used for PRU value. PRU = P2Y12 reaction units

After discontinuation of the infusion (1 to 6 hours before surgery), platelet function prior to surgery was similar for cangrelor and placebo groups (p=0.212). This rapid return of platelet function is consistent with the short half-life of cangrelor (3 to 6 min). Platelet reactivity during the overall study time course is illustrated in Figure E3.

Figure E3: Distribution of platelet reactivity during the BRIDGE study.



No. of patients with valid sample in the ITT population

	Baseline	1	2	3	4	5	6	7	Last on-treatment sample	Last post-treatment pre-CABG
Cangrelor	85	80	70	55	33	7	6	1	84	78
Placebo	86	76	73	57	34	24	14	2	84	75

PRU = P2Y12 reaction units.

2.5.1.3. Discussion on Dose and Efficacy of the BRIDGING indication

The BRIDGE study was submitted to support both the dose for the bridging indication, as well as the indication itself. The study was conducted in two phases: a dose finding phase with dosages up to 1.5 µg/kg/min in which the dose of 0.75 µg/kg/min was selected for further assessment in stage II. Administration of this dose is associated with 100% on-infusion samples <240 PRU, with no significant bleeding events. The choice of a cut off of <240 PRU to assess optimal dose is supported by adequate references, and is defendable. No patients were administered the highest dose of 1.5 µg/kg/min as the endpoint was reached by the previous dose.
The choice of the same endpoint as an efficacy parameter is however not supported. This is a PD parameter that can inform about efficacy, but cannot substitute for it. The results of the second phase shows a significant difference in this parameter between patients who were bridged from clopidogrel to cangrelor, compared to bridging from clopidogrel to placebo. This should have been further confirmed using efficacy parameters such as: death, MI, stroke, stent thrombosis, without tipping the balance by more bleeding. In addition, the chosen dose itself (0.75 µg/kg/min) is much lower than that used in the PCI indication during infusion (4 µg/kg/min), questioning if such a dose would offer adequate protection against major cardiovascular outcomes during the bridging period. The proposed dose of 0.75 ug/kg/min is shown to be associated with a low residual platelet reactivity of < 240 PRU, which is even lower than that achieved with maintenance doses of clopidogrel and comparable to that of ticagrelor and prasugrel.

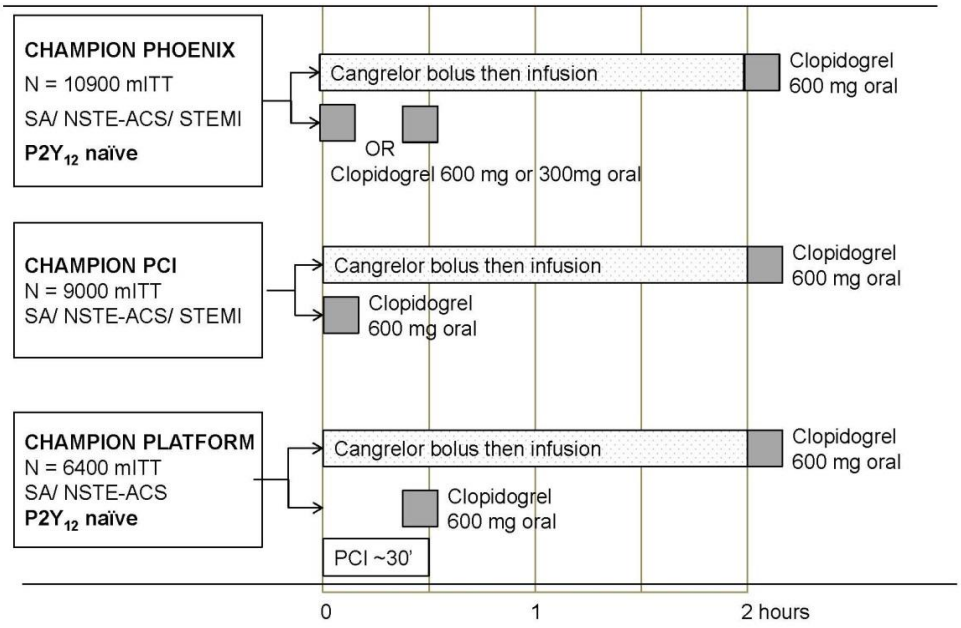
It is acknowledged that doses of antithrombotics in different indications are based on PD data, but confirmation in clinical efficacy and safety data is necessary as direct extrapolation of efficacy and safety is not possible. It can therefore be agreed that the dose in a bridging period could be smaller than that used during PCI, but the exact dose should be further verified by clinical data. There is no actual clinical experience with bridging from ticagrelor or prasugrel to cangrelor. Maintenance of adequate platelet inhibition depends on the PK/PD profile of the oral $P2Y_{12}$ inhibitor. Regarding the duration of infusion, the actual experience in the BRIDGE study includes one patient with the longest administration of 6.7 days. With the relatively low dose investigated in BRIDGE study, the total exposure is smaller than encountered in the CHAMPION studies.

2.5.2. Main studies

Main Studies to support the PCI indication

The CHAMPION trials were three randomized (1:1), double-blind, double-dummy trials designed to test whether cangrelor IV (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 therapy alone at reducing thrombotic events during and immediately after PCI. The three Phase III CHAMPION trials were very similar in design as shown in Figure E4.

Figure E4: The 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. mg = milligrams. mITT = modified intent-to-treat.

CHAMPION PLATFORM and ***CHAMPION PCI*** (implemented 2006 to 2009) 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. However available results showed some efficacy for cangrelor, which led to the hypothesis that the definition of MI was not specific enough to discriminate between MI that was already developing before and those during PCI.

CHAMPION PHOENIX (implemented from 2010 to 2013) applied the contemporary endpoint definitions for MI and ST that had not been published at the time of CHAMPION PCI and CHAMPION PLATFORM study design.

The current AR focuses on the C-PHOENIX study, as it is the only completed phase III study that has achieved its primary objective. Differences in design (timing of clopidogrel administration) and endpoints (definitions of MI and stent thrombosis) between these studies are pointed out as appropriate.

2.5.2.1. CHAMPION PHOENIX

- ***Study design***

Title : A clinical trial comparing cangrelor to clopidogrel standard of care therapy in subjects who require percutaneous coronary intervention: Cangrelor versus standard therapy to achieve optimal management of platelet inhibition.

Methods

The main methods are described above.

Study Participants

The main inclusion criteria for the C-PHOENIX was patients undergoing PCI for:
a. Stable angina (SA) with diagnostic coronary angiography within 90 days prior to randomization demonstrating atherosclerosis.
b. Non-ST-Segment Elevation Acute Coronary Syndrome (NSTE-ACS) with diagnostic coronary angiography within 72 hours prior to randomization demonstrating atherosclerosis.
c. ST-segment elevation MI (STEMI) patients (diagnostic angiography not required).

C-PLATFORM recruited mainly patients requiring PCI for either NSTEMI or unstable angina (UA). C-PCI recruited both NSTEMI and STEMI.

The exclusion criteria included prior stroke (ischaemic or haemorrhagic). In addition, C-PHOENIX excluded patients who were administered any $P2Y_{12}$ inhibitor at any time in the 7 days preceding randomisation.

Treatments

Cangrelor IV was administered as a 30 µg/kg IV bolus followed immediately by a 4 µg /kg/min IV infusion. Cangrelor infusion had to be continued for at least 2 hours or until the end of the index PCI procedure, whichever was longer. Patients were administered a transition dose of 600 mg clopidogrel following the discontinuation of the infusion. The active comparator in the CHAMPION program was **clopidogrel**.

A loading dose of clopidogrel (600 mg or 300 mg) was the control therapy in the CHAMPION programme. In C-PHOENIX, either dose was allowed, per investigator discretion. In the C-PCI and C-PLATFORM trials, clopidogrel loading dose of 600 mg administered either immediately before (C-PCI) or after (C-PLATFORM) PCI, respectively.

Timing of administration. In the CHAMPION programme, 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.

Outcomes/endpoints:

The primary efficacy endpoint of C-PHOENIX was a composite incidence of all-cause mortality, MI, ischaemia-driven revascularization (IDR) and stent thrombosis (ST) in the 48 hours after randomization. Incidence of stent thrombosis at 48 hours post-randomization was a key secondary endpoint. The other CHAMPION studies did not include ST in the primary composite endpoint. In all three of the CHAMPION trials, ST, IDR, and MI were adjudicated by an independent CEC through 30 days after randomization. Mortality was also adjudicated for cardiovascular cause of death in the CHAMPION PHOENIX trial.

Myocardial infarction: The PHOENIX trial was designed with these criteria to avoid confounding peri-procedural MIs with evolving pre-procedural MIs in patients with elevated biomarkers, based on previous experience with the earlier CHAMPION trials. The definition of peri-procedural MI in the 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, according to the Universal Definition of MI (UDMI), were included as PCI-related MI endpoints.

Specifically 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 ischaemic symptoms and 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 ≥3 × 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 ischaemia including ECG changes, angiographic evidence, and ischaemic symptoms) [Brener et al, 2013].

Patients determined to have STEMI at baseline (including patients with normal baseline cardiac markers who were confirmed by CEC adjudication to have baseline STEMI ECG) were not reviewed by the CEC for peri-procedural MI.

Randomisation

Patients were randomized via IV/WRS in the order that they qualified. Patient randomization was stratified by study site, planned clopidogrel loading dose in the clopidogrel treatment arm (600 mg or 300 mg), and patient baseline status (normal ischemic status, abnormal ischemic status) among other factors.

- Blinding (masking)

Placebo in IV and oral form and double-dummy techniques were employed to ensure study blinding.

Statistical Methods

Determination of Sample Size The composite event rate was assumed to be 5.1% in the clopidogrel arm and 3.9% in the cangrelor arm (24.5% reduction in odds ratio) based on results from the CHAMPION PCI and PLATFORM studies. This assumption took into consideration that the interim efficacy analysis was to be performed after 70% of patients had completed 48-hour follow-up and event adjudication, using Gamma family alpha spending function (with gamma = -5). A sample size of approximately 5,450 patients in each arm (approximately 10,900 in total) was considered to provide a power of 85% to detect this estimated difference at the two-sided overall Type I error of 0.05.

The primary analysis is adjusted for baseline patient status, one of the three stratification factors. If more that 15% of the patients were designated to receive a loading dose of 300 mg clopidogrel, then the analysis was also adjusted for designated loading dose. According to the Applicant the primary analysis was not adjusted for the stratification factor study site because of the large number of sites, as adjustment would lead to statistical inefficiency due to many "zero cell" strata. Exploratory subgroup analyses comparing top enrolling sites with other sites did not indicate a significant interaction, and a post-hoc analysis that did adjust for study site did not change the effect on the primary efficacy endpoint. For the same reason, the Applicant would not adjust for stratification factor designated loading dose unless at least 15% of patients had a clopidogrel loading dose of 300 mg. As this was the case, the final SAP was updated accordingly before database lock and the primary analysis was adjusted for this stratification factor.

Interim analysis One interim efficacy analysis was planned for the purpose of overwhelming efficacy and sample size re-estimation after approximately 70% of the enrolled patients had undergone adjudication of the 48-hour primary composite endpoint.

Populations The ITT population was used to summarize patient disposition. The primary efficacy analysis was based on the mITT population with supportive analyses in the ITT and PP populations. All safety analyses were performed on the Safety population.

Efficacy analysis A logistic regression model adjusted for baseline patient ischemic status (normal vs abnormal) and intended clopidogrel loading dose designated by investigators at randomization (600 vs 300 mg) was used to analyze the primary endpoint. As sensitivity analysis, logistic regression without baseline adjustment was also performed. Adjustment for additional risk factors was explored through multivariate

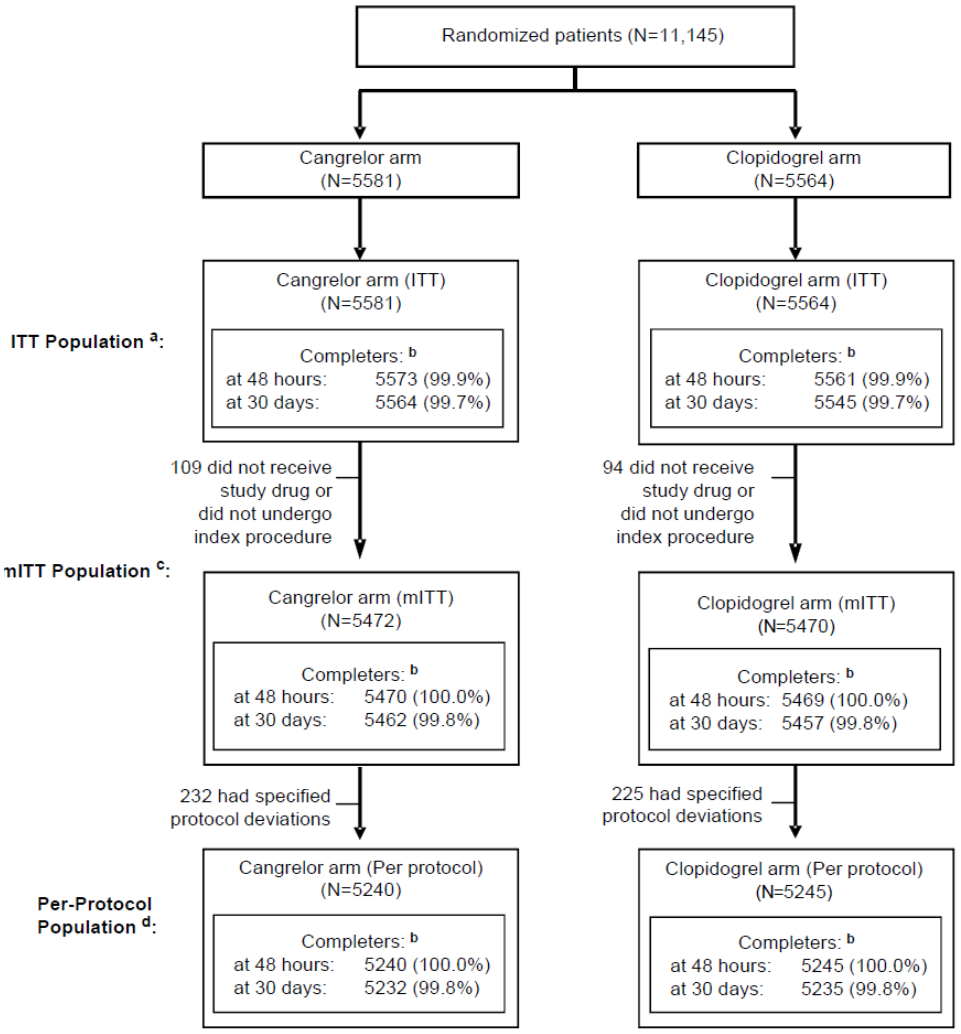
logistic regression. Subgroup analyses were performed on the primary efficacy endpoint. Hierarchical fixed sequence testing methodology was applied to test the key secondary endpoint (ST) and other components of the primary composite endpoints.

- ***Study results***

Participant flow in C-PHOENIX

A total of 11,145 patients were enrolled into the trial and were randomized (Figure E5). No patients in the randomized population were excluded from the ITT population. Among those in the ***ITT population***, 109 patients in the cangrelor arm and 94 patients in the placebo arm did not receive study drug or did not undergo the index PCI procedure and were therefore excluded from the ***mITT population***. Within each of these analysis populations, at least 99.9% of patients in both treatment arms completed the 48-hour time point, and at least 99.7% of patients in both treatment groups were considered to have completed the study at 30 days.

Figure E5: Patient disposition in CHAMPION PHOENIX.



A *ITT population is defined as all patients randomized.*
B *Patients completed scheduled visits or developed a primary endpoint event (death, myocardial infarction, ischaemia-driven revascularisation or stent thrombosis). Percentages represent rounding.*
C *mITT population is defined as all ITT patients who received at least one dose of study drug and underwent the index PCI procedure.*
D *The Per Protocol (PP) population is defined as patients randomized into the trial who received assigned study drug and who underwent the index PCI without specified protocol deviations*
ITT = intent-to-treat; mITT= modified intent-to-treat; N = total number of patients.

Tables E5 and E6 describe the baseline characteristics and medical history of the recruited patients in C-PHOENIX.

Table E5: Patient demographic and other baseline characteristics (ITT population)

Parameter, Statistic Category	Cangrelor (N=5581)	Clopidogrel (N=5564)	Overall (N=11,145)
Age, years			
N	5581	5564	11,145
Mean ± SD	64.0 ± 11.0	63.8 ± 11.0	63.9 ± 11.0
Median (Q1, Q3)	64.0 (56, 72)	64.0 (56, 72)	64.0 (56, 72)
Age group, years			
<65, n (%)	2892 (51.8)	2902 (52.2)	5794 (52.0)
≥65, n (%)	2689 (48.2)	2662 (47.8)	5351 (48.0)
Male, n (%)	3982 (71.3)	4042 (72.6)	8024 (72.0)
Race			
N	5578	5557	11,135
White, n (%)	5231 (93.8)	5206 (93.7)	10,437 (93.7)
Asian, n (%)	173 (3.1)	177 (3.2)	350 (3.1)
Black/African American, n (%)	156 (2.8)	152 (2.7)	308 (2.8)
Native Hawaiian/Pacific Islander, n (%)	13 (0.2)	16 (0.3)	29 (0.3)
American Indian/Alaskan native, n (%)	5 (0.1)	6 (0.1)	11 (0.1)
Weight, kg			
N	5580	5564	11,144
Mean ± SD	85.2 ± 17.8	85.6 ± 17.9	85.4 ± 17.8
Median (Q1, Q3)	84.0 (73, 95)	84.0 (74, 96)	84.0 (73, 96)
Patient types, n (%) [a]			
N	5581	5564	11,145
SA	3158 (56.6)	3059 (55.0)	6217 (55.8)
NSTE-ACS	1401 (25.1)	1424 (25.6)	2825 (25.3)
STEMI	1022 (18.3)	1081 (19.4)	2103 (18.9)
Cardiac markers >ULN			
Troponin I/T	1885/5534 (34.1)	1947/5520 (35.3)	3832/11,054 (34.7)
CK-MB	1190/5270 (22.6)	1230/5280 (23.3)	2420/10,550 (22.9)

Major deviations from the study protocol were limited and comparable between the study treatment arms. The presented baseline data of the recruited patients are in line with the studied population in clinical practice; with the majority of males (72%), and a good representation of patients above 65 years (48%). However, the majority were indicated for elective PCI (55%); with only around 19% of the patients indicated for PCI with STEMI.

A total of 4347/10,942 (39.7%) subjects were enrolled in Europe, with 2172 (39.7%) in the cangrelor arm and 2175 (39.8%) in the clopidogrel arm. This percentage would adequately reflect EU practice in the clinical trial. The associated comorbidities are also reflective of patients with CAD. According to the protocol, patients had to be $P2Y_{12}$ naïve, or discontinued $P2Y_{12}$ for 7 days prior to randomisation. This advice appears at odds with the recruited population, who has previous history of MI/PCI/CABG in almost one third of them. The applicant explained that precise data on recruited patients who may have been candidates for dual antiplatelet therapy is not available. Presented data for patients with previous PCI/MI within 30 days who are candidates for such therapy shows that they were very limitedly recruited (1%). It can be agreed with the company that patients with previous MI/PCI were only included in the trial after they had already completed their guidelines-recommended duration of dual antiplatelet therapy.

Although the protocol excludes patients with prior history of stroke, around 5% of the patients are reported to have had cerebrovascular accidents. The applicant explained that the exclusion criteria were ischemic stroke within the last year or any previous haemorrhagic stroke. However, the CRF did not capture the type of stroke or its timing. Therefore, it should be assumed that all of these other past events were either ischaemic occurring >1 year prior to randomisation or, when occurring within 30 days of randomisation, were an event such as a TIA that did not meet the exclusion criteria.

Table E6: Medical history (ITT population)

	n/N (%)		
Parameter Category	**Cangrelor (N=5581)**	**Clopidogrel (N=5564)**	**Overall (N=11,145)**
Diabetes Mellitus	1546/5571 (27.8)	1559/5555 (28.1)	3105/11126 (27.9)
Current smoker within past 30 days	1533/5444 (28.2)	1573/5428 (29.0)	3106/10872 (28.6)
Hypertension	4460/5566 (80.1)	4406/5546 (79.4)	8866/11112 (79.8)
Hyperlipidemia	3412/4942 (69.0)	3380/4908 (68.9)	6792/9850 (69.0)
Cerebrovascular event	276/5559 (5.0)	252/5543 (4.5)	528/11102 (4.8)
Family history of coronary artery disease	2121/5214 (40.7)	2108/5195 (40.6)	4229/10409 (40.6)
Previous MI	1111/5547 (20.0)	1191/5517 (21.6)	2302/11064 (20.8)
≤30 days before enrollment	55/5547 (1.0)	54/5517 (1.0)	109/11064 (1.0)
Previous PCI	1281/5569 (23.0)	1344/5550 (24.2)	2625/11119 (23.6)
≤30 days before enrollment	13/5569 (0.2)	19/5550 (0.3)	32/11119 (0.3)
Previous CABG	581/5574 (10.4)	509/5553 (9.2)	1090/11127 (9.8)
≤30 days before enrollment	581/5574 (10.4)	509/5553 (9.2)	1090/11127 (9.8)
Congestive heart failure	565/5567 (10.1)	592/5546 (10.7)	1157/11113 (10.4)
Peripheral artery disease	449/5513 (8.1)	390/5509 (7.1)	839/11022 (7.6)

Characteristics of the index PCI are summarized in table E7. CABG was performed as the index procedure for only 0.3% of cangrelor-treated patients and 0.2% of clopidogrel-treated patients during the trial, most often due to the patient's coronary anatomy being evaluated as unsuitable for PCI (11/19 cangrelor patients, 4/9 clopidogrel).

Table E7: Index PCI procedure (ITT population)

	Cangrelor (N=5581)	**Clopidogrel (N=5564)**
Patients with PCI procedure, n (%)	5490 (98.4)	5481 (98.5)
Patients with IVUS used, n (%)	311 (5.6)	326 (5.9)
# of vessels per patient having index PCI, n/N (%)		
0 (None)	49/5490 (0.9)	50/5481 (0.9)
1	4561/5490 (83.1)	4612/5481 (84.1)
2	769/5490 (14.0)	725/5481 (13.2)
3	104/5490 (1.9)	89/5481 (1.6)
4	7/5490 (0.1)	5/5481 (0.1)
Vessels treated per patient [b], n/N (%)		
RCA	1960/5490 (35.7)	1966/5481 (35.9)
LAD	2746/5490 (50.0)	2683/5481 (49.0)
LCX	1584/5490 (28.9)	1573/5481 (28.7)
Left main	149/5490 (2.7)	127/5481 (2.3)
Left main coronary artery bifurcation treated, n/N (%)	85/5460 (1.6)	46/5452 (0.8)
Intervention type, n/N (%)		
Drug-eluting stent	3073/5490 (56.0)	3029/5481 (55.3)
Bare metal stent	2312/5490 (42.1)	2345/5481 (42.8)
Balloon angioplasty	293/5490 (5.3)	274/5481 (5.0)

Concomitant Medications

***Prior medications*.** Nearly all patients were reported to be treated with aspirin (95% cangrelor-treated patients, 94% clopidogrel-treated patients). Unfractionated heparin was the next most common concomitant anticoagulant medication administered (78% of patients for both treatment arms) followed by bivalirudin (23% for both treatment arms).

Periprocedural GP IIb/IIIa inhibitor administration for use as bailout was reported for 129/5581 (2.3%) cangrelor patients, and for 194/5564 (3.5%) clopidogrel patients. The numerical increase in GP IIb/IIIa inhibitor bailout for clopidogrel-treated patients suggests numerically fewer procedural complications leading to GP IIb/IIIa inhibitor bailout occurred in the cangrelor treatment arm.

Post-procedural concomitant medications were balanced between treatment groups, with nearly all patients (97% in each treatment group) received clopidogrel 75 mg for 48 hours post-PCI and the majority of patients (79% in both groups) received post-procedural aspirin.

At discharge, nearly all patients were receiving aspirin (99% in both groups) and long-term maintenance clopidogrel therapy (96% in both groups). Prasugrel was administered to 1.5% of cangrelor-treated patients and 1.6% of clopidogrel-treated patients, and ticagrelor was administered to 0.4% of patients in both treatment groups, among other therapeutic options reported by investigators.

There is a comparable use of prior medications. Most of the patients were co-administered ASA. A slightly higher increase of peri-procedural GP IIb/IIIa inhibitor use is recorded in the clopidogrel arm.

Primary efficacy endpoint

The composite incidence of death/MI/IDR/stent thrombosis among mITT patients was 4.7% in the cangrelor treatment arm and 5.9% in the clopidogrel treatment arm. For adjusted analysis using logistic regression to control for the potential confounding factors of patient baseline status and clopidogrel loading dose, OR: 0.78 (95% CI: 0.66, 0.93), p=0.005; for unadjusted analysis, OR: 0.79 (95% CI: 0.67, 0.93), p=0.006 (table E8).

Table E8: Primary efficacy endpoint (48-hour composite of death, MI, IDR, and stent thrombosis) based on CEC-adjudicated results (mITT population)

	n (%) of patients			
	Cangrelor (N=5472)	Clopidogrel (N=5470)	OR and 95% CI	P value [a]
Death/MI/IDR/ST (adjusted analysis)	257/5470 (4.7)	322/5469 (5.9)	0.78 (0.66, 0.93)	0.005 LR
Death/MI/IDR/ST [b] (non-adjusted analysis)	257/5470 (4.7)	322/5469 (5.9)	0.79 (0.67, 0.93)	0.006

A P-value for the odds ratio comparing cangrelor versus clopidogrel. B RR (95% CI): 0.80 (0.68,0.94). CI = confidence interval. RR = relative risk. OR = odds ratio. LR = logistic regression. mITT = modified intent-to-treat. MI = myocardial infarction. ST = stent thrombosis. IDR = ischaemia-driven revascularisation.

Analyses of the primary efficacy endpoint in the ITT and PP populations provided similar results.

Secondary endpoints. Analysis of the individual incidence of the components of the primary efficacy composite endpoint and related secondary endpoints demonstrated a significant difference in the incidence of MI between cangrelor-treated patients (3.8%) and clopidogrel-treated patients (4.7%), with OR 0.80, 95% CI: 0.67, 0.97; p=0.022, in addition to the significantly lower incidence of stent thrombosis for cangrelor-treated patients (Table E11). Numerical differences between treatment groups for Q-wave MI and IDR were consistent

with these results. The incidence of all-cause mortality and cardiovascular death was the same (0.3%) between treatment groups, with all deaths adjudicated as cardiovascular deaths (Table E9).

Table E9: Individual efficacy endpoints at 48 hours based on CEC-adjudicated results (mITT population)

	n (%) of patients				
	Cangrelor (N=5472)	Clopidogrel (N=5470)	RR and 95% CI	OR and 95% CI	P-value [a]
N	5470	5469			
Primary endpoint					
Death/MI/IDR/ST	257 (4.7)	322 (5.9)	0.80 (0.68, 0.94)	0.79 (0.67, 0.93)	0.006
Key secondary endpoint					
Stent thrombosis	46 (0.8)	74 (1.4)	0.62 (0.43, 0.90)	0.62 (0.43, 0.90)	0.010
Death	18 (0.3)	18 (0.3)	1.00 (0.52, 1.92)	1.00 (0.52, 1.92)	>0.999
CV Death	18 (0.3)	18 (0.3)	1.00 (0.52, 1.92)	1.00 (0.52, 1.92)	>0.999
MI	207 (3.8)	255 (4.7)	0.81 (0.68, 0.97)	0.80 (0.67, 0.97)	0.022
Q-wave MI	11 (0.2)	18 (0.3)	0.61 (0.29, 1.29)	0.61 (0.29, 1.29)	0.193
IDR	28 (0.5)	38 (0.7)	0.74 (0.45, 1.20)	0.74 (0.45, 1.20)	0.217

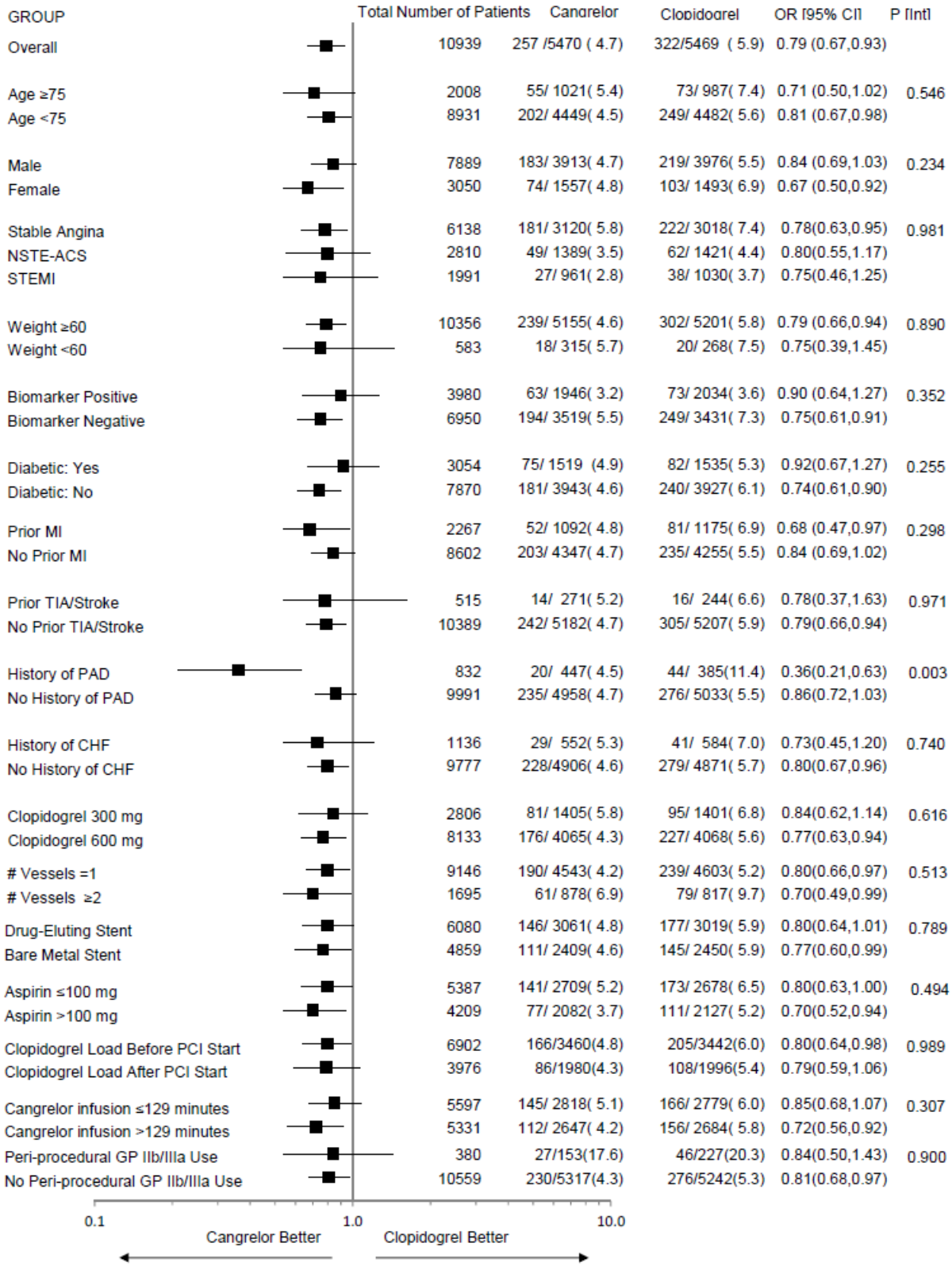
A P-value for the odds ratio comparing cangrelor versus clopidogrel. CI = confidence interval; RR = relative risk; OR = odds ratio; mITT = modified intent-to-treat. MI = myocardial infarction. CABG = coronary artery bypass graft. ST = stent thrombosis. IPST = intraprocedural stent thrombosis. IDR = ischaemia-driven revascularisation.

A) Subgroup analyses

A number of subgroup analyses at 48hours and at D30 were performed by the applicant or requested during the assessment. There are presented below.

Cangrelor efficacy was demonstrated in subgroup analysis 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 (Figure E6). Of note, medical history of peripheral artery disease showed a statistically significant interaction with cangrelor (p=0.003) without adjustment for multiplicity although cangrelor's protective effect remained evident in both groups (with or without PAD history).

Figure E6: Subgroup analysis of death/MI/IDR/ST in 48 hours (mITT Population)



Clopidogrel dose. A total 74% patients were assigned a 600 mg clopidogrel loading dose by investigators at randomization. In this subgroup, the composite incidence of the primary endpoint was significantly reduced in patients who received cangrelor compared with patients receiving clopidogrel 600 mg loading dose (4.3% vs. 5.6%; OR: 0.77; CI: 0.63,0.94; p=0.009)(Table E10).

Table E10: 48-hour composite efficacy endpoint based on CEC-adjudicated results, by clopidogrel loading dose, patient type of and timing of loading dose (mITT)

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

Table E11: Stent thrombosis events at 48 hours in CHAMPION PHOENIX (mITT population)

			Cangrelor vs Clopidogrel	
	Cangrelor N=5470 n (%)	Clopidogrel N=5469 n (%)	OR (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

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.

Note: 3 patients have no efficacy data at 48 h.

Further analysis of C-PHOENIX shows that efficacy outcomes are significantly worse in patients with IPST at 30 days (Table E12), which could support their importance.

Table E12: 30-day efficacy outcomes in patients with and without IPST during index PCI (mITT population)

	n (%) of patients			
30 day endpoint	**IPST (N=89)**	**No IPST (N=10,850[a])**	**RR (95% CI)**	**p value**
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

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

ARC = Academic Research Consortium; CI = confidence interval; IDR = ischaemia-driven revascularization; IPST = intraprocedural stent thrombosis; MI = myocardial infarction; mITT = modified intent-to-treat; PCI = percutaneous coronary intervention; RR = risk ratio; ST = stent thrombosis.

For MI, using a higher threshold of post-PCI elevation of CK-MB of ≥ 10xULN, the results show the superiority of cangrelor (0.7%) over clopidogrel (1.1%) (table E13). These results are reassuring, although the absolute difference is quite small.

Table E13: PHOENIX: Incidence of Type 4a MI categorised by magnitude of CK-MB elevation

	Incidence at 48 hours n (%) of patients		
UDMI Size	**Cangrelor N=5470**	**Clopidogrel N=5469**	**Odds ratio (95% CI)**
≥3x ULN	194 (3.5)	239 (4.4)	0.80 (0.66, 0.98)
≥5x ULN	106 (1.9)	129 (2.4)	0.82 (0.63, 1.06)
≥10x ULN	37 (0.7)	62 (1.1)	0.59 (0.39, 0.89)

CI = confidence interval; MI = myocardial infarction; OR = odds ratio; ULN = upper limit of normal.

The incidence of death was comparable between the treatment groups, and numerically worse at day 30.

The applicant submitted several sensitivity analysis of the primary endpoint to confirm the robustness of the results. (Table E14)

Table E14: Sensitivity analyses of CHAMPION-PHOENIX primary endpoints at 48 hours (mITT population)

	n (%) of patients				
	Cangrelor N=5472	Clopidogrel N=5470	OR (95% CI)	p value	% Omitted Events
Protocol-Defined Primary Endpoint					
Death/MI/IDR/ST	257/5470 (4.7)	322/5469 (5.9)	0.79 (0.67,0.93)	0.0055	N/A
Sensitivity Analyses					
1. Removing IPST					
Death/MI/IDR/ARC-ST	230/5470 (4.2)	286/5469 (5.2)	0.80 (0.67,0.95)	0.0115	11%
2. Removing IPST and MIs solely identified by CKMB >3x ULN but <10x ULN without accompanying ECG changes					
Death/MI ≥10xULN or Symptom or ECG/IDR/ARC-ST	106/5470 (1.9)	161/5469 (2.9)	0.65 (0.51,0.83)	0.0007	54%
3. Removing IPST and all MIs identified solely on the basis of an increase in CK-MB					
Death/MI with Symptom or ECG/IDR/ARC-ST	86/5470 (1.6)	130/5469 (2.4)	0.66 (0.50,0.86)	0.0025	63%

Importantly, the second analysis, which includes the clinically relevant events of death/MI≥ 10 ULN or symptom or ECG/IDR/ARC-ST and excludes 54% of other events, still maintains the superiority of cangrelor (1.9%) against clopidogrel (2.9%) [OR:0.65 (0.51- 0.83); p <0.0007].

Ancillary Analysis

The incidence of the **30-day composite efficacy endpoint of all-cause mortality, MI, IDR or stent thrombosis** remained significantly lower among cangrelor-treated patients (6%) than clopidogrel-treated patients (7%; OR 0.85, 95% CI: 0.73, 0.99; p=0.035)(table E15). By protocol, patients were to be treated with maintenance $P2Y_{12}$ inhibition on the morning after the index PCI procedure and through 30 days, and most mITT patients (96.5% in the cangrelor treatment arm, and 96.6% in the clopidogrel treatment arm) were discharged with clopidogrel as P2Y12 inhibition therapy.

Table E15: 30-day efficacy endpoint (death, MI, IDR, and stent thrombosis) based on CEC-adjudicated results (mITT population)

	n/N (%) of patients				
	Cangrelor (N=5472)	Clopidogrel (N=5470)	RR and 95% CI	OR and 95% CI	P-value [a]
N	5462	5457			
Death/MI/IDR/ST	326/5462 (6.0)	380/5457 (7.0)	0.86 (0.74, 0.99)	0.85 (0.73, 0.99)	0.035
Stent thrombosis	71/5462 (1.3)	104/5457 (1.9)	0.68 (0.51, 0.92)	0.68 (0.50, 0.92)	0.012
IPST	35 (0.6)	54 (1.0)	0.65 (0.42, 0.99)	0.65 (0.42, 0.99)	0.043
Definite ST	27 (0.5)	38 (0.7)	0.71 (0.43, 1.16)	0.71 (0.43, 1.16)	0.170
Probable ST	12 (0.2)	15 (0.3)	0.80 (0.37, 1.71)	0.80 (0.37, 1.71)	0.562
Possible ST	0 (0.0)	0 (0.0)	N/A	N/A	N/A
Subacute ST	28 (0.5)	32 (0.6)	0.87 (0.53, 1.45)	0.87 (0.53, 1.45)	0.602
Death	60/5462 (1.1)	55/5457 (1.0)	1.09 (0.76, 1.57)	1.09 (0.76, 1.58)	0.643
CV Death	48/5462 (0.9)	46/5457 (0.8)	1.04 (0.70, 1.56)	1.04 (0.69, 1.57)	0.839
MI	225/5462 (4.1)	272/5457 (5.0)	0.83 (0.70, 0.98)	0.82 (0.68, 0.98)	0.030
Q-wave MI	14/5462 (0.3)	22/5457 (0.4)	0.64 (0.33, 1.24)	0.63 (0.32, 1.24)	0.181
IDR	56/5462 (1.0)	66/5457 (1.2)	0.85 (0.59, 1.21)	0.85 (0.59, 1.21)	0.360

IPST: intraprocedural stent thrombosis IDR = ischaemia-driven revascularisation. ST = stent thrombosis. NA = not applicable.

Subgroup analysis. Analysis of the primary endpoint in different subgroups showed general consistency in benefits as observed with the main cohort. There was interaction only for patients with history of peripheral artery disease (PAD)(p=0.003) with cangrelor showing more benefits in these patients. The Forest plot shows that the superiority is mainly driven by the results of the subgroup of stable CAD, while the subgroup of STEMI showed non-significant results, but in the same direction of the main cohort (OR 0.75; 95% CI: 0.46- 1.25**).** Even when combining STEMI/NSTEMI and increasing the database (table E16), the results are still not significant, though favouring cangrelor.

Table E16: 48-hour composite efficacy endpoint based on CEC-adjudicated results, by patient type (mITT)

	n/N (%) of patients			
Death/MI/IDR/ST	**Cangrelor**	**Clopidogrel**	**OR (95% CI)**	**p interaction**
All patients	257/5470 (4.7)	322/5469 (5.9)	0.78 (0.67, 0.93)	
Stable angina patients	181/3120 (5.8)	222/3018 (7.4)	0.78 (0.63,0.95)	
NSTE-ACS patients	49/1389 (3.5)	62/1421 (4.4)	0.80 (0.55,1.17)	0.981
STEMI patients	27/961 (2.8)	38/1030 (3.7)	0.75 (0.46, 1.25)	
NSTE-ACS and STEMI	76/2350 (3.2)	100/2451 (4.1)	0.79 (0.58,1.06)	

The presented net clinical benefit is in line with the efficacy results (table E17).

Table E17: Post-hoc analysis of net clinical benefit from CHAMPION PHOENIX, by patient type (mITT and safety populations)

	n/N (%) of patients			
Death/MI/IDR/ST/ GUSTO Severe / Moderate bleeding	**Cangrelor**	**Clopidogrel**	**OR (95% CI)**	**p value**
All patients	284/5470(5.2)	340/5469(6.2)	0.83 (0.70, 0.97)	0.021
Stable angina patients	191/3120 (6.1)	229/3018 (7.6)	0.79 (0.65, 0.97)	0.023
NSTE-ACS patients	56/1389 (4.0)	66/1421(4.6)	0.86 (0.60, 1.24)	0.425
STEMI patients	37/961 (3.9)	45/1030 (4.4)	0.88 (0.56, 1.37)	0.561
NSTE-ACS and STEMI	93/2350 (4.0)	111/2451(4.5)	0.87 (0.66, 1.15)	0.327

Ancillary Analysis. Generally the beneficial results of primary composite endpoint observed at 48 hours, were maintained at 30 days. There were significantly lower incidences of MI and stent thrombosis in the cangrelor group. However, there is a slight numerical increase in the reported CV deaths in the cangrelor group (0.9%; 48/5462) compared to the clopidogrel group (0.8%; 46/5457; RR:1.04 95% CI:0.69-1.57). It is acknowledged that the observed difference in mortality at 30 days is not significant and the incidence is comparable. Longer term results (1 year) are available from the 2 other CHAMPION studies, which show better mortality results for cangrelor (3.3%) vs clopidogrel (3.7%). This is reassuring. The most frequent causes of death according to the study report (table E18) are reported as follows:

Table E18: Deaths within 30 days, reported for ≥ 2 patients in each treatment arm, by preferred term, sorted by frequency (safety population)

	Number (%) of patients	
Preferred Term	**Cangrelor (N=5529)**	**Clopidogrel (N=5527)**
Any deaths within 30 days	**61 (1.1)**	**57 (1.0)**
Cardiogenic shock	9 (0.2)	5 (0.1)
Myocardial infarction	8 (0.1)	1 (0.0)
Acute myocardial infarction	5 (0.1)	3 (0.1)
Cardiac arrest	5 (0.1)	6 (0.1)
Thrombosis in device	3 (0.1)	3 (0.1)
Unknown cause of death	2 (0.0)	6 (0.1)
Cardiac failure congestive	2 (0.0)	4 (0.1)
Sudden cardiac death	2 (0.0)	4 (0.1)
Cerebrovascular accident	2 (0.0)	2 (0.0)
Multi-organ failure	2 (0.0)	1 (0.0)
Myocardial rupture	1 (0.0)	3 (0.1)
Sudden death	1 (0.0)	3 (0.1)
Cardiac failure	1 (0.0)	2 (0.0)
Ventricular fibrillation	1 (0.0)	2 (0.0)
Coronary artery occlusion	0 (0.0)	2 (0.0)

The most frequent Death related events (cardiogenic shock and MI) are described below:

Cardiogenic shock

A total of nine deaths were reported under cardiogenic shock in PHOENIX. Of these the majority (six patients) presented to the hospital with STEMI. The remainder included one patient with NSTE-ACS and two with stable angina. The medical history in all nine of these patients was typical of patients with coronary artery disease. Of the six patients with STEMI, four were from the same site in Russia. All had risk factors for cardiogenic shock including female gender, a medical history of hypertension and a presentation with STEMI. Two of the 4 patients had a history of prior MI or prior PCI, and one patient had a history of insulin dependent diabetes.

One patient who was admitted with NSTE-ACS and underwent PCI of the left anterior descending artery developed dyspnoea followed by rapid progression to pulmonary oedema. The patient died from cardiogenic shock two days after presentation.

Of the two patients with stable angina, one subject was a 62 year old female who suffered a coronary artery perforation of the left anterior descending artery during the PCI resulting in ACUITY Major/GUSTO moderate bleeding and a myocardial infarction. The coronary artery perforation was a procedural complication secondary to a guidewire that led to cardiac tamponade, bradycardia and respiratory arrest. The cardiac tamponade may have been exacerbated by treatment with cangrelor. She died three days after the PCI.

Another SA patient was 55 year old female who suffered a stent thrombosis after PCI, requiring an IDR and resulting in an MI. She died within 48 hours of the PCI.

Myocardial Infarction

A total of eight deaths were reported under myocardial infarction in PHOENIX. Of these, three patients presented to the hospital with STEMI, two with NSTE-ACS and three with stable angina. The medical history in all eight of these patients was typical of patients with coronary artery disease.

Four patients had stent thrombosis between 48 hours and 30 days and subsequently died. One subject was a 46 year old female who underwent PCI for stable angina. After stent placement she experienced abrupt closure with severe spasm which would not resolve, resulting in ventricular fibrillation, cardiac arrest and death. The patient died in the catheterisation laboratory.

Another patient was an 81 year old male with NSTE-ACS. His medical history included hypertension, prior history of smoking, and family history of coronary artery disease. Nine days after discharge from hospital the patient died due to sudden cardiac death and MI, as reported from an autopsy result.

Of the bleeding events that occurred, 2 patients had a $\geq$ 5cm haematoma, which may have been associated with cangrelor treatment but are not known to be clinically correlated with adverse outcomes.

In conclusion, cangrelor may have contributed to the events of cardiac tamponade subsequent to coronary artery perforation and retroperitoneal haematoma resulting in cardiogenic shock and death. Cangrelor may also have contributed to the events of $\geq$ 5cm haematoma but it is unlikely these events were associated with the subsequent myocardial infarction and death in these patients.

Table E19 presents the 48 hrs and 30 days deaths for the different PCI subgroups. The differences whether favouring cangrelor in ACS in 48 hours, or favouring clopidogrel in the same group at 30 days are very marginal. In conclusion the CHMP considered that the numbers are too limited and it is difficult to draw robust conclusions.

Table E19: Death and CV deaths in C-PHOENIX at 48 hours and 30 days in different subgroups (miTT)

	Cangrelor	Clopidogrel	Cangrelor vs Clopidogrel		
			RR and 95% CI	OR and 95% CI	p-value for OR
48 hour post randomization					
(mITT+SA/NSTE-ACS/STEMI)					
Death	18/ 5470(0.3)	18/ 5469(0.3)	1.00(0.52,1.92)	1.00(0.52,1.92)	0.9996
CV Death	18/ 5470(0.3)	18/ 5469(0.3)	1.00(0.52,1.92)	1.00(0.52,1.92)	0.9996
(mITT+SA)					
Death	4/ 3120(0.1)	0/ 3018(0.0)	.(.,.)	.(.,.)	0.0491
CV Death	4/ 3120(0.1)	0/ 3018(0.0)	.(.,.)	.(.,.)	0.0491
(mITT+NSTEMI)					
Death	4/ 1072(0.4)	7/ 1117(0.6)	0.60(0.17,2.03)	0.59(0.17,2.03)	0.4017
CV Death	4/ 1072(0.4)	7/ 1117(0.6)	0.60(0.17,2.03)	0.59(0.17,2.03)	0.4017
(mITT+STEMI)					
Death	9/ 961(0.9)	11/ 1030(1.1)	0.88(0.36,2.11)	0.88(0.36,2.12)	0.7688
CV Death	9/ 961(0.9)	11/ 1030(1.1)	0.88(0.36,2.11)	0.88(0.36,2.12)	0.7688
30 days post randomization					
(mITT+SA/NSTE-ACS/STEMI)					
Death	60/ 5462(1.1)	55/ 5457(1.0)	1.09(0.76,1.57)	1.09(0.76,1.58)	0.6428
CV Death	48/ 5462(0.9)	46/ 5457(0.8)	1.04(0.70,1.56)	1.04(0.69,1.57)	0.8394
(mITT+SA)					
Death	15/ 3115(0.5)	7/ 3012(0.2)	2.07(0.85,5.07)	2.08(0.85,5.10)	0.1031
CV Death	11/ 3115(0.4)	3/ 3012(0.1)	3.55(0.99,12.70)	3.55(0.99,12.75)	0.0377
(mITT+NSTEMI)					
Death	17/ 1387(1.2)	23/ 1418(1.6)	0.76(0.41,1.41)	0.75(0.40,1.41)	0.3761
CV Death	14/ 1387(1.0)	21/ 1418(1.5)	0.68(0.35,1.33)	0.68(0.34,1.34)	0.2606
(mITT+STEMI)					
Death	28/ 960(2.9)	25/ 1027(2.4)	1.20(0.70,2.04)	1.20(0.70,2.08)	0.5048
CV Death	23/ 960(2.4)	22/ 1027(2.1)	1.12(0.63,1.99)	1.12(0.62,2.03)	0.7041

Analysis performed across trials

The applicant presented data from the CHAMPION pooled efficacy analysis (N=24,910 mITT) to further support efficacy of C-PHOENIX. The MI component for the integrated efficacy analysis of the CHAMPION trials included, MI as defined per protocol in CHAMPION PHOENIX and, as ascertained retrospectively from CHAMPION PLATFORM and CHAMPION PCI using the UDMI definition based on adjudicated results. 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 P2Y12 inhibitor therapy prior to PCI.

Two formal interim analyses were conducted in both trials. The first interim review was conducted by the Data Safety and Monitoring Board (DSMB) when approximately 50% of subjects were enrolled and included a stopping rule for both efficacy and futility. The second interim review was conducted when approximately 70% of patients were enrolled and included additional rules for adaptation of the study that included sample size re-estimation and enrichment, as defined in the Interim Analysis Review Committee (IARC) charter.

Demographic and baseline characteristics observed within the individual CHAMPION trials were similar to those observed in the pooled population. The proportion of SA patients (56%) was higher in the CHAMPION PHOENIX [TMC-CAN-10-01] trial compared to the CHAMPION Pooled population.

Results. A significant 19% reduction in the incidence of death/MI/IDR/ST at 48 hours was also observed, p=0.001 (table E20).

Table E20: Incidence of thrombotic events at 48 hours in the CHAMPION pooled analyses (CEC-adjudicated results – mITT Population)

	n (%) of Patients		Cangrelor vs Clopidogrel	
Endpoint	**Cangrelor**	**Clopidogrel**	**OR (95% CI)**	**p value [a] for OR**
CHAMPION Pooled, N	12459	12422		
Death/MI/IDR/ST	473 (3.8)	579 (4.7)	0.81 (0.71, 0.91)	0.001
ST	62 (0.5)	105 (0.8)	0.59 (0.43, 0.80)	0.001
Death	33 (0.3)	45 (0.4)	0.73 (0.47, 1.15)	0.169
MI	387 (3.1)	453 (3.6)	0.85 (0.74, 0.97)	0.018
IDR	66 (0.5)	92 (0.7)	0.71 (0.52, 0.98)	0.036

a P-values based on adjusted logistic regression model (PHOENIX death/MI/IDR/ST analysis) or Chi-squared test (all other analyses presented in table). CI = confidence interval. MI = myocardial infarction. mITT = modified intent-to-treat. CEC = Clinical Events Committee. ST = stent thrombosis. OR = odds ratio. IDR = ischaemia-driven revascularization.

The results from the pooled analysis of the CHAMPION trials demonstrated similar efficacy at 30 days and are presented in Table E21.

Table E21: Incidence of thrombotic events at 30 days in the CHAMPION trials (CEC-adjudicated results – mITT Population)

	n (%) of Patients		Cangrelor vs Clopidogrel	
Endpoint	**Cangrelor**	**Clopidogrel**	**OR (95% CI)**	**p value [a] for OR**
CHAMPION Pooled, N	12407	12357		
Death/MI/IDR/ST	657 (5.3)	748 (6.1)	0.87 (0.78, 0.97)	0.010
ST	113 (0.9)	162 (1.3)	0.69 (0.54, 0.88)	0.003
Death	137 (1.1)	141 (1.1)	0.97 (0.76, 1.23)	0.783
MI	418 (3.4)	487 (3.9)	0.85 (0.74, 0.97)	0.017
IDR	153 (1.2)	178 (1.4)	0.85 (0.69, 1.06)	0.156

a P values based on Chi-squared test. CI = confidence interval; IDR = ischaemic-driven revascularization; MI = myocardial infarction; mITT = modified intent-to-treat; CEC = Clinical Events Committee; ST = stent thrombosis; OR = odds ratio; IDR = ischaemia-driven revascularization.

Supportive study

N/A

2.5.1.2 Summary of main efficacy results

Title: A clinical trial comparing cangrelor to clopidogrel standard of care therapy in subjects who require percutaneous coronary intervention: CHAMPION PHOENIX. Cangrelor versus standard therapy to achieve optimal management of platelet inhibition.		
Study identifier	CHAMPION PHOENIX	
Design	A randomized, double-blind, parallel-group, superiority study of cangrelor efficacy compared with clopidogrel.	
	Duration of main phase:	Date first patient enrolled: 30 September 2010 Date last patient completed: 14 November 2012
Hypothesis	Superiority of cangrelor over clopidogrel	
Treatments groups	Cangrelor	administered as a 30 µg/kg intravenous (IV) bolus followed immediately by 4 µg/kg/min IV infusion.
	Clopidogrel	oral loading dose 300 mg or 600 mg was administered in patients undergoing PCI as soon as possible following randomization as directed by the investigator.
Endpoints and definitions	Primary endpoint	Composite incidence of all-cause mortality, MI, IDR and stent thrombosis, assessed 48 hours after randomization.
	Secondary endpoint	Incidence of stent thrombosis at 48 hours after randomization.
	Other endpoints	Individual incidence of the other components of the composite (all-cause mortality, MI, and IDR) at 48 hours post-randomization ☐ Incidence of cardiovascular mortality at 48 hours and 30 days post-randomization ☐ Incidence of Q-wave MI at 48 hours and 30 days post-randomization
Database lock	4 Jan 2013	

Results and Analysis

Analysis description	
Analysis population and time point description	ITT population: 11,145 patients (5581 cangrelor; 5564 clopidogrel) mITT population: 10,942 patients (5472 cangrelor; 5470 clopidogrel) PP population: 10,485 patients (5240 cangrelor; 5245 clopidogrel) Safety population: 11,056 patients (5529 cangrelor; 5527 clopidogrel)

Descriptive statistics and estimate variability

	Cangrelor N=5470 n (%)	**Clopidogrel N=5469 n (%)**	**OR and 95% CI**	**p-value[a] for OR**
All-cause mortality/MI/IDR/ST	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

2.5.3. Discussion on Clinical Efficacy

Clinical efficacy in the bridge indication:

The BRIDGE study was designed to demonstrate that cangrelor can maintain a low level of platelet reactivity without increasing the bleeding risk, when oral $P2Y_{12}$ inhibitors have to be discontinued prior to surgery.

In the cangrelor group, 44 of 93 (47.3%) patients presented with ACS versus 54 of 90 (60%) patients in the placebo group. In the cangrelor group, 49 of 93 (52.7%) presented with stents while 36 of 90 (40%) in the placebo group had stents. Overall, approximately 13.5% of patients enrolled were STEMI patients.

In this study, the primary efficacy endpoint was met with 98.8% of cangrelor-treated patients maintaining target levels of platelet inhibition (<240 PRU, as determined by Verify*Now*™ P2Y12 test) 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).

The chosen **dose** is much lower than that recommended for the PCI indication (30 µg bolus+ 4 µg/kg/min). However, the currently proposed dose (0.75 µg/kg/min) is not adequately defined.

The choice of a PD parameter as **primary endpoint** to support efficacy in the BRIDGING indication is not accepted by the CHMP. Inhibition of platelet aggregation is a relevant parameter but can not substitute for clinical data indicating thrombosis like myocardial infarction. This point is even more critical considering the low dose used.

BRIDGING data from **ticagrelor** and **prasugrel** are missing; in the BRIDGE study patients were mainly on clopidogrel.

Clinical efficacy in PCI indication:

The three CHAMPION studies are submitted to support the indication of PCI. Both C-PCI and C-PLATFORM are incomplete studies, prematurely terminated due to the low likelihood of achieving their primary aim (superiority of cangrelor to clopidogrel). The discussion will mainly focus on C- PHOENIX, the only complete study which has achieved its primary objective.

Design of clinical studies

The C-PHOENIX recruited the three categories indicated for PCI (stable CAD, STEMI and NSTEMI). This is not an optimal design considering the different risk factors and thrombotic risk in the chronic (stable CAD) versus the acute setting (STEMI/NSTEMI), in addition to the difference in the standard of care. The exclusion of patients with prior stroke limits the external validity of the study, and this is reflected in the SmPC (section 4.3).

Choice of active comparator

The choice of clopidogrel as the only active comparator across the different indications for PCI is debatable. According to the relevant ESC guidelines, either ticagrelor or prasugrel are the preferred agents because of their superior efficacy to clopidogrel. Clopidogrel should only be used when these agents are not available. However, it can be agreed, based on utilization data, that clopidogrel is still currently used for PCI in EU across the different subgroups. In addition, clinical guideline differ regarding the preference of prasugrel/ticagrelor over clopidogrel in the acute PCI setting: the American guidelines give no preference, whereas the ESC favours prasugrel/clopidogrel. Specifically ticagrelor was not available at the time of initiation of C-PHOENIX. Accordingly, the CHMP questioned, whether clopidogrel was a valid comparator in the acute setting and this issue was discussed with the CV SAG experts. (see later)

Dose of and timing clopidogrel used in the study

Regarding the chosen clopidogrel dose, it can be agreed with the MAH that the current EU SmPC recommends a loading dose of 300 mg. However, as already mentioned in most recent guidelines the superior efficacy of the 600 mg is acknowledged. For example, 600 mg loading dose/150 mg maintenance dose in the first week was

superior to the 300/75 mg regimen in the subset of patients undergoing PCI in (OASIS) 7 trial (Mehta et al., 2010). High clopidogrel loading doses have been demonstrated to achieve more rapid inhibition of the ADP receptor. Likewise, in PCI for NSTEMI, 600-mg loading dose of clopidogrel (or a supplementary 300-mg dose at PCI following an initial 300-mg loading dose) is recommended for patients scheduled for an invasive strategy. The results comparing cangrelor to 600 mg clopidogrel are therefore more relevant. In comparison, all patients in the cangrelor arm received 600 mg clopidogrel directly following the cangrelor infusion. The possible disadvantages for the clopidogrel arm with the chosen dose and time of initiation was further addressed by the applicant. Analyses by dose show comparable results, with even better results when the 600 mg dose is used (table E22).

Table E22: Primary endpoint for 'clopidogrel loading dose' subgroups in CHAMPION PHOENIX (mITT population)

	Primary endpoint incidence at 48 hours			
	n/N (%) of patients			
	Cangrelor	Clopidogrel	OR (95% CI)	p value (interaction)
All patients	257/5470 (4.7)	322/5469 (5.9)	0.78 (0.66-0.93)	
300 mg	81/1405 (5.8)	95/1401 (6.8)	0.84 (0.62-1.14)	
600 mg	176/4065 (4.3)	227/4068 (5.6)	0.77 (0.63-0.94)	0.62

CI = confidence interval; OR = odds ratio

Significant results for the primary endpoint in favour of cangrelor were shown against the clopidogrel 600 mg loading dose [cangrelor (4.3%) vs clopidogrel (5.6%) OR: 0.77 (95% CI: 0.63, 0.94)]; but not against the clopidogrel 300 mg loading dose [cangrelor (5.8%) vs clopidogrel (6.8%) OR: 0.84 (95% CI: 0.62, 1.14)]. Significant results were shown when clopidogrel was administered before PCI start [cangrelor (4.8%) vs clopidogrel (6.0%) OR: 0.80 (95% CI: 0.64, 0.98)] but not when administered after PCI start, but with consistent effect on the OR [cangrelor (4.3%) vs clopidogrel (5.4%). OR: 0.79 (95% CI: 0.59, 1.06)].

The switch dose in the cangrelor arm was consistently 600 mg, which may have favoured the results in this arm. However, the applicant explained that most of the events occurred before this dose was given (90% of the events occurred during the first 2 hours after randomisation).

Regarding the possible influence of time of clopidogrel administration, most of the patients were administered clopidogrel before PCI (63.4%), with less than a third administered it during PCI (36.5%), and almost none after PCI (0.1%). These data compare favourably with those from TRITON-38 where clopidogrel was administered mostly during PCI (74%).

The results presented by time of clopidogrel administration (table E23) show that superiority of cangrelor is not dependent on the timing of clopidogrel administration. Further analysis show that clopidogrel efficacy in C-PHOENIX is not compromised by later administration. These data are reassuring.

Table E23: Primary endpoint for 'clopidogrel timing' subgroups in CHAMPION PHOENIX (mITT population)

	Primary endpoint incidence at 48 hours			
	n/N (%) of patients			
	Cangrelor	Clopidogrel	OR (95% CI)	p value (interaction)
All patients	257/5470 (4.7)	322/5469 (5.9)	0.78 (0.66, 0.93)	
Before guide wire insertion	166/3460 (4.8)	205/3442 (6.0)	0.80 (0.64, 0.98)	0.99
After guide wire insertion	86/1980 (4.3)	108/1996 (5.4)	0.79 (0.59, 1.06)	

CI = confidence interval; mITT = modified intent-to-treat; OR = odds ratio.

Further analysis of the dose and time of initiation of clopidogrel was submitted.

The timing of clopidogrel administration in relation to PCI by patient type is represented in table E16. In the acute situations clopidogrel was mostly administered before or during PCI; while in the stable angina subgroup, it was almost equally divided between before and during PCI. The results generally do not point to any trend regarding later administration of clopidogrel, which would have biased the results favouring cangrelor. In addition, considering the time of onset of action of clopidogrel (2-4 hours), it should be administered well upfront of the PCI which may not always be possible in the acute setting. The SAG experts were also invited to comment on the dose and timing of clopidogrel administration.

Table E24: Timing of clopidogrel administration relating to PCI in PHOENIX by Patient Type

	Patient Type		
Timing	**SA**	**NSTE-ACS**	**STEMI**
Before PCI	54.0%	72.1%	83.8%
During PCI (after guide up to 1 hour after cath lab)	45.9%	27.9%	16.1%
1 hour or more after cath lab	0.1%	0%	0.1%

PCI = percutaneous coronary intervention; SA = stable angina; NSTE-ACS = non-ST segment elevation acute coronary syndrome; STEMI = ST segment elevation

Efficacy Endpoints.

The definitions used for the endpoints are overall acceptable. The endpoints were adjudicated, which is important for endpoints like IDR. The MI definition is in line with the third universal definition of MI.

The prognostic value of the type 4a MI definition is, however, contested in medical literature. Peri-procedural myocardial injury or infarction may occur at some stages in the instrumentation of the heart that is required during mechanical revascularization procedures, manifesting as elevated cTn values.

C- PHOENIX used a threshold of 3x ULN elevation in CK-MB to diagnose a new Type 4a MI, based on the available literature at the time. The "Third universal definition of MI" (Thygesen et al., 2012) proposed an arbitrary definition of elevation of cTn values >5 x 99th percentile URL in patients with normal baseline values or a rise of cTn values >20% if the baseline values are elevated. This is in addition to symptomatic, new ECG, angiographic or imagining evidence of new MI. However, the prognostic value of such parameters is debated in an Expert consensus document supporting a higher threshold of post-PCI elevation of CK-MB of $\geqslant$ 10xULN.

Additionally, the inclusion of stent thrombosis as a separate component of the primary composite endpoint with other clinical outcome measures is debatable. In the older CHAMPION studies, it was assessed only in patients with IDR, which appears to be the more appropriate approach. Furthermore, there is limited regulatory experience with investigating ST as a part of the primary endpoint, (eg, registration studies: PLATO, TIMI-38 or HORIZONS-AMI). In ATLAS-ACS, stent thrombosis was analyzed retrospectively. Furthermore, the ARC document addressing clinical trial endpoints did not propose inclusion of ST in the primary composite endpoints (Cutlip et al., 2007).

The applicant clarified that the protocol-defined ST comprised 2 entities: ARC ST (definite) and intraprocedural stent thrombosis IPST. The current duration of 48 hours covers the acute period (0-24 hours), but not the subacute period (>24 hours to 30 days), during which ST has a more prognostic value (Heestermans et al. J Thromb Haemost 2010; 8: 2385–93).

There is limited experienced with IPST in clinical literature. However, 2 recent publications adequately describe the prognostic value of IPST, even if resolved within the procedure (Brener et al 2013 and Xu et al. 2013), which supports the collection of such data. However till further evidence is established about the clinical relevance of IPST, it would be preferable to address them separately from ST.

In the relevant EMA guideline [Point to Consider on the clinical investigation of new medicinal products for the treatment of acute coronary syndrome without persistent ST segment elevation (CPWP/EWP/570/98)], the recommended endpoint is a composite of death and MI. If refractory angina is added to the composite it should be very strictly defined. Neither IDR nor ST were components of the primary endpoints in the PLATO, TRITON–TIMI 38 or HORIZONS-AMI investigating the use of ticagrelor prasugrel or bivaliurdin respectively in PCI. These studies used the composite of cardiovascular death, non-fatal MI, or stroke (and revascularisation in HORIZONS-AMI).

Additionally, the applicant explained that stroke was excluded as the trial duration was only 48 hours; a period where stroke was not expected to contribute to the outcome. This argumentation is not totally supported, as the duration of the study is considered too short in the first place to capture all events that can be temporally attributed to the administration of cangrelor. The SAG discussed further the clinical relevance of the investigated endpoints, see later.

Statistical methods and sample size

The statistical methods and sample size are considered acceptable. The primary analysis was based on the mITT population, with supportive analyses on the ITT and PP population. Definitions of the analysis sets are considered acceptable.

Results.

Major deviations from the study protocol were limited and comparable between the study treatment arms. The recruited patients are in line with the studied population in clinical practice. However, the majority were indicated for elective PCI (55%); with only around 19% of the patients indicated for PCI with STEMI. This is quite limited considering that this is expected to be the main target population.

According to the protocol, patients had to be $P2Y_{12}$ naïve, or discontinued $P2Y_{12}$ for 7 days prior to randomisation. Presented data for patients with previous PCI/MI within 30 days who are candidates for such therapy shows that they were very limitedly recruited (1%). It can be agreed with the company that patients with previous MI/PCI were only included in the trial after they had already completed their guidelines-recommended duration of dual antiplatelet therapy.

Regarding experience in emergency situations of ACS where patients are already on oral $P2Y_{12}$ and cangrelor has to be given, the applicant referred to C-PCI data, where patients on $P2Y_{12}$ inhibition therapy where included.

Efficacy results show superiority of cangrelor over clopidogrel in the primary efficacy endpoint measuring the composite of death, MI, IDR, and stent thrombosis at 48 hours. (4.7% versus 5.9%). Using logistic regression to control for the potential confounding factors of patient baseline status and clopidogrel loading dose in the adjusted analysis was OR: 0.78 (95% CI: 0.66, 0.93), p=0.005; and in the unadjusted analysis, OR: 0.79 (95% CI: 0.67, 0.93), p=0.006.

Benefits were shown for the subgroups of stable angina SA, STEMI and NSTEMI but significance was only shown for the SA subgroup [cangrelor (5.8%) vs clopidogrel (7.4%) OR: 0.78 (95% CI: 0.63, 0.95); STEMI: cangrelor (2.8%) vs clopidogrel (3.7%) OR: 0.75 (95% CI: 0.46, 1.25) and NSTEMI: cangrelor (3.5%) vs clopidogrel (4.4%) OR: 0.80 (95% CI: 0.55, 1.17)].

Results are mainly driven by the significantly lower incidence of stent thrombosis and MI. Definite ST which has some prognostic importance represented only a minority, and results were not significant (table E18) questioning the clinical relevance of the results. Significant results are mainly driven by the IPST. (refer to previous discussion).

There was a significant difference in the incidence of ST between cangrelor-treated patients (0.8%) and clopidogrel-treated patients (1.4%) [OR 0.62, 95% CI: 0.43, 0.90; p=0.010], in addition to the significantly lower incidence of MI [cangrelor-treated patients (3.8%) and clopidogrel-treated patients (4.7%) [OR 0.80, 95% CI: 0.67, 0.97; p=0.022]. No significant difference was demonstrated in the incidence of death [0.3% for each of the cangrelor and clopidogrel groups; OR 1.00, 95% CI: 0.52-1.92; p>0.999] or IDR [cangrelor-treated patients (0.5%) and clopidogrel-treated patients (0.7%), with OR 0.74, 95% CI: 0.45, 1.2; p=0.217].

The data on safety outcomes in patients receiving prior prasugrel or ticagrelor is limited and this is currently reflected in the SmPC. Most of the patients were co-administered ASA, which is reflected in the indication. A slightly higher increase of peri-procedural GP IIb/IIIa inhibitor use is recorded in the clopidogrel arm, which could reflect lower efficacy as mentioned by the applicant, but no firm conclusions can be made on this observation.

Studies comparing ticagrelol or prasugrel with clopidogrel were event-driven long term studies, so direct comparisons with results of the C-PHOENIX are not possible. However, using the same endpoints also that used in HORIZONS-AMI, show superiority of cangrelor was still maintained over clopidogrel, which is considered reassuring. (Table E25).

Table E25: Post-hoc analysis of primary endpoint for PLATO, TRITON TIMI 38 and HORIZONS AMI at 48 hours (mITT population)

	n (%) of patients			
	Cangrelor N=5470	**Clopidogrel N=5469**	**OR (95% CI)**	**p value [a]**
PHOENIX primary endpoint[b]	257 (4.7)	322 (5.9)	0.78 (0.66, 0.93)	0.005
CV mortality/MI/Stroke[c]	226 (4.1)	275 (5.0)	0.81 (0.68, 0.97)	0.025
All-cause mortality/MI/TVR/Stroke[d]	236 (4.3)	289 (5.3)	0.81 (0.68, 0.96)	0.018

a p values based on Chi-squared test.

b Adjusted analysis.

c Post-hoc sensitivity analysis according to PLATO and TRITON TIMI-38 primary endpoint

d Post-hoc sensitivity analysis according to HORIZONS AMI primary endpoint

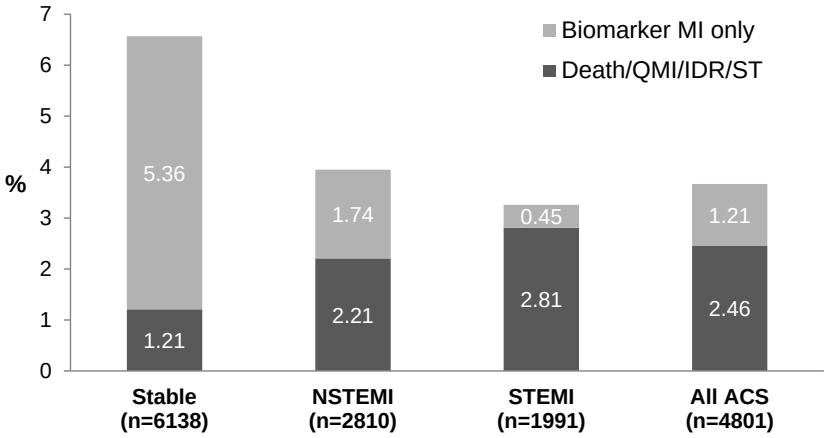
CI = confidence interval; CV = cardiovascular; MI = myocardial infarction; mITT = modified intent-to-treat; TVR = target vessel revascularization. OR = odds ratio.

Nevertheless, these results are presented at 48 hours which is not accepted by the CHMP since clinical trials investigating acute administration of medicinal products are expected to cover a period beyond the time of administration/metabolism of the drug. For example the HORIZONS-AMI measured the efficacy at 30 days. CURRENT-OASIS 7 a randomised factorial trial investigating leading doses of clopidogrel and aspirin measured the outcome at 30 days. The applicant provided further efficacy data at D30, and results were overall comparable.

Subgroup analysis. Efficacy results presented at 48 hours show that cangrelor was significantly better than clopidogrel; the results were also significant for the subgroup with stable CAD; results for STEMI or NSTEMI separately or combined were in the same favorable direction, but not statistically significant. This can be due to the smaller number of patients recruited in these subgroups. It is acknowledged that the study was not powered to show efficacy in each of the investigated subgroups. However, further reassurance is needed regarding efficacy in ACS as this is expected to be the main target for cangrelor. In addition, it was also shown that clinical outcomes are different following PCI for stable CAD than STEMI based on the platelet reactivity to clopidogrel (Park et al., Am Heart J 2013;165:34-42.e1.). Presentation with ACS is also an independent predictor of stent thrombosis (Daemen et al., Lancet 2007;369:667–78).

As pointed out by the applicant the results showing more events in the stable category than ACS setting are unexpected. The explanation is illustrated in figure E8. Although the total number of events was indeed higher in the SA group, these are mainly biochemically diagnosed MIs which could be ascertained in the SA group, but not in the STEMI group due to high baseline CKMB levels. On the other hand, the composite of death/QMI/IDR/ST constitutes most of the events in the STEMI group, which is to be expected.

Figure E8: Analysis separating CK-MB elevation based MIs and non–CK-MB elevation based endpoints from CHAMPION PHOENIX, by patient type (mITT, Final diagnosis)



The generalisability of the results of C-PHOENIX to all subgroups is further discussed by the SAG, see later.

Pooled analysis of the CHAMPION studies.

The three CHAMPION studies shared common properties in the study design, such as the posology of cangrelor, using clopidogrel as the active comparator, the setting of the PCI across its spectrum (stable CAD, STEMI and NSTEMI). However, the value of the C-PCI and C-PLATFORM are limited as they were not completed due to pre-specified futility analysis. Had the studies been completed as planned their weight would have been bigger and the relative weight of C-PHOENIX smaller. Two bodies overseeing the study conduct were set up. A DSMB was established and was responsible for monitoring the trial according to the protocol, to ensure the safety of

patients in the trial. An Interim Analysis Review Committee was responsible for making recommendations to modify the trial using pre-specified adaptation rules, as well as stopping rules for efficacy and futility at the 70% interim analysis. The IARC members were independent of the sponsor and distinct from the DSMB. The roles of the two committees have been detailed. It seems improbable that their use would have hampered the safety oversight of the trials. In addition, a single DSMB was used in the PHOENIX pivotal trial. Importantly also the definition of MI used in the pooling was implemented retrospectively on the results of these studies. There was also no pre-specified pooling/metanalysis planned. As such the data are only presented for descriptive purposes.

During the assessment, taking into account the major objections raised, the applicant proposed to restrict the indication of PCI to patients for whom oral $P2Y_{12}$ inhibitors is not feasible or desirable. These may include 1) patients in the acute phase of cardiovascular illness who may experience reduced bioavailability consequent to nausea, use of opiates or impaired gastrointestinal perfusion resulting in reduced absorption, 2) patients presenting with an unclear aetiology of chest pain and where early administration of a long acting $P2Y_{12}$ inhibitor may increase clinical risk (ie, aortic dissection, aortic rupture, oesophageal tear, pericarditis, 3) patients referred for angiography and possible PCI who have a likelihood of requiring urgent or emergent coronary artery bypass graft (CABG) surgery, and 4) patients requiring PCI while also suffering an active concomitant underlying condition that may require urgent surgery that would be delayed by long acting $P2Y_{12}$ inhibitors (i.e., hip fracture complicated by unstable angina, NSTEMI or even STEMI).

Recognising the ongoing debate regarding time of administration of antiplatelet administration in relation to PCI; differences between the acute and elective PCI and the possible impact on bleeding, the CHMP requested further clarification on this point to the MAH and this issue was discussed with the CV SAG experts for further advice to the CHMP.

Additional expert consultation.

1. The SAG is asked to comment on the benefits and risks of cangrelor during PCI, taking the following points into consideration:

a. The use of clopidogrel as the active comparator in PCI for acute coronary syndromes (PCI-ACS), and the lack of comparator data against ticagrelor/prasugrel which are currently propagated as the preferred antithrombotic agents by the ESC guideline in this situation.

The SAG experts agreed that the ESC guidelines provide recommendation for the use of platelet inhibitors during PCI in patients with both acute coronary syndromes (ACS) and chronic stable angina. The combined use of aspirin and clopidogrel is the standard of care for PCI in stable angina patients whereas for unstable patients (ACS, non-STEMI and STEMI), aspirin with either ticagrelor or prasugrel represent the standard of care. Aspirin, clopidogrel, ticagrelor and prasugrel are given orally, while cangrelor is administered intravenously. However, the SAG experts agreed that ticagrelor and prasugrel were not available at the initiation of the PHOENIX CHAMPION study, thus the use of clopidogrel as a comparator in all three subgroups of patients (stable CAD, non-STEMI AND STEMI) is acceptable. It was also appreciated that use of ticagrelor and prasugrel in patients with ACS remains limited in some European countries, but is increasing. Clopidogrel is still used in clinical practice even in ACS patients undergoing PCI.

In conclusion, the SAG experts considered that the use of clopidogrel as active comparator is acceptable for patients with stable angina and also for patients with non-STEMI and STEMI undergoing PCI. Nevertheless, the improved outcome with ticagrelor of prasugrel versus clopidogrel should be accounted for.

b. Dose and timing of clopidogrel administration in relation to the PCI and the way it affects the outcome of the pivotal study.

In CHAMPION PHOENIX study, all patients were $P2Y_{12}$-inhibitor naive (defined as no $P2Y_{12}$-inhibitor during 7 days prior to randomisation). Cangrelor was administered before guidewire insertion (which defines the start of a PCI procedure) as bolus (30µg/kg) followed by infusion (4 µg/kg/min) for 2 hours. Subsequently oral therapy with clopidogrel 600mg was started at the end of the infusion. In the comparator group clopidogrel 300 mg or 600 mg was administered either before or immediately after PCI, at the discretion of the clinician. In both groups clopidogrel was continued with 75 mg according to the local protocols.

The low dose (300 mg) and late administration of clopidogrel allowed in the protocol raised questions among the SAG experts because these favour the study drug, even though this was not observed in the analysis provided by the company. Earlier studies have shown that optimal protection with clopidogrel is achieved if a high dose (600 mg) is administered before a PCI procedure. Nevertheless, it should be noted that, although a high starting dose of 600 mg clopidogrel is recommended in current guidelines, the registered starting dose is 300 mg in some countries.

In the CHAMPION PHOENIX study 63.4% of patients received clopidogrel before PCI, and 36.5 % during or after PCI (after guidewire insertion up to 1 hour after leaving the cath lab). The numerical difference observed in the study between cangrelor and the two clopidogrel dose groups is counter intuitive (OR 0.84 in 300mg group versus OR 0.77 in the 600mg group) as the 600 mg clopidogrel dose would be expected to provide better efficacy.

In conclusion, all SAG experts agreed that the design of the CHAMPION PHOENIX study favoured cangrelor. Nevertheless, the study is considered reliable and representative of current clinical practice. The incidence of events at 48 hours is lower with cangrelor in the relevant subgroups: administration of clopidogrel before or after guidewire insertion [OR 0.80 (0.64-0.98) and 0.79 (0.59-1.06) respectively] and low (300mg) or high dose (600mg) of clopidogrel [OR 0.84 (0.62-1.14) and 0.77 (0.63-0.94) respectively].

c. The generalisability of the main over-all study results to the subgroups of stable CAD, STEMI and non-STEMI.

The majority of the randomised patients suffered from stable angina (3120 versus 3180 in cangrelor and clopidogrel groups respectively compared with non-STEMI (1389 versus 1421) and STEMI (961 versus 1030). In stable patients pre-treatment with a high dose of clopidogrel is feasible, while the use of cangrelor in clinical practice, once registered, would be mainly in immediate PCI for STEMI which represented only 1/6 of the patients in the CHAMPION PHOENIX trial. Nevertheless, in many hospitals pre-treatment before diagnostic angiography is not done. Accordingly, the trial also investigates cangrelor in the very early phase of PCI when $P2Y_{12}$ inhibition is not yet active in part of the patients.

The results are significant only for the stable angina patients (5.4% versus 7.7% of events compared with the 600mg dose). As the study was not powered to show superiority for all three subgroups the similar trend observed in all subgroups without significant interaction and with point estimates of the same magnitude (0.74 - 0.80) is considered reassuring. Furthermore, the SAG found no arguments in the pharmacology or pathophysiology why cangrelor would have different efficacy in these subgroups.

The observed benefit at 48 hour should be maintained at follow-up (day 30), with no increased risk of mortality or MI. Indeed the 30 day composite efficacy endpoint is marginally favourable for cangrelor over clopidogrel (6% versus 7% of events), although a numerical excess of death in the cangrelor group (60 versus 55) was noted at 30 day follow-up. In contrast, numerically lower mortality was reported in the combined data of the three CHAMPION studies.

In conclusion the SAG experts agreed with the generalisation of the results showing a reduction of thrombotic complications during or immediately after PCI, for the three subgroups of CAD patients (stable angina, non-STEMI and STEMI).

e. The proposed restriction by the MAH to patients with coronary artery disease undergoing percutaneous coronary intervention (PCI) in whom oral therapy with P2Y12 inhibitors is not feasible or desirable.

The SAG experts unanimously considered that the proposed indication is not well defined. The indication should also mention that cangrelor should only be used in patients who have not been pre-treated with $P2Y_{12}$ inhibitors, reflecting the CHAMPION PHOENIX patient population (naïve to $P2Y_{12}$ inhibitors 7 days prior to randomisation). There are little data with non-naïve patients. In CHAMPION PCI the SAG Experts noted lower efficacy results in patients pre-treated with clopidogrel.

The SAG unanimously agreed that:

- cangrelor could be considered as an alternative when $P2Y_{12}$ blockers have not been initiated prior to PCI.

- cangrelor could be a treatment option during PCI for all three subgroups whether stable CAD or non stable ACS (non-STEMI and STEMI).

The SAG experts discussed whom would in practice initiate cangrelor therapy and when. Considering the diversity of clinical practice in EU, it is agreed that it would be an interventional cardiologist, for example when the patient is referred to an ad hoc PCI procedure, or when oral therapy is omitted / forgotten for other reasons. Protocols should be developed in each hospital to define the appropriate use of cangrelor in their setting.

In practice, if a patient has not been pre-treated with $P2Y_{12}$ inhibitors and requires immediate PCI intervention, this patient could be eligible for cangrelor therapy, whether suffering from stable or non stable CAD. The most critical element in the decision of therapy would be the need to start $P2Y_{12}$ inhibition immediately. It was mentioned that also a short acting GP-IIb/IIIa receptor blocker (e.g. Abciximab or Integrilin) could be used in this setting, although it has not been registered for this specific purpose. It takes about 30 minutes (ticagrelor) or up to several hours (clopidogrel) before maximum platelet inhibition is achieved with an oral agent.

In conclusion, the SAG recommended that the indication should reflect the use as an alternative when $P2Y_{12}$ has not been initiated and recommended the following indication: "*patients who have not received an oral $P2Y_{12}$ inhibitor prior to the PCI procedure and in whom oral therapy with a $P2Y_{12}$ inhibitor at the time of PCI is not feasible or desirable. In those patients an oral $P2Y_{12}$ inhibitor should be started after the procedure, as soon as the patient's condition allows".*

2. The SAG is invited to comment on the clinical relevance of the investigated endpoints, mainly: myocardial infarction type 4a and stent thrombosis. In particular:

a. The value of using stricter definitions of MI type 4a based on higher cut off CK-MB (for example ≥ 10x ULN)

The SAG agreed that there is no commonly agreed threshold for biomarker elevation, CK-MB or troponin, above which the risk for impaired outcome is evident. In fact, the risk increases gradually with higher values of these markers, reflecting larger amounts of myocardial damage during the procedure In the absence of such objective evidence, any cut-off represents an arbitrary decision and the proposed definition (CK-MB ≥ 10x ULN or both clinical signs/symptoms and CK-MB > 5 x ULN) is acceptable. It is reassuring that the same trend is observed in the PHOENIX study for all different types of MI and when using different MI definitions (e.g. SCAI definition) and cut offs.

It was noted that the rate of peri-procedural MI reported in PHOENIX for patients with stable angina was higher than for ACS. It is likely that peri-procedural MI in the latter is underestimated because of the challenge to distinguish such complication from the on-going infarction (ACS), which was the indication for PCI.

b. The definition of stent thrombosis which included both ST as defined by the ARC and intraprocedural ST.

The Experts agreed that stent thrombosis is a valid and acceptable endpoint in a PCI setting. Indeed stent thrombosis represents a serious, though relatively rare risk of the PCI intervention and should be avoided. The vast majority of these events (90%) occur within the first 2 days of the procedure thus the study design is acceptable. The end point at 30 days provides complementary information to ensure that the same magnitude of benefit is maintained at follow-up.

It is recognised that both ticagrelor and prasugrel studies (TRITON, PLATO) did not use stent thrombosis as a primary endpoint but a secondary endpoint. The experts also noted the careful analysis made in the champion phoenix trial as the stent thrombosis endpoint was validated by an independent adjudication Committee which reviewed all angiograms recorded during the procedures. A stent thrombosis endpoint based on the observations of the local investigators, without core-lab assessment, would not be reliable.

The efficacy data at 30 days are relevant and it is considered adequate to combine results of the three studies C PCI, C PLATFORM and C-PHOENIX studies to assess safety of cangrelor.

3. The SAG is asked to express a view on the discontinued studies "C-PCI" and "C-PLATFORM".

The Applicant explained that the indiscriminate definition of MI may have been the cause of failure to show superiority of cangrelor in these studies. Does the SAG support this view and accept not to take these results into consideration when the B/R of cangrelor is assessed?

The detection of peri-procedural MI in the PCI and PLATFORM studies depended on cardiac markers alone while in PHOENIX a combination of cardiac markers and other evidence of ischaemia was required to define PCI related MI. In the first two studies only one sample was taken before PCI, thus it was not possible to adequately distinguish elevated markers of necrosis (MI) related to the event, which triggered the PCI (non-STEMI of STEMI) from elevation due to the procedure.

The experts considered the results of C-PCI and C-PLATFORM of relevance. In particular the experts considered it reassuring that the numerically higher mortality observed in one trial (PHOENIX) is not observed in the other trials.

In summary, the SAG experts agreed that the two studies discontinued for futility should be regarded as supportive since the additional analyses (using SCAI definition of MI) are all pointing in the same direction, which is reassuring.

4. Based on all available evidence, the SAG is invited to comment on the positioning of cangrelor in the pharmacological armamentarium of PCI.

Cangrelor is a very short acting agent (T1/2 3- 6min) with a structure similar to ticagrelor. It has a more rapid and greater inhibitory effect than existing therapies ticagrelor, prasugrel and clopidogrel.

Cangrelor is a suitable alternative for the existing antiplatelet agents, especially in situations where an ad hoc PCI would be considered in patients who have not yet received double anti-platelet therapy. In addition, the IV administration is considered useful in patients who cannot swallow (e.g. intubated) or who are vomiting. The fast offset of action is also considered useful in order to manage major bleeding if such would occur during the procedure and to terminate platelet inhibition in patients who are referred for immediate surgery, although this will be very rare.

The benefit of cangrelor is modest, mainly a reduction of peri-procedural MI and stent thrombosis and the effect is likely of similar magnitude as that of ticagrelor or prasugrel compared to clopidogrel. The therapeutic advantage of cangrelor combined with ticagrelor or prasugrel has not been investigated.

The Experts debated the use of the clopidogrel as pre-loading dose prior to PCI intervention. It appears that major differences in medical practice exist in Europe in particular for the treatment of patients with stable angina pectoris. For example whereas in the UK, it is estimated that 95% of stable patients would be pre-loaded with a $P2Y_{12}$ inhibitor, in France and Germany stable angina patients would often not be pre-treated but treatment would start after a decision to proceed with PCI has been taken, based on the angiogram.

In ACS (non-STEMI and STEMI), ESC guidelines recommend a treatment with aspirin and an oral $P2Y_{12}$ inhibitor as soon as possible, The experts agreed that for pre-treated patients there is no place for cangrelor. Patients who come to the cath lab and have not been pre-treated are potential candidates for cangrelor IV therapy. This is reflected in the proposed formulation of the indication in 1e, above.

Discussion following SAG advice

Clopidogrel dose and timing of its administration

The time of administration of clopidogrel presented per indication: stable angina, NSTEMI and STEMI, showed that in the acute situations clopidogrel was mostly administered before or during PCI; while in the stable one, it was almost equally divided between before and during PCI. The results generally do not point to any trend regarding later administration of clopidogrel, which would have biased the results favouring cangrelor.

It is agreed that, considering the time of onset of action of clopidogrel (2-4 hours), it should be administered well upfront of the PCI which may not be possible in the acute setting, as also acknowledged by the SAG experts.

In conclusion, the design of the C-PHOENIX study may have favoured cangrelor compared to clopidogrel arm; nevertheless, the study is considered reliable and representative of current EU clinical practice as confirmed by the Experts, acknowledging the variability of the medical practice across EU.

Validity of end points used (MI definition and stent thrombosis)

Regarding the MI definition used (type4a MI), in the absence of a commonly agreed threshold definition for biomarker elevation, the Experts view agreed to the proposed definition of CK-MB $\geq$ 10x ULN or both clinical signs/symptoms and CK-MB > 5 x ULN, which was reassuring. It was also considered reassuring that the same trend is observed in the PHOENIX study for all different types of MI and when using different MI definitions (e.g. SCAI definition) and cut offs.

The CHMP was also reassured that stent thrombosis may be a valid and acceptable endpoint in a PCI setting as agreed by the SAG experts. Indeed, a careful analysis was made in the C-PHOENIX as the stent thrombosis endpoint was validated by an independent adjudication Committee that reviewed all angiograms recorded during the procedures (IPST).

Generalisability of the study results to the subgroups of stable angina, STEMI and non-STEMI.

The benefits shown in C-PHOENIX are applicable for the subgroup with stable CAD. In this subgroup, clopidogrel is the recommended agent for elective PCI due to lack of data with the newer anti-platelet agents like ticagrelor and prasugrel (ESC, 2013). Superiority of cangrelor was shown over clopidogrel. However, for PCI performed on STEMI and NSTEMI patients, the results are consistent, but did not reach statistical significance. This can be due to the limited representation of these subgroups in the study. The choice of clopidogrel as the active comparator is also not in line with the ESC guideline, but submitted utilisation data in EU show that clopidogrel is still the major antithrombotic used in the acute setting, validating its use as the active comparator in C-PHOENIX when ticagrelor and prasugrel were not available. It was also appreciated by the SAG experts that use of ticagrelor and prasugrel in patients with ACS remains limited in some European countries, although it is increasing. Furthermore, efficacy of ticagrelor and prasugrel is based on long term efficacy data; their efficacy at 48 hours

is not specifically investigated. In summary, the use of clopidogrel as a comparator in all three subgroups of patients (stable CAD, non-STEMI AND STEMI) is considered acceptable for the submitted study.

Furthermore, the CHMP took into account the experts view regarding C-PCI and C-PLATFORM studies and agreed that the two studies discontinued for futility should be regarded as supportive since the additional analyses are all pointing in the same direction, which is reassuring. In particular the experts considered it reassuring that the numerically higher mortality observed in one trial (PHOENIX) is not observed in the other trials.

Following discussion in the SAG experts, cangrelor was further restricted to patients who have not been pre-treated with $P2Y_{12}$ inhibitors, reflecting the CHAMPION PHOENIX patient population (naïve to $P2Y_{12}$ inhibitors 7 days prior to randomisation).

With these restrictions, the efficacy of cangrelor is considered to be demonstrated as an alternative to existing treatments if a patient has not been pre-treated with $P2Y_{12}$ inhibitors.

In summary, the CHMP agreed that efficacy of cangrelor, co administered with acetylsalicylic acid was demonstrated for the below group of patients undergoing PCI in a restricted setting (see below) :

Cangrelor, co-administered with acetylsalicylic acid (ASA), is indicated for the reduction of thrombotic cardiovascular events in adult patients with coronary artery disease undergoing percutaneous coronary intervention (PCI) who have not received an oral $P2Y_{12}$ inhibitor prior to the PCI procedure and in whom oral therapy with $P2Y_{12}$ inhibitors is not feasible or desirable.

2.5.4. Conclusions on clinical efficacy

Cangrelor is a rapidly acting $P2Y_{12}$ inhibitor developed for use during PCI and bridging.

For the bridging indication, the investigated primary endpoints are PD parameters that are not considered sufficient for proof of efficacy. In addition, the proposed dose may not be adequate, especially in light of the doses used in PCI. Nevertheless, this indication was withdrawn during the assessment.

For the PCI indication, the study design with inclusion of all three subgroups indicated for PCI in one study is not optimal. The use of clopidogrel as the active comparable is defendable. The primary efficacy endpoint included MI type 4a, which is of limited clinical relevance, but its relevance was verified by further analysis. The inclusion of stent thrombosis could be acceptable; the results of ST are driven by peri-procedural type, which are of some value, but should have been investigated separately. Further to SAG advice received on the relevance of the stent thrombosis and MI definition used for the primary endpoint, the CHMP was reassured and considered overall the data reliable and relevant in the PCI setting. Additionally, sensitivity analysis submitted including clinically relevant endpoints, showed that the superiority of cangrelor over clopidogrel is maintained at 48 hours which is reassuring, and the efficacy data at 30 days are comparable with the 48 hours efficacy results.

In C-PHOENIX cangrelor was co administered with acid acetylsalicylic and the vast majority of patients were $P2Y_{12}$ naïve or did not receive prior $P2Y_{12}$ therapy prior to PCI. This was further taken into account by the applicant in the amended restricted indication. Therefore, the CHMP considered the efficacy demonstrated in the amended indication

Cangrelor, co-administered with acetylsalicylic acid (ASA), is indicated for the reduction of thrombotic cardiovascular events in adult patients with coronary artery disease undergoing percutaneous coronary intervention (PCI) who have not received an oral $P2Y_{12}$ inhibitor prior to the PCI procedure and in whom oral therapy with $P2Y_{12}$ inhibitors is not feasible or desirable.

2.6. Clinical safety

The overall safety of cangrelor for its intended use in the PCI and Bridging settings is based on a safety dataset of over 26,000 subjects from 16 clinical studies (Phase I through Phase III), of which more than 25,000 were studied in the CHAMPION and BRIDGE studies.

The clinical safety data are presented separately for the CHAMPION and BRIDGE studies which is acceptable by the CHMP.

Patient exposure

Exposure to cangrelor across the different studies is presented in table S1.

Table S1: Summary of cangrelor exposure

Analysis Set	Patients randomised/ entered	Patients exposed/dosed	Patients exposed to Proposed drug range (≥4 ug/kg/min)	Patients with long term safety data (30 or more days)
All Studies	13472	13301	12941	12759
All Studies except Volunteers	13274	13105	12819	12737
All Controlled Studies	13278	13109	12814	12742
All Placebo Controlled Studies	363	354	102	168
All Active Controlled Studies	12915	12755	12712	12574
Champion Studies	12711	12565	12565	12495

The patients receiving the highest dose (4.0 µg/kg/min) for short duration (<24 hours) represent the majority of exposures (12,787, 99.12%), as they originate predominantly in the pooled CHAMPION studies. Patients receiving the 0.75 mg/kg/min dose represent patients from the BRIDGE study, with the duration of exposures ranging from <24 hours up to ≥72 hours (table S2).

Table S2: Cangrelor infusion duration by pre-specified dose (safety population)

Infusion duration groups	≤0.5µg/kg/min N=50 n (%)	0.75µg/kg/min N=112 n (%)	1.0µg/kg/min N=53 n (%)	2.0µg/kg/min N=145 n (%)	≥4.0µg/kg/min N=12901 n (%)
<24 hours	28 (56)	9 (8.04)	43 (81.13)	98 (67.59)	12787 (99.12)
24-<48 hours	15 (30)	10 (8.93)	10 (18.87)	31 (21.38)	56 (0.43)
48-<72 hours	3 (6)	41 (36.61)	NA	8 (5.52)	21 (0.16)
≥72 hours	4 (8)	52 (46.43)	NA	8 (5.52)	37 (0.29)

µg = microgram(s). kg = kilogram(s). min = minutes.

Adverse events

In the CHAMPION Pooled studies, the pattern of overall incidence of AEs, death, SAEs, and AEs leading to study drug discontinuation was similar to that of All Studies and well balanced in both treatment groups (Table S3).

Table S3: Summary of reported TEAEs in pooled CHAMPION studies and in pooled placebo-controlled studies

Patients with at least one AE	CHAMPION studies		Placebo-controlled studies	
	Cangrelor N=12,565 n (%)	Clopidogrel N=12,542 n (%)	Cangrelor N= 354 n (%)	Control N=218 n (%)
Patients with any bleeding event / AE	2253 (17.9)	1755 (14.0)	221 (62.4)	97 (44.5)
Patients with any AE	2900 (23.1)	2745 (21.9)	266 (75.1)	158 (72.5)
Patients who died	298 (2.4)	323 (2.6)	4 (1.1)	5 (2.3)
Patients with any SAEs	281 (2.2)	270 (2.2)	33 (9.3)	16 (7.3)
Patients with any AE leading to study drug discontinuation	74 (0.6)	51 (0.4)	21 (5.9)	11 (5.0)

AE = adverse event; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Table S4: Overview of adverse events in the BRIDGE study (safety population)

Parameter	Stage II	
	Cangrelor (N=106) n/N (%)	Placebo (N=101) n/N (%)
Patients with any AEs		
Pre-surgery	32/106 (30.2)	29/101 (28.7)
Post-surgery	48/102 (47.1)	44/96 (45.8)
Pre and Post-surgery	58/106 (54.7)	56/101 (55.4)
Patients with any bleeding event / AEs	58/106 (54.7)	48/101 (47.5)
Patients with any SAEs		
Pre-surgery	5/106 (4.7)	4/101 (4.0)
Post-surgery	8/102 (7.8)	5/96 (5.2)
Pre and Post-surgery	11/106 (10.4)	9/101 (8.9)
Patients who Died		
Pre-surgery	1/106 (0.9)	3/101 (3.0)
Post-surgery	1/102 (1.0)	2/96 (2.1)
Pre- and Post-surgery	2/106 (1.9)	5/101 (5.0)
Patients with AE leading to study drug discontinuation		
Pre-surgery	6/106 (5.7)	3/101 (3.0)
Post-surgery	0	0
Pre- and Post-surgery	6/106 (5.7)	3/101 (3.0)

AE = adverse event; SAE = serious adverse event.

The most common AE is **bleeding**, which is addressed separately later in this report. The most common AEs reported in the cangrelor arm in the All Studies population were similar in type and frequency as those reported for the CHAMPION pooled studies (Table S5). The type and frequency of the events are balanced between cangrelor and control arms, with the exception of dyspnoea and injection site haematoma.

Table S5: Summary of reported TEAEs (≥1.0% of patients in either treatment arm) in the CHAMPION studies (safety population)

Preferred Term	Cangrelor (N=12565) n (%)	Clopidogrel (N=12542) n (%)
Patients with any AE	**2900 (23.1)**	**2745 (21.9)**
Back pain	401 (3.2)	398 (3.2)
Chest pain	306 (2.4)	323 (2.6)
Nausea	296 (2.4)	316 (2.5)
Headache	253 (2.0)	274 (2.2)
Hypotension	201 (1.6)	165 (1.3)
Vomiting	177 (1.4)	161 (1.3)
Hypertension	168 (1.3)	149 (1.2)
Dyspnoea	143 (1.1)	48 (0.4)

TEAE = treatment-emergent adverse event. AE = adverse event.

Serious adverse events and deaths

SAEs

The frequency of patients with SAEs in the C-PHOENIX trial was low and balanced between treatment groups, at 2.2% vs 1.9% for cangrelor- and clopidogrel-treated patients respectively. These results were consistent with the type and frequency of SAEs in the CHAMPION program and the frequency across treatment groups (Table S6), as would be expected.

Table S6: Serious TEAEs occurring in ≥0.1% of cangrelor-treated patients in CHAMPION studies (safety population)

Preferred Term	Cangrelor (N=12565) n (%)	Clopidogrel (N=12542) n (%)
Patients with at least one SAE	**281 (2.2)**	**270 (2.2)**
Cardiogenic shock	24 (0.2)	25 (0.2)
Ventricular fibrillation	18 (0.1)	14 (0.1)
Hypotension	15 (0.1)	12 (0.1)
Chest pain	14 (0.1)	12 (0.1)
Coronary artery dissection	14 (0.1)	10 (0.1)
Renal failure acute	12 (0.1)	7 (0.1)
Ventricular tachycardia	10 (0.1)	8 (0.1)
Cardiac failure congestive	10 (0.1)	7 (0.1)
Cardiac arrest	9 (0.1)	16 (0.1)
Pulmonary oedema	9 (0.1)	8 (0.1)
Coronary artery perforation	8 (0.1)	5 (0.0)
Acute pulmonary oedema	7 (0.1)	0 (0.0)

No SAEs were reported in Stage I of the BRIDGE study. In stage II, the overall frequency of BRIDGE patients with pre-procedural or post-procedural SAEs was balanced between treatment groups (tables S7 and S8).

Table S7: Pre-procedure SAEs reported for Stage II patients, in BRIDGE – (safety population)

	Stage II	
Preferred Term	**Cangrelor (N=106) n (%)**	**Control (N=101) n (%)**
Subjects with at least one SAE	**5 (4.7)**	**4 (4.0)**
Angina pectoris	1 (0.9)	0
Arterial thrombosis limb	1 (0.9)	0
Cardiac arrest	1 (0.9)	1 (1.0)
Cardiogenic shock	1 (0.9)	0
Bronchospasm	1 (0.9)	0
Papillary muscle rupture	1 (0.9)	0
Cardiac asthma	0	1 (1.0)
Cardiac failure	0	2 (2.0)
Cardiopulmonary failure	0	1 (1.0)
Gastroenteritis norovirus	0	1 (1.0)

Table S8: Post-procedure SAEs reported for Stage II patients in BRIDGE – (safety population)

	Stage II	
Preferred Term	**Cangrelor (N=102) n (%)**	**Control (N=96) n (%)**
Subjects with at least one SAE	**8 (7.8)**	**5 (5.2)**
Cardiogenic shock	3 (2.9)	1 (1.0)
Respiratory failure	2 (2.0)	1 (1.0)
Cardiac arrest	2 (2.0)	0
Chest pain	1 (1.0)	0
Coronary artery thrombosis	1 (1.0)	0
Beta haemolytic streptococcal infection	1 (1.0)	0
Hypoxia	1 (1.0)	0
Mediastinitis	1 (1.0)	0
Systemic inflammatory response syndrome	1 (1.0)	0
Renal failure acute	1 (1.0)	0
Vasoplegia syndrome	1 (1.0)	0
Ventricular arrhythmia	1 (1.0)	0
Abdominal sepsis	0	1 (1.0)
Atrial fibrillation	0	1 (1.0)
Multi-organ failure	0	1 (1.0)

Deaths

The overall incidence of death in All Studies pooled was low and numerically lower in the cangrelor group (2.3%) than the comparator group in the All Studies population (2.6%), including C- PHOENIX (0.3% and 0.4% respectively) and BRIDGE (1.9% and 5% respectively) (table S9).

Table S9: Summary of deaths by SOC and preferred term occurring in ≥0.1% of patients in the CHAMPION studies (safety population)

	Cangrelor N=12565	Clopidogrel N=12542
System Organ Class/Preferred Term	**n (%)**	**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)
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)

Adverse events of Special Interest

In addition to bleeding, dyspnoea, renal impairment, and hypersensitivity were considered as adverse events of special interests (AESI) based on the preclinical and clinical data and pharmacological effects.

1. Bleeding

Bleeding events were reported more frequently with cangrelor than with the control in the CHAMPION trials (Table S10) and in the BRIDGE trial (Table S11).

Table S10: Frequent bleeding-related adverse events occurring in ≥0.5% of patients by preferred term in CHAMPION Pooled studies within 30 days from dosing start (safety population)

	CHAMPION studies	
	Cangrelor N=12565	**Clopidogrel N=12542**
Preferred Terms	**n (%)**	**n (%)**
Patients with any bleeding-related AE	2253 (17.9)	1755 (14.0)
Traumatic haematoma	807 (6.4)	607 (4.8)
Vessel puncture site discharge	763 (6.1)	569 (4.5)
Ecchymosis	593 (4.7)	409 (3.3)
Haematoma	273 (2.2)	201 (1.6)
Haemoglobin decreased	141 (1.1)	105 (0.8)
Haematocrit decreased	135 (1.1)	95 (0.8)
Transfusion	101 (0.8)	76 (0.6)
Haemorrhage	61 (0.5)	43 (0.3)
Haematuria	57 (0.5)	45 (0.4)

Table S11: Summary of non-CABG- and CABG-related bleeding events in BRIDGE trial (safety population)

	Pre-procedure (non-CABG)		Post-Procedure (CABG-related)	
	Cangrelor (N=106) n (%)	**Placebo (N=101) n (%)**	**Cangrelor (N=106) n (%)**	**Placebo (N=101) n (%)**
Access site bleeding	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)
Clinically overt bleed	1 (0.9)	0 (0.0)	1 (1.0)	2 (2.1)
Haematoma ≥5 cm at puncture site	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)
Haemodynamic compromise	0 (0.0)	0 (0.0)	3 (2.9)	1 (1.0)
Intracranial haemorrhage	0 (0.0)	0 (0.0)	0 (0.0.)	0 (0.0)
Intraocular	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Blood transfusion	2 (1.9)	1 (1.0)	26 (**25.5**)	31 (**32.3**)
Reoperation for bleeding	0 (0.0)	0 (0.0)	2 (2.0)	2 (2.1)
Retroperitoneal	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
Ecchymosis	13 (12.3)	6 (5.9)	2 (2.0)	2 (2.1)
Epistaxis	2 (1.9)	2 (2.0)	0 (0.0)	0 (0.0)
Haematoma <5 cm at puncture site	2 (1.9)	0 (0.0)	1 (1.0)	0 (0.0)
Oozing at puncture site	3 (2.8)	0 (0.0)	3 (2.9)	0 (0.0)
Drop in haemoglobin and/or haematocrit	3 (2.8)	0 (0.0)	17 (**16.7**)	22 (**22.9**)
Drop in haemoglobin	3 (2.8)	0 (0.0)	17 (16.7)	20 (20.8)
3 g/dL to ≤4 g/dL	0 (0.0)	0 (0.0)	5 (4.9)	5 (5.2)
>4 g/dL to ≤5 g/dL	2 (1.9)	0 (0.0)	3 (2.9)	4 (4.2)
>5 g/dL	1 (0.9)	0 (0.0)	9 (8.8)	11 (11.5)
Drop in haematocrit percent	3 (2.8)	0 (0.0)	12 (**11.8**)	20 (**20.8**)
9 to ≤12	0 (0.0)	0 (0.0)	4 (3.9)	3 (3.1)
>12 to ≤15	1 (0.9)	0 (0.0)	1 (1.0)	4 (4.2)
>15	2 (1.9)	0 (0.0)	7 (6.9)	13 (13.5)
Thrombocytopenia	0 (0.0)	1 (1.0)	2 (2.0)	4 (4.2)
Platelet count <100,000	0 (0.0)	1 (1.0)	2 (2.0)	4 (4.2)
Platelet count <50,000	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Platelet count <25,000	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	5 (4.7)	2 (2.0)	11 (10.8)	9 (9.4)

Fatal Bleeding. In the total pooled safety population, fatal bleeding events within 30 days of dosing were low and balanced in cangrelor (8/12565, 0.1%) vs control group (9/12542, 0.1%). Five of the 17 combined fatalities were due to bleeding in the nervous system, with four in the cangrelor arm and one in the clopidpgrel arm (table S12). Deaths after 30 days were low and were similar in both the cangrelor and control groups (5 vs 6, respectively).

Table S12: Summary of bleeding-related death within 30 days from dosing start [CHAMPION Pooled, safety population]

	n (%) of patients		
System Organ Class Preferred Term	**Cangrelor (N=12,565)**	**Clopidogrel (N=12,542)**	**p-value**
Patients Died	8 (0.1)	9 (0.1)	0.8054
Cardiac disorders	3 (0.0)	4 (0.0)	0.7036
Cardiac tamponade	1 (0.0)	0 (0.0)	
Myocardial rupture	1 (0.0)	4 (0.0)	0.1790
Ventricle rupture	1 (0.0)	0 (0.0)	
Gastrointestinal disorders	1 (0.0)	2 (0.0)	0.5626
Retroperitoneal haemorrhage	1 (0.0)	0 (0.0)	
Gastrointestinal haemorrhage	0 (0.0)	2 (0.0)	
Neoplasms benign, malignant and unspecified [incl cysts and polyps]	0 (0.0)	1 (0.0)	
Tumour haemorrhage	0 (0.0)	1 (0.0)	
Nervous system disorders	4 (0.0)	1 (0.0)	0.1803
Haemorrhage intracranial	2 (0.0)	0 (0.0)	
Cerebral haemorrhage	1 (0.0)	0 (0.0)	
Haemorrhagic stroke	1 (0.0)	1 (0.0)	0.9990
Vascular disorders	0 (0.0)	1 (0.0)	
Shock haemorrhagic	0 (0.0)	1 (0.0)	

Bleeding events were reported as endpoints in the CHAMPION and BRIDGE studies. Bleeding events were captured in the CHAMPION studies for 48 hours after randomization, and in the BRIDGE study during surgery and through hospital discharge. The bleeding endpoints were collected on the electronic case report forms (eCRFs) and were programmatically imputed into three bleeding scales:

- Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO),
- Thrombolysis in Myocardial Infarction (TIMI) and
- Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) scales.

In C-PHOENIX, there was no significant increase in the primary safety outcome of GUSTO severe/life-threatening bleeding or GUSTO moderate bleeding (Table S13). There was a significant increase in GUSTO mild bleeding, driven primarily by ecchymosis, oozing, and <5 cm haematoma. There was a significant increase in ACUITY major bleeding that was primarily driven by an increase in ⩾5 cm haematoma at the puncture site. Results of the pooled CHAMPION studies showed comparable results (table S14).

Table S13: Analysis of non–CABG-related bleeding complications from CHAMPION PHOENIX (safety population))

	n (%) of patients			
	Cangrelor N=5529	Clopidogrel N=5527	OR (95% CI)	p value
GUSTO				
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 haematoma <5 cm	98 (1.8)	51 (0.9)	1.94 (1.38, 2.72)	0.0001
ACUITY				
Major	235 (4.3)	139 (2.5)	1.72 (1.39, 2.13)	<0.001
Major w/o haematoma ≥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 haematoma <5 cm	106 (1.9)	81 (1.5)	1.31 (0.98, 1.76)	0.0656
Blood and blood product utilization				
Patients with any transfusion	25 (0.5)	16 (0.3)	1.56 (0.83, 2.93)	0.1594

Table S14: Analysis of non–CABG-related bleeding complications from the pooled CHAMPION program (safety population)

	n (%) of patients			
	Cangrelor N=12,565	Control N=12,542	OR (95% CI)	p value
GUSTO				
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 haematoma <5 cm	707 (5.6)	515 (4.1)	1.39 (1.24, 1.56)	<0.001
ACUITY				
Major	534 (4.2)	353 (2.8)	1.53 (1.34, 1.76)	<0.001
Major w/o haematoma ≥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 haematoma <5 cm	293 (2.3)	255 (2.0)	1.15 (0.97, 1.36)	0.1053
Blood and blood product utilization				
Patients with any transfusion	90 (0.7)	70 (0.6)	1.29 (0.94, 1.76)	0.1154

Table S15 presented the main safety endpoint per type of patient showing no significant difference in stable, NSTEMI or STEMI subpopulations.

Table S15: Analysis of non–CABG-related GUSTO severe/life-threatening and moderate bleeding complications from CHAMPION PHOENIX, by patient type (safety population)

	n/N (%) of patients			
GUSTO severe/life-threatening and moderate bleeding	**Cangrelor**	**Clopidogrel**	**OR (95% CI)**	**p-value (interaction)**
All patients	31/5529 (0.6)	19/5527 (0.3)	1.63 (0.92, 2.90)	
Stable angina patients	12/3137 (0.4)	8/3036 (0.3)	1.45 (0.59, 3.56)	
NSTE-ACS patients	7/1392 (0.5)	4/1421 (0.3)	1.79 (0.52, 6.13)	0.929
STEMI patients	12/1000 (1.2)	7/1070 (0.7)	1.84 (0.72, 4.70)	
NSTE-ACS and STEMI	19/2392 (0.8)	11/2491 (0.4)	1.81 (0.86, 3.80)	

Frequencies of adverse events of intracranial haemorrhage and of gastrointestinal bleeding for the CHAMPION pooled database are presented by SOC and PT in Table S16.

Table S16: Summary of bleeding related adverse events within 30 days from dosing start by system organ class and preferred terms related to gastrointestinal disorders and nervous system disorders (CHAMPION pooled, safety population)

	n (%) of patients		
System Organ Class Preferred Term	**Cangrelor (N=12,565)**	**Clopidogrel (N=12,542)**	**p-value**
Subjects with at least one bleeding related AE	111 (0.9)	71 (0.6)	0.0030
Gastrointestinal disorders	98 (0.8)	67 (0.5)	0.0160
Retroperitoneal haemorrhage	27 (0.2)	15 (0.1)	0.0647
Gastrointestinal haemorrhage	20 (0.2)	15 (0.1)	0.4007
Gingival bleeding	20 (0.2)	12 (0.1)	0.1586
Haematemesis	11 (0.1)	12 (0.1)	0.8313
Mouth haemorrhage	8 (0.1)	1 (0.0)	0.0198
Rectal haemorrhage	3 (0.0)	0 (0.0)	
Lip haemorrhage	2 (0.0)	0 (0.0)	
Duodenal ulcer haemorrhage	1 (0.0)	0 (0.0)	
Haematochezia	1 (0.0)	3 (0.0)	0.3164
Haemorrhoidal haemorrhage	1 (0.0)	1 (0.0)	0.9990
Lower gastrointestinal haemorrhage	1 (0.0)	0 (0.0)	
Oesophageal haemorrhage	1 (0.0)	0 (0.0)	
Peritoneal haematoma	1 (0.0)	0 (0.0)	
Upper gastrointestinal haemorrhage	1 (0.0)	0 (0.0)	
Diverticulum intestinal haemorrhagic	0 (0.0)	1 (0.0)	
Gastric haemorrhage	0 (0.0)	1 (0.0)	
Haemorrhagic erosive gastritis	0 (0.0)	1 (0.0)	
Intra-abdominal haematoma	0 (0.0)	1 (0.0)	
Melaena	0 (0.0)	3 (0.0)	
Rectal fissure	0 (0.0)	1 (0.0)	
Nervous system disorders	13 (0.1)	4 (0.0)	0.0293
Haemorrhage intracranial	9 (0.1)	3 (0.0)	0.0838
Cerebral haemorrhage	2 (0.0)	0 (0.0)	
Cerebrovascular accident	1 (0.0)	0 (0.0)	
Haemorrhagic stroke	1 (0.0)	1 (0.0)	0.9990

Source: Appendix Table 16.6.21.4.1.9.

In the pooled CHAMPION studies which were PCI trials, CABG was infrequent occurring in 164/25,107 (0.6%) of patients (82/12,565 in the cangrelor and 82/12,542 in the clopidogrel treatment arms, respectively). No GUSTO Severe/Life threatening bleeding occurred. ACUITY Major and Minor as well as GUSTO Moderate and Mild bleeding was balanced in each treatment arm. There was no difference in CABG related blood and blood product utilization between cangrelor and clopidogrel treated subjects (table S17).

Table S17: Analysis of CABG-related bleeding complications from pooled CHAMPION studies (safety population)

	n (%) of patients			
	Cangrelor N=82	Clopidogrel N=82	OR (95% CI)	p value
GUSTO				
Severe/Life Threatening	0 (0.0)	0 (0.0)	-	-
Moderate	9 (11.0)	6 (7.3)	1.56 (0.53, 4.61)	0.4164
Mild	4 (4.9)	4 (4.9)	1.00 (0.24, 4.14)	1.0000
ACUITY				
Major	10 (12.2)	10 (12.2)	1.00 (0.39, 2.55)	1.0000
Minor	3 (3.7)	0 (0.0)	-	0.0804
Blood and blood product utilization				
Patients with any transfusion	9 (11.0)	6 (7.3)	1.56 (0.53, 4.61)	0.4164

In the BRIDGE study, there were generally more non-CABG bleeding events in the cangrelor treated group (table S18). The frequency of major bleeding endpoints was low with the increase in frequency of bleeding driven mostly by ecchymosis, haematoma and puncture site bleeding, but results were not significant. The frequency of CABG-related bleeding endpoints measured was overall higher than pre-CABG, but balanced between treatment arms (table S19).

Table S18: Non-CABG- and CABG-related bleeding by bleeding scales and transfusion in BRIDGE study (safety population)

	Pre-procedure (non-CABG-related)		Post-procedure (CABG-related)	
	Cangrelor (N=106) n (%)	Placebo (N=101) n (%)	Cangrelor (N=102) n (%)	Placebo (N=96) n (%)
GUSTO	20 (18.9)	11 (10.9)	40 (39.2)	42 (43.8)
Severe/life-threatening	0 (0.0)	0 (0.0)	3 (2.9)	1 (1.0)
Moderate	2 (1.9)	1 (1.0)	24 (23.5)	31 (32.3)
Mild	19 (17.9)	10 (9.9)	21 (20.6)	17 (17.7)
Mild w/o ecchymosis, oozing at puncture site, and <5 cm haematoma at puncture site	6 (5.7)	5 (5.0)	18 (17.6)	17 (17.7)
ACUITY	20 (18.9)	11 (10.9)	40 (39.2)	42 (43.8)
Major	3 (2.8)	1 (1.0)	30 (29.4)	34 (35.4)
Minor	19 (17.9)	10 (9.9)	17 (16.7)	14 (14.6)
Minor w/o ecchymosis, oozing at puncture site, and <5 cm haematoma at puncture site	5 (4.7)	5 (5.0)	14 (13.7)	14 (14.6)

	Pre-procedure (non-CABG-related)		Post-procedure (CABG-related)	
	Cangrelor (N=106) n (%)	Placebo (N=101) n (%)	Cangrelor (N=102) n (%)	Placebo (N=96) n (%)
Major excluding haematoma ≥5 cm	3 (2.8)	1 (1.0)	30 (29.4)	34 (35.4)
Any Blood Transfusion	2 (1.9)	1 (1.0)	26 (25.5)	31 (32.3)

Table S19: CABG-related bleeding and transfusion in the BRIDGE trial (Stage II safety population)

	Cangrelor	Placebo	OR (95% CI)	p value
Protocol-defined excessive, n/N (%)	12/102 (11.8)	10/96 (10.4)	1.15 (0.47, 2.79)	0.7630
Surgical re-exploration	2/102 (2.0)	2/96 (2.1)	0.94 (0.13, 6.81)	0.9512
24-hour chest tube output of >1.5 liters	8/102 (7.8)	5/96 (5.2)	1.55 (0.49, 4.91)	0.4574
PRBC transfusions >4 units	6/102 (5.9)	8/96 (8.3)	0.69 (0.23, 2.06)	0.5033
Consistent with BARC-defined, n/N (%)	10/102 (9.8)	10/96 (10.4)	0.93 (0.37, 2.36)	0.8863
Fatal bleeding	0/102 (0.0)	0/96 (0.0)	NA	NA
Peri-operative intracranial bleeding within 48 hours	0/102 (0.0)	0/96 (0.0)	NA	NA
Reoperation for the purpose of controlling bleeding	2/102 (2.0)	2/96 (2.1)	0.94 (0.13, 6.81)	0.9512
Transfusion of ≥5 units of whole blood or PRBC within a 48-hour period	7/102 (6.9)	8/96 (8.3)	0.81 (0.28, 2.33)	0.6963
Chest tube output ≥2 liters within a 24-hour period	3/102 (2.9)	4/96 (4.2)	0.70 (0.15, 3.20)	0.6424
Chest tube output (mL) (mean ± SD)				
4 hour	325.4 ± 265.6	297.1 ± 200.2	NA	0.9851
24 hour	830.4 ± 557.3	805.2 ± 440.4	NA	0.8188
Blood and blood product utilization				
Patients with any transfusion, n/N (%)	26/102 (25.5)	31/96 (32.3)	0.72 (0.39, 1.33)	0.2908
Units of whole blood/PRBC, mean ± SD (n)	3.45 ± 2.09 (22)	3.73 ± 2.56 (30)	NA	0.8359
Units of platelets mean ± SD (n)	1.85 ± 0.90 (13)	2.62 ± 2.63 (13)	NA	0.8485
Units of FFP mean ± SD (n)	4.09 ± 2.12 (11)	4.67 ± 3.96 (15)	NA	0.9781

The SAG was also requested to provide their input on the bleeding profile of cangrelor as follows:

d. The bleeding profile of cangrelor and the need for further characterisation, in particular in the patients undergoing PCI-ACS where a larger bleeding difference was found in STEMI and non-STEMI patients, taking also into account the profile obtained with other antiplatelet agents.

The SAG considered the safety profile of cangrelor acceptable even though a higher bleeding risk is observed compared to clopidogrel [OR 1.63 (0.92-2.90) for all subgroups]. This increase in bleeding has to be balanced with the higher pharmacological efficacy of cangrelor in inhibiting platelet aggregation, and subsequently in reducing thrombosis risk.

The majority of the bleeding events observed in the cangrelor group are ecchymosis and haematomas >5 cm at puncture sites and manageable. No intracranial haemorrhages were observed in either group.

The bleeding rate is higher in non-STEMI and STEMI patients (1.2 and 0.8 versus 0.7 and 0.4 in cangrelor and clopidogrel groups respectively). This may be due in part to the concomitant use of anticoagulants in these patients. It should be appreciated that also the risk of thrombotic events is higher in patients with ACS, although the development of infarction during treatment in patients with ACS is difficult to ascertain. The relative bleeding risk was similar in stable and unstable patients.

With regards to bleeding related death within 30 days, the SAG noted a numerically higher rate of patients with cardiac tamponade with cangrelor (n=2 of which one case was fatal in the cangrelor group versus no cases in the clopidogrel group) which is of concern and recommends an appropriate warning in the SmPC. This could be due to guidewire perforation, a risk inherent to the procedure itself. Accordingly, special care should be recommended.

The increased numbers of death at day 30 due to cardiogenic shock (9 versus 5 with cangrelor and clopidogrel respectively) and myocardial infarction (8 versus 1) need to be further investigated according to the SAG experts. Furthermore, there is a need to look at the totality of the data related to death at day 30 from all three trials.

The SAG also noted that few patients with high bleeding risk were included in the study (low body weight, elderly, females) and that the mean age of the study population is rather low (65 years of age) which is younger than the patient population in current practice. The SAG recommended that this should be addressed with appropriate warnings.

In the CHAMPION PHOENIX study, any patient with stroke or TIA within the last 6 months was excluded. Thus, the SmPC recommends a contra-indication in these patients. The Experts considered this to be more applicable with the US practice and the Experts were not convinced about the need to contra-indicate the use of cangrelor in these patients. Nevertheless, this is justified as it represents the study population excluded from the study.

2. Renal Function

Cangrelor was shown to be associated with reversible AEs in rats and dogs in the upper urinary tract.

In all reported studies, there was a numerical increase in renal-related AEs for cangrelor of 93/13,301 (0.7%) vs 64/12,861 (0.5%) (Table S20).

Table S20: Summary of renal TEAEs of special interest by SOC and preferred term in all studies (safety population)

SMQ or System Organ Class	Preferred Term	Cangrelor (N=13301) n (%)	Control (N=12861) n (%)
Patients with any renal AE		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)
	Renal failure	15 (0.1)	7 (0.1)
	Proteinuria	12 (0.1)	9 (0.1)
	Nephropathy toxic	4 (0.0)	5 (0.0)
	Oliguria	3 (0.0)	3 (0.0)
	Renal impairment	2 (0.0)	4 (0.0)
	Azotaemia	2 (0.0)	0 (0.0)
	Anuria	1 (0.0)	0 (0.0)
	Renal tubular necrosis	0 (0.0)	1 (0.0)

There were a total of 13 deaths reported in patients with the SMQ of Acute Renal Failure; 7 of the deaths occurred in cangrelor-treated patients and 6 in the control group.

Baseline and post-baseline creatinine level data were obtained in the C-PCI and C-PLATFORM but were not captured in C-PHOENIX trial. The incidence of SMQ of Acute Renal Failure appeared to increase with worsening baseline renal function (table S21).

Table S21: TEAE frequency (SMQ) by baseline renal function in the CHAMPION pooled studies, and in placebo-controlled studies (safety population)

	CHAMPION Pooled [a]		Placebo-controlled	
	Cangrelor (N=12565) n (%)	Clopidogrel (N=12542) n (%)	Cangrelor N=354 n (%)	Control N=218 n (%)
Patients with at least one event in the SMQ of **Acute Renal Failure**	68 (0.5)	50 (0.4)	13 (3.7)	12 (5.5)
Severe (<30 mL/min/ 1.73 m^2)	10/281 (3.6)	5/282 (1.8)	0/5 (0.0)	0/3 (0.0)
Table 4. Moderate (30 to <60 mL/min/ 1.73 m^2)	25/2197 (1.1)	14/2159 (0.6)	9/80 (11.3)	8/52 (15.4)
Table 5. Mild (60 to ⩽90 mL/min/ 1.73 m^2)	5/2809 (0.2)	11/2790 (0.4)	4/180 (2.2)	2/107 (1.9)
Normal (>90 mL/min/ 1.73 m^2)	1/1552 (0.1)	0/1577 (0.0)	0/78 (0.0)	2/55 (3.6)

[a] Glomerular filtration rate data from CHAMPION PCI/PLATFORM only.

3. Dyspnoea

Dyspnoea has been reported with reversible inhibitors of $P2Y_{12}$. In C- PHOENIX study, dyspnoea was reported in 1.2% of patients in the cangrelor arm vs 0.3% in the clopidogrel arm, which is consistent with the incidence in the All Studies group. In BRIDGE, the incidence of dyspnoea was 2.8% (3/106) in the cangrelor group versus 0.9% (1/101) in the placebo group. The majority of dyspnoea was non-serious (98%), mild (66%), with only a few cases (n=3) severe. The median time of the event was 2 hours. Few patients discontinued the study drug due to dyspnoea (10/179, 5.6%). No patient died of dyspnea.

4. Hypersensitivity

There were similar overall rates of hypersensitivity events reported with cangrelor (0.7%) vs control (0.6%) in all studies, but a higher rate of SAEs with cangrelor vs control (7 vs 2) (Table **S22**).

Table S22: Serious TEAEs of hypersensitivity, all studies (safety population)

Preferred Term	Cangrelor (N=13301) n (%)	Control (N=12861) n (%)
Patients with any SAE of hypersensitivity	7 (0.1)	2 (0.0)
Anaphylactic reaction	2 (0.0)	0 (0.0)
Angioedema	2 (0.0)	0 (0.0)
Anaphylactic shock	1 (0.0)	0 (0.0)
Bronchospasm	1 (0.0)	0 (0.0)
Laryngeal oedema	1 (0.0)	0 (0.0)
Stridor	1 (0.0)	0 (0.0)
Hypersensitivity	0 (0.0)	2 (0.0)

Laboratory findings

In All Studies and in the CHAMPION programme, the potentially clinically significant test values in haematology between the cangrelor and control treatment groups were consistent with the findings in the bleeding events (Table S23). Clinical chemistry parameters were also balanced except for a higher creatinine level (>1×ULN) in the cangrelor group compared to the clopidogrel or control (table S24). In the placebo controlled studies, there were numerically more patients with post-baseline changes in AST (>1×ULN).

Table S23: Potentially clinical significant tests in haematology parameters in CHAMPION programme and placebo-controlled studies (safety population)

	CHAMPION		Placebo Controlled	
Haematology Parameters	Cangrelor (N=12565) n/N (%)	Clopidogrel (N=12542) n/N (%)	Cangrelor (N=354) n/N (%)	Control (N=218) n/N (%)
Haematocrit (g/dL) ≤0.8 × LLN	440/11673 (3.8)	382/11659 (3.3)	86/337 (25.5)	60/206 (29.1)
Haemoglobin (%) ≤ 0.8 × LLN	423/11658 (3.6)	330/11660 (2.8)	87/338 (25.7)	66/209 (31.6)
Platelets ≥700 k/µL	3/11914 (0.0)	1/11889 (0.0)	0/340 (0.0)	0/213 (0.0)
Platelets ≤75 k/µL	16/11914 (0.1)	18/11889 (0.2)	11/340 (3.2)	6/213 (2.8)
WBC ≥16 k/µL	113/6268 (1.8)	106/6290 (1.7)	37/342 (10.8)	29/211 (13.7)
WBC [a] ≤2.8 k/µL	4/6268 (0.1)	1/6290 (0.0)	0/342 (0.0)	0/211 (0.0)

LLN: lower limit normal

Table S24: Post-baseline changes in serum chemistry parameters from normal at baseline to >1×ULN in CHAMPION program and placebo controlled studies (safety population)

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

ULN = upper limit of normal. U/L = units/litre.

Vital signs

Only the C-PCI and C-PLATFORM studies collected vital signs and no significant differences between treatment groups in systolic and diastolic blood pressure and heart rate were observed.

Safety in special populations

Table S25 presents a summary of AE distributed by age.

Table S25: Overall summary of AEs by age group, all studies (safety population)

	Cangrelor				Clopidogrel			
	<65 y (n=7312)	65-74 y (n=3786)	75-84 y (n=1972)	85+ y (n=231)	<65 y (n=7057)	65-74 y (n=3644)	75-84 y (n=1927)	85+ y (n=233)
All AEs	1925 (26.3)	968 (25.6)	570 (28.9)	62 (26.8)	1630 (23.1)	825 (22.6)	496 (25.7)	80 (34.3)
Fatal AEs	20 (0.3)	23 (0.6)	12 (0.6)	2 (0.9)	19 (0.3)	22 (0.6)	14 (0.7)	5 (2.1)
SAE	187 (2.6)	104 (2.7)	64 (3.2)	15 (6.5)	130 (1.8)	101 (2.8)	66 (3.4)	19 (8.2)
Discontinuation	55 (0.8)	35 (0.9)	25 (1.3)	1 (0.4)	29 (0.4)	24 (0.7)	15 (0.8)	1 (0.4)
CNS	26 (0.4)	18 (0.5)	16 (0.8)	2 (0.9)	19 (0.3)	10 (0.3)	19 (1.0)	4 (1.7)
AE related to falling	2 (0.0)	8 (0.2)	4 (0.2)	0 (0.0)	3 (0.0)	2 (0.1)	4 (0.2)	0 (0.0)
Cardiovascular Events	548 (7.5)	326 (8.6)	204 (10.3)	24 (10.4)	466 (6.6)	290 (8.0)	168 (8.7)	31 (13.3)
Cerebrovascular Events	7 (0.1)	2 (0.1)	5 (0.3)	1 (0.4)	4 (0.1)	6 (0.2)	5 (0.3)	0 (0.0)
Infections	43 (0.6)	30 (0.8)	24 (1.2)	0 (0.0)	35 (0.5)	19 (0.5)	5 (0.3)	5 (2.1)

An interaction analysis of a number of intrinsic and extrinsic factors was performed on the CHAMPION pooled data and revealed a significant interaction for gender and smoking.

Immunological events

N/A

Discontinuation due to AES

The incidence of patients with AEs leading to discontinuation from the study drug in the C-PHOENIX study and in the CHAMPION program (Table S26) was low and similar in the cangrelor-treated and clopidogrel-treated patients.

Table S26: AEs (occurring in ≥2 patients) leading to discontinuation of study drug in CHAMPION pooled studies (safety population)

	CHAMPION studies	
Preferred Term	**Cangrelor (N=12565) n (%)**	**Clopidogrel (N=12542) n (%)**
Patients with at least one AE causing study drug discontinuation	**75 (0.6)**	**52 (0.4)**
Coronary artery perforation	14 (0.1)	7 (0.1)
Coronary artery dissection	11 (0.1)	8 (0.1)
Dyspnoea	8 (0.1)	1 (0.0)
Hypotension	5 (0.0)	6 (0.0)
Vomiting	4 (0.0)	4 (0.0)
Cardiac arrest	3 (0.0)	3 (0.0)
Nausea	3 (0.0)	3 (0.0)
Acute pulmonary oedema	3 (0.0)	0 (0.0)
Cardio-respiratory arrest	3 (0.0)	0 (0.0)
Cardiogenic shock	2 (0.0)	5 (0.0)
Anaphylactic reaction	2 (0.0)	0 (0.0)
Cardiac tamponade	2 (0.0)	0 (0.0)
Arterial rupture	1 (0.0)	3 (0.0)
Bradycardia	1 (0.0)	2 (0.0)
Thrombosis in device	1 (0.0)	2 (0.0)
Chest pain	0 (0.0)	2 (0.0)
Hypersensitivity	0 (0.0)	3 (0.0)

The overall incidence of patients with AEs leading to discontinuation from study drug in the BRIDGE study was numerically higher among cangrelor-treated patients (table S27).

Table S27: AEs leading to discontinuation of study drug in BRIDGE (safety population)

	Stage II	
Preferred Term	**Cangrelor (N=106) n (%)**	**Placebo (N=101) n (%)**
Subjects with at least one AE leading to study drug discontinuation	**6 (5.7)**	**3 (3.0)**
Angina pectoris	1 (0.9)	0 (0.0)

Preferred Term	Stage II	
	Cangrelor (N=106) n (%)	Placebo (N=101) n (%)
Cardiogenic shock	1 (0.9)	0 (0.0)
Papillary muscle rupture	1 (0.9)	0 (0.0)
Pericarditis	1 (0.9)	0 (0.0)
Bronchospasm	1 (0.9)	0 (0.0)
Dyspnoea	1 (0.9)	0 (0.0)
Cardiopulmonary failure	0 (0.0)	1 (1.0)
Hypoglycemia	0 (0.0)	1 (1.0)
Nephropathy toxic	0 (0.0)	1 (1.0)

The most common AEs leading to discontinuation were in the SOC of Cardiac disorders. The top two most common AEs leading to discontinuation were coronary artery dissection and coronary artery perforation, both of which were procedure related. Dyspnoea also led to discontinuation and was reported by more patients in the cangrelor group than in the clopidogrel group.

2.6.1. Discussion on clinical safety

Patient Exposure. The safety database is adequate for the PCI indication, for both the dose (4.0µg/kg/min) and the maximum duration indicated in the SmPC of 4 hours. For the bridging indication, patient exposure is very limited to those recruited in the BRIDGE study (stage II: cangrelor n=93 ; placebo, n=90).

The SmPC mentioned that experience is available for administration up to 7 days. The applicant explained that the duration of 7 days referred to the period of disruption of oral $P2Y_{12}$ antiplatelets. However, the actual experience in the BRIDGE study is limited to one patient with the longest administration of 6.7 days. Based on these data, the inclusion of the reference to 7 days in the SmPC is not supported (Reference to the Bridging indication is removed from the label).

Focus on the current assessment will be on the safety data from the pooled CHAMPION studies as the included patient populations, and posology were comparable to that of C-PHOENIX, nevertheless a wider database can help identify the safety profile. Post CABG bleeding data from the BRIDGE study is important to clarify the bleeding risks associated with bridging.

Adverse Events. The reported AE are generally balanced and reflect the studied population, and the pharmacological class of cangrelor.

Serious adverse events. The frequency of SAEs in the CHAMPION studies is low and balanced between the treatment groups, which is reassuring. In the BRIDGE study, the frequency of SAEs is higher in the cangrelor group compared to the placebo group, specially post CABG (7.8% vs 5.2 respectively). There was one case of coronary artery thrombosis reported in the cangrelor group. Reviewing the case narrative, it is difficult to assess causality (lack of efficacy during bridging) of cangrelor in relation to the stent thrombosis, as the event occurred 4 days following the CABG surgery. In addition, no outcome data are collected in the BRIDGE study that could further clarify this event.

Deaths. The death rate in the cangrelor group was comparable to that reported in the clopidogrel group in the CHAMPION studies. This is in line with the efficacy data discussed before. In the BRIDGE study the death rate in the cangrelor group (1.9%) was much lower than that in placebo (5%).

In all studies, the major cause of death was cardiovascular-related, its overall incidence being comparable in the cangrelor group (2.3% for 4 pooled studies and 2.4% in the CHAMPION studies) than in the comparator group (2.6%). In C-PHOENIX at day 30, 61 deaths were reported in the cangrelor group (1.1%) versus 57 deaths in the clopidogrel group (1.0%). An imbalance in the reported incidence of deaths due to cardiogenic shock and myocardial infarction is noted (9 and 8 cases in the cangrelor group versus 5 and 1 in the clopidogrel group respectively). There are also 5 additional cases of death related to acute MI in the cangrelor arm versus 3 in the clopidogrel arm. Opposite trends were shown in C-PCI and C-PLATFORM. Deaths related to cardiogenic shock, MI and AMI were reported less in the cangrelor arm (for C- PCI 4, 2, 0 and C-PLATFORM 4, 0 and 2 respectively) than in the clopidogrel arm (for C-PCI 6, 6, 2, and C-PLATFORM 12, 2, and 1 respectively).

Bleeding. There is a slightly higher bleeding risk associated with cangrelor (17.9%) compared to clopidogrel (14%) in the CHAMPION studies due to higher rates of traumatic haematoma (6.4% vs 4.8% respectively); vessel puncture site discharge (6.1% vs 4.5%); ecchymosis (4.7% vs 3.3%) and haematoma (2.2% vs. 1.6%). Intracranial haemorrhage was recorded in a higher frequency in the cangrelor group than clopidogrel. This is currently reflected as a warning in section 4.4 of the SmPC. The frequency of GI bleeding and fatal bleedings were comparable, which is reassuring. CABG-related bleedings in patients who had CABG in the CHAMPIONS trials showed comparable trends as in the non-CABG bleedings, with higher frequencies in the cangrelor group recorded in GUSTO moderate bleeding, and ACUITY minor bleedings. In the BRIDGE study, presented bleeding data are reassuring considering that the comparator is placebo. For this reason, it also appears unexpected to observe higher frequencies of blood transfusions, drop in haemoglobin or haematocrite reported in the placebo group compared to the cangrelor group (25.5 vs 32.3% and 16.7 vs 22.9 respectively). The company did not clarify the possible reasons for such differences. However, it can be agreed that the study was not powered to address the differences in components, and that the results were not significantly different precluding any conclusions.

A numerically higher rate of patients with cardiac tamponade with cangrelor (n=2 of which one case was fatal in the cangrelor group versus no cases in the clopidogrel group) was observed which is of concern; a warning is currently included in the SmPC.

Fatal bleeding. The incidence of fatal bleeding appears to be balanced between the cangrelor and the control groups. This is reassuring. However, there were 5 cases of bleeding in the nervous system, 4 in the cangrelor arm and 1 in the control arm. Assessment of the 4 fatal cases shows that in 3/4 there is a history of stroke, or possibly TIA. There is no mention of the time of onset in relation to cangrelor administration. To address the fatal cases, the contraindication proposed by the applicant of " Any history of intracranial haemorrhage or ischaemic stroke within the last year" is modified to 'History of stroke or TIA" without any reference to timing. An interaction between cangrelor and a specific anticoagulant leading to a higher intracranial haemorrhage can not be ruled out, but is not clear from the submitted narratives. A general warning is included in the SmPC.

Bleeding scales. It is considered a disadvantage that the bleeding events were not adjudicated by a blinded committee. Using the ISTH definitions to classify bleedings would have also been preferred (Schulman at al., 2005). The ACUITY[1] bleeding definitions are the most comparable to those used by the ISTH, and so the assessment will focus on their results.

Bleeding complications are about 1.5 times more frequent with cangrelor compared to clopidogrel but seem to be mostly of non-severe nature. In C-PHOENIX there was no significant increase in the primary safety outcome

[1] Non-CABG major bleeding that included any one of the following: intracranial, retroperitoneal, intraocular, ≥5 cm diameter haematoma at puncture site, reduction in haemoglobin concentration of >4 g/dL without an overt source of bleeding, reduction in haemoglobin concentration of >3 g/dL with an overt source of bleeding, re-operation for bleeding, use of any blood product transfusion.

of GUSTO severe/life-threatening bleeding or GUSTO moderate bleeding. There was a significant increase in GUSTO mild bleeding, driven primarily by ecchymosis, oozing, and <5 cm haematoma. There were significant increases in ACUITY major and minor bleedings. The former was primarily driven by an increase in ⩾5 cm haematoma at the puncture site. Comparable results are observed for the pooled CHAMPION studies. Nevertheless, the data on bleeds may be incomplete due to 1) the restrictive definition for GUSTO mild and 2) for the investigator report based counts of changes in Hgb/Hct without re-confirming e.g. by assessing the collected laboratory values (affecting e.g. the TIMI defined bleeding cases) as well as 3) reliance in the bleeding related death counts on the investigator reports only and not investigating the relation of all reported deaths and possible preceding bleeds. Additional assessment is asked from the company in this regard (LOI).It was observed that different frequencies were reported in the C-PHOENIX study when using GUSTO vs ACUITY bleeding scale, whereas frequencies are comparable in the pooled CHAMPION analysis. The applicant explained that the observed differences were related to the different definitions used throughout the CHAMPION program. Using the same definitions resulted in comparable results.

It is noticeable that for stable CAD, bleeding rate appears comparable between cangrelor (0.4%) and clopidogrel (0.3%). However, the risk appears to increase more in the acute setting in the side of cangrelor (0.8%) compared to clopidogrel (0.4%). Further analysis of the bleeding data was requested. In the response the applicant clarified that in all three CHAMPION trials bleeding outcomes were only collected until 48-hours, therefore, no bleeding data is available at 30 days or 1 year. Considering the limited duration of administration of cangrelor of 4 hours and duration of pharmacodynamic action, bleeding data beyond 48 hours may not be directly relevant to the safety assessment of cangrelor. Using the GUSTO definitions it can be observed that the numbers of severe/life threatening events are limited across the different strata, precluding a robust conclusion. Using the ACUITY major bleeding, results are significantly better in the clopidogrel group. However, it can be agreed with the applicant that excluding haematoma > 5 cm leads to similar trends, but not significant differences, making it difficult to draw robust conclusions.

Table S28: Analysis of non–CABG-related ACUITY bleeding complications from CHAMPION PHOENIX, by patient type (safety population)

	n/N (%) of patients			
ACUITY bleeding	**Cangrelor**	**Clopidogrel**	**OR (95% CI)**	**p value (interaction)**
ACUITY Major				
All patients	235/5529 (4.3)	139/5527 (2.5)	1.72 (1.39, 2.13)	
Stable angina	103/3201 (3.2)	58/3184 (1.8)	1.79 (1.29, 2.48)	
NSTE-ACS	69/1468 (4.7)	40/1433 (2.8)	1.72 (1.16, 2.55)	0.9662
STEMI	63/860 (7.3)	41/910 (4.5)	1.68 (1.12, 2.51)	
NSTE-ACS and STEMI	132/2328 (5.7)	81/2343 (3.5)	1.68 (1.27, 2.23)	
ACUITY Major w/o >5cm haematoma				
All patients	42/5529 (0.8)	26/5527(0.5)	1.62 (0.99, 2.64)	
Stable angina	21/3201 (0.7)	15/3184(0.5)	1.40 (0.72, 2.71)	
NSTE-ACS	7/1468 (0.5)	3/1433(0.2)	2.28 (0.59, 8.85)	0.7620
STEMI	14/860 (1.6)	8/910(0.9)	1.87 (0.78, 4.47)	
NSTE-ACS and STEMI	21/2328 (0.9)	11/2343(0.5)	1.93 (0.93, 4.01)	
ACUITY Minor				
All patients	653/5529 (11.8)	475/5527 (8.6)	1.42 (1.26, 1.61)	
Stable angina	388/3201 (12.1)	272/3184 (8.5)	1.48 (1.25, 1.74)	
NSTE-ACS	168/1468 (11.4)	125/1433 (8.7)	1.35 (1.06, 1.73)	0.7963
STEMI	97/860 (11.3)	78/910 (8.6)	1.36 (0.99, 1.86)	
NSTE-ACS and STEMI	265/2328 (11.4)	203/2343 (8.7)	1.35 (1.12, 1.64)	

ACUITY = Acute Catheterization and Urgent Intervention Triage strateg; CABG = coronary artery bypass graft surgery; CI = confidence interval; NSTE-ACS = non-ST segment elevation acute coronary syndrome; OR = odds ratio; STEMI = ST-segment elevation myocardial infarction; cm = centimeter.

In the BRIDGE study, pre-CABG, the presented results by GUSTO and ACUITY scale does not show significant differences.

Renal Function. Pre clinical data show some deleterious effects of cangrelor on the upper urinary tract. Data were not collected in C-PHOENIX, which is disappointing. In the whole safety database, the main concern appears to be increased blood creatinine (0.2% vs 0.1%), although the actual numbers are limited. In addition, more cases of acute renal failure are reported in the cangrelor treatment arm compared to clopidogrel in the C-PCI and C-PLATFORM studies in patients with baseline severe or moderate renal impairment. However, this was not seen in the placebo-controlled studies. Data of patients with different degrees of renal impairment pertaining to progression of renal function and bleeding in the pooled C-PCI and PLATFORM studies were submitted, as in C-PHOENIX such data was not collected. There is a trend for deterioration of renal function as measured by creatinine clearance and GFR mostly in patients with baseline severe renal impairment in the cangrelor group compared to the clopidogrel group. Likewise, in such patients, there is a higher incidence of moderate GUSTO and major ACUITY bleeding rates reported. This is adequately addressed in the SmPC section 4.4.

Dyspnoea. There is a higher incidence of dyspnea reported with cangrelor than with clopidogrel, which is a class effect for direct P2Y12 antagonists (reported with ticagrelor as well). A warning on the risk of dyspnea is therefore included in section 4.4 of the SmPC.

Hypersensitivity. The general incidence of hypersensitivity was balanced between cangrelor and the control groups. However there is a slightly higher incidence of serious cases of hypersensitivity reported with cangrelor. None of these cases were fatal. Assessment of the 7 cases led to the conclusion that the causality of cangrelor cannot be excluded, as all the cases are confounded by the co-administration by other agents e.g contrast agents. The reported cases were serious but because they all occur during hospitalization or the catheterization laboratory, they were all managed successfully. The overall incidence is comparable. Some changes in section 4.4 are proposed to highlight the seriousness of these cases.

Laboratory findings. The recorded haematology results appear to be in line with the bleeding profile of cangrelor. There is a slight increase in the level of serum creatinine compared to clopidogrel, which has been discussed before. The applicant discussed the differences in the mechanism of action of ticagrelor compared to cangrelor which support a differential effect on uric acid. Data from the CHAMPION studies showed that the incidence of AEs relating to uric acid increase was generally low and similar between cangrelor and control [7/12565 (0.1%) vs 5/12542 (0.0%) respectively.

Vital signs. The applicant discussed available data pertaining to ventricular pauses. Preclinical data did not indicate that cangrelor can be associated with such AEs, unlike ticagrelor. The thorough QT study also did not point to any arrhythmogenic potential. Lastly, the applicant presented data pooled from the CHAMPION studies which are all reassuring and showing comparable incidence to the comparator.

Eye disorders. One case of serious eye disorder was reported in the cangrelor arm (SCS). The applicant discussed the pre-clinical and clinical findings pertaining to ocular AEs. Regarding the pre-clinical data, it can be agreed that their clinical relevance are limited. This is mainly because they occurred in a dog tissue that is not found in humans. Also the findings were apparent after long term dosing (28 days) which is much longer than the clinical use (2 hours to 7 days).

In the cangrelor clinical program, there was a higher frequency of ocular related AEs in the cangrelor group. It can not be excluded that this is related to the higher rate of minor bleedings. The serious cases discussed by the applicant pertain to one case of blurred vision, and another case of central retinal artery occlusion. In both cases the direct deleterious effect of cangrelor on the ocular tissues is considered unlikely.

Special populations. Analysis of the incidence of AEs based on different subgroups showed a significant interaction by gender and smoking. It is difficult to explain this finding based on clinical grounds. It can be agreed that a chance finding can not be excluded, considering the multiple interactions tested and the higher chances of false positive results of the statistical analysis. Further analysis based on individual AE resulted in small numbers and does not show a clear pattern. The incidence of the different types of AEs is shown to be comparable between cangrelor and clopidogrel for the respective age groups, with increasing frequency by age as would be expected.

AE leading to discontinuation. The reported AE leading to discontinuation appear to be balanced in the whole program. Dyspnoea is frequently reported as the AE leading to discontinuation.

In conclusion, from the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Additionally during the assessment, the CHMP sought the SAG advive in relation to the bleeding. (see below)

Additional Expert consultation

1. The SAG is asked to comment on the benefits and risks of cangrelor during PCI, taking the following points into consideration:

d. The bleeding profile of cangrelor and the need for further characterisation, in particular in the patients undergoing PCI-ACS where a larger bleeding difference was found in STEMI and non-STEMI patients, taking also into account the profile obtained with other antiplatelet agents.

The SAG considered the safety profile of cangrelor acceptable even though a higher bleeding risk is observed compared to clopidogrel [OR 1.63 (0.92-2.90) for all subgroups]. This increase in bleeding has to be balanced with the higher pharmacological efficacy of cangrelor in inhibiting platelet aggregation, and subsequently in reducing thrombosis risk.

The majority of the bleeding events observed in the cangrelor group are ecchymosis and haematomas >5 cm at puncture sites and manageable. No intracranial haemorrhages were observed in either group.

The bleeding rate is higher in non-STEMI and STEMI patients (1.2 and 0.8 versus 0.7 and 0.4 in cangrelor and clopidogrel groups respectively). This may be due in part to the concomitant use of anticoagulants in these patients. It should be appreciated that also the risk of thrombotic events is higher in patients with ACS, although the development of infarction during treatment in patients with ACS is difficult to ascertain. The relative bleeding risk was similar in stable and unstable patients.

With regards to bleeding related death within 30 days, the SAG noted a numerically higher rate of patients with cardiac tamponade with cangrelor (n=2 of which one case was fatal in the cangrelor group versus no cases in the clopidogrel group) which is of concern and recommends an appropriate warning in the SmPC. This could be due to guidewire perforation, a risk inherent to the procedure itself. Accordingly, special care should be recommended.

The increased numbers of death at day 30 due to cardiogenic shock (9 versus 5 with cangrelor and clopidogrel respectively) and myocardial infarction (8 versus 1) need to be further investigated according to the SAG experts. Furthermore, there is a need to look at the totality of the data related to death at day 30 from all three trials.

The SAG also noted that few patients with high bleeding risk were included in the study (low body weight, elderly, females) and that the mean age of the study population is rather low (65 years of age) which is younger than the patient population in current practice. The SAG recommended that this should be addressed with appropriate warnings.

In the CHAMPION PHOENIX study, any patient with stroke or TIA within the last 6 months was excluded. Thus, the SmPC recommends a contra-indication in these patients. The Experts considered this to be more applicable with the US practice and the Experts were not convinced about the need to contra-indicate the use of cangrelor in these patients. Nevertheless, this is justified as it represents the study population excluded from the study.

The CHMP took note of the advice in its assessment (see above).

2.6.2. Conclusions on the clinical safety

The safety database of cangrelor is considered adequate for the proposed indication. The identified risks of bleeding and dyspnea are related to its mechanism of action and pharmacological class. In the PCI indication, incidence of bleeding is somewhat higher for cangrelor compared to clopidogrel, particularly for intracranial bleedings. The difference is not significant, however a warning is included in the labelling. Bleeding rates are comparable between cangrelor and clopidogrel in the three major subgroups (Stable, NSTEMI and STEMI) when using GUSTO severe/life-threatening and moderate bleeding. Using the ACUITY scale, there is a significant

increase in bleeding in the ACS group administered cangrelor, but that is less evident with the exclusion of haematomas of > 5 cm.

In the BRIDGE study, compared to placebo, the bleeding results are reassuring, although the database is limited.

In patients with severe renal impairment a deterioration in renal function compared to clopidogrel is noticed, in addition to a higher rate of GUSTO moderate bleeding. The effects on renal function are adequately addressed in section 4.4 of the SmPC. Further analysis of data did not reveal AEs related to ventricular pauses or elevations of uric acids, unlike what is reported with ticagrelor.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 1.2 could be acceptable provided minor changes are implemented.

The CHMP endorsed the Risk Management Plan version 1.4 implementing the requested changes with the following content:

Safety concerns

Summary of safety concerns	
Important identified risk	Serious bleeding
	Hypersensitivity
	Dyspnoea
	Renal impairment
Important potential risks	Inadequate antiplatelet effect of clopidogrel or prasugrel caused by the mistiming of the cangrelor transition to thienopyridines
Missing information	Exposure to cangrelor during pregnancy and lactation
	Use of cangrelor in the paediatric population (<18 years of age)
	Use of cangrelor in patients with increased risk of bleeding [eg history of gastrointestinal bleeding, major surgery within 30 days, clinically relevant thrombocytopaenia or anaemia and patients affected by cerebral arteriovenous malformation (AVM)]
	Use of ticagrelor and prasugrel before, during and after the cangrelor infusion

Pharmacovigilance plan

Study/activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status (planned, started)**	**Date for submission of interim or final reports (planned or actual)**
A multicentre retrospective observational study of patients undergoing PCI who receive cangrelor and transition to either clopidogrel, prasugrel or ticagrelor	To describe bleeding and MACE event rates in patients undergoing PCI that require treatment with IV cangrelor switching to either prasugrel or ticagrelor including any association between mistiming of administration of clopidogrel or prasugrel and MACE.	Bleeding and MACE in patients with inadequate antiplatelet effect of clopidogrel or prasugrel caused by the mistiming of the cangrelor transition to thienopyridines Bleeding and MACE with the use of ticagrelor and prasugrel before, during and after the cangrelor infusion	Planned.	Interim safety analysis planned Q4 2016, Q4 2017; Final study report Q3 2018

Risk minimisation measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Important Identified Risk		
Serious bleeding	The proposed SmPC contains the following: Section 4.3 Contraindications Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects Section 4.9 Overdose	None.
Hypersensitivity	The proposed SmPC contains the following: Section 4.3 Contraindications Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects	None.
Dyspnoea	The proposed SmPC contains the following: Section 4.4 Special warnings and	None.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	precautions for use Section 4.8 Undesirable effects	
Renal impairment	The proposed SmPC contains the following: Section 4.2 Posology and method of administration Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects Section 5.2 Pharmacokinetic properties Section 5.3 Preclinical safety data	None.
Important Potential Risk		
Inadequate antiplatelet effect of clopidogrel or prasugrel caused by the mistiming of the cangrelor transition to thienopyridines	The proposed SmPC contains the following: Section 4.2 Posology and method of administration Section 4.5 Interaction with other medicinal products and other forms of interaction	None.
Missing Information		
Exposure to cangrelor during pregnancy and lactation	The proposed SmPC contains the following: Section 4.6 Fertility, pregnancy and lactation Section 5.3 Preclinical safety data	None.
Use of cangrelor in the paediatric population (<18 years of age)	The proposed SmPC contains the following: Section 4.2 Posology and method of administration Section 5.1 Pharmacodynamic properties Section 5.2 Pharmacokinetic properties	None.
Use of cangrelor in patients with increased risk of bleeding [eg history of gastrointestinal bleeding, major surgery within 30 days, clinically relevant thrombocytopaenia or anaemia and patients affected by cerebral arteriovenous malformation (AVM)]	The proposed SmPC contains the following: Section 4.3 Contraindications Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effect Section 4.9 Overdose	None.
Use of ticagrelor and prasugrel	The proposed SmPC contains the	None.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
before, during and after the cangrelor infusion	following: Section 4.2 Posology and method of administration Section 4.5 Interaction with other medicinal products and other forms of interaction	

The CHMP endorsed this advice without changes.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

Cangrelor is a novel, intravenous, direct-acting P2Y12 receptor antagonist. It was developed for two indications: Percutaneous Coronary Intervention (PCI) indication to prevent thrombotic cardiovascular events and Bridging indication, in the pre-operative period when anti-thrombotic agents are interrupted. The latter was withdrawn at D180 due to major objections raised on the lack of clinical evidence, thus not described below.

The PCI indication is based mainly on CHAMPION PHOENIX (C-PHOENIX), the only complete and positive study from the CHAMPION triad (C-PCI and C-PLATFORM).

The pivotal C-PHOENIX study was a randomized, double-blind, double-dummy trial designed to test whether cangrelor at the time of PCI followed by transition to oral clopidogrel is superior to oral clopidogrel therapy alone at reducing thrombotic events during and immediately after PCI. In this trial, 11.185 patients where included with stable angina (SA), ST segment elevation myocardial infarction (STEMI) or non-ST segment elevation myocardial infarction (NSTEMI), among them around 40% recruited in EU, which is reassuring regarding the applicability to EU clinical practices.

The composite incidence of death/MI/IDR/stent thrombosis among mITT patients was 4.7% in the cangrelor treatment arm and 5.9% in the clopidogrel treatment arm. For adjusted analysis using logistic regression to control for the potential confounding factors of patient baseline status and clopidogrel loading dose, OR: 0.78 (95% CI: 0.66, 0.93), p=0.005; for unadjusted analysis, OR: 0.79 (95% CI: 0.67, 0.93), p=0.006.

Benefits were shown for the subgroups of stable angina SA, STEMI and NSTEMI but significance was only shown for the SA subgroup [cangrelor (5.8%) vs clopidogrel (7.4%) OR: 0.78 (95% CI: 0.63, 0.95); STEMI: cangrelor (2.8%) vs clopidogrel (3.7%) OR: 0.75 (95% CI: 0.46, 1.25) and NSTEMI: cangrelor (3.5%) vs clopidogrel (4.4%) OR: 0.8 (95% CI: 0.55, 0.1.17)].

Significant results were shown against the clopidogrel 600 mg loading dose [cangrelor (4.3%) vs clopidogrel (5.6%) OR: 0.77 (95% CI: 0.63, 0.94)]; but not the clopidogrel 300 mg loading dose [cangrelor (5.8%) vs clopidogrel (6.8%) OR: 0.84 (95% CI: 0.62, 1.14)]. Significant results were shown when clopidogrel was administered before PCI start [cangrelor (4.8%) vs clopidogrel (6.0%) OR: 0.80 (95% CI: 0.64, 0.98)] but not when administered after PCI start, but with consistent effect on the OR [cangrelor (4.3%) vs clopidogrel (5.4%) OR: 0.79 (95% CI: 0.59, 1.06)].

There was a significant difference in the incidence of **ST** between cangrelor-treated patients (0.8%) and clopidogrel-treated patients (1.4%) [OR 0.62, 95% CI: 0.43, 0.90; p=0.010], in addition to the significantly lower incidence of **MI** [cangrelor-treated patients (3.8%) and clopidogrel-treated patients (4.7%) [OR 0.80, 95% CI: 0.67, 0.97; p=0.022]. No significant difference was demonstrated in the incidence of death or IDR.

Uncertainty in the knowledge about the beneficial effects

The inclusion of stent thrombosis as a separate component of the primary composite endpoint with other "harder" clinical outcome measures is debatable. This is a radiographic diagnosis that may not necessarily lead to a clinical intervention. ST included both ARC ST (definite) and intraprocedural stent thrombosis IPST. Significant results of stent thrombosis are mainly driven by the IPST, which is of questionable clinical relevance. Likewise, the measurement of PCI-related MI is questioned; it would have been better to capture all types of MIs, and analyse them separately according to their prognostic value.

The measurement of the primary endpoint at 48 hours alone is not sufficient. The study period should cover an adequate period to include efficacy and safety events that have a temporal relation to the investigated agent. Further analysis was requested to include a 30 days period.

The choice of **clopidogre**l as the active comparator for the subgroups of STEMI and NSTEMI is debatable. Prasugrel or ticagrelor may have been more valid comparators according to the current ESC guideline. Allowing the use of either 300 or 600 mg clopidogrel as a loading dose in the control group, while a fixed 600 mg was given following PCI in the cangrelor group is debatable. The SAG experts agreed that such design may have favoured cangrelor. Still it was acknowledged that there are major differences in EU regarding clopidogrel use.

The majority of **studied population** in C-PHOENIX was indicated for elective PCI (56%); 25% indicated for PCI with NSTEMI and only around 19% of the patients indicated for PCI with STEMI, which is quite limited representation. Results were only positive for the elective PCI, but not the ACS related PCI. In the general cohort no significant improvement was demonstrated in death or IDR. There is a slight numerical increase in the reported CV deaths in the cangrelor group (0.9%; 48/5462) compared to the clopidogrel group (0.8%; 46/5457; RR:1.04 95% CI:0.69-1.57).

The three CHAMPION studies shared common properties. In the current application focus is mainly given to C-PHOENIX; the value of the two other studies is limited due to the issued associated with the definitions of MI. The studies were not completed due to pre-specified futility analysis. There was also no pre-specified pooling/metanalysis planned. As such the data are only presented for descriptive purposes. Reanalysis of data from C-PCI and C-PLATFORM using the updated definition of MI generally support the results of the C-PHOENIX study.

Unfavourable effects

The overall safety of cangrelor is based on the exposure in the CHAMPION studies of 24,107 patients, of whom 12,565 were administered cangrelor. The incidence of any **AE** was comparable in the cangrelor (23.1%) and clopidogrel arms (21.9%). The most common AE was bleeding. The frequency of **SAEs** was similar in the cangrelor group and clopidogrel groups (2.2% each), with also similar frequencies reported for cardiogenic shock, ventricular fibrillation, hypotension, chest pain, coronary artery dissection. The overall incidence of **death** was lower in the cangrelor group (2.4% versus 2.6% in the clopidogrel group). The major cause of death was cardiovascular-related (1.1% and 1.2% in the cangrelor and clopidogrel groups respectively), with similar incidence reported for myocardial infarction, cardiac arrest and cardiogenic shock. In C-PHOENIX at day 30, there was a comparable rate of deaths reported in the cangrelor group (1.1%) and the clopidogrel group (1.0%). There was a slight imbalance in the reported incidence of deaths due to cardiogenic shock, MI and acute MI favouring clopidogrel. Opposite trends were shown in C-PCI and C-PLATFORM.

Patients with any **bleeding-related AE** were more frequently reported in the cangrelor group (17.9%) than the clopidogrel group (14%) due to higher rates of minor bleedings. GI bleedings were slightly more frequent in the cangrelor group (0.2%) than the clopidogrel group (0.1%). Nervous system related bleedings were also higher in the cangrelor group (0.1%) than the clopidogrel group (0). A numerically higher rate of patients with cardiac tamponade with cangrelor (n=2 of which one case was fatal in the cangrelor group versus no cases in the clopidogrel group); a warning is currently included in the SmPC. The incidence of fatal bleeding is balanced in all studies between the cangrelor and the control groups (0.1% each). The most frequently reported fatal bleeding in the cangrelor arm was in the nervous system (n=4) compared to one case reported in the control group.

Using the GUSTO bleeding scale, more bleedings were reported in the cangrelor group (17.5%) than in the clopidogrel group (13.5%); with the highest frequency reported in the mild GUSTO (16.8% vs. 13% respectively; $p<0.001$). The severe/life threatening GUSTO was comparable in both groups at 0.2%. Using the ACUITY scale, both major and minor bleedings were significantly more frequent in the cangrelor group compared to the clopidogrel group. Bleeding frequency was comparable in the treatment arms across the CAD subgroups with the GUSTO classification.

AEs reported in the different **age** groups shows comparable rates between cangrelor and the comparator, with increasing frequency by increasing age. In all reported studies, there was a numerical increase in renal-related AEs for cangrelor of 93/13,301 (0.7%) vs 64/12,861 (0.5%) in the comparator arm. There is a trend for deterioration of renal function as measured by creatinine clearance and GFR mostly in patients with baseline severe renal impairment in the cangrelor group compared to the clopidogrel group. Likewise, in such patients, there is a higher incidence of moderate GUSTO and major ACUITY bleeding rates reported.

In CHAMPION studies, **dyspnoea** was reported in 1.2% of patients in the cangrelor arm vs 0.4% in the clopidogrel arm. There were similar overall rates of **hypersensitivity** events reported with cangrelor (0.7%) vs control (0.6%) in all studies, but with a slightly higher incidence of serious cases reported with cangrelor (n=7 vs. 2 in the control group). None of these cases were fatal. Analysis of these cases could not exclude the causality of cangrelor.

Further analysis of data did not reveal AEs related to ventricular pauses or elevations of uric acids, unlike what is reported with ticagrelor.

The incidence of patients with AEs leading to **discontinuation** from the study drug in the CHAMPION studies was low and comparable in the cangrelor-treated (0.6%) and clopidogrel-treated patients (0.4%). The most frequently reported causes were coronary artery dissection/perforation and dyspnea.

Uncertainty in the knowledge about the unfavourable effects

Bleeding events were not adjudicated by a blinded committee, which is an important point to prevent bias and ensure consistency in a global trial. Using the ISTH definitions to classify bleedings would have also been preferred to the GUSTO scale currently used, as it is more universally accepted.

Balance

Importance of favourable and unfavourable effects

The mechanism of action of cangrelor as a reversible $P2Y_{12}$ receptor antagonist with a rapid onset and offset of action makes it an attractive option to currently available $P2Y_{12}$ antagonists used during PCI which take from 2-4 hours (clopidogrel) to 30 minutes (prasugrel and ticagrelor) to act with a longer duration of action after discontinuation. This is especially important in acute situations. Also, it could be an alternative when patients can not tolerate oral medication. The rapid offset of action is also advantageous in case CABG is considered necessary instead of a PCI.

In the **PCI indication**, reduction in stent thrombosis contributed to the positive results, specifically (IPST). Stent thrombosis may be a valid and acceptable endpoint in a PCI setting as also agreed by the SAG experts. It represents a serious, though relatively rare risk of the PCI intervention and should be avoided. ST was validated by an independent adjudication Committee that reviewed all angiograms recorded during the procedures.

Two recent publications adequately describe the prognostic value of IPST, even if resolved within the procedure (Brener et al 2013 and Xu et al. 2013). Also, in C-PHOENIX patients who had IPST had a worse prognosis. It can be agreed that counting IPST is valuable, but that should be separate from ST.

Using a more stringent cut-off value of enzyme elevations to define MI, further confirmation of the relevance of the positive results was obtained. There is no commonly agreed threshold for biomarker elevation, CK-MB or troponin, above which the risk for impaired outcome is evident. It is reassuring that the same trend is observed in the PHOENIX study for all different types of MI and when using different MI definitions (e.g. SCAI definition) and cut offs.

Further analysis of the dose and time of initiation of clopidogrel was submitted. Analyses by dose show comparable results, with even better results when the 600 mg dose is used. The switch dose in the cangrelor arm was consistently 600 mg, which may have favoured the results in this arm. However, the applicant explained that 90% of the events occurred during the first 2 hours after randomisation, i.e. before this dose was administered. In most of the patients clopidogrel was administered before PCI, with less than a third administered it during PCI, and almost none after PCI. These data compare favourably with those from TRITON-38 where clopidogrel was administered mostly during PCI. Results presented by time of clopidogrel administration show that superiority of cangrelor is not dependent to the timing of clopidogrel administration. Further analysis show that clopidogrel efficacy in C-PHOENIX is not compromised by later administration. The data are reassuring. The applicant presented the time of administration of clopidogrel per indication: stable angina, NSTEMI and STEMI. The results generally do not point to any trend regarding later administration of clopidogrel, which would have biased the results favouring cangrelor. In addition, considering the time of onset of action of clopidogrel (2-4 hours), it should be administered well upfront of the PCI which may not be possible in the acute setting, as also acknowledged by the SAG experts. The design of the C-PHOENIX study may have favoured cangrelor; nevertheless, the study is considered reliable and representative of current clinical practice.

Benefits are more robustly shown for for the subgroup with stable CAD, but not for STEMI and NSTEMI patients. This can be due to the limited representation of these subgroups in the study. The choice of clopidogrel as the active comparator in ACS is also not in line with the ESC guideline, but submitted utilisation data in EU show that

clopidogrel is still the major antithrombotic used in the acute setting, validating its use as the active comparator in C-PHOENIX when ticagrelor and prasugrel were not available. It was also appreciated by the SAG experts that use of ticagrelor and prasugrel in patients with ACS remains limited in some European countries, although it is increasing. Furthermore, efficacy of ticagrelor and prasugrel is based on long term efficacy data; their efficacy at 48 hours is not specifically investigated. In summary, the use of clopidogrel as a comparator in all three subgroups of patients (stable CAD, non-STEMI AND STEMI) is acceptable. Benefits was maintained at 30 days.

The value of C-PCI and C-PLATFORM studies is limited due to issues associated with the definitions of MI. Detection of peri-procedural MI in these studies depended on cardiac markers alone, also only one sample was taken before PCI, thus it was not possible to adequately distinguish elevated markers of necrosis (MI) related to the event, which triggered the PCI (non-STEMI of STEMI) from elevation due to the procedure. Reanalysis of their data using the updated definition of MI generally support the results of the C-PHOENIX study. The SAG experts considered the results of C-PCI and C-PLATFORM of relevance. In particular it was considered reassuring that the numerically higher mortality observed in one trial (PHOENIX) is not observed in the other trials.

Exposure to support safety in the PCI indication is adequate as it is based on a wide database from the C-PHOENIX supported by that from C-PCI and C-PLATFORM. The most common AE is bleeding which is expected in such studies. The somewhat higher bleeding rate reported in the cangrelor group compared to clopidogrel is to be anticipated, considering the superiority in efficacy A significant increase in ACUITY MAJOR bleeding was noticed in the ACS subgroup, but this was mainly driven by haematoma $\geq$ 5 cm at the puncture site. This is reassuring. Data at 30 days are not conclusive; in C-PHOENIX a slight increase in total mortality, especially deaths related to cardiogenic shock, MI and AMI is shown in the cangrelor arm while an opposite trend is shown in both P-PCI and P-PLATFORM. It is difficult to draw any robust conclusions as the data is inconsistent and is not supported by significant results but only occasional trends. Also a direct causal pathway denoting lack of efficacy or an associated risk can not be always detected.

Submitted analysis of net clinical benefit shows that the results are in favour of a benefit for cangrelor.

Benefit-risk balance

In the PCI indication, significant benefit is shown in the whole cohort and in the subgroup of stable CAD. The benefit in the ACS patients (STEMI and non-STEMI) is less clearly defined.

During the assessment, the applicant proposed to restrict the indication of PCI to patients for whom oral $P2Y_{12}$ inhibitors is not feasible or desirable. These may include 1) patients in the acute phase of cardiovascular illness who may experience reduced bioavailability consequent to nausea, use of opiates or impaired gastrointestinal perfusion resulting in reduced absorption, 2) patients presenting with an unclear aetiology of chest pain and where early administration of a long acting $P2Y_{12}$ inhibitor may increase clinical risk (ie, aortic dissection, aortic rupture, oesophageal tear, pericarditis, 3) patients referred for angiography and possible PCI who have a likelihood of requiring urgent or emergent coronary artery bypass graft (CABG) surgery, and 4) patients requiring PCI while also suffering an active concomitant underlying condition that may require urgent surgery that would be delayed by long acting $P2Y_{12}$ inhibitors (i.e., hip fracture complicated by unstable angina, NSTEMI or even STEMI.

Following discussion and advice received from the SAG experts, cangrelor was further restricted to patients who have not been pre-treated with $P2Y_{12}$ inhibitors, reflecting the CHAMPION PHOENIX patient population (naïve to $P2Y_{12}$ inhibitors 7 days prior to randomisation).

With these restrictions, the benefit risk of cangrelor is considered to be positive.

Discussion on the benefit-risk assessment

Initial assessment of cangrelor in PCI was hampered by the chosen endpoints, the choice of the comparator and the duration of the study. Another issue are the implications of the other two studies (C-PCI and C-PLATFORM) that were discontinued prematurely due to reasons of futility.

The above limitations precluded positioning cangrelor as an alternative to the current oral $P2Y_{12}$ inhibitors. However, the proposed restriction of the indication to patients who were not or can not be administered oral $P2Y_{12}$ inhibitors, adequately positions cangrelor in clinical practice. If a patient has not been pre-treated with $P2Y_{12}$ inhibitors and requires immediate PCI intervention, this patient could be eligible for cangrelor therapy, whether suffering from stable or non stable CAD. The most critical element in the decision of therapy would be the need to start $P2Y_{12}$ inhibition immediately as in situations where an ad hoc PCI would be considered in patients who have not yet received double anti-platelet therapy. In addition, the IV administration is considered useful in patients who cannot swallow (e.g. intubated) or who are vomiting. The fast offset of action is also considered useful in order to manage major bleeding if such would occur during the procedure and to terminate platelet inhibition in patients who are referred for immediate surgery, although this will be very rare. In all other PCI, oral $P2Y_{12}$ inhibitors should constitute the first line choice in patients undergoing PCI due to the robust evidence of their B/R, also documented in the relevant ESC guideline.

Conclusion

The overall B/R of cangrelor in the revised indication is positive.

4. Recommendations

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by majority decision that the risk-benefit balance of Kengrexal, is favourable in the indication*, "co-administered with acetylsalicylic acid (ASA), for the reduction of thrombotic cardiovascular events in adult patients with coronary artery disease undergoing percutaneous coronary intervention (PCI) who have not received an oral $P2Y_{12}$ inhibitor prior to the PCI procedure and in whom oral therapy with $P2Y_{12}$ inhibitors is not feasible or desirable."*
and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**
  Not applicable

- **Obligation to complete post-authorisation measures>**

  Not applicable

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

These conditions fully reflect the advice received from the PRAC.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that cangrelor is qualified as a new active substance.

APPENDIX

DIVERGENT POSITION

The undersigned member(s) of the CHMP did not agree with the CHMP's positive opinion recommending the granting of the marketing authorisation of Kengrexal indicated as follows:

Kengrexal, co-administered with acetylsalicylic acid (ASA), is indicated for the reduction of thrombotic cardiovascular events in adult patients with coronary artery disease undergoing percutaneous coronary intervention (PCI) who have not received an oral $P2Y_{12}$ inhibitor prior to the PCI procedure and in whom oral therapy with $P2Y_{12}$ inhibitors is not feasible or desirable.

The overall benefit-risk balance for Kengrexal in the claimed indication is considered negative based on the following :

This application is based on three pivotal studies (CHAMPION PCI, CHAMPION PLATFORM and CHAMPION PHOENIX). Two of the studies were statistically negative.

The benefit observed in the only positive study (CHAMPION PHOENIX) was obtained at the expenses of 1) Myocarcial Infaction which were diagnosed mainly based on biochemical markers and 2) intraprocedural stent thrombosis.

The marginal benefit observed in the CHAMPION PHOENIX study need to be counterbalanced by a clear increase in major bleeding in cangrelor arm.
The narrow major bleeding definition used in the cangrelor clinical development (GUSTO severe/life-threatening definition) compared to the ACUITY definition may have play a role favor to this new compound.

Recent studies have shown that post procedural bleeding has an important prognostic role that is at least not inferior to that shown for post-procedural myocardial infarction [Mehran et al. Eur Heart J 2009;30:1457-66; Ndrepepa et al. J Am Coll Cardiol 2008;51:690-7].

In addition, ACS patients, who will be the main target of cangrelor in standard practice, were very limited and not adequately represented in the study.
There are other issues with regards to the study design of CHAMPION PHOENIX that need consideration in particular, whether the comparator clopidogrel and its dosing where appropriate, may be debatable. The lack of comparison data with prasugrel or ticagrelor remains an issue.

In this study, the lack of net clinical benefit is also reflected in the lack of trend in benefit with respect to all-cause mortality.

London, 22 January 2015

……..……

Conception Prieto