

RISK MANAGEMENT PLAN CANGRELOR (Kengrexal[®])

RMP Version Number: 5.2

Data Lock Point for this RMP: 30 Oct 2022

EU Risk Management Plan for Kengrexal (CANGRELOR)

RMP version to be assessed as part of this application:

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Rationale for submitting an updated RMP:

- Updates in the Additional Pharmacovigilance Activities by removing ARCANGELO-PASS study (Final Report submitted).
- Changes and updates per the recommendation of PRAC Rapporteur in Type II variation assessment report.

Summary of significant changes in this RMP:

- Changes in the Additional Pharmacovigilance Activities section (Part III, Section III.2).
- Changes related to the Post-Authorisation Safety Study ARCANGELO in Part III.2, Part III.3, Part V.3, Part VI II.B and II.C.2, Annex 2, Annex 3.
- Removal of the following from the safety concerns as advised by PRAC Rapporteur in Type II variation assessment report:
 - *Important potential risks:* Inadequate antiplatelet effect of clopidogrel or prasugrel caused by the mistiming of the cangrelor transition to thienopyridines.
 - *Missing information:* Use of cangrelor in the paediatric population (<18 years of age); Use of cangrelor in patients with increased risk of bleeding (e.g. history of gastrointestinal bleeding, major surgery within 30 days, clinically relevant thrombocytopaenia or anaemia and patients affected by cerebral arteriovenous malformation); Use of ticagrelor and prasugrel before, during and after the cangrelor infusion.
- Removal of Specific adverse drug reaction follow-up questionnaires for Thrombotic Events.
- Changes related to the removal of safety concerns in Part II Module SVII, SVIII, Part III.1, Part V.1 and V.3, Part VI II.A and II.B, Annex 4.

Other RMP versions under evaluation: Not applicable

Details of the currently approved RMP:

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LIST OF ABBREVIATIONS

ACS	acute coronary syndrome
ACS-I	first Euro Heart Survey of patients with ACS
ACS-II	second Euro Heart Survey of patients with ACS
ACUITY	Acute Catheterization and Urgent Intervention Triage Strategy
ADP	adenosine diphosphate
ADR	adverse drug reactions
AE	adverse event(s)
ALT	alanine aminotransferase
ASA	acetylsalicylic acid
AST	aspartate aminotransferase
AVM	arteriovenous malformation
BARC	Bleeding Academic Research Consortium
BMI	body mass index
bpm	beats per minute
CABG	coronary artery bypass graft
CAD	coronary artery disease
CI	confidence interval
CNS	central nervous system
cm	centimetre(s)
C _{max}	maximum concentration
CVD	coronary vascular disease
dL	decilitre
ECG	electrocardiogram(s)
EEA	European Economic Area
eGFR	estimated glomerular filtration rate
EPAR	European Public Assessment Report
EU	European Union
GFR	glomerular filtration rate
GPI	glycoprotein IIb/IIIa receptor inhibitor
GUSTO	Global Use of Strategies to Open Occluded Arteries
H	hour(s)
HDL	high-density lipoprotein

IABP	intra-aortic balloon pump
IBD	International birthday
ICH	intracranial haemorrhage
IDR	ischaemia-driven revascularisation
IHD	ischaemic heart disease
INR	international normalised ratio
IV	intravenous
kg	kilogram(s)
L	litre(s)
LDL	Low-density lipoprotein
MACE	Major Adverse Cardiovascular Events
Max	maximum
mcg	microgram(s)
µg	microgram(s)
µM	micrometre(s)
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram(s)
MI	myocardial infarction
min	minute(s)
Min	minimum
mL	millilitre(s)
NA	not applicable
NNH	number needed to harm
NOAEL	no observed adverse effect level
NSTE-ACS	non-ST-elevation acute coronary syndrome
NSTEMI	non-ST-segment elevation myocardial infarction
OR	odds ratio
PCI	percutaneous coronary intervention
PD	pharmacodynamic(s)
PhV	pharmacovigilance
PK	pharmacokinetic(s)
PL	package leaflet
PSUR	Periodic Safety Update Report
PTCA	percutaneous transluminal coronary angioplasty

SA	stable angina
SmPC	Summary of Product Characteristics
ST	stent thrombosis
UA	unstable angina

Part I: Products Overview

Table Part I.1 - Product Overview

Active substance (s) (INN or common name)	Cangrelor
Pharmacotherapeutic group (s) (ATC Code)	Platelet aggregation inhibitors excluding heparin (B01AC25)
Marketing Authorisation Holder	Chiesi Farmaceutici S.p.A.
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Kengrexal 50 mg powder for concentrate for solution for injection/infusion
Marketing Authorisation procedure	Centralised
Brief description of the product	Chemical class Cangrelor is a novel, intravenous (IV), direct-acting, P2Y₁₂ receptor inhibitor that blocks adenosine diphosphate (ADP)-induced platelet activation and aggregation. Cangrelor is a synthetic substance manufactured using synthetic processes.
Hyperlink to the Product Information	Kengrexal European Medicines Agency (europa.eu)
Indication(s) in the EEA	Current: 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 P2Y₁₂ inhibitor prior to the PCI procedure and in whom oral therapy with P2Y₁₂ inhibitors is not feasible or desirable. Proposed: Not applicable

Dosage in the EEA	Current: <u>Posology</u> The recommended dosage of cangrelor is a 30 mcg/kg IV bolus followed immediately by a 4 mcg/kg/min IV infusion. Initiate the bolus infusion prior to PCI. The maintenance infusion should ordinarily be continued for at least 2 hours or for the duration of PCI, whichever is longer. At the discretion of the physician, the infusion may be continued for a total duration of up to four hours. Patients should be transitioned to oral P2Y12 therapy for chronic treatment. For transition, a loading dose of oral P2Y12 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. <u>Method of administration</u> Cangrelor is intended for intravenous use, only after reconstitution and dilution. Cangrelor should be administered via a dedicated intravenous line. Administer the bolus volume rapidly (<1 minute), from the diluted bag via manual intravenous push or pump. Ensure the bolus is completely administered before the start of PCI. Start the infusion immediately after administration of the bolus. Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: Powder for concentrate for solution for injection / infusion. White to off-white lyophilised powder. Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety Specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

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 P2Y12 inhibitor prior to the PCI procedure and in whom oral therapy with P2Y12 inhibitors is not feasible or desirable.

Incidence and prevalence

Coronary heart disease is one of the most common causes of death worldwide. In Europe and other industrialised countries, it is the leading cause of death among men and women. Approximately 2.5 to 3 million patients are admitted annually with ACS to hospitals in the European Union (EU) and the United States of America (USA).

ACS is a major health problem in industrialised and increasingly in non-industrialised countries and represents a significant number of hospitalisations annually in Europe. In the second Euro Heart ACS Survey ^[1] conducted in 190 medical centres from 32 European countries the in-hospital and 30-day mortality rates for patients presenting with STEMI were 5.3% and 6.4%, respectively. For patients presenting with NSTEMI, in-hospital and 30-day mortality rates were 2.5% and 3.4%, respectively.

Demographics of the population in the authorised indication

The incidence of CAD increases with age, with a higher incidence among men until the age of 70. Many studies have found gender-related differences in the presentations, prevalence, and clinical outcomes of CAD ^{[2][3][4]}. Coronary artery disease first presents itself in women approximately 10 years later than in men, most commonly after menopause ^[5]. The worldwide INTERHEART study, a large study of more than 52000 individuals with MI, first demonstrated that this approximate 8 to 10-year difference in age at onset holds widely around the world, across various socioeconomic, climatic, and cultural environments. Although CAD in general is manifested earlier in less developed countries, the age gap in time of onset between men and women is universal ^[6]. Women who are 15 years post menopause are equally likely as men to develop CAD. About 90% of patients with coronary heart disease report at least one of the major risk factors, including cigarette smoking, dyslipidaemia, hypertension, and diabetes.

Baseline demographic data from the second Euro Heart Survey on ACS in 2004 (ACS-II) involving 6385 European patients with a final diagnosis of ACS are shown in [Table 1](#), with data from the first Euro Heart Survey on ACS in 2000-2001 (ACS-I) for comparison.

Table 1: Baseline, demographic, and clinical characteristics of ACS-I and ACS-II patients on the basis of the initial electrocardiographic pattern

	ST-elevation		No ST-elevation	
	ACS-I (n = 4431)	ACS-II (n = 3004)	ACS-I (n = 5367)	ACS-II (n = 3063)
Age (years)	63.4±13.0	62.5±13.1	65.8±12.0	66.1±12.1
Male gender (%)	71.6	74.1	64.4	67.0
BMI (mean)	27.0±4.1	27.0±4.3	27.4±4.4	27.4±4.8
Prior MI (%)	22.3	15.7	35.6	29.3
Prior PCI/CABG (%)	9.5	8.9	22.2	21.5
Diabetes mellitus (%)	21.1	21.4	23.5	26.7
Current smoker	42.8	45.6	27.0	28.0
Past smokers	20.3	22.6	26.8	29.8
Hypertension (%)	51.6	50.0	63.5	64.6
Hyperlipidaemia (%)	46.8	43.2	54.6	51.9
Family history of CAD (%)	27.4	29.8	29.3	32.6
Prior stroke/TIA (%)	5.9	5.2	8.1	7.3
Renal failure (%)	3.4	3.8	5.8	7.1
Heart rate (mean bpm)	79±20	78±19	79±19	79±20
Killip Class II, III, IV (%)	22.7	20.4	16.1	19.7

Source: Table 1 ^[1].

Continuous variables are presented as mean ± SD. ACS = acute coronary syndromes; BMI = body mass index; bpm = beats per minute; CABG = coronary artery bypass graft (surgery); CAD = coronary artery disease.

MI = myocardial infarction; PCI = percutaneous coronary intervention; SD = standard deviation; TIA = transient ischaemic attack.

These data provide a comparison between the first survey in 2000 and the second in 2004. Within both surveys, a considerable degree of similarity is shown with respect to mean age (65.2 in ACS-I vs 64.7 in ACS-II), and the proportion of men affected (67.5% in ACS-I vs 70.1% in ACS-II) ^[1].

There are estimated to be 87 distinct ethnic groups residing in Europe, of which 33 form the majority population in at least one sovereign state, while the remaining 54 constitute ethnic minorities. The total number of national minority populations in Europe is estimated at 105 million people, or 14% of 770 million Europeans ^[7].

It is clear that each population group, either that determined by religion or ethnicity, has differences in terms of illness behaviour, seeking assistance with health matters, and beliefs about illness.

Furthermore, some diseases are more prevalent in certain ethnic groups – or example, cardiovascular-related illnesses are more prevalent in men from the Indian subcontinent. Migrants of South Asian descent worldwide have elevated risks of morbid and mortal events due to ischaemic heart disease (IHD) ^[8].

In the United Kingdom (UK), mortality from IHD in both South Asian men and women is 1.5 times that of the general population, and South Asians have not benefited to the same extent from the general decline in deaths caused by IHD over the last few decades ^[9]. These ethnic differences are greatest in the youngest age groups. These ethnic differences have been extensively studied, and while classical risk factors, such as smoking, blood pressure, obesity, and cholesterol vary substantially between subgroups of South Asians—such that in some

cases, levels are equivalent to, or lower than, a comparable European population—levels of glucose intolerance, central obesity (as measured by waist to hip ratio), fasting triglyceride, and insulin are uniformly elevated compared to Europeans^[8].

Risk factors for the disease

Well-established risk factors are associated with the development of CAD and ACS. Non-modifiable factors influencing risk include age, gender, family history, and race/ethnicity.

Age is the most powerful independent predictor for the development of ACS. Men are at greater risk than women; men older than age 45, women older than age 55, and anyone with a first-degree male or female relative who developed CAD before age 55 or 65, respectively, are also at increased risk.

Modifiable risk factors include elevated levels of serum cholesterol, low-density lipoprotein cholesterol, and triglycerides; lower levels of high-density lipoprotein cholesterol; and the presence of Type 2 diabetes, cigarette smoking, obesity, a sedentary lifestyle, and hypertension.

The main existing treatment options

ACS is an unstable coronary condition prone to ischaemic recurrences and other complications that may lead to death or MI in the short and long term. The management of ACS patients, which includes anti-ischaemic and antithrombotic pharmacological treatments as well as various strategies for coronary revascularisation, is directed at preventing or reducing complications and to improving outcomes.

The timing and intensity of interventions are tailored to an individual patient's risk. Early invasive strategies in moderate- and high-risk patients consist of angiography followed by PCI (with stent implantation), coronary artery bypass graft (CABG) surgery, or medical management. Those strategies result in improved event-free survival compared to conservative care and are recommended by the European Society of Cardiology^{[10] [11] [12]} and the American College of Cardiology/American Heart Association^{[13] [14] [15]}.

Revascularisation for NSTEMI- and STEMI-ACS relieves symptoms, shortens hospital stay, and improves prognosis. The indications and timing for myocardial revascularisation and choice of preferred approach (PCI or CABG) depend on many factors including the patient's condition, the presence of risk features, comorbidities, and the extent and severity of the lesions as identified by coronary angiography.

Worldwide, more than 2.5 million patients undergo PCI each year including more than 700,000 patients in both the USA and in the EU^[16] and 900,000 patients in total for the Asia Pacific region^{[17] [18] [19]}. PCI is used extensively to treat patients with stable and unstable CAD. Despite important advancements in PCI techniques, ischaemic complications of PCI are well characterised and include death, MI, stent thrombosis (ST), and the need for urgent repeat revascularisation. Thrombosis associated with vessel injury resulting from spontaneous or mechanical disruption of atherosclerotic plaque is a common pathogenic mechanism of these complications^[20]. Additionally, in catheter procedures and with placement of intracoronary devices, platelet deposition and stimulation of thrombosis can occur. Before and during the PCI procedure, pharmacologic antithrombotic regimens consist of an anticoagulant, aspirin, and an oral P2Y₁₂ inhibitor.

For patients with moderate- or high-risk CAD, an invasive approach requiring PCI, dual antiplatelet therapy (aspirin and an ADP receptor blocker)^[21] and concomitant antithrombotic therapy (bivalirudin, and unfractionated or low molecular weight heparin) is recommended^[11].

Other than aspirin, pharmacological antiplatelet therapy may include clopidogrel, prasugrel, or ticagrelor. In patients who receive dual antiplatelet therapy, glycoprotein IIb/IIIa receptor antagonists (abciximab, eptifibatide, tirofiban) are also recommended as bail out therapy for high-risk patients undergoing PCI^[11].

The choice of combination of oral antiplatelet agents, a glycoprotein IIb/IIIa receptor inhibitor (GPI), and anticoagulants is made in relation to the risk of ischaemic and bleeding event^{[22] [23]}.

In addition to antithrombotic and antiplatelet therapy, pharmacological anti-ischaemic therapy may include nitrates, calcium channel blockers, and beta blockers. Morphine is prescribed as an analgesic.

Comorbidities including hypertension, hypercholesterolemia and diabetes mellitus are common in patients with CAD and often require additional medical management^[24].

Management of hypertension in patients with CAD is exceedingly important. Control of blood pressure reduces myocardial oxygen consumption and thereby reduces angina, and it also lowers the incidence of cardiovascular events. Beta blockers devoid of intrinsic sympathomimetic activity represent first-line antihypertensive therapy for patients with a history of MI or CAD with angina. Angiotensin-converting enzyme inhibitors are indicated for all patients with diabetes mellitus or a history of MI with impaired left ventricular systolic function. Calcium channel blockers are useful for patients with hypertension and angina despite maximum tolerable administration of beta blockers.

Guidelines have recommended a low-density lipoprotein (LDL) cholesterol level <70 mg/dL for all patients with coronary artery or other atherosclerotic disease. Patients whose LDL levels are >100 mg/dL should start pharmaceutical therapy. 3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are the recommended first-line agents for patients who have CAD and elevated total and LDL cholesterol levels. Guidelines also recommend a target high-density lipoprotein (HDL) cholesterol level >45 mg/dL for men with CAD and >55 mg/dL for women.

Diabetic patients with CAD have a particularly high risk for recurrent cardiovascular events, and they should be targeted for aggressive risk-factor modification. Recommendations include enhanced blood glucose control and monitoring with a haemoglobin A1c level lower than 7%.

Current guidelines for patients with CAD recommend medical management and/or intervention, depending on severity and patient risk^{[24] [11]}.

Natural history of the indicated condition in the target population, including mortality and morbidity

Atherosclerosis is the primary underlying condition associated with coronary artery disease (CAD)^[25]. Atherosclerosis is a progressive disease that affects nearly all individuals in the developed world and is considered one of the primary causes of death in Europe^[26].

Atherosclerosis progresses from initial intimal thickening to development of more advanced plaque lesions in adulthood. Atherosclerotic plaques can remain stable or become vulnerable to rupture, leading to platelet activation and aggregation, and subsequent activation of the coagulation pathway culminating in coronary intraluminal thrombosis and variable degrees of vascular occlusion.

Stable coronary disease can be treated with PCI if the atherosclerotic plaque becomes occlusive (even without rupture). In some cases, stable coronary vascular disease (CVD) may result in acute coronary syndrome (ACS) in the absence of plaque rupture and thrombosis when physiological stress (e.g., trauma, blood loss, anaemia, infection, tachyarrhythmias) increases demands on the heart^[25]. ACS refers to a spectrum of clinical presentations ranging from unstable angina (UA); (i.e., ACS without release of biomarkers of myocardial

necrosis) to non–ST-segment elevation myocardial infarction (NSTEMI) and to ST-segment elevation myocardial infarction (STEMI)^[25].

Coronary plaque rupture is responsible for approximately 75% of coronary vessel thrombi that lead to myocardial infarction (MI) and/or death in ACS^[26].

Coronary artery disease is the single most common cause of death in Europe: accounting for 1.8 million deaths in Europe each year. Over one in five women (22%) and one in five men (20%) die from the disease. Coronary artery disease is also the single most common cause of death in the EU, accounting for over 681,000 deaths in the EU each year: 15% of deaths among men, and 13% of deaths among women^[27].

Coronary artery disease remains the main cause of death for women in all 27 countries of the EU and it is the main cause of death for men in all these countries except France, the Netherlands, Slovenia, and Spain. For men living in EU countries CVD causes between 60% (Bulgaria) and 25% (France) of deaths, and for women between 70% (Bulgaria) and 30% (France and the Netherlands) of deaths^[27].

Over the past 30 years death rates from CAD have been consistently falling in most Northern and Western European countries, however trends in Central and Eastern European countries have been mixed, including relative stability in some places (e.g., Bulgaria) and rapid increases in other countries including Ukraine and Belarus. Since around 2000 to 2005, however, rates are now also falling in the majority of Central and Eastern European countries. Between 1999 and 2009, death rates for men aged under 65 living in Iceland and the Netherlands fell by 57% and 55% respectively, while in countries such as Ukraine, the Russian Federation and Lithuania, small decreases in death rates for that decade overall (up to 10% decreases from 1999 rates) hide a pattern of steep increases until the mid-2000s, followed by equally steep falls in recent years. Among women, Estonia recorded a remarkable decrease of 60% in death rates from CAD between 1999 and 2009, while the Netherlands and Norway showed a halving of rates over the same period. Only in Lithuania and Kyrgyzstan were death rates from CAD for women higher in 2009 than in 1999^[27].

Important co-morbidities

Comorbidities are an important factor in the progression of CAD. Conventional risk factors for the development of CAD include hypertension, hypercholesterolaemia, diabetes, sedentary lifestyle, obesity, smoking, and a family history of CAD, and have an adverse influence on prognosis in those with established disease, presumably through their effect on the progression of atherosclerotic disease processes. However, appropriate treatment can reduce these risks. In general, the outcome is worse in patients with reduced left ventricular ejection fraction and heart failure, a greater number of diseased vessels, more proximal locations of coronary stenosis, greater severity of lesions, more extensive ischaemia, more impaired functional capacity, older age, significant depression, and more severe angina^[24]. An elevated resting heart rate is also indicative of a worse prognosis in those with suspected or proven CAD.

Part II: Module SII - Non-clinical part of the safety specification

The toxicity profile of cangrelor has been investigated in mice, rats, and dogs, and utilised single-dose, seven-day, and one-month continuous intravenous (IV) dosing regimens.

The reproductive toxicity of cangrelor has been investigated in a series of fertility and embryo-foetal development studies in rats and rabbits.

The genotoxicity of cangrelor has been investigated in a standard battery of in vitro and in vivo assays.

Cangrelor is not intended for long-term administration and therefore no studies of long-term carcinogenic potential have been conducted.

The exposure safety margins at the no observed adverse effect level (NOAEL) doses in the pivotal toxicity studies range from 34- to 103-fold for cangrelor. The safety margins are several-fold higher with regard to exposure at doses that were not associated with histological changes to kidney and urinary tracts. In rats and dogs, there were no histological changes at doses of 12 µg/kg/min and 15 µg/kg/min, respectively, which are associated with safety margins ranging from 140- to 229-fold. Importantly, these safety margins are based on exposures generated from repeat-dose studies of one-month duration, which are considerably longer than the acute exposures anticipated for humans in the PCI setting.

Non-clinical toxicology findings

The results of single- and repeat-dose toxicity studies in rats and dogs indicate that the kidney and urinary tract are the principal target tissues associated with cangrelor administration. The safety margins for the renal toxicity associated with administration of single doses of cangrelor are greater than 1000-fold based on extrapolated exposures and the safety margins associated with the renal and urinary tract toxicity following repeat administration of lower doses of cangrelor range from 13- to 21-fold.

Investigative studies in rats established that cangrelor-related renal toxicity is essentially of two types distinguished by absolute exposure and duration of exposure. The predominant lesions associated with single bolus IV infusion of high doses (200 mg/kg) of cangrelor are cortical tubular changes and the predominant lesions observed following continuous IV infusion of lower doses (48 µg/kg/min) cangrelor for 7-28 days are inflammation-based and involve the renal pelvis and ureter. Investigative studies showed that the inflammatory lesions associated with lower doses occur after 7-28 days of repeat administration, are reversible, and are not associated with the primary human urinary metabolite.

Liver enzyme (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) changes have been documented consistently in all animal species investigated. In rats these changes were reversible following cessation of treatment. There is no clear association of these changes with organ damage in rats and dogs, although liver changes noted in rabbits may be associated with the compound. Notably, the plasma concentration of cangrelor observed in rabbits is considerably higher, dose for dose, than in rats and dogs.

Non-clinical data pertaining to reproductive and developmental toxicity

Reproductive toxicity - cangrelor produced dose-related foetal growth retardation characterised by increased incidences of incomplete ossification and unossified hind limb metatarsals in rats. In rabbits, cangrelor was associated with increased incidences of abortion and intrauterine losses, as well as foetal growth retardation at higher doses which may have been secondary to maternal toxicity. Cangrelor did not produce malformations in either the rat or rabbit reproductive studies.

Impairment of Fertility

Fertility – the effects on fertility, the ability to produce a pregnancy with female partner(s), sperm morphology and sperm motility were observed in the male rat fertility study when cangrelor was administered at 48 µg/kg/min. These effects were not apparent at lower doses (3 and 12 µg/kg/min) and were reversible following cessation of dosing. In this study, semen analysis was conducted after eight weeks of continuous treatment. In a one-month toxicity study in rats, semen analysis conducted after four weeks of treatment had shown no abnormalities. Together, these studies indicate that the observed effects are produced only after prolonged continuous dosing of cangrelor (greater than four weeks) and that the effects are reversible.

Female fertility parameters (oestrous cycles, mating performance, preimplantation losses) were unaffected by cangrelor at doses up to 12 µg/kg/min. There was a statistically significant decrease in mean % post-implantation survival of embryos in animals in the 48 µg/kg/min dose group which could have been secondary to maternal toxicity, although a direct effect on the embryo cannot be ruled out.

Non-clinical data pertaining to mutagenicity and genotoxicity

Neither cangrelor nor its metabolites were mutagenic in the Ames or Mouse Lymphoma L5178Y cell assays. Cangrelor was not clastogenic when tested for its ability to induce chromosomal aberrations in human peripheral blood lymphocytes in vitro, nor was it genotoxic in the mouse micronucleus test.

Non-clinical pharmacologic findings

Cangrelor produced no apparent adverse pharmacological effects in any organ system that indicative of a clinical safety concern. Cangrelor did not affect adenosine uptake into erythrocytes. There was no indication of an increased risk of bleeding in any of the general safety and toxicity studies conducted in the nonclinical program.

Safety pharmacology studies indicated cangrelor induced transient hypothermia, which is an expected class effect associated with administration of adenosine and adenosine analogues. In addition, cangrelor exhibited central nervous system (CNS) effects involving motor coordination and respiration in conscious mice, but there is a greater than 50-fold safety margin when compared to therapeutic doses on a mg/mm² basis.

Cardiovascular System

There were no treatment-related effects of cangrelor on the cardiovascular or respiratory systems in anaesthetised rats. In addition, there were no effects on cardiovascular parameters or the autonomic nervous system in anaesthetised cats. Telemetry studies show that cangrelor does not have any adverse effects on haemodynamic and cardiovascular parameters including QRS and QT intervals in anaesthetised dogs.

Nervous System

Adverse effects on the CNS were observed with cangrelor in a modified Irwin test when administered to mice at supratherapeutic doses. Effects were only observed at dose levels considered sufficiently in excess of human exposure (>50-fold safety margin on a mg/mm² basis).

Non-clinical data pertaining to drug interactions

The potential of cangrelor and the major metabolites, AR-C69712MX and AR-C90439XX, to inhibit individual cytochrome P450 (CYP) isozymes was evaluated in vitro [SC-102858-1]. Cangrelor did not inhibit any CYP studied: IC₅₀ >100 µM for CP1A2, 2A6, 2C9, 2D6, 2E1, or 3A4; IC₅₀ >50 µM

for CYP 2C1. Metabolites AR-C69712XX and AR-C90439XX showed potential to inhibit one isoform, CYP2C19, at high concentrations with IC₅₀s of 58 and 59 μ M, respectively.

The potential interaction between cangrelor and standard therapy with aspirin (A), heparin (H), and GTN (N) was evaluated [Study SC-30178]. The pharmacodynamics (PD) effects of cangrelor were not altered on a background of A/H/N. There was no evidence that the primary effects of any component of standard triple therapy were affected by cangrelor.

In view of its PK properties, the effects of cangrelor and its metabolites are likely to be rapidly reversible on slowing or stopping the infusion. No interactions are expected with regularly used cardiovascular, antihypertensive, lipid lowering, antihyperglycemic, or antithrombotic drugs.

Other toxicity-related information or data

ADME - Steady state levels of cangrelor are achieved rapidly after administration, and importantly, 90% of the dose is cleared from plasma within minutes after cessation of treatment. These characteristics of cangrelor are consistent with a drug designed to have a short duration of action. In addition, cangrelor is not incorporated into macromolecules and is eliminated by rapid, complete metabolism to inactive metabolites with the majority of an administered dose excreted within 24 hours.

Tissue distribution studies in rats showed a rapid decrease in exposure such that by six hours post dose, radiolabel in these tissues including liver was close to background levels.

Conclusions on non-clinical data

Steady state levels of cangrelor are achieved rapidly after administration, and importantly, 90% of the dose is cleared from plasma within minutes after cessation of treatment. These characteristics of cangrelor are consistent with a drug designed to have a short duration of action. In addition, cangrelor is not incorporated into macromolecules and is eliminated by rapid, complete metabolism to inactive metabolites with the majority of an administered dose excreted within 24 hours.

The nonclinical data support the use of cangrelor in the proposed PCI indication.

There are no safety concerns that have not been adequately addressed by clinical data.

Part II: Module SIII – Clinical trials exposure

SIII.1 Brief overview of development

The goal of the cangrelor clinical development plan was to demonstrate that rapid and reversible platelet inhibition with cangrelor in the acute care setting improves ischaemic outcomes in patients with CAD while maintaining an acceptable safety profile.

The study populations evaluated in the clinical development program included:

- Patients with CAD, from SA to ACS who required P2Y₁₂ inhibition while undergoing PCI who were investigated in three Phase III studies (CHAMPION program)
- The complete clinical development program includes 20 clinical studies (eight Phase I studies, nine Phase II studies and three Phase III studies) and 13,340 cangrelor-treated subjects. A summary of the pivotal studies is provided in [Table 2](#).

Table 2: Cangrelor development programme

Study	Study Number	Patient Population	N=ITT	Cangrelor Infusion Dose	Dose duration (hour) ^d	Comparator
CHAMPION PHOENIX	TMC-CAN-10-01	ACS/CAD undergoing PCI	11,145	(30 µg/kg bolus) 4 µg/kg/min	2.15 (0.02- 6.17)	Clopidogrel 600 or 300 mg ^a
CHAMPION PLATFORM	TMC-CAN-05-03	ACS/CAD undergoing PCI	5,362	(30 µg/kg bolus) 4 µg/kg/min	2.05 (0.02-8.18)	Clopidogrel 600 mg ^b
CHAMPION PCI	TMC-CAN-05-02	ACS/CAD undergoing PCI	8,877	(30 µg/kg bolus) 4 µg/kg/min	2.05 (0.07- 5.25)	Clopidogrel 600 mg ^c

Sources: TMC-CAN-05-02: Table 1.1 and Table 3.1.2.3; TMC-CAN-05-03: Table 1.1 and Table 3.1.4.1; TMC-CAN- 10-01: Table 1.1 and Table 3.1.4.1.

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

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

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

^c All patients randomised to the comparator arm received clopidogrel 600 mg at the time of PCI.

^d Median (min – max)

SIII.2 Clinical trial exposure

In order to characterise the safety profile of cangrelor in patients with CAD undergoing PCI a grouping algorithm for summary presentation of data was developed. The pooling strategy for the cangrelor safety population is as follows:

- **CHAMPION studies (3)**, providing a complete pooled safety dataset in all studies comparing cangrelor versus clopidogrel in 25,107 CAD patients (12,565 cangrelor-treated) undergoing PCI.
- **All studies (21)**, providing the entire pooled safety dataset in 26,201 patients (13,340 cangrelor-exposed) across all patient populations, regardless of dose and duration of therapy.

Studies Supporting the Safety of Cangrelor in the PCI Indication

Three Phase III Studies - CHAMPION PHOENIX, PLATFORM, and PCI: The CHAMPION programme was designed to demonstrate that a rapid and potent platelet inhibition strategy with cangrelor at the time of PCI is superior to a loading dose of clopidogrel in preventing thrombotic events, without causing excessive bleeding. This programme was composed of three adequate and well-controlled studies, CHAMPION PHOENIX [TMC-CAN-10-01], CHAMPION PLATFORM [TMC-CAN-05-03] and CHAMPION PCI [TMC-CAN-05-02]. The CHAMPION PHOENIX trial confirmed that P2Y₁₂ inhibition with IV cangrelor at the time of PCI, compared to clopidogrel, significantly reduced the incidence of thrombotic events (including ST) in patients undergoing PCI. The pivotal safety analyses for cangrelor are based on the three pooled Phase III CHAMPION studies (N=12,565 cangrelor; 25,107 all CAD patients undergoing PCI). The study population was consistent between all three trials and included all types of patients with CAD, from those with SA to ACS, including patients with prior stents.

Clinical Trial Exposure

Clinical trial exposure is derived from twenty-one (21) clinical studies of cangrelor that comprise the clinical programme. In these trials, cangrelor was administered as a bolus dose plus continuous IV infusion or a continuous IV infusion alone. In order to characterise the safety profile of cangrelor in patients with CAD, a grouping algorithm for summary presentation of data was developed. In the cangrelor development programme patients/subjects were treated with at least one dose of cangrelor across a range of cumulative doses and included healthy subjects, renally-impaired patients, and CAD patients that provided a complete analysis of the overall safety. Patients treated in the clinical programme are representative of those who would be expected to receive the medicinal product upon marketing.

Relevant features of the patient populations include different presentations of CAD (SA, NSTEMI-ACS, STEMI), different comorbidities, demographics, and other potentially important covariates. The elderly (≥ 65) were included in the studies, but no studies have been performed in children.

The pooling strategy for the cangrelor safety population is as follows:

- **PCI Indication: Derived from pooled CHAMPION studies (3)**, providing a complete pooled safety dataset in all studies comparing cangrelor versus clopidogrel in 25,107 CAD patients (12,565 cangrelor-treated) undergoing PCI.

- **Total Exposure: All studies (21)**, providing the entire pooled safety dataset in 26,201 patients (13,340 cangrelor-exposed) across all patient populations, regardless of dose and duration of therapy.

SIII.2.1 Duration of exposure

A broad spectrum of cangrelor drug exposures have been studied in the clinical development programme (15 µg/kg to 60 µg/kg bolus doses and 0.01 µg/kg/min to 8 µg/kg/min infusions) and duration of continuous use (from one hour up to seven days) in patients including UA, STEMI, and those patients amenable to PCI (with or without stent implantation) with either PCI/percutaneous transluminal coronary angioplasty (PTCA) or CABG. The population exposed to cangrelor in this clinical development programme is representative of those expected to receive cangrelor when it is marketed.

As shown in [Table 3](#), 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. Duration of exposure for the PCI indication is shown in [Table 4](#).

Table 3: Cangrelor infusion duration by pre-specified dose, reported as number and percentage of patients treated in all studies (safety population)

Infusion duration groups	≤0.5 µg/kg/min N=50 n (%)	0.75 µg/kg/min N=112 n (%)	1.0 µg/kg/min N=53 n (%)	2.0 µg/kg/min N=145 n (%)	≥4.0 µg/kg/min N=12901 n (%)
<24 h	28 (56)	9 (8.04)	43 (81.13)	98 (67.59)	12,787 (99.12)
24-<48 h	15 (30)	10 (8.93)	10 (18.87)	31 (21.38)	56 (0.43)
48-<72 h	3 (6)	41 (36.61)	NA	8 (5.52)	21 (0.16)
≥72 h	4 (8)	52 (46.43)	NA	8 (5.52)	37 (0.29)

Source: Annex 7, Summary of Clinical Safety (SCS) Section 2.7.4.9.2.1, Table 11.3.1.4.1.

µg = µg. kg = kilograms. min = minutes. h = hours. NA = not applicable.

The CHAMPION studies employed a uniform dosing regimen of 30 µg/kg IV bolus followed by IV infusion of 4 µg/kg/min (N=12,901).

Table 4: Duration of exposure (for PCI indication) – CHAMPION pooled population

Duration of exposure (hours)	Persons	Person hours
<2	492	
2 to < 4	11,893	
At least 4	140	
Total person hour	12,525	27,937

Source: Annex 7, Summary of Clinical Safety (SCS) Section 2.7.4.9.2.3, Tables 16.3.1.4.1.1

SIII.2.2 Dose

Table 5 summarises the cangrelor infusion rate and duration within each pooled dataset and for all studies pooled. The majority of patients treated received a cangrelor infusion of 4 µg/kg/min in the CHAMPION trials.

Table 5: Exposure by dose (for PCI indication)

Clinical Setting	≤0.5 µg/kg/min N=50	0.75 µg/kg/min N=112	1.0 µg/kg/min N=53	2.0 µg/kg/min N=145	≥4.0 µg/kg/min N=12933
PCI setting	N	N	N	N	12,525 (96.8)

Sources: Annex 7, SCS, Section 2.7.4.9.2.3, Table 16.3.1.4.1.

µg = microgram(s). kg = kilogram(s). min = minutes. PCI = percutaneous coronary intervention. NA = not applicable.

SIII.2.3 Age group and gender

Table 6: Exposure by age group and gender (for PCI indication)

Age group	Persons (cangrelor-treated; N=12565)		
	Male	Female	Total
<55 years	2,442 (26.9)	513 (14.8)	2,955 (23.5)
55 - <65 years	3,002 (33.0)	873 (25.1)	3,875 (30.8)
65 - <75 years	2,433 (26.8)	1,168 (33.6)	3,601 (28.7)
≥75 years	1,213 (13.3)	921 (26.5)	2,134 (17.0)
Total	9,090 (72.3)	3,475 (27.7)	12,565 (100.0)

Sources: Annex 7, SCS Section 2.7.4.9.2.3, Table 16.2.1.4.1. PCI

= percutaneous coronary intervention

SIII.2.4 Ethnic origin

Table 7: Exposure by ethnic or racial origin (for PCI indication)

Ethnic/racial origin	Persons (cangrelor-treated; N = 12565)
American Indian or Alaskan native	20 (0.2)
Asian	958 (7.6)
Black or African American	433 (3.4)
Hispanic or Latino	281 (2.2)
Native Hawaiian or Pacific Islander	41 (0.3)
Caucasian	10,815 (86.1)
Missing	17 (0.1)
Total	12,565 (99.9)

Sources: Annex 7, SCS Section 2.7.4.9.2.3, Table 16.2.1.4.1.

Note: Due to rounding, individual percentages in table may not total to 100%. PCI = percutaneous coronary intervention

Table 8: Special populations (for PCI indication)

Renal impairment (GFR) ^a	Persons
Severe (<30 mL/min/ 1.73 m ²)	281
Moderate (30 to <60 mL/min/1.73 m ²)	2,197
Mild (60 to ≤90 mL/min/1.73 m ²)	2,809
Normal (>90 mL/min/1.73 m ²)	1,552
Total	6,839

^a Glomerular filtration rate (GFR) data from CHAMPION PCI/PLATFORM only. Source: Annex 7, SCS Section 2.7.4.9.2.3, Table 16.6.24.4.18, Table 16.6.24.4.19, Table 16.6.24.4.20, Table 16.6.24.4.21

Part II: Module SIV – Populations not studied in clinical trials

The clinical program enrolled a broad spectrum of CAD patients (SA and ACS). These patients are representative of those intended to receive cangrelor in the real-world setting; patients with CAD who require prevention of thrombotic cardiovascular events (including ST) while undergoing PCI.

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Exclusion criteria for the cangrelor development programme were based on pre-existing morbidities and were based on a consideration of bleeding risk e.g., patients known to have active bleeding or to be at increased bleeding risk; patients at increased risk of cerebrovascular accident (including ischaemic or haemorrhagic stroke), patients with cerebral arteriovenous malformation, intracranial aneurysm, trauma, tumour, or who have had major surgery, and patients with known impaired haemostasis (including congenital and acquired bleeding disorders), thrombocytopenia or neutropenia associated with clopidogrel. Exclusions for some trials also included patients with severe hypertension not adequately controlled by antihypertensive therapy at the time of randomisation.

Exclusion criteria based on pharmacological considerations included, prior GPI use (within 12 hours or seven days depending on the agent) and receipt of fibrinolytic therapy 12 hours prior to randomisation or receipt of warfarin.

Since the studies were comparing cangrelor to clopidogrel loading doses, the CHAMPION PLATFORM and PHOENIX trials excluded pre-treatment of any P2Y₁₂ inhibitor seven days preceding randomisation and the CHAMPION PCI trial excluded any dose higher than maintenance dose (75 mg clopidogrel) within five days preceding randomisation.

Procedural exclusions for CHAMPION trials included patients intended for staged PCI procedures (where the second stage would occur within 30 days after the first intervention); and patients for whom admission was planned for less than 12 hours following PCI.

Standard exclusion criteria were also applied in studies of cangrelor (e.g., lactating females or females known or suspected to be pregnant, hypersensitivities to investigational agents, inability to provide informed consent; active treatment with other investigational agents or devices at the time of randomisation or planned use during the 30-day follow-up period).

In summary, the exclusion criteria for the cangrelor clinical development programme were largely based on considerations of cangrelor's pharmacology and potential risks for patients due to their pre-existing comorbidities or concomitant medications. The exclusion criteria that will remain as contraindications, e.g., history of active bleeding, intracranial haemorrhage (ICH), impaired haemostasis or hypersensitivity, will help to minimise the risk of bleeding or hypersensitivity. Overall, the exclusion criteria were clinically appropriate to the use of a P2Y₁₂ inhibitor in the target PCI population.

SIV.1.1 Exclusion criteria which will to remain as contraindications

Criterion	Implications for target population
Active pathological bleeding such as peptic ulcer, intracranial	Cangrelor is known to increase Global Use of Strategies to Open Occluded Arteries (GUSTO) mild and Acute Catheterisation and Urgent

haemorrhage, cerebral arteriovenous malformation, Patients who have had major surgery or trauma, or uncontrolled severe hypertension.	Intervention Triage Strategy (ACUITY) major and minor bleeding complications in patients undergoing PCI. This contraindication will help to minimise the risk of further bleeding in patients at increased risk of bleeding complications.
History of ischaemic stroke within the last year, any history of ICH.	This contraindication will help to minimise the risk of ICH in cangrelor-treated patients. In the overall cangrelor clinical programme (N=13,301), there were 10 cangrelor-treated patients and three clopidogrel-treated patients who experienced ICH. Among the 10 cangrelor-treated patients, nine were from CHAMPION pooled studies (N=12,565). Within 48 hours Eight (0.06%) cangrelor-treated patients experienced ICH, including four with haemorrhagic stroke within 48 hours after randomisation. These eight patients ranged in age from 53 to 76 years old. Of these eight patients, two had a medical history of stroke. The onset time of the bleeding events was 1.2 to 25 hours (four within six hours, four from 12 to 25 hours) after cangrelor infusion started. Three patients died from ICH (one within 48 hours, two between 48 hours to 30 days); One patient died from cardiac arrest beyond 48 hours; three patients were fully recovered; one patient survived (no additional information available). None of the eight patients had bleeding in other locations or an MI endpoint. In the clopidogrel arm, two patients experienced ICH (one haemorrhagic stroke). Neither patient had a prior medical history of stroke. One patient died >48 h, another was recovering but remained hospitalised. Beyond 48 hours and within 30 days One cangrelor-treated patient and one clopidogrel-treated patient experienced ICH (haemorrhagic stroke in clopidogrel arm) between 48 hours and 30 days following randomisation. Neither patient had a prior medical history of stroke. The cangrelor-treated patient died from ICH. Between 30 days and 1 year One cangrelor-treated patient and three clopidogrel-treated patients experienced fatal ICH (two patients with haemorrhagic stroke in clopidogrel arm) between 30 days and 1 year.
Impaired haemostasis	Drugs that affect coagulation (such as heparin and bivalirudin) and inhibit platelet function (such as cangrelor and GPIs), can increase the risk of bleeding especially when given together in combination. This contraindication will help to minimise the risk of potential bleeding in patients with impaired haemostasis.
Hypersensitivity to the active substance or to any of the excipients.	In the overall cangrelor clinical programme, there were 93 (0.7%) subjects in cangrelor arm and 75 (0.6%) subjects in comparator arm who experienced hypersensitivity. The clinical manifestations varied from anaphylactic reaction/shock, bronchospasm, angioedema to urticarial, pruritus, or rash.

	To minimise the potential for hypersensitivity reactions to cangrelor, known hypersensitivity to cangrelor or any of the excipients will be contraindicated. This will have minimal impact on the target population as other oral treatment options are available.
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SIV.1.2 Exclusion criteria which are NOT proposed to remain as contraindications

Criteria	Reason for being an exclusion criterion	Justification for not being a contraindication
Tumour	Related to the potential impact of bleeding risk associated with certain types of tumours as well as impact of morbidity associated with the malignancy to impact on clinical trial results and interpretation in an investigational setting.	Use will not be in an investigational study setting and potential risk versus benefit can be adequately assessed by the treating clinician on a case-by- case basis.
Patients intended for staged PCI	Related to re-exposure to the investigational compound prior to the end of the study evaluation follow-up period.	Use will not be in an investigational study setting.
Prior receipt of P2Y12 inhibitor	Some of the trials in a PCI setting compared cangrelor to oral P2Y12 inhibitor therapy administered at a standardised time window so use prior to randomisation could confound the results.	Cangrelor has been given to patients who have received prior clopidogrel in CHAMPION PCI with no known implications for patient safety. Bleeding and other AEs were similar in patients with and without prior exposure to oral P2Y12 inhibitors [Table 16.9.28.4.1 and Table 16.7.28.4.1]. However, in CHAMPION PHOENIX all randomised patients were naïve to prior oral P2Y12 therapy. The target patient population and the indication reflect this: Section 4.1 (Therapeutic Indications) 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 P2Y12 inhibitor prior to the PCI procedure and in whom oral

SIV.1.2 Exclusion criteria which are NOT proposed to remain as contraindications

		therapy with P2Y12 inhibitors is not feasible or desirable.
Prior GPI use	Restricted to “bail-out use” only during the study.	When cangrelor is used in combination with routine GPI there may be an increased risk of bleeding complications [Data on File: Table 9.110.4.1]. The following statements in the SmPC reflect this: Section 4.2 Use with other anticoagulant agents Kengrexal has been administered with unfractionated and low- molecular weight heparin, bivalirudin, fondaparinux and GP IIb/IIIa inhibitors. Section 4.4 Special warnings and precautions for use Risk of bleeding Cangrelor should be used with caution in patients taking medicines that may increase the risk of bleeding.
Prior warfarin	Exclusion was based on use in an investigational setting where an international normalised ratio (INR) result of >1.5 could potentially lead to an increased risk of bleeding.	Use will not be in an investigational setting, however, to optimise prescribing information for clinicians the following statement is included in the SmPC: Section 4.4 Risk of bleeding Cangrelor should be used with caution in patients taking medicines that may increase the risk of bleeding.
Prior fibrinolytic therapy	Use was in a clinical study setting and could confound the study results and put the patient at an increased risk of bleeding.	Use will not be in an investigational setting, however institutional practices regarding the use of lytics and other adjunctive agents and procedures should be considered to minimise any risk of bleeding. The following statement reflects this in the SmPC: Section 4.4 Special warnings and precautions for use <i>Risk of bleeding</i>

SIV.1.2 Exclusion criteria which are NOT proposed to remain as contraindications

		Cangrelor should be used with caution in patients taking medicines that may increase the risk of bleeding.
Planned admission for <12 hours	Hospitalisation >12 hours was needed in the study to acquire the needed study-related assessments.	Use will not be in an investigational study setting.
Refusal to receive a blood transfusion	Bleeding and transfusion as assessed in the study setting and refusal could bias results.	Use will not be in an investigational study setting.
Requirement for dialysis treatment	These types of patients have a higher risk of post-operative complications, so enrolment in a clinical study could confound results.	Use will not be in an investigational study setting and since cangrelor is not renally metabolised and renal impairment does not impact on PK / PD, use would not be prohibited in this population.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

Limitation to detect ADR in clinical trial development programmes

Ability to detect adverse reactions	Limitation of trial programme	Discussion of implications for target population
That are uncommon in the PCI setting	In the PCI setting, 12,565 patients were exposed to cangrelor.	Adverse drug reactions (ADRs) with a frequency greater than 1 in 4,188 could be detected with a 95% confidence limit if there were no background incidence.
Due to prolonged exposure	Cangrelor is not intended for prolonged exposure as it is intended for use in a hospital or acute setting only. A broad spectrum of cangrelor drug exposures have been studied in the clinical development programme (15 µg/kg to 60 µg/kg bolus doses and 0.01 µg/kg/min – 8 µg/kg/min infusions) and duration of continuous use (from one hour up to seven days) in patients including UA, STEMI, and those patients amenable to PCI (with or without	The incidence of adverse events (AEs) did not increase with increased cangrelor exposure. The nature of the AEs was generally consistent with those expected in these patient populations with CAD undergoing PCI and CABG.

	stent implantation) with either PCI/PTCA or CABG. The population exposed to cangrelor in this clinical development programme is representative of those expected to receive cangrelor when it is marketed.	
Due to cumulative effects	Cangrelor clearance varied with weight (higher clearance in heavier patients). The impact of weight on drug exposure is minimal with the predicted shift in exposure (steady-state concentration or area under the curve) of less than 20% for patients ranging from 40- 140kg, with no observed clinical impact.	Cumulative effects of cangrelor are of little concern due to the short terminal half-life (three to six minutes) and that clearance is independent of organ function.
That have a long latency	Total duration from study drug initiation through the follow-up period was planned to be no more than a maximum of approximately 35 days per protocol across the pivotal studies.	Considered of little relevance given the short duration of therapeutic effect and no evidence of accumulation.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Type of special population	Exposure
Pregnant women Breastfeeding women	There are no data on the use of cangrelor in women who are pregnant or lactating. Of the 3,693 subjects who received cangrelor in clinical studies, none were reported to be pregnant or breastfeeding. Given the clinical context of cangrelor as an acute, short-duration treatment, the Sponsor does not intend to engage in any specific studies in this population.
Elderly	Of the 12,565 patients who received cangrelor in the PCI setting, 46% of the patients were ≥ 65 years of age, with 17% ≥ 75 years. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

Children	The safety and effectiveness of cangrelor in patients less than 18 years of age has not been established. Based on the results of adult studies, the condition of non-site-specific embolism and thrombosis is clinically relevant to paediatric patients and includes several underlying conditions where cangrelor may be effective as an inhibitor of platelet activation. These conditions include thrombosis occurring both in the arterial and venous vasculature, as well as clot formation occurring on devices used for therapeutic purposes. Based on current understanding of thrombotic and embolic conditions, cangrelor is not anticipated to be useful in conditions unrelated to platelet activation such as non-thrombotic embolic events including infective, air, or fat emboli. Furthermore, cangrelor, if used during surgical procedures, may increase the risk of haemorrhagic complications and P2Y₁₂ inhibitors are not currently recommended for use in this setting. Due to its IV route of administration, mechanism of action, and short half-life, cangrelor is only suitable as a short-term (hours to a few days) adjunct therapy to current procedural anticoagulant therapies to prevent procedural and early post-procedural thrombotic events in paediatric patients undergoing percutaneous vascular procedures. These patients are at risk of both arterial, venous, and device-mediated thrombotic complications that cangrelor may be able to minimize or prevent. With the intent of using cangrelor as an adjunct to an anticoagulant, it is important to note that there is considerable experience in the adult population of coadministration of cangrelor with concomitant anticoagulation with no identified safety/tolerability consequences, which is expected to be similar in the paediatric population.
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Patients with relevant comorbidities:	
Patients with hepatic impairment	Cangrelor is not metabolised by hepatic enzymes and therefore involvement with the cytochrome P450 systems is likely to be minimal. Based upon its metabolism, no dosage adjustment is required for patients with hepatic impairment. Patients with hepatic impairment were not excluded from the cangrelor clinical development program. However, cangrelor has not been specifically studied in patients with hepatic impairment.

Patients with renal impairment	Cangrelor is not metabolised or excreted by the kidneys and therefore the implications of renal impairment on cangrelor PK/PD and safety are likely to be minimal. Based upon its metabolism, no dosage adjustment is required for patients with renal impairment. Cangrelor has been studied in a dose-ranging study [SC-931-5109] in patients with renal impairment, the PK, safety, and tolerability of cangrelor was studied. Plasma concentration-time profiles for cangrelor were comparable to those observed previously in healthy volunteers and there was no specific relationship between infused dose, concentration and measured safety variables observed. Patients with renal impairment were not excluded from the cangrelor clinical development program.
Immunocompromised patients	There is no information on these patients' groups from clinical programmes.
Patients with a disease severity different from inclusion criteria in clinical trials	Patients in the cangrelor program were not excluded based on severity of CAD. The clinical program enrolled a broad spectrum of CAD patients (SA and ACS). These patients are representative of those intended to receive cangrelor in the marketing setting: patients with CAD who require prevention of thrombotic cardiovascular events while undergoing PCI. Using subgroup analysis of pooled data cangrelor efficacy in reducing thrombotic events compared with clopidogrel was maintained across multiple patient types, according to subgroup analysis of the composite efficacy endpoint (Death, MI, ischaemia driven revascularisation [IDR], ST) at 48 hours. Odds ratios (OR) for important subgroups consistently favoured cangrelor efficacy, with many comparisons at the subgroup category level reaching significance. For subgroups based on sex (male or female), age (<75 or ≥75 years), and race (Caucasian or non-Caucasian), cangrelor efficacy was consistent with that observed for the total population. Cangrelor efficacy was also consistent in subgroup analysis among patients presenting with SA, NSTEMI-ACS, and STEMI, and among patients with either 600 mg or 300 mg clopidogrel loading dose, or clopidogrel loading before or after PCI start. The subgroups of patients within the USA or in other countries including Europe showed similar benefit from cangrelor treatment effect.
Population with relevant different ethnic origin	Patients of different racial and/or ethnic origins enrolled in the cangrelor studies included: Caucasian, American Indian or Alaskan native, Asian, Black or African American, Native Hawaiian or Pacific Islander, and Hispanic or Latino. Caucasian patients dominated in the studies (approximately 85%). No meaningful difference in the benefit-risk profile of cangrelor has been observed in any ethnic group in clinical investigations carried out to date and no dose adjustment is required. Furthermore, as cangrelor does not require metabolism to an active metabolite there is no reason to expect a difference in PK or PD on a pharmacogenomics basis.

Subpopulations carrying relevant genetic polymorphisms	Use of cangrelor in patients with active bleeding or increased risk of bleeding, because of impaired haemostasis and/or irreversible coagulation disorders is contraindicated. This includes genetically induced disorders of this nature. Cangrelor is not a pro-drug that requires hepatic metabolism and has clearance independent of organ function. Since the PK/PD profile of cangrelor is not influenced by such systems to any significant extent (Summary of Clinical Pharmacology, Module 2, Section 2.7.2.2.7), genetic polymorphisms involved in drug metabolism would not be expected to influence outcomes in patients administered cangrelor.
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Part II: Module SV – Post-authorisation experience

SV.1 Post-authorisation exposure

The patient exposure calculation is based on the World Health Organization Defined Daily Dose (DDD).

SV.2 Exposure

The estimated number of patients exposed is calculated based on sales volume of Kengrexal sold divided by an estimated average number of vials used to treat each patient (1.4 vials/patient). The table below represents market exposure for the period from IBD of the product 23 March 2015 to 30 October 2022.

Region/ Country	Number of vials sold cumulatively	Patients exposed cumulatively
US	352,540	251,814
Europe	139,940	99,959
Austria	14,180	10,129
Belgium	1,840	1,314
France	20,060	14,329
GB	5,450	3,893
Germany	14,660	10,471
Greece	1,080	771
Italy	40,360	28,829
Netherlands	4,900	3,500
Spain	6,550	4,679
CEE	1,800	1,286
Nordics	20,900	14,929
Switzerland	7,970	5,693
Turkey	190	136
Total	492,480	351,773

Part II: Module SVI – Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

The proposed supply classification for cangrelor is subject to medicinal prescription in an acute care setting. The potential for misuse for illegal purposes is therefore no greater than for other products in this supply category. No psychoactive effects have been observed that would lead to potential abuse with cangrelor.

Part II: Module SVII – Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

SVII.1.1.1 Potential for harm overdose

Bleeding is a potential expected pharmacological effect of overdose. Since cangrelor is administered by health care providers in an acute care setting, overdoses would occur only in the context of administration to a patient. There is no antidote to cangrelor. Should a major bleeding event occur, the PD effect of cangrelor can be rapidly reversed by discontinuing the infusion with a return to normal platelet function within 60 minutes [TMC-CAN-04-02]. Any effects may therefore be short-lived after treatment is discontinued. If bleeding occurs, appropriate supportive measures should be taken including discontinuing treatment.

In the cangrelor clinical programme overdose was defined for cangrelor as administration of 20% (allowing the variations in the weight-based dose calculation) more than either the bolus or infusion dose as described in a clinical study protocol.

Out of 12,565 cangrelor-treated patients, a total of 36 instances of overdose of cangrelor occurred in the CHAMPION program [TMC CAN-05-02 PCI, TMC-CAN-05-03 PLATFORM and TMC-CAN-10-01 PHOENIX] [Table 9](#). All instances were related to accidental user errors, e.g., dose calculation based on weight in pounds instead of kilograms (kg); all occurred outside Europe; bolus administration directly from reconstituted cangrelor instead of diluted solution; pump rates set to higher than the protocol-defined rate.

The maximum doses delivered were approximately 10 times greater for the bolus [TMC-CAN-05-03, Patient 327010005] and 3.5 times greater for the infusion dose [TMC-CAN-05-02, Patient 048018007] for the PCI indication.

Table 9: Cangrelor dose administered in 36 overdosed patients in CHAMPION studies

Cangrelor bolus						
Dose range (µg/kg)	< 36	36 – <60	60 - <70	70 - < 90	Around 300	
Recommended dose multiple	No overdose	1.2–2 x	2– 2.5x	2.5–3x	10x	
Number of patients (N)	11	13	8	1	3*	Total = 36
Cangrelor infusion						
Dose range (µg/kg/min)	< 4.8	4.8 - < 8	8 - <10	10 - <12	12 - <14	
Recommended dose multiple	No overdose	1.2 – 2 x	2 – 2.5 x	2.5 – 3x	3 -3.5x	

Number of patients (N)	5	19	8	3**	1**	Total = 36
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* These patients were overdosed with only cangrelor bolus. ** These patients were overdosed with only cangrelor infusion.

Source: Data on File: Table

16.3.1.4.1.E $\mu\text{g} = \mu\text{g}; \text{kg} =$

kilograms; min = min.

The bleeding AEs that occurred in the 36 patients are summarised in Table 10. The frequencies of bleeding events were balanced between both treatment arms and are consistent with those in the overall CHAMPION patient population. There was no correlation between the bleeding events and the magnitude of the cangrelor overdose: no bleeding events occurred in the patients who received the greatest overdose of bolus (10 times the proposed PCI bolus dose) or infusion (3.5 times the proposed PCI infusion dose); the patient (TMC-CAN-05-02, 001064075) who experienced a retroperitoneal bleeding event (classified as GUSTO moderate, ACUITY major and Thrombolysis In Myocardial Infarction (TIMI major) received 1.35 times the proposed PCI dose. Two patients who experienced GUSTO mild bleeding received 2 times the bolus dose (TMC-CAN-05-02, 001086051) and 2.7 times the infusion dose (TMC-CAN-05-02, 043007001) respectively.

Table 10: Summary of all bleeding in overdosed patients in CHAMPION studies

	Cangrelor N=36 n (%)	Clopidogrel N=30 n (%)
Any GUSTO bleeding	3 (8.3)	4 (13.3)
Severe/life threatening	0 (0.0)	0 (0.0)
Moderate ^a	1 (2.8)	0 (0.0)
Mild	2 (5.6)	4 (13.3)
Mild excluding ecchymosis, oozing, and <5 cm haematoma	1 (2.8)	2 (6.7)
Any TIMI bleeding	1 (2.8)	1 (3.3)
Major ^a	1 (2.8)	0 (0.0)
Minor	0 (0.0)	1 (3.3)
Mild excluding ecchymosis, oozing, and <5 cm haematoma	0 (0.0)	1 (3.3)
Any ACUITY bleeding	3 (8.3)	4 (13.3)
Major ^a	2 (5.6)	1 (3.3)
Major excluding haematoma ≥ 5 cm	1 (2.8)	0 (0.0)
Minor	1 (2.8)	3 (10.0)
Minor excluding ecchymosis, oozing, and <5 cm haematoma	0 (0.0)	1 (3.3)
Any blood transfusion	1 (2.8)	0 (0.0)

Source: Annex 7, Summary of Clinical Safety (SCS), Section 2.7.4.9.2.3, Table 16.6.1.4.9

^a This patient (TMC-CAN-05-02-001064075) received 1.35 times of the protocol defined cangrelor dose and experienced retroperitoneal bleeding, which was classified as GUSTO moderate, ACUITY Major, and TIMI major bleeding.

GUSTO = Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; TIMI

= Thrombolysis in Myocardial Infarction; ACUITY = Acute Catheterization and Urgent Intervention Triage Strategy; cm = centimetre

The overall incidence and pattern of non-bleeding AEs is consistent with those in the overall CHAMPION patient population. No serious adverse events (SAEs) were reported, and no AEs caused study drug discontinuation in the 36 overdosed patients. The majority of non-bleeding AEs were reported as recovered. A review of the non-bleeding AEs occurring in the overdosed patients did not suggest a correlation between the overdose and non-bleeding AEs.

In the cangrelor QTc study [TMC-CAN-08-01], none of the 58 healthy subjects who received up to two times the proposed daily dose of cangrelor in the PCI setting (60 µg/kg IV bolus followed by 8 µg/kg/min infusion for three hours) experienced an increased risk of bleeding. The percentages of subjects reporting more than one AE were similar across all treatment groups. The half-life of cangrelor of three to six minutes is not dependent on dose; cangrelor is rapidly metabolised in the circulation.

SVII.1.1.2 Potential for transmission of infectious agent

Assurance has been obtained from the manufacturers of cangrelor drug substance that the product is manufactured in accordance with the requirements described in the European Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products.

Cangrelor is a lyophilised powder intended for reconstitution and dilution prior to IV injection or infusion. The potential for the introduction of infectious contaminants from the use of cangrelor is no greater than for any other parenteral agent used in an acute care setting.

SVII.1.1.3 Potential for off -label use

The potential for off-label use exists with all medications. However, the more likely off-label uses for cangrelor include upstream use in patients with ACS prior to undergoing angiography, use in patients undergoing peripheral intervention as opposed to coronary intervention, and intracoronary injection during PCI, especially in high-risk patients such as those with STEMI undergoing primary PCI. No safety or efficacy data exists to support these uses.

SVII.1.1.4 Potential for infusion site irritation

Kengrexal was generally not associated with infusion site irritation in patients. The risk of this ADR has a low clinical consequence in relation to severity of indication and do not impact the risk benefit profile.

SVII.1.1.5 Potential for medication errors

Description of medication errors during the clinical trial programme

Product name: Cangrelor				
Description of error	Number of occurrence	Analysis of cause	Steps taken to prevent	Comment

Cangrelor was given hours and 15 minutes outside of the stability window.	N=1	Human error	Relevant study site staffs were retrained.	No AE resulted from the error.
Cangrelor was mixed in a 100 mL normal saline IV bag but ran the intravenous infusion as a 250 mL bag.	N=1	Human error	Relevant study site staffs were retrained.	No AE resulted from the error.
Two vials instead of one vial of cangrelor were added into one 100 mL bag of 0.9% sodium chloride.	N=1	Human error	Relevant study site staffs were retrained.	No AE resulted from the error.
Overdose In CHAMPION studies, 20 were overdosed with both the bolus and infusion, 5 were overdosed with only the bolus and 11 were overdosed with only the infusion (See Section SVI.1 for more details).	N=36	All instances were related to accidental user errors, e.g., dose calculation based on weight in pounds instead of kg (all occurred outside Europe); bolus administration directly from reconstituted cangrelor instead of diluted solution; pump rates set to higher than protocol defined rate.	Relevant study site staffs were retrained.	A review of these occurrences did not reveal a significantly increased bleeding risk: most of these overdosed patients (33/36) did not experience bleeding although 3/36 did experience bleeding (1 GUSTO moderate; 2 GUSTO mild). Of note, the two patients who received the most significant overdoses (bolus or infusion) did not experience bleeding events. A review of the AEs occurring in the patients who received overdoses did not suggest a correlation between the overdose and non-bleeding AEs.

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Important identified risks

Important identified risks	Identification and benefit-risk impact
Serious bleeding	Bleeding is the most common AE in cangrelor- versus clopidogrel- treated patients undergoing PCI (17.5% vs 13.5%, respectively: OR 1.35 [95% CI 1.26-1.45] $p < 0.0001$). Bleeding events were reported as endpoints and measured with bleeding scales in the CHAMPION pooled studies (captured for 48 hours after randomisation). The severity of bleeding events varied from mild, moderate, to severe. In the CHAMPION pooled studies, the majority of the bleeding events were mild (96%, 2109/2196, GUSTO mild), or minor (71%, 77/109, TIMI minor); severe bleeding was as shown in the table above. The nature of the bleeding varied from ecchymosis or oozing to intracranial bleeding, cardiac tamponade, gastrointestinal, and retroperitoneal bleeding. In the overall cangrelor clinical programme, the major bleeding events (the incidence rate for cangrelor vs comparators) included but were not limited to: ICH including haemorrhagic stroke, 10 (0.1%) vs 3 (0.0%); cardiac tamponade, 16 (0.1%) vs 3 (0.0%); pulmonary haemorrhage, 2 (0.0%) vs 1 (0.0%); gastrointestinal haemorrhage, 22 (0.2%) vs 17 (0.1%); and retroperitoneal haemorrhage, 26 (0.2%) vs 15 (0.1%). Haemorrhagic complications have emerged as an independent risk factor for subsequent mortality in patients with ACS and in those undergoing PCI, representing a hazard equivalent to or greater than that for MI Serious bleeding can result in fatal outcome and it may have a negative impact on the benefit risk balance of the product.
Hypersensitivity	In the entire cangrelor clinical programme (N=13,301), hypersensitivity occurred in 93 (0.7%) subjects in the cangrelor arm and 75 (0.6%) subjects in the comparator arm; OR 1.20 (95% CI 0.88 – 1.63) $p = 0.24$. Serious adverse event (SAE) of hypersensitivity occurred in 7 (0.1%) cangrelor-treated patients vs 2 (0.0%) comparator-treated patients; OR 3.39 (95% CI 0.70 – 16.30) $p = 0.18$. In the CHAMPION pooled studies, hypersensitivity occurred in 71 (0.6%) patients for cangrelor vs 65 (0.5%) for clopidogrel; OR 1.09 (95% CI 0.78-1.53), $p = 0.6134$. Serious hypersensitivity occurred in 5 (0.04%) cangrelor-treated patients vs 2 (0.02%) clopidogrel-treated patients; OR 2.50 (95% CI 0.48-12.87), $p = 0.2578$. In the overall cangrelor clinical programme, among the 93 cangrelor-treated subjects who experienced AEs of hypersensitivity, most were reported with mild (64/93, 69%) or moderate (23/93, 25%) events; six patients (6%) had

	severe events. In the CHAMPION pooled studies, most patients who had AEs of hypersensitivity were reported with mild (70%) or moderate (24%) events; 6% had severe events. The clinical manifestations of hypersensitivity varied from serious in form including anaphylactic reaction/shock, bronchospasm, angioedema, laryngeal oedema, and stridor to non-serious in form, e.g., urticarial, pruritus or rash. There was a higher number of SAEs with cangrelor vs control (seven vs two). A review of the narratives of seven cangrelor treated patients suggested that cangrelor may have contributed to the occurrences of some of the SAEs, e.g., anaphylactic reaction, anaphylactic shock and bronchospasm. However, the patients received multiple drugs and many received contrast agents when undergoing PCI. These confounding factors may have also contributed to the occurrence of hypersensitivity. Hypersensitivity is considered as important identified risks for the purpose of this RMP.
Dyspnoea	In the CHAMPION pooled safety population dyspnoea (including exertional dyspnoea) was reported in 1.2% (148/12,565) cangrelor treated patients, OR 0.01 (95% CI 0.01 – 0.01). In the CHAMPION PHOENIX trial, dyspnoea was reported in 1.2% (65/5529) of cangrelor treated patients, OR 0.01 (95% CI 0.01 – 0.01). Among the 148 cangrelor-treated patients in the CHAMPION pooled safety population who had dyspnoea, most events were considered mild (96/148, 64.9%) or moderate (51/148, 34.5%) and the event in one patient was considered severe. The median duration of dyspnoea was 1.9 hours in the cangrelor-treated group and 3.4 hours in the clopidogrel-treated group. No patient deaths were reported due to dyspnoea. In CHAMPION PHOENIX most events of dyspnoea in cangrelor- treated patients were considered mild (46, 70.59%) or moderate (18, 27.94%) and one event was considered severe. In the CHAMPION pooled safety population SAEs of dyspnoea occurred rarely in only three cangrelor-treated patients vs one clopidogrel-treated patient. The implications of dyspnoea on the patient are likely to be minimal as only 10 cangrelor-treated vs 3 clopidogrel-treated patients discontinued due to dyspnoea. Among the 148 cangrelor-treated patients who had dyspnoea, most events were considered mild 96 (64.9%) or moderate 51 (34.5%) and only in 1 patient was the event considered severe. The median duration of dyspnoea was short at 1.9 hours in the cangrelor treated group and 3.4 hours in the clopidogrel-treated group. No patient deaths were reported due to dyspnoea.

Renal impairment	In the CHAMPION pooled studies, AEs that were identified using SMQ of acute renal failure occurred in 68/12,565 (0.5%) patients for cangrelor vs 50/12,542 (0.4%) patients for clopidogrel; OR 1.3595 (95% CI 0.9428-1.9602), p=0.0987. In the CHAMPION pooled studies, one third of the AEs (searched by the SMQ) were serious (33.8%). Majority were recovered (54.4%) or recovering (20.6%); 4.4% recovered with sequelae; one patient died. Majority of the AEs were mild (54.4%) or moderate (36.8%); 8.8% were severe. The renal AEs ranged from increased serum creatinine and proteinuria to acute renal failure. Events of renal impairment may vary in terms of severity from mild transient rises in blood creatinine not requiring further intervention to more serious events such as acute renal failure that may require further intervention including haemodialysis. Renal impairment is considered as important identified risks for the purpose of this RMP
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Important potential risks

Important potential risk	Identification and benefit-risk impact																												
Inadequate antiplatelet effect of clopidogrel or prasugrel caused by the mistiming of the cangrelor transition to thienopyridines	Due to the controlled conditions under which the CHAMPION trials were conducted there are minimal available clinical data to guide on the frequency of thrombotic events occurring after mistiming the transitioning from cangrelor to clopidogrel.																												
	Clinical thrombotic events from the pooled CHAMPION studies occurring in the limited number of patients who mistimed (took clopidogrel any time before the cangrelor infusion had discontinued) versus those who took clopidogrel correctly (after the end of the infusion) are presented below:																												
	48-hour efficacy outcomes in patients with mistiming and correct transition from cangrelor to clopidogrel																												
	<table><tr><th>48-hour endpoint</th><th>Mistiming</th><th>Correct</th><th>OR (95%CI)</th></tr><tr><td>Efficacy (mITT)</td><td>(N=75)</td><td>N=12,185)</td><td></td></tr><tr><td>Death/MI/IDR/ST</td><td>6 (8.0%)</td><td>439 (3.6%)</td><td>2.33(1.00,5.39)</td></tr><tr><td>Death</td><td>0 (0%)</td><td>20 (0.2%)</td><td></td></tr><tr><td>MI</td><td>6 (8.0%)</td><td>370 (3.0%)</td><td>2.78(1.20,6.44)</td></tr><tr><td>IDR</td><td>1 (1.3%)</td><td>53 (0.4%)</td><td>3.09(0.42,22.66)</td></tr><tr><td>ST</td><td>1 (1.3%)</td><td>58 (0.5%)</td><td>2.83(0.39,20.67)</td></tr></table>	48-hour endpoint	Mistiming	Correct	OR (95%CI)	Efficacy (mITT)	(N=75)	N=12,185)		Death/MI/IDR/ST	6 (8.0%)	439 (3.6%)	2.33(1.00,5.39)	Death	0 (0%)	20 (0.2%)		MI	6 (8.0%)	370 (3.0%)	2.78(1.20,6.44)	IDR	1 (1.3%)	53 (0.4%)	3.09(0.42,22.66)	ST	1 (1.3%)	58 (0.5%)	2.83(0.39,20.67)
48-hour endpoint	Mistiming	Correct	OR (95%CI)																										
Efficacy (mITT)	(N=75)	N=12,185)																											
Death/MI/IDR/ST	6 (8.0%)	439 (3.6%)	2.33(1.00,5.39)																										
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IDR	1 (1.3%)	53 (0.4%)	3.09(0.42,22.66)																										
ST	1 (1.3%)	58 (0.5%)	2.83(0.39,20.67)																										
	Source: CHAMPION Pooled, Table 16.5.9.48.2																												

	No deaths were reported among the 75 patients who took clopidogrel before the cangrelor infusion had discontinued. The potential outcome of mistiming of administration of clopidogrel or prasugrel when transitioning from a cangrelor infusion would be a loss of some or all of the pharmacodynamic effect of the first transition dose. This would potentially increase the risk of serious or life-threatening thrombotic events (such as ST) in a patient who has just undergone PCI and not correctly transitioned to chronic oral therapy with a thienopyridine (clopidogrel or prasugrel) P2Y₁₂ inhibitor. Embolitic and thrombotic events may have a negative impact on the benefit risk balance of the product. Therefore, it is considered as important potential risk for the purpose of this RMP.
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Missing information

Missing information	Identification and benefit risk impact
Exposure to cangrelor during pregnancy and lactation	There are no data on the use of cangrelor in women who are pregnant or lactating. Of the 3,693 subjects who received cangrelor in clinical studies, none were reported to be pregnant or breastfeeding. Due to the lack of information on effects of the active substances on the newborn, a serious impact cannot be entirely ruled out. “Use in Pregnancy and Lactation” will be considered a Missing Information.
Use of cangrelor in patients with increased risk of bleeding (history of gastrointestinal bleeding, major surgery within 30 days, clinically relevant thrombocytopenia or anaemia and patients affected by cerebral arteriovenous malformation)	Related to the potential impact of bleeding risk associated with active pathological bleeding such as peptic ulcer, intracranial haemorrhage, cerebral arteriovenous malformation in patients who have had major surgery or trauma, or uncontrolled severe hypertension is considered a contraindication for the product. The safety of use of cangrelor in patients with increased risk of bleeding is not known. Therefore, it will be considered a missing information for the RMP purpose.
Use of ticagrelor and prasugrel before, during and after the cangrelor infusion	The safety of the use of ticagrelor and prasugrel before, during and after the cangrelor infusion is not known and therefore will be considered a missing information for the purpose of the RMP.

Use of cangrelor in the paediatric population (<18 years of age)	Cangrelor has not yet been studied in the paediatric population. However, the intent is to study its use in the condition of “prevention of thromboembolic events” during general percutaneous vascular procedures. Although other oral platelet inhibitors are available, there remains difficulty in dosing and administration of these agents to paediatric patients, therefore it is possible that clinicians may consider use of cangrelor in this population when administration of oral agents is not desirable or feasible.
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SVII.2 New safety concerns and re-classification with a submission of an updated RMP

The list of safety concerns included in the previous version (v 5.0) of the RMP have been revised and re-evaluated based on the definition of important identified/potential risks and missing information given in the GVP Module V (Rev.2) and final results from the ARCANGELO study. The following important potential risk and missing information have been removed from the list of safety concerns as they are no longer considered as important potential risks and missing information:

Removed potential risk

Inadequate antiplatelet effect of clopidogrel or prasugrel caused by the mistiming of the cangrelor transition to thienopyridines, previously classified as important potential risks, was removed from the list of safety concerns based on the results of the completed category 3 PASS ARCANGELO study.

It is to be noted that the transition time of cangrelor to thienopyridines is adequately addressed in the SmPC (sections 4.2, 4.4 and 4.5) and PIL (section 2). This event will be monitored through routine PV activities.

Removed missing information

Use of cangrelor in the paediatric population (<18 years of age), Use of cangrelor in patients with increased risk of bleeding (e.g. history of gastrointestinal bleeding, major surgery within 30 days, clinically relevant thrombocytopenia or anaemia and patients affected by cerebral arteriovenous malformation) and Use of ticagrelor an prasugrel before, during and after the cangrelor infusion previously classified as missing information have been removed from the list of safety concerns.

Cumulatively, four cases of *Use of cangrelor in the paediatric population* (age groups - one adolescent, two children and one infant) were collected in the company's database; these cases include twelve reported adverse events, of which one was reported as serious with the causality assessment of possibly related and eleven as non-serious. In addition, Cangrelor is currently approved for use in adults only. In total, 9 serious bleeding cases in *Use of cangrelor in patients with increased risk of bleeding* were identified, which included 5 patients with thrombocytopenia, 2 with anaemia and 2 post surgery patients. No case with usage of cangrelor in patient with history of gastrointestinal bleeding or with cerebral arteriovenous malformation was found. The concern *Use of ticagrelor an prasugrel before, during and after the cangrelor infusion* was addressed well in the completed category 3 PASS ARCANGELO study and is no longer considered as missing information.

All the above-mentioned events are adequately addressed in the SmPC (Section 4.2, 4.3, 4.4, 4.5, 4.9, 5.1 and 5.2) and PIL (Section 2). As there are no additional PhV activities are in place to further characterise these issues, these events will be monitored through regular PV activities; the concern *Use of cangrelor in patients with increased risk of bleeding* will be followed-up routinely in the list of concerns in PSURs.

SVII.3 Details of important identified risks, important potential risks, and missing information**SVII. 3.1. Presentation of important identified risks and important potential risk****Important identified risks**

Important identified risk	Serious bleeding
MedDRA PT Term (code)	Haemorrhages (10055798).
Potential mechanisms	Antiplatelet agents are used to reduce the risk of ischaemic complications. As a function of their anticoagulant activity, they are known to increase the risk of bleeding. Bleeding complications are mostly iatrogenic, attributable to vessel puncture and femoral arterial access in concert with use of potent antiplatelet and anticoagulant medications.
Evidence source	SCS Section 2.7.4.9.2.3, Table 16.6.1.4.1 and SCS Section 2.7.4.9.2.1, Table 11.6.21.4.1

Characterisation of the risk: - frequency with 95 % CI	Bleeding is the most common AE in cangrelor- versus clopidogrel- treated patients undergoing PCI (17.5% vs 13.5%, respectively: OR 1.35 [95% CI 1.26-1.45] p<0.0001). Bleeding events were reported as endpoints and measured with bleeding scales in the CHAMPION pooled studies (captured for 48 hours after randomisation). The frequencies of non-CABG related bleeding events which represent serious bleeding are presented in the table below: <table><tr><th colspan="4">In the CHAMPION pooled studies within 48 hours of randomisation</th></tr><tr><th></th><th>Cangrelor N=12,565 n (%)</th><th>Clopidogrel N=12,542 N (%)</th><th>Odds ratio (95% CI)</th></tr><tr><td>GUSTO severe/life threatening</td><td>28 (0.2)</td><td>23 (0.2)</td><td>1.22 (0.70,2.11)</td></tr><tr><td>GUSTO severe/moderate</td><td>103 (0.8)</td><td>79 (0.6)</td><td>1.30 (0.97,1.75)</td></tr><tr><td>TIMI Major</td><td>32 (0.3)</td><td>28 (0.2)</td><td>1.14 (0.69,1.90)</td></tr><tr><td>ACUITY Major</td><td>534 (4.2)</td><td>353 (2.8)</td><td>1.53 (1.34,1.76)</td></tr><tr><td>ACUITY Major excluding haematoma ≥5cm</td><td>169 (1.3)</td><td>123 (1.0)</td><td>1.38 (1.09,1.74)</td></tr></table>	In the CHAMPION pooled studies within 48 hours of randomisation					Cangrelor N=12,565 n (%)	Clopidogrel N=12,542 N (%)	Odds ratio (95% CI)	GUSTO severe/life threatening	28 (0.2)	23 (0.2)	1.22 (0.70,2.11)	GUSTO severe/moderate	103 (0.8)	79 (0.6)	1.30 (0.97,1.75)	TIMI Major	32 (0.3)	28 (0.2)	1.14 (0.69,1.90)	ACUITY Major	534 (4.2)	353 (2.8)	1.53 (1.34,1.76)	ACUITY Major excluding haematoma ≥5cm	169 (1.3)	123 (1.0)	1.38 (1.09,1.74)
In the CHAMPION pooled studies within 48 hours of randomisation																													
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ACUITY Major	534 (4.2)	353 (2.8)	1.53 (1.34,1.76)																										
ACUITY Major excluding haematoma ≥5cm	169 (1.3)	123 (1.0)	1.38 (1.09,1.74)																										
- Severity and nature of risk	Due to the nature of the intervention along with the use of potent antiplatelet and anticoagulant agents, bleeding related to PCI occurs relatively frequently in the general population. In one retrospective study of 10,974 patients who underwent PCI, TIMI major bleeding occurred in 588 patients (5.4%), TIMI minor bleeding in 1394 patients (12.7%) and no bleeding occurred in 8992 patients (81.9%). Major bleeding episodes included 15 haemorrhagic strokes, 370 haematomas, 63 gastrointestinal bleeds, and 30 retroperitoneal bleeds. Minor bleeding included were 823 haematomas, 88 gastrointestinal bleeds, and 11 retroperitoneal bleeds^[28].																												
- Seriousness/outcomes	The seriousness of bleeding events varied from non-serious to life-threatening or fatal.																												
Risk factors or risk groups	Patients with major bleeding are generally older than patients with minor or no bleeding (67.8 ± 11 vs 65.9 ± 11 vs 63.6 ± 11 years respectively, p <0.001); and more often experience intraprocedural complications such as emergency use of an intra-aortic balloon pump (IABP), at 13.6% vs 6.5% vs 2.3% respectively, p <0.001^[28]. The proportion of women experiencing major bleeding (228 of 3307; 6.9%) is reported to be 1.5 times higher than in men (360 of 7635; 4.7%)^[28]. Multivariate logistic regression analysis identified the use of an IABP (odds ratio [OR] 3.0, p <0.0001), procedural hypotension (OR 2.9, p <0.001), and age >80 years (OR 1.9 compared with age <50 years, p < 0.001) as the strongest predictors for major bleeding^[28].																												

	Other contemporary large-scale studies have consistently identified elderly patients, women, and patients with impaired renal function and/or baseline anaemia to be at increased risk for bleeding ^{[29] [30] [31]} .
Preventability	Patients at increased risk of bleeding are contraindicated from receiving cangrelor as documented in the SmPC in Section 4.3. Further attempts to decrease bleeding complications require enhanced utilisation of bleeding avoidance strategies — bivalirudin, vascular closure devices, and radial artery approaches are examples of bleeding avoidance strategies ^{[32] [33] [34]} .
Impact on the risk-benefit balance of the product:	Haemorrhagic complications have emerged as an independent risk factor for subsequent mortality in patients with ACS and in those undergoing PCI, representing a hazard equivalent to or greater than that for MI^{[28] [35] [36] [37] [30] [31] [38] [39]}. The impact on the benefit risk balance is not expected to be significant nevertheless the risk needs to be monitored on routine basis.
Public health impact	Major bleeding also considerably prolongs the hospital stay and increases resource consumption, representing an important source of excess expenditures^[40]. For every 1,844 patients undergoing PCI with cangrelor compared to conventional therapy, one GUSTO severe/life-threatening bleed might occur resulting in a number needed to harm (NNH) of 1844 in CHAMPION PHOENIX.

Missing information

Missing information: 1 MedDRA PT Term (code)	Exposure to cangrelor during pregnancy and lactation (10073513), (10071402)
There are no data on the use of cangrelor in women who are pregnant or lactating. Due to the lack of information on effects of the active substances on the newborn, a serious impact cannot be entirely ruled out. Therefore, this population is in need of further characterisation. They can be obtained using routine pharmacovigilance activities and do not require any additional minimization measures.	

Part II: Module SVIII – Summary of the safety concerns**Summary of safety concerns**

Important Identified risks	• Serious bleeding
Important Potential risks	• None
Missing information	• Exposure to cangrelor during pregnancy and lactation

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine Pharmacovigilance activities

Chiesi routine pharmacovigilance activities are described in the Company Pharmacovigilance System Master File (PSMF) document (ref. no. MFL2815).

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for Serious bleeding; This questionnaire has the purpose of obtaining structured information and improve quality of data collected, to evaluate any new risk factors and characterise serious bleeding events to further characterise the safety concern. [Annex 4](#) included the full version of the questionnaire.

III.2 Additional pharmacovigilance activities

None.

III.3 Summary Table of additional Pharmacovigilance activities

Beside routine pharmacovigilance practices, no additional PV activities have been planned for Kengrexal®.

Part IV: Plan for Post - Authorisation Efficacy Studies

No post-authorisation efficacy studies are planned or ongoing for Kengrexal®.

Part V: Risk Minimisation Measures (including evaluation of the effectiveness of risk minimisation activities)

V.1 Risk minimisation measures

All of the identified or potential safety concerns and missing information are addressed using standard pharmacovigilance measures and routine risk management measures, such as pharmacovigilance monitoring, detection and evaluation of safety signals, appropriate labelling and good communication with regulators and other stakeholders. Accordingly, no risk minimisation measures, additional to product information provided through the SmPC and PIL are considered necessary.

Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Serious bleeding (Important identified risk)	<u>Routine risk communication</u> SmPC section 4.3 SmPC section 4.4 SmPC section 4.8 SmPC section 4.9 PL section 2 PL section 4 Legal status: Special medical prescription and reserved for acute hospital settings.
Exposure to cangrelor during pregnancy and lactation (Missing information)	<u>Routine risk communication</u> SmPC section 4.6 SmPC section 5.3 PL section 2 Legal status: Special medical prescription and reserved for acute hospital settings.

Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Through routine pharmacovigilance, including preparation of Periodic Safety Update Reports (PSURs) and signal detection analysis
Criteria for judging the success of the proposed risk minimisation measures	Analysis of each case collected. No significant increase in reporting rates.
Planned dates for assessment	1-monthly during signal detection and according to PSUR periodicity.
Results of effectiveness measurement	Not applicable

Effectiveness of risk minimisation measures	
Impact of risk minimisation	Fully informed prescriber and patient in order that appropriate management can be started if required. No negative impact from these measures is anticipated.
Comment	None

V.2 Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of risk minimisation measures

Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Important Identified Risk		
Safety concern	Risk minimisation measures	Pharmacovigilance activities
Serious bleeding	<u>Routine risk minimisation measures:</u> <i>SmPC section 4.3</i> <i>SmPC section 4.4</i> <i>SmPC section 4.8</i> <i>SmPC section 4.9</i> <i>PL section 2</i> <i>PL section 4</i> Legal status: Special medical prescription and reserved for acute hospital settings. <u>Additional risk minimisation measures:</u> none	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire for Serious bleeding. Additional pharmacovigilance activities: None
Missing Information		

Exposure to cangrelor during pregnancy and lactation	<u>Routine risk minimisation measures:</u> <i>SmPC section 4.6</i> <i>SmPC section 5.3</i> <i>PL section 2</i> Legal status: Special medical prescription and reserved for acute hospital settings. <u>Additional risk minimisation measures:</u> none	Routine pharmacovigilance activities. Additional pharmacovigilance activities: None
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Part VI: Summary of the Risk management plan

SUMMARY OF THE RISK MANAGEMENT PLAN FOR KENGREXAL[®] (CANGRELOR)

This is a summary of the risk management plan (RMP) for Kengrexal[®]. The RMP details important risks of Kengrexal[®], how these risks can be minimised, and how more information will be obtained about Kengrexal[®]'s risks, and uncertainties (missing information).

Kengrexal summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Kengrexal[®] should be used.

This summary of the RMP for Kengrexal[®] should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Kengrexal[®]'s RMP.

I. The medicine and what is it used for

Kengrexal[®] co-administered with acetylsalicylic acid (ASA), is authorised 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 P2Y₁₂ inhibitor prior to the PCI procedure and in whom oral therapy with P2Y₁₂ inhibitors is not feasible or desirable. It contains cangrelor as the active substance, and it is given by intravenous infusion; Kengrexal is available as powder for concentrate for solution for injection / infusion.

Further information about the evaluation of Kengrexal[®]'s benefits can be found in Kengrexal[®]'s EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage [Kengrexal | European Medicines Agency \(europa.eu\)](https://www.ema.europa.eu/en/medicines/humans/kt/Kengrexal)

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Kengrexal[®], together with measures to minimise such risks are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and product information addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;

- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

If important information that may affect the safe use of Kengrexal is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Kengrexal® are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Kengrexal®. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

Important Identified risks:	• Serious bleeding
Important Potential risks:	• None
Missing information:	• Exposure to cangrelor during pregnancy and lactation

II.B Summary of important risks and missing information

Important identified risk

Serious bleeding	
Evidence for linking the risk to the medicine	Antiplatelet agents are used to reduce the risk of ischaemic complications. As a function of their anticoagulant activity, they are known to increase the risk of bleeding. During clinical studies, bleeding was the most common AE in cangrelor-versus clopidogrel- treated patients undergoing PCI (a surgical procedure used to unblock narrowed blood vessels that supply the heart).
Risk factors and risk groups	Patients with major bleeding are generally older than patients with minor or no bleeding and more often experience intraprocedural complications such as emergency use of an intra-aortic balloon pump.

Risk minimisation measures	<u>Routine risk minimisation measures:</u> <i>SmPC section 4.3, 4.4, 4.8 and 4.9</i> <i>PL section 2 and 4</i> Legal status: Special medical prescription and reserved for acute hospital settings. <u>Additional risk minimisation measures:</u> none
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Missing information

Exposure to cangrelor during pregnancy and lactation	
Risk minimisation measures	<u>Routine risk minimisation measures:</u> <i>SmPC section 4.6 and 5.3</i> <i>PL section 2</i> Legal status: Special medical prescription and reserved for acute hospital settings. <u>Additional risk minimisation measures:</u> none

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Kengrexal®.

II.C.2 Other studies in post-authorization development plan

There are no studies required for Kengrexal®.

Part VII: Annexes

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Annex 5- Protocols for proposed and on-going studies in RMP part IV.....	59
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Annex 1- EudraVigilance Interface

The completed document was provided to the following e-mail address:

h-eurmp-evinterface@emea.europa.eu

Annex 2- Tabulated summary of planned, ongoing, and completed Pharmacovigilance study programme

Completed studies

Study (Study short name, and title) Status (planned/on-going/completed)	Summary of objectives	Safety concerns addressed	Protocol link Milestones
Post-Authorisation Safety Study Category 3 Completed	<u>Primary Objective</u> To assess the safety of cangrelor in a real-world setting, when administered in patients with acute coronary syndromes undergoing PCI. The safety of cangrelor will be based on the incidence of any haemorrhage 30 days post-PCI. <u>Secondary objectives</u> - To describe the incidence of type 1-2 (mild) and type 3-5 (moderate-severe) bleedings, according to the Bleeding Academic Research Consortium [BARC] both at 48 hours and 30 days post-PCI. - To assess the efficacy of cangrelor in terms of incidence of major adverse cardiac events (MACE) at 48 hours and 30 days post-PCI including death, myocardial infarction, ischaemia-driven revascularisation, and stent thrombosis. - To stratify the results on bleedings and major adverse cardiac events by the specific oral platelet P2Y12 receptor (prasugrel /ticagrelor /clopidogrel). - To assess the management of transitions from cangrelor to oral platelet P2Y12 receptor, in term of type (prasugrel/ticagrelor/clopidogrel) and timing of administration. - To describe the use of glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors.	Inadequate antiplatelet effect of clopidogrel or prasugrel caused by the mistiming of the cangrelor transition to thienopyridines (Important potential risk) -Use of ticagrelor and prasugrel before, during and after the cangrelor infusion (Missing information)	FPFV: 23 Oct 2020 LPLV: 17 Jan 2022 Final report submission: 27 Jan 2023 Request for Supplementary Information: 14 Apr 2023

Annex 3- Protocols for proposed, ongoing and completed studies in the pharmacovigilance plan

NA

Annex 4- Specific adverse drug reaction follow-up forms**Cangrelor Bleeding Adverse Events**

Please provide the following additional information if not previously reported. Feel free to attach additional pages.

- Did the bleeding event occur during or after the PCI procedure? ☐ During PCI ☐ After PCI
- Did the bleeding event occur during or after the Cangrelor infusion?
☐ During infusion ☐ After infusion; how long after? _____ ☐ min _____ ☐ hr
- What was the route of vascular access used during PCI? ☐ Radial ☐ Femoral
- Was a closure device used? ☐ No ☐ Yes (specify) _____
- Did the patient experience any complications during the PCI? (check all that apply)
☐ Arterial perforation at access site ☐ Coronary arterial perforation
☐ Cardiac perforation ☐ Vascular dissection (specify: ☐ coronary ☐ access site)
☐ Complications deploying stents ☐ Other _____
- Did the patient receive any of the following medication(s) prior to the event? (check all that apply)
☐ Aspirin (acetylsalicylic acid) ☐ Clopidogrel ☐ Prasugrel ☐ Ticagrelor ☐ Ticlopidine
☐ Abciximab ☐ Eptifibatide ☐ Tirofiban ☐ UFH ☐ Enoxaparin ☐ Dalteparin
☐ Fondaparinux ☐ Bivalirudin ☐ Desirudin ☐ Dabigatran ☐ Rivaroxaban ☐ Argatroban
☐ Warfarin ☐ Alteplase ☐ Urokinase ☐ Streptokinase ☐ Other _____
- What was the most recent pre-Cangrelor platelet count? _____ units _____
- Were any actions taken or treatments administered to help stop the bleeding? ☐ No
☐ Stop Cangrelor infusion ☐ Blood product transfusion
☐ Further interventions (specify) _____
- Does the patient have a history of any of the following conditions that may have contributed to bleeding? (check all that apply)
☐ Haemorrhagic stroke ☐ Ischaemic stroke ☐ Cerebral arteriovenous malformation
☐ Gastrointestinal bleeding ☐ Severe hypertension ☐ Coagulation disorder
☐ Thrombocytopenia ☐ Anaemia ☐ Renal impairment
☐ Excessive bleeding related to procedure ☐ Recent injuries (accidents, falls, head traumas, etc.)
☐ Recent (within 30 days) procedures/surgeries (specify) _____
☐ Other _____
- Does the patient have a family history of excessive bleeding related to procedure?
☐ No ☐ Yes (specify) _____

Please provide any additional details about this report that have not already been provided elsewhere. Feel free to attach additional pages by referencing the CHIESI reference number listed above.

Annex 5- Protocols for proposed and on-going studies in RMP part IV

Not applicable, no post-authorisation efficacy trials are on-going or proposed.

Annex 6- Details of proposed additional risk minimisation measures.

None.

Annex 7- Other supporting data (including referenced material)

1. Referenced Data Tables and Figures

2.7.4 Summary of Clinical Safety, Section 2.7.4.9.2.1 (All Studies Pooled)

Table 11.3.1.4.1	Summary of IV Study Drug Administration, Safety Population
Table 11.6.21.4.1	Summary of Bleeding Related Adverse Events within 30 Days from Dosing Start by System Organ Class and Preferred Term, Safety Population
Table 11.6.24.4.1	Summary of Reported Treatment Emergent Adverse Events of Special Interest by System Organ Class, and Preferred Term Safety Population
Table 11.6.24.4.2	Summary of Reported Treatment Emergent Adverse Events of Special Interest, Hypersensitivity by Preferred Term, Safety Population
Table 11.6.24.4.3	Summary of Reported Treatment Emergent Serious Adverse Events of Special Interest, Hypersensitivity by Preferred Term, Safety Population
Table 11.6.27.4.1	Descriptive Summary of Treatment Emergent Adverse Events of Special Interest, Hypersensitivity, Safety Population

2.7.4 Summary of Clinical Safety, Section 2.7.4.9.2.2 (Placebo-controlled studies)

Table 14.6.8.4.1	Incidence of Potentially Clinically Significant Tests in Serum Chemistry Parameters, Safety Population
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2.7.4 Summary of Clinical Safety, Section 2.7.4.9.2.3 (CHAMPION studies pooled)

Table 16.2.1.4.1	Patient Demographics, Safety Population
Table 16.3.1.4.1	Summary of IV Study Drug Administration, Safety Population
Table 16.3.1.4.1.1	Summary of IV Study Drug Administration, Safety Population (Champion Pooled)

Table 16.5.9.48.2	Summary of Efficacy Endpoints by Treatment by Blue pill timing (mITT) (Champion Pooled)
Table 16.6.1.4.1	Summary of Bleeding, Safety Population
Table 16.6.1.4.9	Summary of Bleeding, Safety+Overdosed Patients

2.7.4 Summary of Clinical Safety, Section 2.7.4.9.2.3 (CHAMPION studies pooled)

Table 16.6.8.4.1	Incidence of Potentially Clinically Significant Tests in Serum Chemistry Parameters, Safety Population
Table 16.6.24.4.1	Summary of Treatment Emergent Adverse Events of Special Interest by System Organ Class, Preferred Term Safety
Table 16.6.24.4.4	Summary of Reported Treatment Emergent Adverse Events of Special Interest, Hypersensitivity by Preferred Term, Safety Population
Table 16.6.24.4.5	Summary of Reported Treatment Emergent Serious Adverse Events of Special Interest, Hypersensitivity by Preferred Term, Safety Population
Table 16.6.24.4.6	Summary of Reported Treatment Emergent Serious Adverse Events of Special Interest, Renal Failure by Preferred Term, Safety Population
Table 16.6.24.4.18	Summary of Treatment Emergent Adverse Events of Special Interest, Renal Failure by System Organ Class, Preferred Term, Safety Population: Baseline GFR Severe (<30 mL/min/1.73 m ²)
Table 16.6.24.4.19	Summary of Treatment Emergent Adverse Events of Special Interest, Renal Failure by System Organ Class, Preferred Term, Safety Population: Baseline GFR Moderate (30-<60 mL/min/1.73 m ²)
Table 16.6.24.4.20	Summary of Treatment Emergent Adverse Events of Special Interest, Renal Failure by System Organ Class, Preferred Term, Safety Population: Baseline GFR Mild (60-90 mL/min/1.73 m ²)
Table 16.6.24.4.21	Summary of Treatment Emergent Adverse Events of Special Interest, Renal Failure by System Organ Class, Preferred Term, Safety Population: Baseline GFR Normal (>90 mL/min/1.73 m ²)
Table 16.6.25.4.1	Descriptive Summary of Treatment Emergent Adverse Events of Special Interest, Dyspnoea Safety Population

Table 16.6.26.4.1	Descriptive Summary of Treatment Emergent Adverse Events of Special Interest, Renal Failure, Safety Population
Table 16.6.27.4.1	Descriptive Summary of Treatment Emergent Adverse Events of Special Interest, Hypersensitivity, Safety Population
Table 16.7.28.4.1	Summary of Bleeding by Prior vs Non-Prior Thienopyridine Use, Safety Population
Table 16.9.28.4.1	Summary of Treatment Emergent Adverse Events by Prior vs Non-Prior Thienopyridine Use, Safety Population

Summary of Clinical Efficacy

Figure 12	Subgroup analysis of death/MI/IDR/ST in 48 hours (mITT Population)
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TMC-CAN-10-01 PHOENIX

Table 1.1	Patient Disposition by Treatment Group, All Randomized Subjects
Table 2.1.4.1	Patient Demographics, Safety Population
Table 3.1.2.1	Summary of IV Study Drug Administration, ITT Population
Table 5.0.1.1	Analysis of 48-hour Composite Endpoint Based on CEC Adjudicated Results (mITT, SA/NSTE-ACS/STEMI)
Table 5.1.1.1	Summary of 48-hour Efficacy Endpoint Based on CEC Adjudicated Results (mITT, SA/NSTE-ACS/STEMI)
Table 8.2.4.1	Summary of Adverse Events by System Organ Class and Preferred Term (Safety, SA/NSTE-ACS/STEMI)
Figure 8 (CSR in-text figure)	Subgroup analysis of death/MI/IDR/ST in 48 hours (mITT Population)

TMC-CAN-05-03 PLATFORM

Table 1.1	Patient Disposition, Randomized Patients
Table 3.1.2.1	Summary of IV Study Drug Administration, ITT Population

TMC-CAN-05-02 PCI

Table 1.1	Patient Disposition, Randomized Patients
Table 3.1.2.3	Summary of IV Study Drug Administration, ITT Population

Data on file

Table 9.110.4.1	Summary of Bleeding by GPIIb/IIIa use - Used vs Not Used (TMC- CAN-10-01 PHOENIX post hoc analysis)
Table 16.3.1.4.1.E	Cangrelor dose administered in 36 overdosed patients in CHAMPION studies

2. Referenced Study Reports

1. Report MDCO-CAN-12-03 (TRANSITION). A study of the transition from IV cangrelor to oral ticagrelor, and ticagrelor to cangrelor, in patients with coronary artery disease. 09 Apr 2013.
2. Report MDCO-CAN-13-01 (TRANSITION II). A study of the transition from IV cangrelor to oral prasugrel, and prasugrel to cangrelor, in patients with coronary artery disease. 26 August 2013.
3. Report SC-30178. The effect of intravenous infusion of AR-C69931MX on arterial thrombosis and haemostasis in the anaesthetized dog: interaction with aspirin, heparin and glyceryl trinitrate. 14 July 1998.
4. Report SC-102858-1. AR-C69931MX: The potential of AR-C69931MX, AR-C69712XX and AR-C90439XX to inhibit human cytochrome P450 (CYP). 29 March 2000.
5. Report SC-931-5014. An ascending dose step-plateau infusion study to investigate the tolerability, safety, activity and pharmacokinetics of AR- C69931MX, an antiplatelet agent, in healthy male volunteers. 14 March 1998.
6. Report SC-931-5036. An ascending dose, step-plateau infusion study to investigate the tolerability, safety, activity and pharmacokinetics of AR- C69931MX, an antiplatelet agent in healthy female volunteers. 27 March 1998.
7. Report SC-931-5037. A double-blind placebo controlled two-way crossover study to investigate the combined effects and interactions of aspirin, heparin and glyceryl trinitrate pre-treatment with stepped infusions of AR 69931MX in healthy male volunteers. Astra Charnwood, 13 May 1998.
8. Report SC-931-5058. An open multi-centre study to assess the safety, tolerability and activity of intravenous AR-C69931MX in unstable angina pectoris and/or non-Q-wave myocardial infarction. 9 December 1998.
9. Report SC-931-5060. A double-blind, placebo-controlled, multi-centre study to assess the safety and tolerability of intravenous AR-C69931MX and placebo in unstable angina pectoris or non-Q-wave myocardial infarction. 26 August 1999.
10. Report SC-931-5109. An open, group comparative study of the pharmacokinetics, safety and tolerability of AR-C69931MX, administered as ascending infusions ($50 - 4000 \text{ ng} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) for 5 hours to subjects with renal impairment and healthy controls. 9 December 1999.
11. Report SC-931-5129 Part 1. A multicentre pilot study to assess the safety and ex vivo platelet aggregation of response of intravenous AR-C69931MX in patients undergoing PTCA, with or without intracoronary stent placement (Part 1 double-blind vs placebo). 16 February 2001.
12. Report SC-931-5129 Part 2. A multicentre pilot study to assess the safety and ex vivo platelet aggregation of response of intravenous AR-C69931MX in patients undergoing PTCA, with or without intracoronary stent placement (Part 2 open-label, multi-centre). 16 February 2001.
13. Report SC-931-5135. An open study, with blinded end-point assessment, to assess the safety,

tolerability, and the effect on coronary artery patency of intravenous AR-C69931MX as both monotherapy and adjunct to activase in patients with ST-elevation myocardial infarction. 16 August 2002.

14. Report SC-931-9017. The metabolism and disposition of [3H]AR-C69931MX (formerly ARL69931MX) in healthy male volunteers when administered intravenously at 2 µg/kg/min for 2 hours. Astra Charnwood, 06 January 1998.
15. SC-100199 AR-C69931MX: The Metabolism and Disposition of [3H]AR- C69931MX in Healthy Male Volunteers Following Intravenous Infusion (Clinical Study No. CP9017)
16. Report TMC-CAN-04-02. The pharmacokinetics and pharmacodynamics of cangrelor bolus plus infusion in healthy volunteers. 06 February 2009.
17. Report TMC-CAN-08-01. QTc Study: A double-blind, placebo-controlled, positive-controlled, randomized crossover study to assess the effect of cangrelor at the therapeutic dose and a supratherapeutic dose level on the QT/QTc interval in healthy volunteers.
18. Report TMC-CAN-08-02 (BRIDGE) Clinical Study Report. Maintenance of platelet inhibition with cangrelor after discontinuation of thienopyridines in patients undergoing surgery: The BRIDGE Trial. 29 March 2013.
19. Report TMC-CAN-05-02 (CHAMPION PCI) Clinical Study Report. A clinical trial comparing cangrelor to clopidogrel in subjects who require percutaneous coronary intervention. 14 February 2013.
20. Report TMC-CAN-05-03 (CHAMPION PLATFORM) Clinical Study Report. A clinical trial comparing treatment with cangrelor (in combination with usual care) to usual care, in subjects who require percutaneous coronary intervention. 14 February 2013.
21. Report TMC-CAN-05-02-S1, TMC-CAN-05-03-S1. The effect of cangrelor on the pharmacodynamics of clopidogrel. A sub study to Protocol Nos. TMC-CAN-05-02 and TMC-CAN-05-03. 13 March 2013.
22. Report TMC-CAN-10-01 (CHAMPION PHOENIX) Clinical Study Report. A clinical trial comparing cangrelor to clopidogrel standard of care therapy in subjects who require percutaneous coronary intervention. 11 April 2013.
23. MDCO-CAN-13-02 A Study of the Transition from Cangrelor to Clopidogrel or Prasugrel in Patients with Coronary Artery Disease. 03 Nov 2014.

Annex 8– Summary of changes to Risk Management Plan over time

Version	Approval date procedure	Change
01	NA	First issue of the EU-RMP
1.5	March 2015	Changes following the PRAC assessment of the initial version
2	NA	- The list of safety concerns included in the previous versions of the RMP have been revised in line with the definition of important identified risks as per GVP Module V (Rev.2). <<<i>Hypersensitivity, dyspnoea and renal impairment</i>>> have been removed from the list of important identified - Reconsideration of the PASS category 3 included in the previous version of the RMP and request a waiver to be issued on the previous commitment for the PASS.
3	NA	- Addition of the PASS (category 3 study) in the pharmacovigilance plan following the PRAC request. - Inclusion on the Protocol synopsis for the PASS
3.1	EMA/H/C/003773/II/0015	- Inclusion of the requested PASS as additional pharmacovigilance activity (category 3 study) - Inclusion of the protocol synopsis of the PASS in the relevant Annex of the RMP
3.2	NA	Changes in the protocol synopsis as per PRAC's recommendation
3.3	NA	Changes in the protocol synopsis as per PRAC's recommendation
4.0	May 2020	Changes in the protocol synopsis as per PRAC's recommendation

Version	Approval date procedure	Change
4.1	October 2021	- Changes in Part I, Part II SI, SIII, SV, SVI, S VII, S VIII, Part III, Part IV, Part V, Part VI and Annexes for alignment with the new template EMA/164014/2018 Rev.2.0.1, which accompanies the GVP Module V Rev.2 including the new exposure data. - Update of timelines for the post-authorisation safety study Arcangelo the post-authorisation safety study Arcangelo, including the Non-Substantial, General Amendment.
4.2	November 2021	Response to Rapporteur assessment from 02 November 2021
5.0	EMA/H/C/003773/IB/0024 21 DEC 2021	- No safety concerns have been added and/or removed from the RMP. - Changes related to authority's further request
5.1	January 2023	- Changes in the Additional Pharmacovigilance Activities section (Part III, Section III.2). - Changes related to the Post-Authorisation Safety Study ARCANGELO in Part III.2, Part III.3, Part V.3, Part VI II.B and II.C.2, Annex 2, Annex 3. - New post-marketing exposure data.
5.2	April 2023 EMA/H/C/003773/II/0031	Response to PRAC Rapporteur's preliminary assessment report. Removal of: <i>Important potential risks:</i> Inadequate antiplatelet effect of clopidogrel or prasugrel caused by the mistiming of the cangrelor transition to thienopyridines. <i>Missing information:</i> Use of cangrelor in the paediatric population (<18 years of age); Use of cangrelor in patients with increased risk of bleeding (e.g. history of gastrointestinal bleeding, major surgery within 30 days, clinically relevant thrombocytopenia or anaemia and patients affected by cerebral arteriovenous malformation); Use of ticagrelor and prasugrel before, during and after the cangrelor infusion. Specific adverse drug reaction follow-up questionnaires for Thrombotic Events.

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