CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204958Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA Number:	204958
Submission Type:	Resubmission – Class 2
Submission Date:	December 23, 2014
PDUFA goal date:	June 23, 2015
Drug Name:	Cangrelor
Trade Name:	(b) (4)
Drug Class:	$P2Y_{12}$ antagonist
Proposed Indication:	Reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with coronary artery disease undergoing percutaneous coronary intervention (PCI)
Applicant:	The Medicines Company
OCP Division:	DCP1
OND Division:	Division of Cardiovascular and Renal Products (DCRP)
Reviewer:	Sreedharan Sabarinath, PhD
Team Leaders:	Jeffry Florian, PhD Rajanikanth Madabushi, PhD

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INTRODUCTION

Cangrelor is an intravenous, reversible $P2Y_{12}$ platelet receptor antagonist that blocks adenosine diphosphate (ADP) induced plate activation and aggregation. The original new drug application (NDA) for cangrelor was submitted on 04/30/2013 and received a Complete Response letter on 04/30/2014. The applicant resubmitted the NDA on 12/23/2014 addressing the issues raised in the Complete Response letter. In addition, the current submission includes clinical pharmacology studies addressing or confirming transition strategies proposed for switching patients from cangrelor to two other oral $P2Y_{12}$ drugs: clopidogrel and prasugrel.

This review is an addendum to the clinical pharmacology review (DARRTS dated 1/10/2014), from the first review cycle, which includes detailed information on the clinical pharmacology of cangrelor. The focus of this review is primarily on labeling recommendations for transitioning patients from cangrelor to oral antiplatelet agents. The review also addresses the utility of cangrelor in patients on glycoprotein IIb/IIIa (Gp IIb/IIIa) inhibitors.

RECOMMENDATIONS:

The recommended strategies for transitioning from cangrelor infusion to oral antiplatelet therapy and for Gp IIb/IIa inhibitors (GPIs) are as follows:

- Ticagrelor: administer a 180 mg loading dose during or immediately after discontinuation of cangrelor infusion. This transition represents the best choice in terms of the impact on the antiplatelet activity.
- Clopidogrel: Administer 600 mg loading dose immediately after discontinuation of cangrelor infusion. While there is a loss of antiplatelet activity for a short duration following the switch, there is clinical trial experience with this transition strategy form Phase 3.
- Prasugrel: Administer 60 mg loading dose immediately after discontinuation of cangrelor infusion.

(b) (4)

Antiplatelet Effects of clopidogrel, prasugrel and ticagrelor

Clopidogrel and prasugrel are irreversible oral $P2Y_{12}$ drugs while ticagrelor is a reversible $P2Y_{12}$ receptor blocker. The reported average pharmacological effects of these drugs, based on percentage inhibition of platelet aggregation measured using light transmittance aggregometry with 20 µM ADP as agonist, are illustrated in Figure 1 below.

Prasugrel and ticagrelor attain maximum platelet inhibition relatively faster compared to clopidogrel after a single dose administration. Similarly the maximum platelet inhibition seen with ticagrelor and prasugrel were higher relative to that observed with clopidogrel.

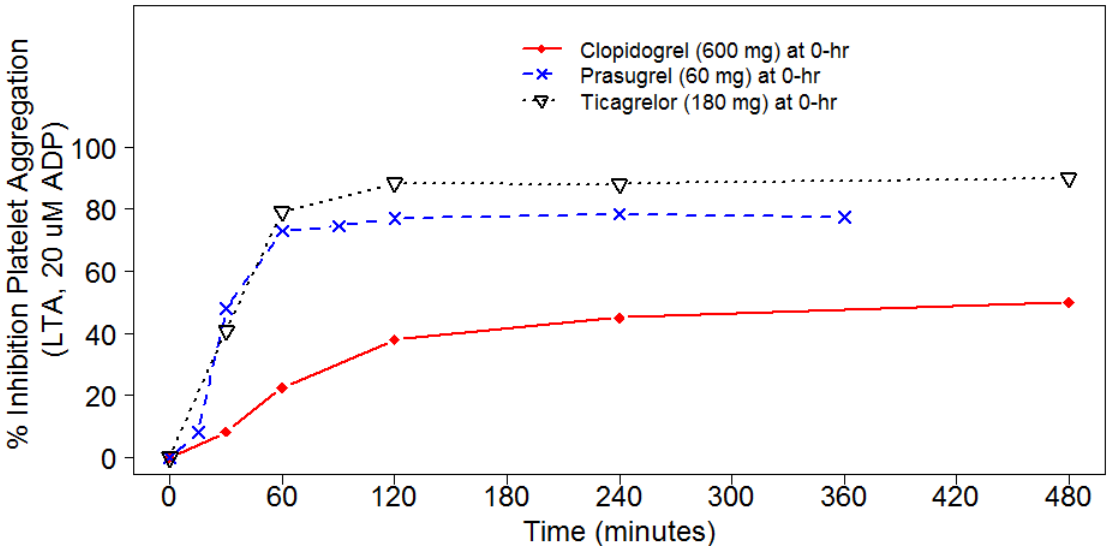

Figure 1 Percentage inhibition in platelet aggregation for clopidogrel, prasugrel and ticagrelor loading doses. Source: Adapted from approved USPI of Brilinta®[1] [ticagrelor and clopidogrel profile] and Effient®[2] [prasugrel profile].

Transition to Ticagrelor

The transition from cangrelor to ticagrelor was evaluated in study MDCO-CAN-12-13 in patients with stable coronary artery disease (reviewed previously[3]). Cangrelor was administered as 30 µg/kg IV bolus and 4 µg/kg/min 2 h infusion (note: all cangrelor administrations in the figures and descriptions below use the same bolus and infusion doses, but for brevity are referred as a

[1] Ticagrelor USPI: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022433s010lbl.pdf

[2] Prasugrel USPI: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022307s010lbl.pdf

[3] Clinical Pharmacology Review, DARRTS date 01/10/2014

'cangrelor infusion'). A 180 mg loading dose of ticagrelor was given at 30 minutes (90 minutes prior to the end of infusion) or 75 minutes (45 minutes prior to the end of infusion) (N=6). The inhibitory effects of cangrelor and ticagrelor were preserved when both products were co-administered (Figure 2). After discontinuing cangrelor infusion, there was a slight decrease in platelet inhibition for about 30 minutes, which is considered as not significant. Therefore, our recommendation is to administer loading dose of ticagrelor (180 mg) during or immediately after the cangrelor infusion (Figure 3).

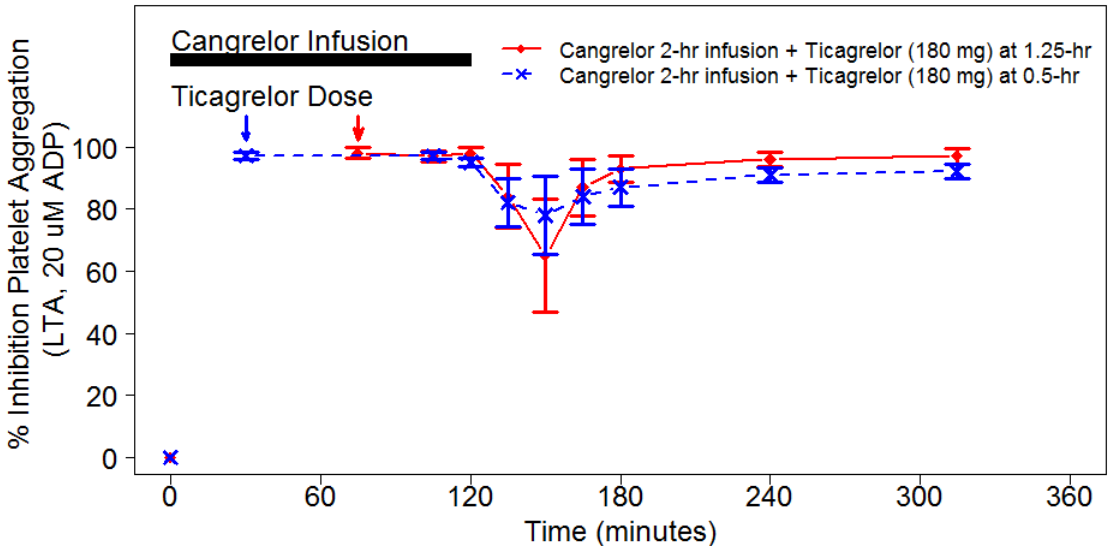

Figure 2 Transition from cangrelor to ticagrelor. The horizontal black bar indicates 2 h-infusion duration for cangrelor. The down arrows color matched to the plot lines indicate administration of ticagrelor 180 mg dose. Error bars represent 90 % confidence intervals. Source: Prepared by FDA

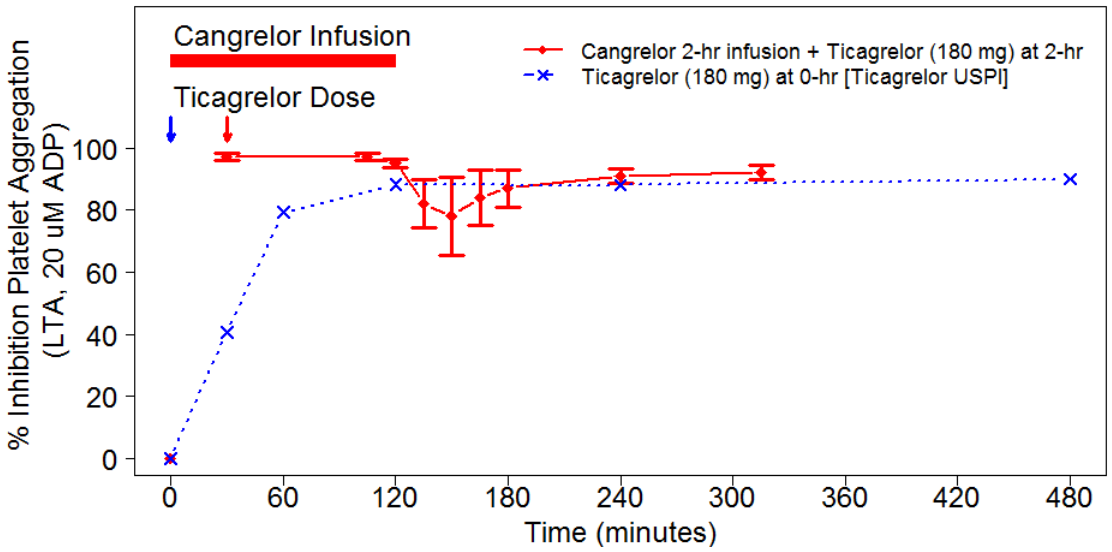

Figure 3 Recommended transition strategy for ticagrelor: administer 180 mg ticagrelor during or at the end of cangrelor infusion. The blue dotted line is a representative time-course of antiplatelet effect seen with 180 mg ticagrelor when given alone, extracted from ticagrelor USPI. The horizontal red bar indicates 2 h-infusion duration for cangrelor. The down arrows color matched to the plot lines indicate administration of ticagrelor 180 mg dose. Error bars represent 90 % confidence intervals. There was no ticagrelor reference treatment group in ticagrelor transition studies. There was a temporary dip in antiplatelet activity for about 30 minutes after cangrelor infusion was stopped, but there was no attenuation in ticagrelor's pharmacological effects. Source: Prepared by FDA

Transition to Clopidogrel

Study TMC-CAN-04-02 (reviewed earlier[4]) was a study in healthy subjects to assess the pharmacokinetics of cangrelor and the pharmacodynamics of either clopidogrel 600 mg alone or clopidogrel 600 mg administered either at the beginning or at the end of cangrelor infusion. Platelet inhibition was measured using whole blood impedance aggregation (WBIA), p-selectin expression measured by flow-cytometry and light transmittance aggregometry (LTA). There was a significant loss in antiplatelet effects of clopidogrel when administered at the beginning of cangrelor infusion possibly because of competitive inhibition at platelet $P2Y_{12}$ receptors. The active metabolite of clopidogrel is short lived and administration of clopidogrel 1-hr prior to the end of the infusion results in maximum exposure of the active metabolite during the period

[4] Clinical Pharmacology Review, Page 29, DARRTS date 01/10/2014

when platelet inhibition with cangrelor is maintained. This minimizes the ability of the active metabolite of clopidogrel to irreversibly bind to platelets, resulting in loss of its pharmacological activity. The recommendation, based on this study, was to administer clopidogrel loading dose at the end of cangrelor infusion. It should also be noted that this transition strategy was employed for clopidogrel in the CHAMPION-PHOENIX pivotal efficacy study.

In study MDCO-CAN-13-02 in patients with stable coronary artery disease (CAD), additional scenarios evaluating clopidogrel loading dose administered during the 2 h cangrelor infusion period were evaluated. The dosing times were at 2 h (end-of-infusion) (N=3), at 1.5 h (0.5 h prior to the end of the infusion) (N=6) and at 1 h (1-h prior to the end of the infusion) (N=3). The study results are shown in Figure 4.

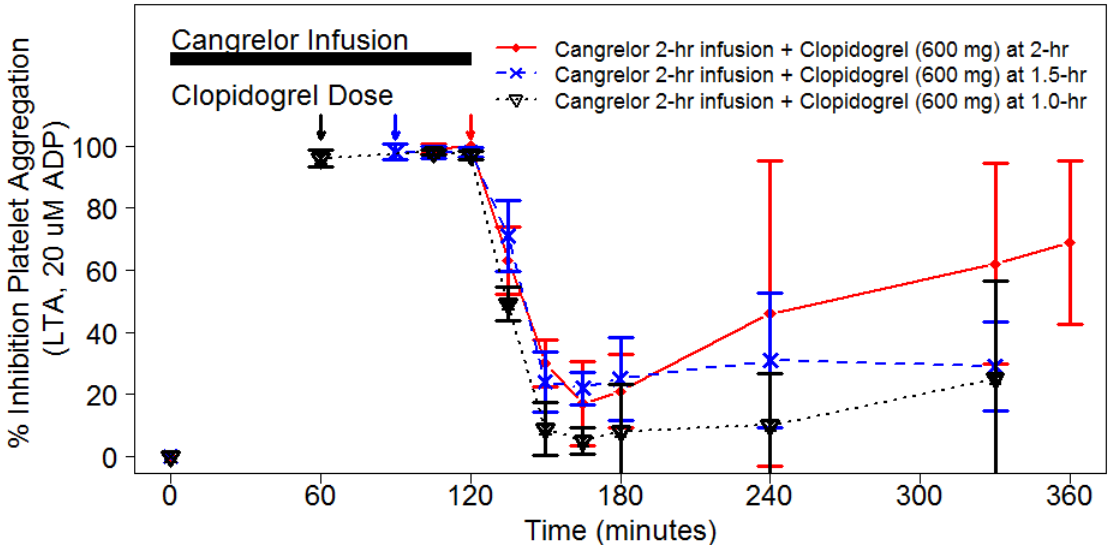

Figure 4 Percentage inhibition in platelet aggregation time-course with cangrelor and clopidogrel measured by LTA. Error bars represent 90 % confidence intervals. The horizontal black bar indicates 2 h-infusion duration for cangrelor. The down arrows color matched to the plot lines indicate administration of clopidogrel 600 mg dose. Baseline measurements at zero time reflect no drug treatment. Administering clopidogrel 600 mg loading dose after stopping cangrelor infusion did not alter its expected pharmacological effect. However, administering clopidogrel during cangrelor infusion resulted in significant attenuation of its antiplatelet effect. Source: Prepared by FDA

When the dosing time for clopidogrel overlapped with cangrelor infusion there was profound attenuation in clopidogrel's antiplatelet effect. These results in CAD patients are in agreement with the previously reviewed transition study TMC-CAN-04-02 in healthy subjects. Therefore,

the recommended transition strategy for clopidogrel is to administer a 600 mg loading dose immediately after stopping cangrelor infusion (Figure 5) as detailed in our previous review[5].

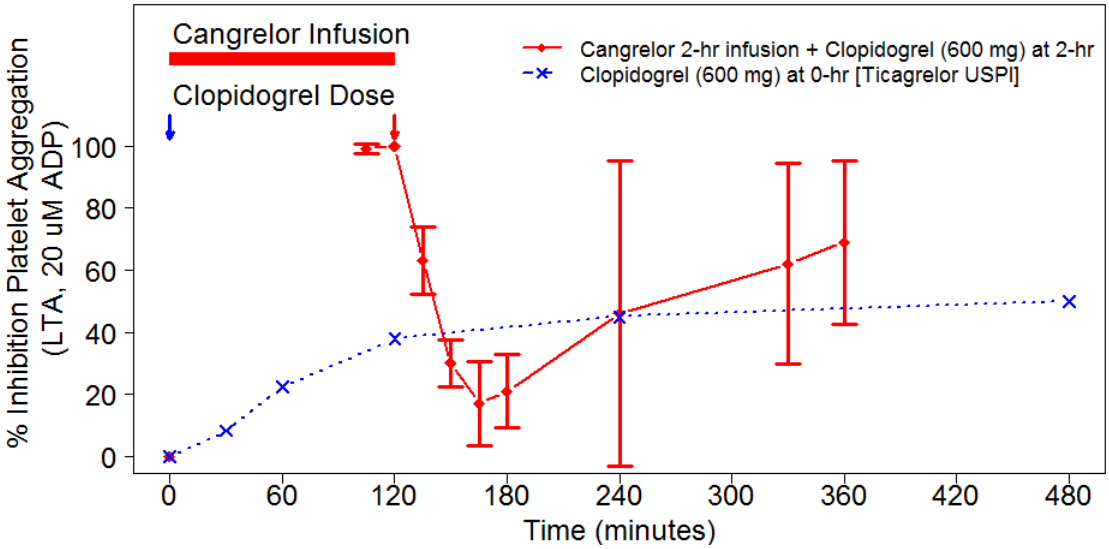

Figure 5 Recommended transition strategy for clopidogrel: administer 600 mg clopidogrel loading dose at the end of cangrelor infusion. The horizontal red bar indicates 2 h-infusion duration for cangrelor. The down arrows color matched to the plot lines indicate administration of clopidogrel 600 mg dose. Error bars represent 90 % confidence intervals. The blue dotted line is a representative time-course of antiplatelet effect seen with 600 mg clopidogrel when given alone, extracted from ticagrelor USPI. There was no clopidogrel reference treatment group in study MDCO-CAN-13-02. There was a temporary dip in antiplatelet activity after cangrelor infusion was stopped, but there was no attenuation in clopidogrel's pharmacological effects. Source: Prepared by FDA

[5] Clinical Pharmacology Review, Page 29, DARRTS date 01/10/2014

Transition to Prasugrel

Prasugrel (60 mg) was administered at 1 h (1-h prior to the end of infusion) (N=3) or 1.5 h (0.5-h prior to the end of infusion) (N=6), or 2 h (at the end of the cangrelor infusion) (N=3) in study MDCO-CAN-13-01 in patients with CAD. Study MDCO-CAN-13-02 also tested transition from cangrelor to prasugrel where a prasugrel 60 mg loading dose was given 30 min after end of cangrelor infusion (N=3). The observed time course of platelet response is shown in Figure 6.

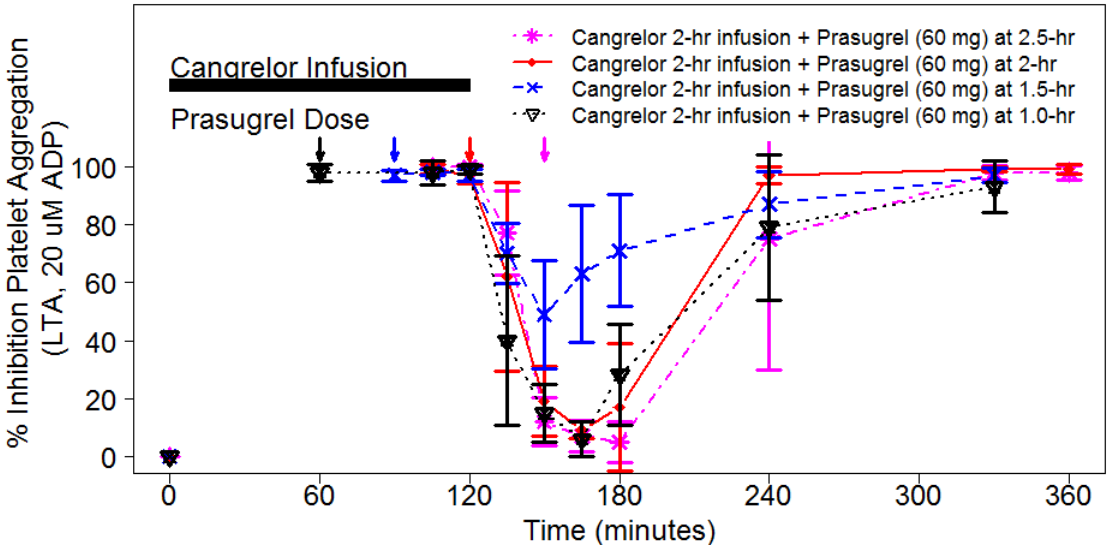

Figure 6 Percentage inhibition of platelet aggregation with prasugrel and cangrelor. The horizontal black bar indicates 2 h-infusion duration for cangrelor. The down arrows color matched to the plot lines indicate administration of prasugrel 60 mg dose. Error bars represent 90 % confidence intervals. This figure includes data from studies MDCO-CAN-13-01 and MDCO-CAN-13-02. Source: Prepared by FDA

Administration of prasugrel at 1.5 h (0.5 h prior to the end of the cangrelor infusion) limited the recovery of platelet activity to a greater extent after stopping cangrelor infusion. Prasugrel dosed at 1 h (1 h prior to the end of infusion) or at 2 h (end of infusion) allowed complete recovery of platelet activity to baseline (drug free) levels at 2-4 h. As seen in MDCO-CAN-13-01 there was also complete recovery of platelet activity to baseline levels when prasugrel was given at 2.5 h (0.5 h after stopping cangrelor infusion). All prasugrel treatment groups showed antiplatelet effects similar to that seen with cangrelor from 4 h time point onwards. Prasugrel showed higher than reported pharmacological response, on par with cangrelor, in this study (Figure 6). However, this is likely due to comparison of results between different studies.

Further, the prasugrel switch study results appear to suggest that administration at 1.5 h (0.5 h prior to the end of the cangrelor infusion) would minimize the period of time when platelet inhibition is less than maximal and that administration at either the end of infusion or 1 h prior to the end of the infusion would result in the similar platelet inhibition profiles. However, the clinical pharmacology review team has difficulty reconciling the observations for prasugrel in MDCO-CAN-13-01 and MDCO-CAN-13-02 with what was observed for clopidogrel in MDCO-CAN-13-02 and TMC-CAN-04-02 and what is known about the clinical pharmacology for prasugrel and clopidogrel.

The active metabolite of prasugrel is reported to have half-life greater than 2 h. As such the metabolite would be expected to be in systemic circulation even if the prasugrel dose was administered 1 h prior to the end of the infusion resulting in a less substantial decrease in platelet inhibition than observed. On the contrary, if the active metabolite was no longer systemically available with administration 1 h prior to the end of the infusion, it is not possible to explain similar platelet inhibition profile to that observed with administration of prasugrel at 2 h (end of the infusion).

Moreover, it's difficult to explain why administering prasugrel 0.5 h prior to the end of the cangrelor infusion would results in greater platelet inhibition given the expected onset time of the active metabolite and as the inhibition in this scenario appear magnified compared to administration at the end of the infusion (as opposed to time-shifted), we consider the observations in this arm a result of small sample size (n=3 or 6) and that making dosing recommendations based on this study is not justified. Since prasugrel belongs to the same class as that of clopidogrel, a reasonable approach would be to use prasugrel the same way as clopidogrel, when transitioning. Therefore, our recommendation is to administer loading dose of prasugrel immediately after stopping cangrelor infusion (Figure 7). An additional study which is appropriately powered would be needed to inform any other transition approaches with prasugrel.

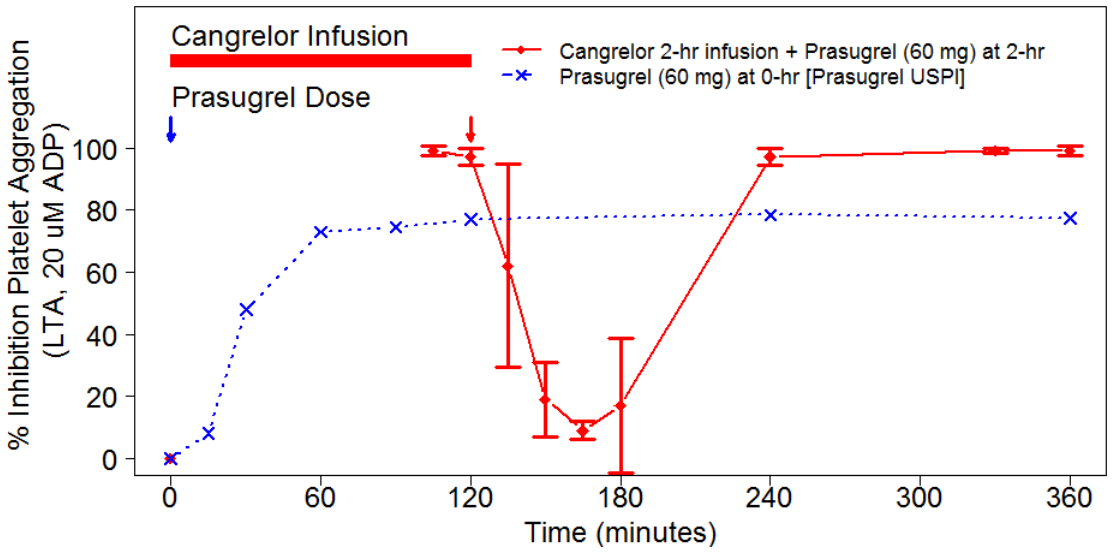

Figure 7 Recommended transition strategy for prasugrel: administer 60 mg prasugrel at the end of cangrelor infusion. The blue dotted line is a representative time-course of antiplatelet effect seen with 600 mg clopidogrel when given alone, extracted from prasugrel USPI. The horizontal red bar indicates 2 h-infusion duration for cangrelor. The down arrows color matched to the plot lines indicate administration of prasugrel 60 mg dose. Error bars represent 90 % confidence intervals. There was no prasugrel reference treatment group in prasugrel transition studies. There was a temporary dip in antiplatelet activity after cangrelor infusion was stopped, but there was no attenuation in prasugrel's pharmacological effects. Source: Prepared by FDA

A plot of time course of antiplatelet effect seen with the recommended transition strategies for all the three drugs are shown in Figure 8.

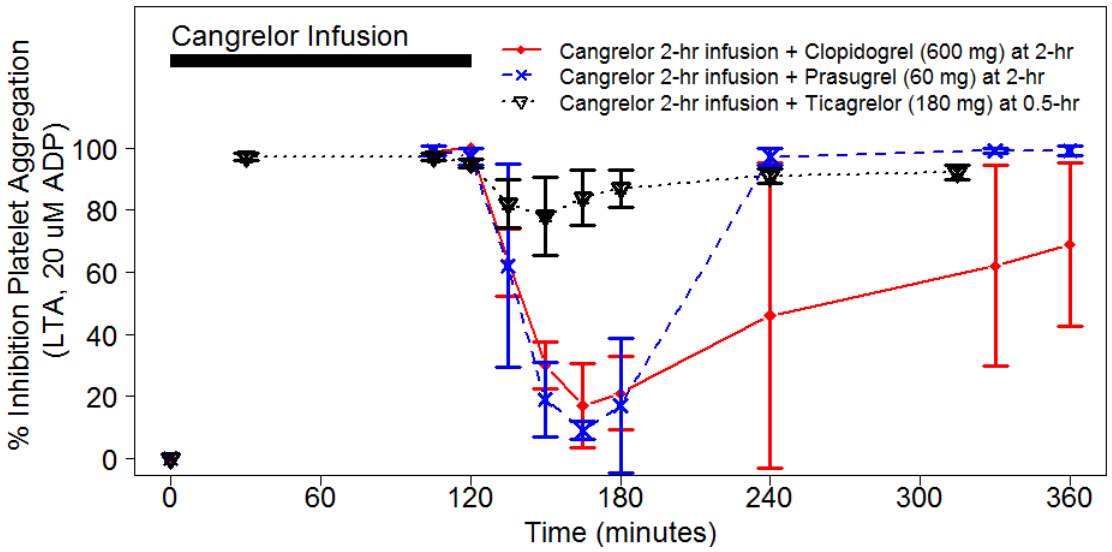

Figure 8 Recommended transition strategies for clopidogrel, prasugrel and ticagrelor. The horizontal black bar indicates 2 h-infusion duration for cangrelor. Error bars represent 90 % confidence intervals. Source: Prepared by FDA

Cangrelor with glycoprotein IIb/IIIa inhibitors

Mechanistic Expectation:

Cangrelor is a reversible platelet inhibitor that blocks binding of ADP to platelet $P2Y_{12}$ receptors, one of the pathways for activation of platelet-Gp IIb/IIIa complex. In a broad sense, drugs that inhibit Gp IIb/IIIa receptors act downstream in the platelet activation/aggregation cascade relative to platelet $P2Y_{12}$ receptor blockers[6]. Therefore, if platelet activation by ADP is blocked (by drugs like clopidogrel, prasugrel, ticagrelor or cangrelor) conformational changes to Gp IIb/IIIa receptors that induce binding to fibrinogen may not occur. Based on this hypothesis, the clinical consequence of administering cangrelor to patients on Gp IIb/IIIa inhibitors (GPIs) is expected to be minimal. However, there are no pharmacokinetic/pharmacodynamic or drug-drug interaction studies in the sponsor's original or current submissions that support this hypothesis.

[6] Circulation, 1995, 92:2373-2380. http://circ.ahajournals.org/content/92/9/2373.full

Clinical Experience:

There is limited clinical data on GPI use from the three CHAMPION Phase III studies. GPIs were allowed only as bail out therapy in the pivotal efficacy study CHAMPION-PHOENIX. The two other Phase III studies that failed to demonstrate clinical benefits for cangrelor, CHAMPION-PLATFORM and CHAMPION-PCI, both initially allowed GPI use at investigator's discretion but later actively discouraged their use by means of protocol amendments. Reported actual GPI use was 2.3 %, 8 % and 22 % in PHOENIX, PLATFORM and PCI studies, respectively[7]. The use of GPIs did not appear to affect treatment effect of cangrelor relative to clopidogrel for primary efficacy endpoint in all these studies, but the observed event rates were relatively higher in patients with GPI use than those without[8].

Observed bleeding events in the first 48 hours from CHAMPION-PCI study for patients with and without GPI use are listed below in Table 1. Patients with GPI use had higher incidence of GUSTO severe/life threatening and TIMI major bleeds for both cangrelor and clopidogrel treatment groups. The PCI study had about 22 % of patients on GPIs. CHAMPION-PLATFORM study also showed a similar trend but had fewer patients on GPIs (8 %). The clinical experience for cangrelor use with GPIs, predominantly from CHAMPION-PCI study, suggests an increase in bleeding risk with concurrent use. This is consistent with the USPIs of GPIs (tirofiban[9], abciximab[10], and eptifibatide[11]) which suggest an increased bleeding risk for GPIs when co-administered with antiplatelet drugs.

Table 1 **Comparison of bleeding events between patients with and without GPI use from CHAMPION-PCI study**

GUSTO Severe/Life Threatening Bleeds n/N (%)		
	Cangrelor	Clopidogrel
GPI use	4/1154 (0.3)	6/1170 (0.5)
No GPI use	6/3219 (0.2)	5/3194 (0.2)
TIMI Major Bleeds		
GPI use	15/1154 (1.3)	10/1170 (0.9)
No GPI use	4/3219 (0.1)	4/3149 (0.1)

Source: Adapted from Clinical Study Report TMC-CAN-05-02, CHAMPION-PCI, Pages 100-102

[7] Division Director Review, Page 3, DARRTS dated 4/30/2014

[8] Statistical Review, Page 8, DARRTS dated 4/23/2014

[9] AGGRASTAT® (tirofiban): http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/020912s019s020lbl.pdf

[10] ReoPro® (abciximab): http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/103575s5126lbl.pdf

[11] INTEGRILIN® (eptifibatide): http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/020718s037lbl.pdf

While the USPIs of ticagrelor[12] and prasugrel[13] allow concomitant use with GPIs, the usage setting is almost similar to the way cangrelor is proposed to be used. Cangrelor and GPIs are intravenous short acting drugs with a quick onset. Hence, there does not seem to be a situation that requires administration of both cangrelor and GPIs at the same time.

Therefore, our recommendation is not to use GPIs concurrently with cangrelor during PCI.

(b) (4)

[redacted]

[12] BRILINTA® (ticagrelor): http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022433s010lbl.pdf

[13] EFFIENT® (prasugrel): http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022307s010lbl.pdf

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/s/

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03/14/2015

JEFFRY FLORIAN
03/15/2015

RAJANIKANTH MADABUSHI
03/15/2015

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 204-958	**Reviewer:** Kareen Riviere, Ph.D.	
Submission Date:	4/30/2013; 2/6/14; 2/14/14; 3/18/14		
Division:	DCRP	**Team Leader:** Angelica Dorantes, Ph.D.	
Applicant:	The Medicines Company	**Acting Supervisor:** Richard Lostritto, Ph.D.	
Trade Name:	Kengreal	**Date Assigned:**	5/2/2013
Generic Name:	cangrelor for injection	**Date of Review:**	3/28/2014
Indication:	1. For the reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with coronary artery disease undergoing PCI. 2. To maintain P2Y12 inhibition in ACS patients or patients with stents who are at increased risk for thrombotic events (such as stent thrombosis) when oral P2Y12 therapy is interrupted due to surgery.	**Type of Submission:** 505(b)(1) NDA	
Formulation/strengths:	Powder for (b) (4) / 50 mg		
Route of Administration:	Intravenous		

SUMMARY:

The proposed to-be-marketed formulation was tested in three pivotal phase 3 efficacy and safety studies. In In these phase 3 clinical trials, encapsulated Plavix® (clopidogrel bisulfate) tablets were the active comparator. The clinical team requested that the Biopharmaceutics team assess whether the encapsulated- and non-encapsulated Plavix® tablets are equivalent.

The focus of this Biopharmaceutics review is on the evaluation of the *in vitro* dissolution profile comparison data supporting the similarity of the dissolution rates of the encapsulated- and non-encapsulated Plavix® tablets.

RECOMMENDATION:

The results from the comparative *in vitro* dissolution study indicate that the encapsulated and non-encapsulated Plavix® tablets do NOT have similar *in vitro* dissolution profiles. There are no available *in vivo* BE data to indicate that these formulations behave similarly or not *in vivo*. From the Biopharmaceutics perspective, it is not expected that the (b) (4) dissolution will cause the encapsulated Plavix® tablets to have significantly different bioavailability as the non-encapsulated Plavix® tablets and therefore we do not expect these products to be bio-inequivalent. However, we defer to the Clinical Team to decide on the clinical implications of this (b) (4) and to determine whether the Applicant will have to conduct an *in vivo* BE study to demonstrate that the encapsulated and non-encapsulated Plavix® tablets are in fact bioequivalent.

Kareen Riviere, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

cc: Dr. Richard Lostritto

ASSESSMENT OF BIOPHARMEUTICS INFORMATION

There was a concern as to whether the in vitro dissolution rate of the encapsulated and non-encapsulated Plavix tablets used in clinical study was similar. Thus, the following IR comments were conveyed to the Applicant on February 10, 2014.

FDA Information Request:
We would like to further clarify our request for additional information regarding the use of over-encapsulated Plavix tablets in all clinical studies, as it is important that your timely response is complete to address our concerns. Please provide the following additional information regarding the over-encapsulated Plavix tablets used in the clinical efficacy and safety studies:

1. *Complete comparative dissolution data (mean, individual, RSD, and profiles) at 5, 10, 15, 20, 30, 60 minute time points for the Plavix tablet versus the over-encapsulated formulation in the regulatory method and at least two other media (e.g. pH 4.5 and 6.8). If you are not using the regulatory dissolution method, please justify your selection of the dissolution testing conditions. Note that the dissolution data for each type of over-encapsulated tablet used should be provided. For example, we note that different capsules may have been used in different studies.*

2. *A tabular summary of the qualitative and quantitative composition of the over-encapsulated formulation used in each of the clinical studies. Also, please specify whether the US marketed Plavix was used for all countries for all trials and provide a copy of the certificate of analysis for each batch used in the clinical studies.*

Table 1. Composition of Clopidogrel Bisulfate Active Comparator Capsules

Component	Amount/Capsule
Plavix® (clopidogrel bisulfate) tablet, 75 mg	Two (2) Plavix® (clopidogrel bisulfate) tablets, 75 mg
	(b) (4)

Applicant's Response dated February 14, 2014

The Applicant stated that the quantitative composition and manufacturing process for the encapsulated Plavix tablets was the same for all the clinical trials. The Plavix® tablets were sourced from US and EU market. The clinical trials in EU countries used Plavix® sourced from EU.

The regulatory dissolution method for Plavix® tablets in current USP monograph is Apparatus II, 50 rpm, pH 2.0 HCL buffer dissolution medium, and 1000 mL volume. The Applicant adapted the USP method for evaluating the comparative dissolution of encapsulated and non-encapsulated Plavix® tablets. In order to eliminate the need for a sinker and mitigate artifacts due to the observed mounding, they chose to use dissolution USP Apparatus I. The 100 rpm agitation speed was selected as this is typical for Apparatus I and is considered a mild agitation condition. The dissolution medium is pH 2.0 HCL buffer and the medium volume is 1000 mL, same as in the regulatory method for Plavix® tablets.

For Plavix® tablets, the dissolution data are taken from a developmental study conducted in triplicate. For encapsulated Plavix® tablets, the data for 10 and 20 minute time points are taken from early development studies. The data for 15, 30 and 45 minutes represents the mean of all batches used in Phoenix clinical trials which included Plavix® tablets sourced from both US and EU (refer to Tables 2 and 3).

Table 2. Comparison of Time Course of Dissolution of Encapsulated Plavix® Tablets and Plavix® Tablets

	Encapsulated Plavix Tablets	Plavix Tablets
Time (Minutes)	Mean %Clopidogrel %RSD Range	Mean %Clopidogrel %RSD Range
10	(b) (4)	
15		
20		
30*		
45		

Table 3. Summary of Clopidogrel Bisulfate Active Comparator Product Batches used in Clinical Studies

Lot Number	Clinical Study Used	Plavix Source
L0302325	PHOENIX	US
L0305334	PHOENIX	US
L0303429	PHOENIX	EU
L0306547	PHOENIX	EU
L0205922	PHOENIX, CHAMPION PCI & PLATFORM	US
L0206649	PHOENIX, CHAMPION PLATFORM	US
KH2005042	CHAMPION PCI & PLATFORM	US
KK2006013	CHAMPION PCI & PLATFORM	US
KM2006033	CHAMPION PCI & PLATFORM	US
L0200997	CHAMPION PCI & PLATFORM	US
KA2006061	CHAMPION PCI & PLATFORM	EU
L0201463	CHAMPION PCI & PLATFORM	EU
L0205158	CHAMPION PCI & PLATFORM	EU
L0206648	CHAMPION PLATFORM	EU

The Applicant stated that they did not evaluate the dissolution of encapsulated and non-encapsulated Plavix® tablets in other pH media requested (4.5 and 6.8) because clopidogrel bisulfate is practically insoluble under these pH conditions and will result in incomplete release without the aid of surfactants.

Reviewer's Assessment:

The Applicant's justification for not using the regulatory dissolution method for the comparative dissolution studies is acceptable. It is known that the Apparatus I (basket) is sometimes better suited for capsule formulation than Apparatus II (paddle). Also, 100 rpm agitation speed is suitable for the basket method.

The Applicant averaged the dissolution data from multiple lots used in the clinical supplies to obtain the dissolution data for the encapsulated tablets presented in Table 2, while the dissolution data for the tablets appears to be recently conducted. These data in Table 2 are incomplete and therefore f2 similarity testing could not be performed.

Additional Data Submitted on March 18, 2014

The Applicant submitted additional dissolution profile data comparing encapsulated and non-encapsulated Plavix® tablets (refer to Tables 5-6 and Figure 1). They claim that the tablets were encapsulated (b) (4) (see Table 4). The applicant

also stated that manufacturing and dissolution testing was conducted (b) (4) using the following dissolution testing conditions (same as above):

USP Apparatus	Rotation Speed	Media Volume	Temp	Medium
I (Baskets)	100 rpm	1000 mL	37°C	pH 2.0 HCl buffer

Table 4. Composition of Encapsulated Plavix Tablet

(b) (4)

Table 5. Dissolution Profiles of Encapsulated Plavix Tablets

(b) (4)

Table 6. Dissolution Profiles of Non-encapsulated Plavix Tablets

(b) (4)

*Each unit contains 2 Plavix tablets.

Figure 1. Comparison of Dissolution Profiles of Encapsulated and Non-encapsulated Plavix®

Reviewer's Assessment:

- ***The same formulation of encapsulated tablets was used in this recent study (compare Table 1 and Table 4). Also, the same dissolution testing conditions as above were used to generate data in this study.***

- ***The dissolution data in Figure 1 was*** (b) (4) ***% RSD) at the*** (b) (4) ***minute time-point for the encapsulated tablets. Due to the*** (b) (4) ***other statistical approaches (parametric/non-parametric) as discussed in the Dissolution Guidance should be used to estimate the similarity of the profiles.***

- ***It is noted that the Applicant did not provide data in other dissolution media as requested since they claimed that clopidogrel bisulfate is practically insoluble under these pH conditions and will result in incomplete release without the aid of surfactants. The Applicant's justification is acceptable.***

- ***The Applicant states that the dissolution rate is the same for both formulations but that there*** (b) (4) ***The Applicant's statement*** (b) (4) ***for the encapsulated formulation is reasonable. Nevertheless, the fact that the dissolution profiles are different should not be ignored.***

- ***In conclusion, the provided comparative in vitro dissolution data indicate that the encapsulated and non-encapsulated Plavix® tablets do not have similar in vitro dissolution profiles. There are not sufficient data to conclude whether or not these formulations behave similarly or not, in vivo. From the Biopharmaceutics perspective, it is not expected that*** (b) (4) ***in dissolution will cause the encapsulated Plavix® tablets to have significantly different pharmacokinetics as the non-encapsulated Plavix® tablets. However, we defer to the Clinical Team to decide on the clinical implications of this*** (b) (4) ***and to determine whether the Applicant will have to conduct an in vivo BE study to demonstrate that the encapsulated and non-encapsulated Plavix® tablets are in fact bioequivalent.***

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/s/

KAREEN RIVIERE
03/28/2014

ANGELICA DORANTES
03/28/2014

CLINICAL PHARMACOLOGY REVIEW

NDA Number:	204958
Submission Dates:	04/30/2013
Submission Type:	Original NDA (NME, Standard Review)
Brand Name:	To be finalized
Generic Name:	Cangrelor for injection
Drug Class:	$P2Y_{12}$ antagonist
Dosage Form/Route:	Lyophilized powder for (b) (4) /intravenous (IV)
Proposed Indications & Dose:	(1) For reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with coronary artery disease undergoing percutaneous coronary intervention (PCI) Proposed dose: 30 µg/kg IV bolus + 4 µg/kg/min IV infusion for at least 2 hours or duration of procedure whichever is longer (2) To maintain $P2Y_{12}$ inhibition in patients with acute coronary syndromes (ACS) or patients with stents who are at increased risk for thrombotic events (such as stent thrombosis) when oral $P2Y_{12}$ therapy is interrupted due to surgery Proposed dose: 0.75 µg/kg/min IV infusion as soon as possible after discontinuation of oral $P2Y_{12}$ inhibitors until 1 hour prior to surgery
Applicant:	The Medicines Company
OCP Division:	DCP1
OND Division:	Division of Cardiovascular and Renal Products (DCRP)
Reviewers:	Sreedharan Sabarinath, PhD Jeffry Florian, PhD
Team Leaders:	Yaning Wang, PhD Rajanikanth Madabushi, PhD

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1. EXECUTIVE SUMMARY

The Medicines Company has submitted an original New Drug Application (NDA 204958) for cangrelor for injection. The applicant is seeking approval for two proposed indications: (1) for the reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with coronary artery disease undergoing percutaneous coronary intervention (PCI), and (2) to maintain $P2Y_{12}$ inhibition in patients with acute coronary syndromes (ACS) or patients with stents who are at increased risk for thrombotic events (such as stent thrombosis) when oral $P2Y_{12}$ therapy is interrupted due to surgery.

Cangrelor is an intravenous (IV), reversible $P2Y_{12}$ antagonist that inhibits adenosine diphosphate (ADP)-induced activation and aggregation of platelets. Cangrelor is a substituted nucleotide and undergoes rapid de-phosphorylation by nucleotidases in the circulation. The effective elimination half-life of cangrelor is about 3-6 minutes and its clearance is independent of the hepatic function.

The clinical development program supporting this NDA included one pivotal efficacy study called CHAMPION-PHOENIX in the PCI setting. There were two other similar Phase III studies (CHAMPION-PCI and CHAMPION-PLATFORM) that were considered as supportive and were used to assess the safety of cangrelor in patients. All these studies used a 30 µg/kg bolus IV dose followed immediately by 4 µg/kg/min continuous IV infusion for at least 2 hours or for the duration of the index procedure, whichever was longer. The CHAMPION-PHOENIX was a double-blind, randomized, controlled study in patients with coronary artery disease (stable angina, ACS and patients with stents) who require P_2Y_{12} inhibition for PCI (N~10939, 1:1 randomization to cangrelor or clopidogrel). Clopidogrel was the comparator for this study. The primary efficacy endpoint was a composite of death/myocardial infarction (MI)/ischemia driven re-vascularization (IDR)/stent thrombosis (ST) at 48 hours post randomization. The applicant reported a 21 % relative risk reduction with cangrelor compared to treatment with clopidogrel (Odds Ratio: 0.79, 95 % CI 0.66-0.93, p=0.005).

A double-blind, randomized, placebo controlled, PK/PD study (BRIDGE) in patients undergoing cardiac surgery (N~183 for stage II, 1:1 randomization to cangrelor or placebo) formed the basis for seeking approval for the second indication. The BRIDGE study tested cangrelor for bridging patients with ACS or patients with stents at increased risk of thrombotic events due to discontinuation of an oral platelet $P2Y_{12}$ inhibitor prior to surgery. Platelet reactivity units (PRU) were measured during the treatment period (about 5 days) and the primary efficacy analysis was the percentage of patients with all samples during the infusion achieving PRU < 240, as determined by *VerifyNow*™ $P2Y_{12}$ test. More than 98 % of patients treated with

cangrelor maintained target platelet reactivity levels (PRU < 240) at all times during the infusion (0.75 µg/kg/min for about 5 days) period compared to about 19 % of placebo treated patients. The threshold platelet reactivity (PRU < 240) used in BRIDGE efficacy analysis is not based on any established pharmacodynamics (PD)-outcome relationships. However, it is not unreasonable to expect that inhibition of platelet reactivity is important for the reduction of thrombotic cardiovascular events. From this perspective the efficacy could be expected to be maintained when platelet reactivity is reduced. Further, upon stopping the IV infusion of cangrelor at least 1 hour before the surgery, the platelet reactivity levels are comparable to that of the control arm (i.e., 5-7 days after stopping oral $P2Y_{12}$ treatment). The results from the PHOENIX trial, even though in a different population with a different dosing regimen for shorter duration, provide some assurance of bridging between antiplatelet activity and efficacy. Cangrelor can therefore be considered as a viable option to provide antiplatelet effect for up to 1 hour prior to surgery compared to the current standard of care, which requires cessation of the treatment with oral $P2Y_{12}$ inhibitors for at least 5-7 days before surgery.

The IV formulation used in the Phase III program was similar to the to-be-marketed formulation and therefore no pivotal BE study was required.

1.1 Recommendations

The Office of Clinical Pharmacology (OCP) has reviewed the clinical pharmacology information submitted to the NDA 204958 (cangrelor for injection). The NDA can be approved from a clinical pharmacology perspective.

1.2 Post Marketing Requirements/Commitments

None.

2. SUMMARY OF OCP FINDINGS

2.1 Background

Cangrelor is a platelet $P2Y_{12}$ antagonist and other approved drugs in this class include ticlopidine, clopidogrel, prasugrel and ticagrelor. Cangrelor reversibly blocks $P2Y_{12}$ receptors and inhibits ADP induced platelet activation and aggregation. The applicant (The Medicines Company) is seeking approval for cangrelor for injection for two indications: 1) for reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with coronary artery disease undergoing PCI, and 2) to maintain $P2Y_{12}$ inhibition in patients with ACS or patients with stents who are at increased risk for thrombotic events (such as stent thrombosis) when oral $P2Y_{12}$ therapy is interrupted due to surgery.

2.2 Current Submission

The current NDA is supported by a single pivotal efficacy study CHAMPION-PHOENIX. There are two other Phase III studies, CHAMPION-PCI and CHAMPION-PLATFORM, which are considered supportive and were used for safety assessments. The clinical pharmacology program for cangrelor comprised of about 16 clinical studies. These studies describe ADME of cangrelor in healthy subjects, PK/PD in healthy subjects and in patients, a renal impairment study, a thorough QT study, PD studies testing transition strategies for cangrelor with clopidogrel and ticagrelor, and characterization of drug-drug interaction with concurrent administration of aspirin, heparin and glyceryl trinitrate.

2.3 Pharmacokinetics

- The pharmacokinetics of cangrelor is linear over the range of 0.025 - 4 µg/kg/min infusion.

- Cangrelor is metabolized rapidly in the systemic circulation by nucleotidases and is considered independent of hepatic function.

- The major circulating metabolite AR-C69712 is several thousand fold less active at human platelet $P2Y_{12}$ receptors. All other metabolites detected are reported to be pharmacologically inactive.

- Upon continuous infusion, steady-state is reached in ~ 30 minutes. Based on this, the average effective elimination half-life of cangrelor is about 3-6 minutes. Upon stopping of the infusion, cangerlor displays a biphasic decline, with a longer terminal elimination half-life of 14-26 hours at higher doses.

- The plasma protein binding of cangrelor is ~ 98 %
- About 58 % and 35 % of the radiolabeled dose is excreted in urine and feces, respectively

2.4 Exposure-Response relationships

There was no pharmacokinetic (PK) data collected in the Phase III studies and the pharmacodynamics (PD) sampling (to assess platelet inhibition) was limited to about 104 patients from the supportive study CHAMPION-PCI and did not include any subjects from the pivotal efficacy study CHAMPION-PHOENIX. Therefore, any potential relationships between cangrelor exposure and its PD with safety or efficacy outcome measures could not be evaluated.

2.5 Intrinsic factors

2.5.1 Body weight, Sex, Age and Race

A population PK analysis indicated that body weight is the only significant covariate for cangrelor exposure. This impact of body weight is already accounted for in the weight-based cangrelor infusion regimen.

2.5.2 Renal Impairment

A dedicated study comparing healthy subjects with normal renal function (creatinine clearance CrCL > 90 mL/min) and patients with renal impairment (CrCL 20-70 mL/min) studied two maximum infusion rates (2 μg/kg/min and 4 μg/kg/min) for cangrelor in an unbalanced design. Direct comparison of exposures between healthy subjects and renally impaired subjects within dose groups was difficult in this study because of the lesser number of subjects in the reference groups (N ~ 3 for the higher infusion rate group). However, the effective elimination half-life and PK/PD for platelet inhibition of cangrelor were not significantly altered in renally impaired subjects. Further, comparison of the PK in patients with renal impairment in this study with pooled healthy controls from the cangrelor development program showed that impairment of renal function did not significantly alter the pharmacokinetics of cangrelor. The Phase III studies for cangrelor included patients with impaired renal function (CHAMPION-PLATFORM: N ~ 623 and CHAMPION-PCI: N ~ 688 patients with CrCL < 60 mL/min) and no significant changes in the safety/efficacy profile of cangrelor was evident in these patients. Therefore, no dose adjustments are proposed for cangrelor in patients with renal impairment.

2.5.3 Hepatic Impairment

Since the biotransformation of cangrelor is believed to be mediated through nucleotidases in systemic circulation, which is considered independent of hepatic function, there was no dedicated hepatic impairment study included in the clinical development program.

2.5.4 Pediatrics

The PK of cangrelor is not studied in pediatrics.

2.6 Drug-Drug Interactions

In vitro studies indicated that cangrelor and its metabolite AR-C69712 have minimal potential to inhibit or induce CYP enzymes at therapeutic concentrations. The PK of cangrelor and AR-C69712 did not alter significantly when co-administered with a combination of aspirin, heparin and glyceryl trinitrate. The inhibition in ADP induced platelet aggregation by cangrelor was comparable between both treatment groups in this study. But there were prolongation in bleeding times and higher incidence of adverse events like purpura and headaches when cangrelor was co-administered with a combination of aspirin, heparin and glyceryl trinitrate.

Clinical studies also evaluated the transition strategies while switching from and to oral $P2Y_{12}$ drugs like clopidogrel and ticagrelor with cangrelor. There is attenuation in clopidogrel pharmacological effects on platelets when co-administered with cangrelor. This could probably be because of the competition between cangrelor and the active metabolite of clopidogrel (which has very short plasma half-life) for $P2Y_{12}$ receptors. However, administering clopidogrel after stopping cangrelor infusion did not alter the anti-platelet effects usually seen with clopidogrel. This is because of the short effective half-life (3-6 minutes) of cangrelor. However, the pharmacological effect of ticagrelor ($t_{1/2}$ ~ 7 hours for ticagrelor and ~ 9 hours for the active metabolite) was not significantly altered when co-administered with cangrelor.

2.7 Biopharmaceutics

The pivotal efficacy study CHAMPION-PHOENIX and the Phase II Study BRIDGE used the same IV formulation (cangrelor diluted in sterile normal saline) as the proposed marketing image formulation.

3. QUESTION BASED REVIEW

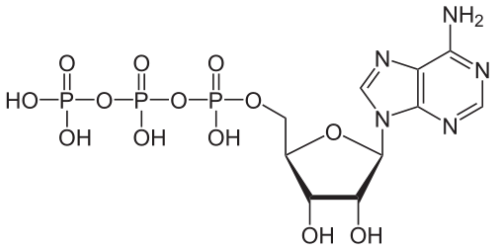
3.1 General Attributes

Cangrelor is a reversible $P2Y_{12}$ antagonist that blocks ADP induced platelet activation and aggregation. The chemical structure of cangrelor is similar to that of adenosine triphosphate, ATP (Figure 1). Other approved drugs in this class include ticlopidine, clopidogrel, prasugrel (all are thienopyridine pro-drugs and are irreversible blockers of platelet $P2Y_{12}$ receptors) and ticagrelor (a reversible blocker).

3.1.1 Drug Substance

Cangrelor for injection is a sterile white to off-white lyophilized powder for IV infusion. The chemical name of cangrelor is tetra sodium salt of N6-[2-(methylthio)ethyl]-2-[(3,3,3,-trifluropropyl)-5'-adenylic acid, monohydride with (dichloromethylene)bisphosphonic acid. It has a molecular formula of $C_{17}H_{21}N_5Cl_2F_3Na_4O_{12}P_3S_2$ and a molecular weight of 864.3 g/mol (See Figure 1B).

A



B

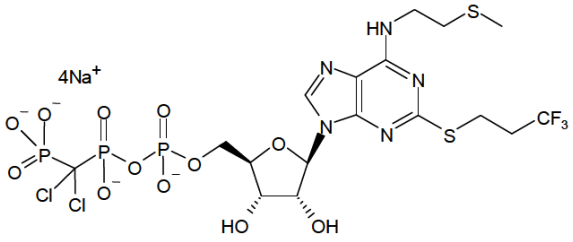


Figure 1 The chemical structures of (**A**) adenosine triphosphate, ATP and (**B**) cangrelor

3.1.2 What are the proposed mechanism of action and therapeutic indication?

Cangrelor reversibly blocks the $P2Y_{12}$ platelet receptors and prevents ADP-induced platelet activation and aggregation. ADP plays a key role in the genesis of physiological platelet-rich hemostatic plugs and of pathological arterial thrombi. The transduction of the ADP signal involves its interaction with 2 platelet receptors, the G_q-coupled $P2Y_1$ receptor and the G_i-

coupled $P2Y_{12}$ receptor. Concomitant activation of both the G_q and G_i pathways by ADP is necessary to elicit normal platelet aggregation (Figure 2).

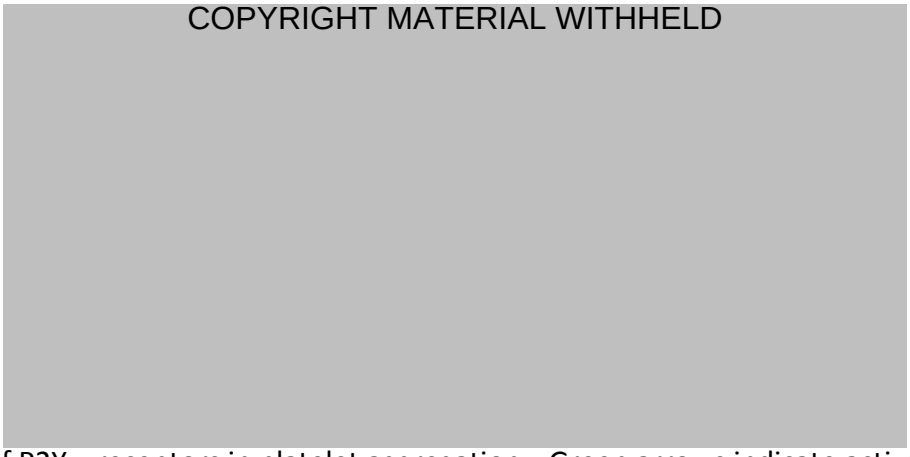


Figure 2 Role of $P2Y_{12}$ receptors in platelet aggregation . Green arrows indicate activation; red line, inhibition; blue line, amplification; and dotted black line, secretion. Ref. Cattaneo M *et al*. Circulation. 2010, 121:171-179

The applicant is seeking approval for cangrelor for the following two indications:

- **PCI:** For the reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with coronary artery disease undergoing percutaneous coronary intervention (PCI), and
- **BRIDGE:** To maintain $P2Y_{12}$ inhibition in patients with acute coronary syndromes (ACS) or patients with stents who are at increased risk for thrombotic events (such as stent thrombosis) when oral $P2Y_{12}$ therapy is interrupted due to surgery

[1] ADP, by interacting with $P2Y_{12}$, a 7-transmembrane receptor that is coupled to the inhibitory G protein G_i, induces platelet aggregation and amplifies the aggregation response that is induced by other agonists or by ADP itself, interacting with its other platelet receptor, $P2Y_1$. In addition, $P2Y_{12}$ stabilizes the platelet aggregates and amplifies the secretion of platelet dense granules stimulated by secretion-inducing agonists (which are coupled to G_q). Although $P2Y_{12}$ is coupled to inhibition of adenylyl cyclase (AC) through G_i, this function does not appear to be directly related to $P2Y_{12}$-mediated platelet activation. However, it could have important implications *in vivo*, where platelets are exposed to the inhibitory prostaglandin PGI2 (prostacyclin), which inhibits platelet aggregation by increasing platelet cAMP through activation of AC mediated by Gs; inhibition of AC by $P2Y_{12}$ counteracts the inhibitory effect of prostacyclin, thereby favoring the formation of platelet aggregates *in vivo*.

3.1.3 What are the current treatments available for the proposed indication?

Several oral $P2Y_{12}$ antiplatelet drugs, such as ticlopidine, clopidogrel, prasugrel, and ticagrelor are available that can reduce thrombotic risks by inhibiting platelet activation and aggregation. The ACCF/AHA/SCAI practice guidelines[2] for PCI recommends the use a loading dose of a $P2Y_{12}$ inhibitor in patients undergoing PCI with stenting (options include clopidogrel 600 mg or prasugrel 60 mg or ticagrelor 180 mg) before the procedure (within 24 hours) and then continue on maintenance oral antiplatelet therapy after the procedure.

Most of the currently approved oral antiplatelet drugs have an onset of pharmacological action of few hours and an offset of up to few days. Patients receiving oral antiplatelet drugs who require elective surgery are currently advised to stop taking their antiplatelet drugs for 5-7 days so as to minimize the risk for bleeding during surgery. Such discontinuation may result in an elevated risk for thrombosis. The applicant is seeking an indication where cangrelor provides continued platelet inhibition while oral $P2Y_{12}$ antiplatelet drugs are stopped, prior to an elective surgery. The offset in pharmacological activity for cangrelor is approximately < 2 hours and the treatment can continue up to few hours prior to surgery without increasing the risk for bleeding during surgery. There are no drugs approved specifically for this proposed indication, even though bridging anticoagulant therapy (*e.g.* heparins) is available for some instances.

3.1.4 What are the proposed dosages and route of administration?

Cangrelor is available as lyophilized powder for IV infusion. Each 10 mL vial containing 50 mg of cangrelor (free acid) is reconstituted with sterile water for injection and further diluted with normal saline (0.9 % NaCl) or 5 % dextrose for intravenous infusion.

The proposed dose for the PCI indication is a bolus IV dose of 30 µg/kg prior to the procedure followed immediately by a continuous IV infusion of 4 µg/kg/min for 2 hours or for the duration of the PCI procedure, whichever is longer.

For the bridge indication a continuous IV infusion of cangrelor at a rate of 0.75 µg/kg/min after stopping oral $P2Y_{12}$ inhibitors and continuing the infusion until one hour prior to administration of anesthesia for surgery is proposed. The bridging period could be up to 7 days.

[2] 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. Journal of the American College of Cardiology, 2011, 58: e44-122

3.2 General Clinical Pharmacology

3.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The primary evidence for efficacy in support of the PCI indication is from CHAMPION-PHOENIX Phase III study (TMC-CAN-10-01) in patients with stable angina (SA), non-ST-segment elevation ACS (NSTE-ACS) and ST-segment elevation myocardial infarction (STEMI). A single placebo-controlled Phase II study called BRIDGE (TMC-CAN-08-02) in patients with ACS or with stents awaiting cardiac surgery supports the bridge indication. The clinical pharmacology program included PK studies in healthy subjects (SC-931-5014, SC-931-5036, SC-931-9064, TMC-CAN-04-02) as well as in patients with UA or myocardial infarction (SC-931-5058, SC-931-5060, SC-931-5135), mass balance and excretion studies (SC-931-9017 and SC-100199), a DDI study with concurrent administration of a combination of aspirin, heparin and glyceryl trinitrate (SC-931-5037), a PK study in patients with impaired renal function (SC-931-5109) and studies assessing transition strategies while switching from or to cangrelor for oral $P2Y_{12}$ drugs like clopidogrel and ticagrelor (MDCO-CAN-12-03, TMC-CAN-04-02, TMC-CAN-08-02). The design features of the Phase III studies are described in section 3.2.3.

3.2.2 Were correct moieties identified and properly measured to access clinical pharmacology?

The applicant measured cangrelor (AR-C69931) and its major circulating metabolite AR-C69712, a nucleoside formed by de-phosphorylation in human plasma using validated analytical methods. This metabolite is reported to be several thousand (~ 70,000) fold less potent than cangrelor at human $P2Y_{12}$ receptors. Some clinical pharmacology studies (*e.g.* SC-931-5014, SC-931-5036 and SC-931-5109) monitored additional pharmacologically inactive metabolites AR-C90439, AR-C90441 and AR-C71301.

3.2.3 What are the key features of the Phase III trials of cangrelor?

The applicant conducted three Phase III studies (CHAMPION-PCI, PLATFORM and PHOENIX) in patients with ACS/coronary artery disease (CAD) undergoing PCI (Figure 3). All these studies used a single dose level of 30 µg/kg/min IV bolus followed by 4 µg/kg/min infusion for cangrelor and had clopidogrel (300 or 600 mg) as comparator.

CHAMPION-PHOENIX was the pivotal efficacy study and used more restrictive criteria to define per-procedural myocardial infarction (MI) in patients for whom baseline MI could not be excluded compared to other two studies, in addition to other subtle design differences. CHAMPION-PHOENIX was a prospective, randomized (1:1), double-blind, double-dummy, comparator controlled (clopidogrel 300 or 600 mg), parallel-group, superiority study in

approximately 11145 patients. The primary efficacy endpoint was a composite of death/MI/IDR/ST assessed at 48 hours after randomization. The components of primary efficacy endpoint were also assessed at 30 days. The safety endpoints included various bleeding assessments, such as GUSTO bleeding. There was no PK/PD assessments included in this study. Details of the dose selection are provided in Section 3.2.4.

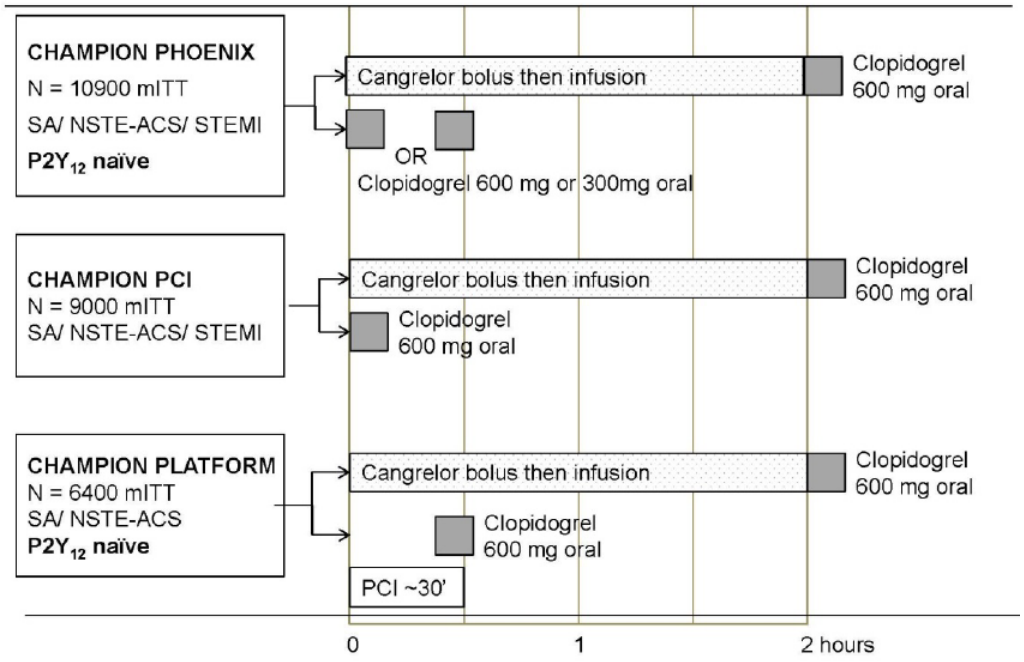


Figure 3. CHAMPION study designs. The shaded square box represents the approximate timing of clopidogrel dose post randomization. CHAMPION-PLATFORM did not include STEMI patients and the clopidogrel dose (600 mg) was administered immediately post-PCI procedure in the comparator arm in this study. The average duration of the PCI procedure is ~ 30 minutes. CHAMPION-PCI study included both P2Y12 naïve and experienced patients. SA - Stable Angina, NSTE-ACS – non-ST segment elevation acute coronary syndrome, STEMI – ST-segment elevation myocardial infarction, PCI – percutaneous coronary intervention, mITT – modified intent-to-treat.

3.2.4 How was the Phase III doses selected?

3.2.4.1 For PCI indication

The cangrelor dose selection was based on results from early phase PK/PD studies. Results from studies in healthy subjects (SC-931-5014 and SC-931-5036) demonstrated the dose-response (platelet inhibition) of cangrelor and provided justification for using an IV bolus dose to achieve steady state cangrelor concentrations (hence, targeted platelet inhibition) faster on

treatment. A Study in patients with unstable angina or non-Q-wave MI (SC-931-5058) provided additional support for 2 and 4 µg/kg/min intravenous infusion rates in a PCI population based on a target of 90 % platelet inhibition in > 80 % of patients. Finally, the study TMC-CAN-04-02 in healthy subjects evaluated a dosing regimen with combined IV bolus and maintenance infusion. This study was used for supporting the use of 30 µg/kg IV bolus dose followed by a 4 µg/kg/min IV infusion based on platelet inhibition assessments.

3.2.4.1.1 Dose-response in healthy volunteers and justification for bolus dosing

The dose-ranging studies conducted in healthy volunteers (SC-931-5014 and SC-931-5036) demonstrated the relationship between inhibition of platelet aggregation and cangrelor infusion rate, with near complete inhibition at infusion rates at or exceeding 1 µg/kg/min (Figure 4). In addition, as steady state exposures of cangrelor are achieved after ~ 30 minutes, there is a period (~ 30 minutes) between the start of the infusion and steady-state where the percentage of platelet inhibition is increasing to near maximum. To eliminate this initial 30-minute period required to achieve complete inhibition, the applicant used a bolus dose that is 7.5-fold higher than the proposed target infusion rate.

The bolus dose necessary to achieve similar exposures to a target infusion rate is calculated as[3]: bolus dose = Target Infusion/CL × V. The Target Infusion rate here is 4 µg/kg/min (See Section 3.2.4.1.2 for details). Based on the clearance (46.1 L/hr) and central volume of distribution (3.4 L) estimates from the population PK model, a bolus dose, which is about 4.4-fold higher than the target infusion rate would be necessary for cangrelor. The bolus dose selected by the applicant will exceed the dose necessary to achieve platelet inhibition expected at steady state for the accompanying target infusion, but will quickly equilibrate given the rapid effective half-life of 3-6 minutes for cangrelor.

[3] Under the assumption of a One-Compartment PK model

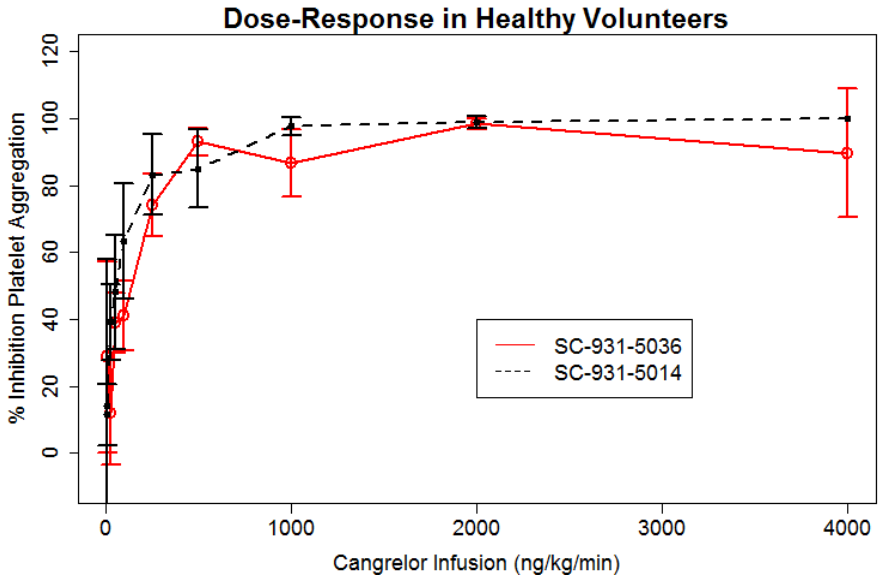


Figure 4. Percent inhibition of platelet aggregation to 3 µM ADP as measured by whole blood impedance assay (WBIA) versus cangrelor infusion rate in healthy male/female volunteers.

3.2.4.1.2 Dose-response in patients and justification for target infusion rate

Study SC-931-5058 evaluated cangrelor at three separate stepped, dose titration schemes followed by a plateau infusion in patients with UA or non-Q-wave MI. For the purpose of this analysis, we will focus on the observed percentage of platelet inhibition 30-minutes following each dose step (0.05, 0.2, 0.5, 1, 2, or 4 µg/kg/min) across the three dose escalation schemes (Parts I & II: 0.05, 0.2, 0.5 and 2 µg/kg/min, Part III: 0.2, 1, 2, 4 µg/kg/min) and treatment duration. Similar to the observations in healthy volunteers, cangrelor doses of 1 µg/kg/min or higher were associated with a mean percentage inhibition of ADP-induced platelet aggregation approaching 100 % (Figure 5). However, a categorical analysis of individual patient platelet inhibition demonstrates that while the mean percentage of platelet inhibition may have been similar at cangrelor doses of 1 µg/kg/min or higher, cangrelor doses of 2 or 4 µg/kg/min were associated with a greater percentage of patients achieving complete (~100 %) inhibition of ADP-induced platelet aggregation (Table 1). This observation supports that while average maximum inhibition may be achieved at lower infusion rates, higher cangrelor doses may be necessary to achieve maximum inhibition in the overall population. The applicant used this observation as a justification for carrying forward a high infusion rate (4 µg/kg/min) to the Phase III studies in the PCI setting.

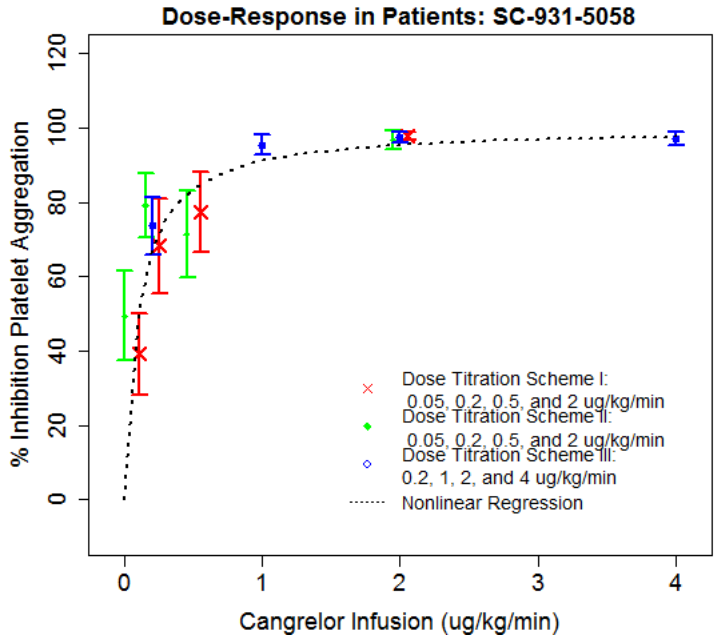


Figure 5. Percent inhibition of platelet aggregation to 3 µM ADP as measured by whole blood impedance assay (WBIA) versus cangrelor infusion rate in patients with unstable angina or non-Q-wave myocardial infarction. Parts I, II and III represent different dose escalation schemes. Values are mean and standard error.

Table 1 Percentage of patients in study SC-931-5058 exhibiting different levels of platelet inhibition with 3 µM ADP as measured by WBIA for various cangrelor infusions (0.05 – 4 µg/kg/min).

Cangrelor IV (µg/kg/min)	N	Number (%) of Patients Exhibiting Different Levels of Platelet Inhibition			
		≤ 60 %	> 60 to 80 %	> 80 to < 100 %	100 %
0.05	24	17 (71 %)	3 (13 %)	4 (17 %)	0
0.2	34	10 (29 %)	9 (26 %)	10 (29 %)	5 (15 %)
0.5	21	6 (29 %)	5 (24 %)	5 (24 %)	5 (24 %)
1	14	0	1 (7 %)	8 (57 %)	5 (36 %)
2	38	0	0	13 (34 %)	25 (66 %)
4	14	0	0	2 (14 %)	12 (86 %)

3.2.4.1.3 Combined IV bolus and maintenance infusion regimen

A combined bolus and infusion maintenance dose was evaluated in study TMC-CAN-04-02. This study was conducted in healthy volunteers and compared platelet inhibition using cangrelor administered as either: 15 µg/kg IV bolus followed by 2 µg/kg/min infusion or 30 µg/kg IV bolus

followed by 4 µg/kg/min infusion. The duration of the cangrelor infusion was 1-hour, and ADP-induced platelet inhibition was assessed using a variety of PD measurements including whole blood impedance aggregation (WBIA) and flow cytometry for platelet activation in response to ADP. Based on WBIA complete inhibition of platelet activation was achieved following bolus administration for both doses and maintained throughout the cangrelor infusion period.

Based on a 5 µM ADP-induced P-Selectin expression assessed by flow cytometry, maximum inhibition was achieved in both treatment arms after the bolus, but it was only maintained during the infusion in the high infusion rate arm while it declined to 85 % by the end of the infusion in the low infusion rate arm. Further separation between the tested regimens was observed at 20 µM ADP-induced P-Selectin expression (Figure 6) with greater maximum inhibition in the high dose arm following the bolus administration and maintained throughout the infusion. Median percent inhibition was about 96 % in the high dose arm and about 87 % in the low dose arm, respectively.

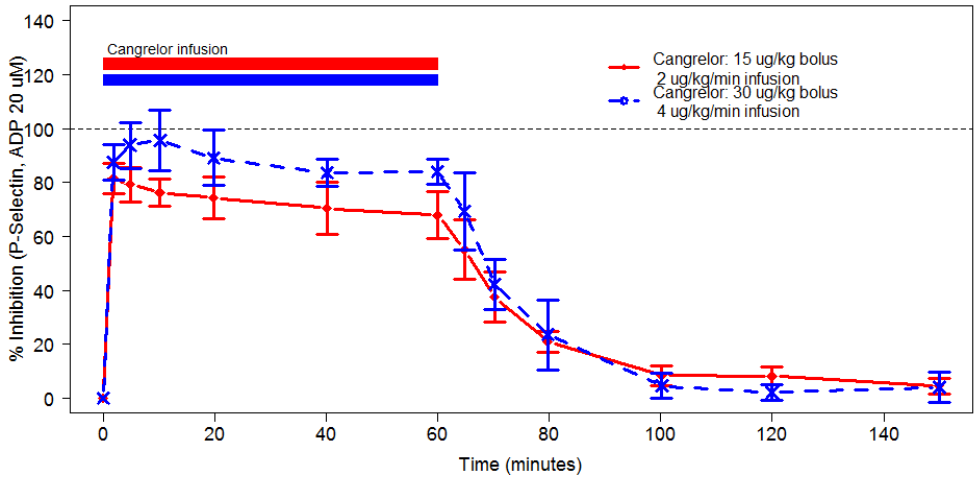


Figure 6. Percent inhibition of platelet response to 20 µM ADP as measured by flow cytometry for the low dose (15 µg/kg IV bolus followed by 2 µg/kg/min infusion) and high dose (30 µg/kg IV bolus followed by 4 µg/kg/min infusion) regimens

3.2.4.2 For BRIDGE indication

The Phase II study TMC-CAN-08-02 (BRIDGE, Stage I) provided supporting evidence for the proposed bridging dose for transitioning patients from oral $P2Y_{12}$ inhibitor therapy to cangrelor while awaiting coronary artery bypass graft (CABG) surgery. Dose-escalating cohorts (n=5) of 0.5, 0.75, 1.0, and 1.5 µg/kg/min IV infusions were planned until > 60 % platelet inhibition (as assessed by *VerifyNow*^{TM} $P2Y_{12}$ assay) was achieved in 80 % of the daily samples. A cangrelor dose of 0.5 µg/kg/min maintained platelet inhibition > 60 % in about 77 % (13/17) of patient

samples. The second dose cohort at 0.75 µg/kg/min maintained platelet inhibition > 60 % in 94 % (17/18) of daily samples and was chosen for testing in Stage II of BRIDGE study. A cumulative distribution plot (Figure 7) of the observations for 0.5 and 0.75 µg/kg/min infusions supports the conclusion that the higher dose cangrelor arm achieved a greater percentage of samples with platelet inhibition > 60%. Both doses achieved a similar percentage of samples with platelet inhibition > 80 %. The conclusion regarding the inadequacy of 0.5 µg/kg/min is based on one additional sample falling below the pre-specified platelet inhibition criteria.

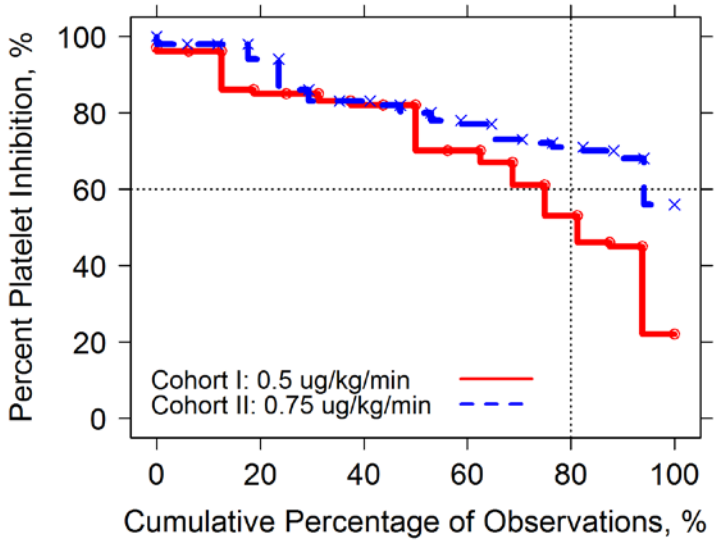


Figure 7. Cumulative frequency of samples with platelet inhibition > 60 % as reported by *VerifyNow*™ $P2Y_{12}$ test for cangrelor infusion rates of 0.5 and 0.75 µg/kg/min in Stage I of BRIDGE study.

Stage II of BRIDGE study was a randomized, double-blind, placebo-controlled trial comparing cangrelor 0.75 µg/kg/min and placebo infusions in patients transitioning from oral $P2Y_{12}$ therapy while awaiting CABG surgery. The PRU value profiles for the two treatment arms from the start of treatment (left) and prior to/following surgery (right) are shown below in Figure 8. In patients randomized to placebo, PRU values increased from baseline reflective of waning effect from their previous oral $P2Y_{12}$ therapy. In contrast, PRU values remained suppressed in the cangrelor treatment arm while on cangrelor infusion. The primary efficacy endpoint for this stage was a comparison of percentage of patients with PRU < 240 as determined by *VerifyNow*™ $P2Y_{12}$ assay between placebo and cangrelor treatment groups. This endpoint was achieved with 99 % of cangrelor patients (83/84) with all PRU samples < 240 compared to 19 % (16/84) in the placebo arm.

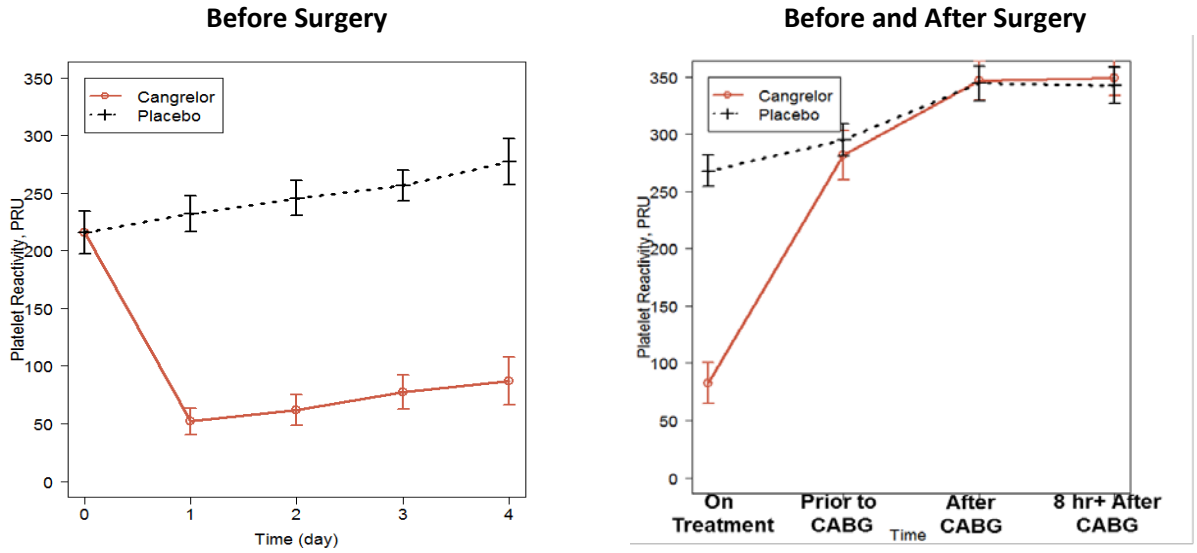


Figure 8. Platelet reactivity measured as *VerifyNow*^{TM} $P2Y_{12}$ PRU versus time from Study TMC-CAN-08-02 for cangrelor (red solid line) and placebo (black dotted line) treatment arms. PRU values from baseline up until the time of CABG surgery are shown on the left pane. PRU values from the last on-treatment assessment, prior to, and following CABG surgery are shown on the right.

Physicians were instructed to discontinue cangrelor treatment 1 to 6 hours prior to surgery to permit recovery of platelet activity prior to surgery. The median time between the end of the cangrelor infusion and the start of surgery was about 3 hours with an interquartile range of about 2-4 hours. Using this approach, the PRU values were similar between cangrelor and placebo treatment arms prior to initiation of surgery (280 versus 298; p-value=0.21). The CABG-related bleeding events were similar between cangrelor (10/102; 10 %) and placebo (10/96; 10 %) treatment arms, though the sample size was not sufficient enough to determine whether there was a difference in CABG-related bleeding events between treatment arms. There were slightly higher non-CABG bleeding events in the cangrelor arm. For GUSTO (severe/life-threatening), TIMI (major), and ACUITY (major) bleeds, there were 2 % (2/102), 0 % (102), and 17 % (12/102) events in the cangrelor arm compared to 1 % (1/96), 0 % (0/96), and 5 % (5/96) events in the placebo arm.

In summary, the proposed dose of 0.75 µg/kg/min IV infusion resulted in significantly greater platelet inhibition based on PRU as assessed by *VerifyNow*^{TM} than placebo while transitioning patients awaiting CABG surgery from oral $P2Y_{12}$ therapy. The study also demonstrated that

discontinuation of 0.75 µg/kg/min cangrelor infusion at a median of 3 hours (interquartile range: 2 to 4 hours) prior to CABG surgery resulted in similar PRU values between the cangrelor and placebo arms just prior to surgery. The selected dose of cangrelor achieved platelet inhibition similar to or greater than that achieved with clopidogrel at steady state as the Day-1 PRU values were significantly lower than baseline. The benefit of achieving PRU values lower than that achieved with the regular maintenance dose of oral $P2Y_{12}$ drugs is not known.

3.2.5 What are the characteristics of the exposure or dose-response relationships for efficacy or safety?

The three Phase III studies (CHAMPION-PCI, PLATFORM, and PHOENIX) included only one dose level (30 µg/kg IV bolus followed by 4 µg/kg/min IV infusion) so a dose-response analysis could not be conducted.

There was no PK data collected from these studies and the PD sampling (to assess platelet inhibition) was limited to about 104 patients from the supportive CHAMPION-PCI and CHAMPION-PLATFORM studies and did not include any subjects from the pivotal efficacy study CHAMPION-PHOENIX. Therefore, any potential relationships between cangrelor exposure or its PD with safety and efficacy outcome measures could not be evaluated.

3.2.6 Does cangrelor prolog QT or QTc interval?

A double-blind, placebo and positive (moxifloxacin 400 mg) controlled, cross-over study assessed the effect of cangrelor at therapeutic (30 µg/kg IV bolus plus 4 µg/kg/min infusion for 3 hours) and supra-therapeutic dose (60 µg/kg IV bolus plus 8 µg/kg/min infusion for 3 hours) levels on QT/QTc interval in healthy volunteers (Study TMC-CAN-08-01). The applicant concluded that cangrelor does not affect cardiac repolarization and the QT-IRT review concurred with this conclusion (Ref. QT-IRT Review, DARRTS dated 11/17/2011).

3.3 Pharmacokinetics of Drug and Metabolite(s)

Cangrelor undergoes rapid de-phosphorylation in systemic circulation and forms its primary circulating metabolite AR-C69712. This metabolite is reported to be 70, 000 times less potent than cangrelor at $P2Y_{12}$ human platelet receptors.

3.3.1 What are the single and multiple dose PK parameters?

Ascending dose PK/PD studies with 4-step IV infusions up to 4 µg/kg/min were performed in healthy male and female subjects (SC-931-5014 and SC-931-5036). The total treatment duration was about 24 hours. The maximum plasma concentrations (C_{max}), AUC and steady state plasma concentrations (C_{ss}) were dose-linear up to the maximum tested infusion rate of 4 µg/kg/min. At the end of infusion, cangrelor concentrations declined in a bi-phasic manner, with an

effective initial half-life of about 3.5 to 6 minutes and a longer terminal elimination half-life up to 14 to 26 hours at the highest dose level. The PK of the primary metabolite AR-C69712 was also linear with dose and showed a $t_{1/2}$ of about 2-3 hours. The molar ratio of AR-C69712 to cangrelor at steady state was approximately 0.8-0.9.

3.3.2 How does the PK of the drug and metabolite(s) in healthy volunteers compare to that in patients?

The PK of cangrelor is comparable in healthy volunteers and in patients included in the clinical development program.

3.3.3 Based on the PK parameters, what is the degree of linearity or non-linearity in dose-concentration relationship?

The maximum plasma concentrations (C_{max}), AUC and steady state plasma concentrations (C_{ss}) were dose-linear up to the maximum tested infusion rate of 4 µg/kg/min in healthy subjects for cangrelor (Figure 9) and its primary circulating metabolite AR-C69712.

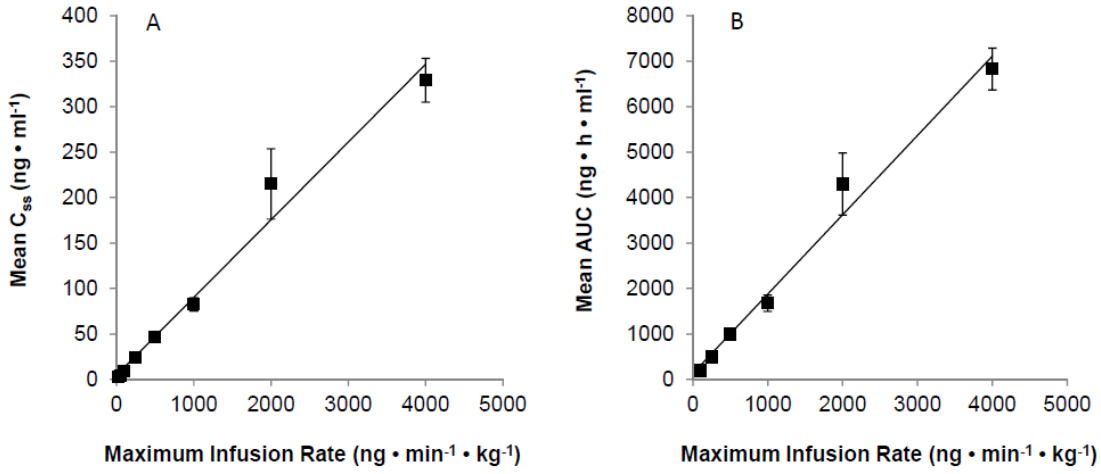


Figure 9. Dose-linearity plots for steady state plasma concentrations (A) and AUC (B) for cangrelor in healthy volunteers. Ref. Study Report SC-931-5014

3.3.4 What is the inter- and intra-subject variability of PK parameters, and what are the major causes of variability?

The inter-individual variability (% CV) for PK parameters in healthy volunteers ranged from 19-32 % for cangrelor (Study TMC-CAN-04-02). Based on the population PK analysis the between subject variability on clearance (CL) and volume of distribution (V_c) were about 19 and 23 % respectively. Since cangrelor is administered as a one-time single dose regimen the within subject variability was not estimated.

3.3.5 What intrinsic factors (age, sex, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

3.3.5.1 Body weight, Sex, Age and Race

Of the demographic and laboratory covariates evaluated, only body weight was identified as having a significant effect on cangrelor pharmacokinetics. The body weight effect was included as an allometric scaling coefficient on all compartmental parameters (coefficient of 0.75 for central compartment clearance [CL] and intra-compartment transit rate [Q]; coefficient of 1.0 for central [V1] and peripheral [V2] volume of distribution). This impact of body weight was already accounted for in the weight-based cangrelor infusion regimen. Over a weight range of 50 to 100 kg and the proposed dosing regimens for the proposed BRIDGE and PCI indications, the range of expected exposures (AUC and steady state plasma concentration) is predicted to be 9 % lower for a patient weighing 50 kg relative to a reference patient with 70 kg body weight, and approximately 9 % higher for a patient weighing 100 kg relative to the same reference patient.

Neither sex nor age was identified as having a significant effect on cangrelor pharmacokinetics. There were insufficient numbers of Asian and African-American subjects in the pharmacokinetic dataset to assess race differences on the pharmacokinetics of cangrelor.

3.3.5.2 Renal Impairment

The current NDA includes a renal impairment study (SC-931-5109) in normal healthy subjects (creatinine clearance > 90 mL/min, N=8) and in subjects with impaired renal function (creatinine clearance of 20-70 mL/min, N=16). Three-step, ascending IV infusions of cangrelor were used in this study, with Part I using a maximum infusion rate of 2 µg/kg/min and Part II using 4 µg/kg/min maximum infusion rate, respectively. The distribution of subjects was not balanced across treatments, with lesser number of subjects (N ~ 3-4) in the reference treatment groups. The plasma concentration profiles of cangrelor and its derived PK parameters were comparable in healthy volunteers and renally impaired subjects in Part I (maximum dose 2 µg/kg/min) of the study. The observed C_{max} and AUC for cangrelor showed an increase of 11 % and 9 % respectively in renally impaired patients relative to healthy subjects in Part I. But the C_{max} and AUC for cangrelor showed an increase of 54 % and 117 %, respectively in renal impairment relative to healthy subjects in the Part II where a maximum infusion rate of 4 µg/kg/min was tested. The steady state plasma concentrations (C_{ss}) were 5 % and 44 % higher in renally impaired subjects for cangrelor infusion rates of 2 µg/kg/min and 4 µg/kg/min,

respectively. Two healthy subjects (16 and 18) had to be excluded from analysis in Part II, making the comparisons less informative. Besides, the cangrelor exposure in healthy volunteers in the Part II of the renal impairment study was lower than that that from previous observations in healthy volunteers who received 4 µg/kg/min infusion rate (Table 2). If a cross-study comparison was used, the increase in cangrelor C_{ss} in renal impairment relative to healthy subjects would be ~ 16 % in contrast to the 44 % increase seen in the dedicated renal impairment study. The PK/PD of cangrelor was also comparable between healthy subjects and subjects with renal impairment in the renal impairment study. Cangrelor treatment was generally well tolerated, but one subject experienced a syncopal attack and was not included in the analysis (subject 16). Another subject (subject 2) had deterioration in renal function and required dialysis. This was considered as progression in the underlying renal disease.

Table 2 Comparison of cangrelor steady-state exposures in healthy subjects and in subjects with renal impairment. Data pooled from three Phase I studies and the renal impairment study.

Infusion Rate (µg/kg/min)	Study	N	Steady State Plasma Concentration (ng/mL)		
			GM (% CV)	Median	Ratio (RIS/HS)
2	Healthy Subjects –Other Studies*	14	222 (22)	241	0.93
	Healthy Subjects –Renal Imp Study**	4	198 (24)	214	1.05
	RIS – Renal Imp Study	8	207 (20)	203	-
4	Healthy Subjects –Other Studies*	18	399 (26)	409	1.16
	Healthy Subjects –Renal Imp Study**	3	322 (10)	321	1.44
	RIS – Renal Imp Study	7	464 (19)	461	-

*Other - Combined Studies SC-931-5014, SC-931-5036, TMC-CAN-04-02
** Renal Impairment Study SC-931-5109
RIS-Renally Impaired Subjects, HS-Healthy Subjects with Normal Renal Function
GM-Geometric Mean, N-Number of Subjects

The Phase III studies for cangrelor included patients with impaired renal function (CHAMPION-PLATFORM: N ~ 623 and CHAMPION-PCI: N ~ 688 patients with CrCL < 60 mL/min) and used the same dosing regimen as CHAMPION-PHOENIX. There was no significant difference in the safety and efficacy profiles of cangrelor in these patients compared to the overall study results. Altogether, the available data supports that no dose adjustments are necessary for cangrelor in renally impaired subjects.

3.3.5.3 Hepatic Impairment

Since the biotransformation of cangrelor is believed to be mediated through nucleotidases in systemic circulation which is considered independent of hepatic function there was no dedicated hepatic impairment study included in the clinical development program.

3.3.6 What are the characteristics of drug absorption (transporters and pH impact)?

The impact of transporters on the PK of cangrelor and vice versa was not studied. Cangrelor is administered by intravenous route for shorter duration (~ 2 hours for PCI indication) as a single use regimen and the expectation for any potential impact in this setting is considered to be low.

3.3.7 What are the characteristics of drug distribution, including plasma protein binding?

In vitro plasma protein binding determined by equilibrium dialysis method (SC-10009) was about 97 - 98 % for cangrelor and 88 - 89 % for its metabolite AR-C69712, respectively. Another *in vitro* study (SC-103039) showed that cangrelor predominantly binds to albumin and reported > 98 % plasma protein binding. The RBC partitioning was up to 5 % for cangrelor and that for AR-C69712 was about 28-34 %.

3.3.8 What are the characteristics of drug metabolism?

Cangrelor is a substituted nucleotide (See Figure 1) and is believed to be inactivated rapidly in the circulation by de-phosphorylation mediated through nucleotidases to a nucleoside metabolite, AR-C69712. This major circulating metabolite is reported to be several thousand fold less potent (~70,000 X) than cangrelor at human $P2Y_{12}$ receptors. After the initial de-phosphorylation, various other sulfoxide metabolites are formed and are considered pharmacologically inactive. The primary enzyme systems responsible for this biotransformation are not yet identified. The proposed metabolic pathway for cangrelor in humans is shown in Figure 10 below.

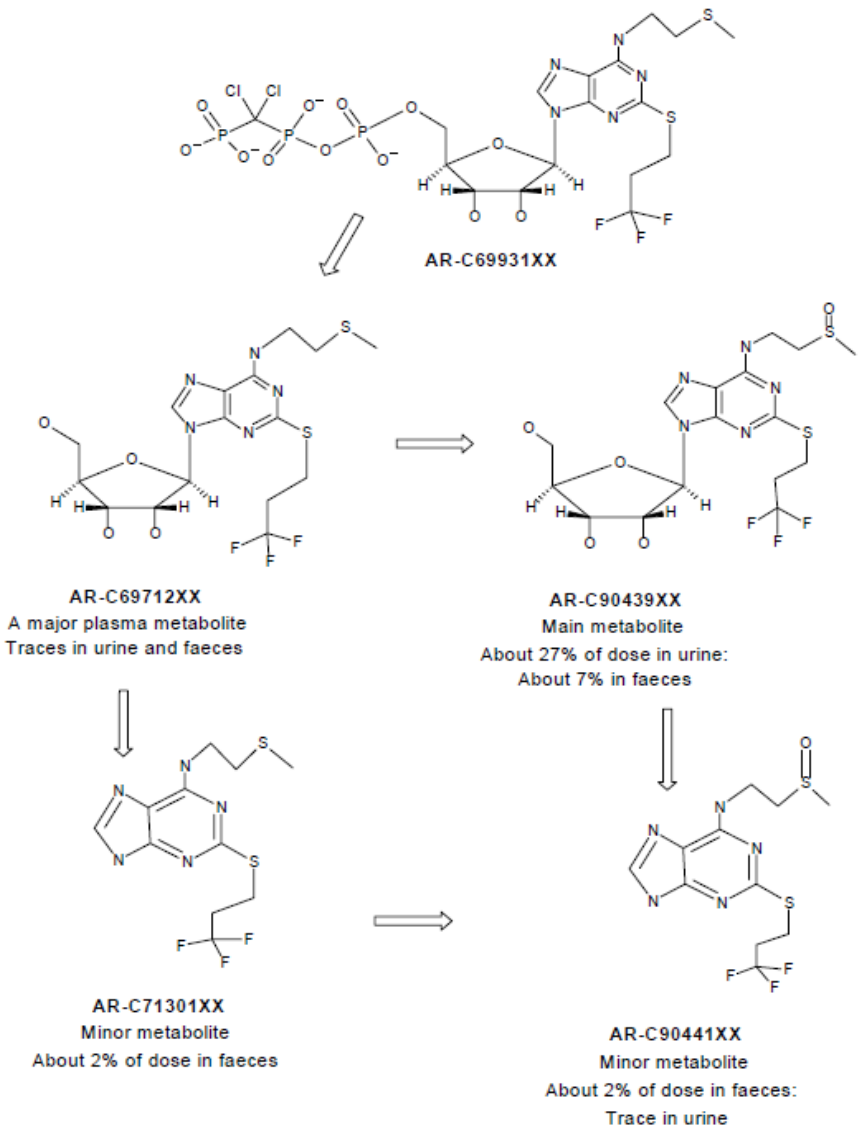


Figure 10. Proposed metabolic pathway for cangrelor in humans
Source: Figure 10, Study Report SC-100199, Page 44

3.3.9 Does the mass balance study suggest renal or hepatic as the major route of elimination for cangrelor?

In the mass balance study (SC-931-9017/SC-100199) with [^{3}H]-cangrelor 2 µg/kg/min infusion for 2 hours in healthy subjects, the mean cumulative recovery of radioactivity was about 93 %, with approximately 58 % and 35 % found in urine and feces, respectively (Table 3). Approximately 50 % of the radioactivity was recovered within the first 24 hours. The chromatographic method used did not differentiate between cangrelor (AR-69931) and one of its metabolite AR-C90439 in this study and so the presence or absence of cangrelor (AR-

C69931) in urine or feces cannot be confirmed. About 10 % and 19 % of the recovered radioactivity was not fully characterized. The Table describes the relative contributions of the moieties identified in urine and feces.

Table 3 Percentage of radioactive dose recovered from urine and feces and relative contribution of various moieties

Identified Moiety/Matrix	Urine	Feces
Cangrelor (AR-C69931)	*	*
AR-C69712	0.6	0.4
AR-C90439	27.3	6.6
AR-C71301	-	2.0
AR-C90441	0.7	1.8
Oxidized AR-C90441 or AR-C69712 derivative	5.1	5.0
Glucuronide-AR-C69712	10.4	-
Sulphone and Glucuronide of AR-C69712	4.4	-
Unidentified^{+}	~ 9.5	~ 19.3
% of Dose Recovered	**~ 58.0**	**~ 35.1**

From Study SC-100199, N=4, [^{3}H]-Cangrelor 2 µg/kg/min IV infusion for 2 hours
*Presence/absence not confirmed in this study; - not detected; $^{+}$ difference between recovered and identified radioactivity

3.3.10 What is the drug-drug interaction (DDI) potential for cangrelor?

3.3.10.1 *In Vitro* Studies

The *in vitro* evaluation of DDI potential focused on CYP inhibition and CYP induction by cangrelor and its primary circulating metabolite AR-C69712. The biotransformation of cangrelor to AR-C69712 is proposed to be mediated by nucleotidases in systemic circulation and is believed to be independent of hepatic function. Induction potential for CYP1A2, 2C9 and 3A4 by were tested in primary cultured human hepatocytes. Cangrelor and AR-C69712 were found to have the potential to induce CYP2C9 and 3A4 at 100 µM concentration level (Studies 300736967 and 300739180) but was significantly lower than that seen with rifampin, the positive control used.

The potential for cangrelor, AR-C69712 and AR-C90439 to inhibit CYP1A2, 2A6, 2C9, 2C19, 2D6, 2E1 and 3A4 were assessed with human liver microsomes (SC-102858). It was reported that cangrelor and its metabolites have no potential to inhibit CYP1A2, 2A6, 2C9, 2D6, 2E1 and 3A4 systems, with observed IC_{50} values of > 100 µM. However, AR-C69712 and AR-C90439 showed a potential to inhibit CYP2C19 at very high concentrations (IC_{50} of 58-59 µM). Based on the

observed therapeutic concentrations of cangrelor and its metabolites no significant clinical DDIs are anticipated at the proposed dose.

3.3.10.2 *In Vivo* Studies

A double-blind, placebo-controlled, two-way cross-over study (AC-931-5037) investigated the combined effects of aspirin, heparin and glyceryl trinitrate pre-treatment with stepped IV infusions of cangrelor (six steps from 50 ng/kg/min to 2 μg/kg/min, with a total infusion duration of 4 hours and 15 minutes) in healthy male subjects. The PK of cangrelor and AR-C69712 did not alter significantly when co-administered with aspirin, heparin and glyceryl trinitrate (given together). The inhibition in ADP induced platelet aggregation by cangrelor was comparable between both treatment groups. But there were prolongation in bleeding times and higher incidence of adverse events like purpura and headaches when cangrelor was co-administered with a combination of aspirin, heparin and glyceryl trinitrate. No major adverse events were reported from this study.

3.3.11 What is the transition strategy while switching from cangrelor to oral $P2Y_{12}$ inhibitors like clopidogrel, prasugrel or ticagrelor?

3.3.11.1 Transition to clopidogrel

Study TMC-CAN-04-02 in healthy subjects included clopidogrel with or without cangrelor administration, offset by different times (See Figures 11-13 below). Platelet inhibition was measured using whole blood impedance aggregation (WBIA), P-Selectin expression measured with flow-cytometry and light transmittance aggregometry (LTA). The antiplatelet effects of clopidogrel was attenuated when administered at the start of cangrelor infusion (about 35 % inhibition of platelets after cangrelor infusion was stopped) while full effect (about 78 % platelet inhibition) was seen when clopidogrel was administered after the cangrelor infusion, compared to clopidogrel administered alone in the control, group (about 82 % platelet inhibition).

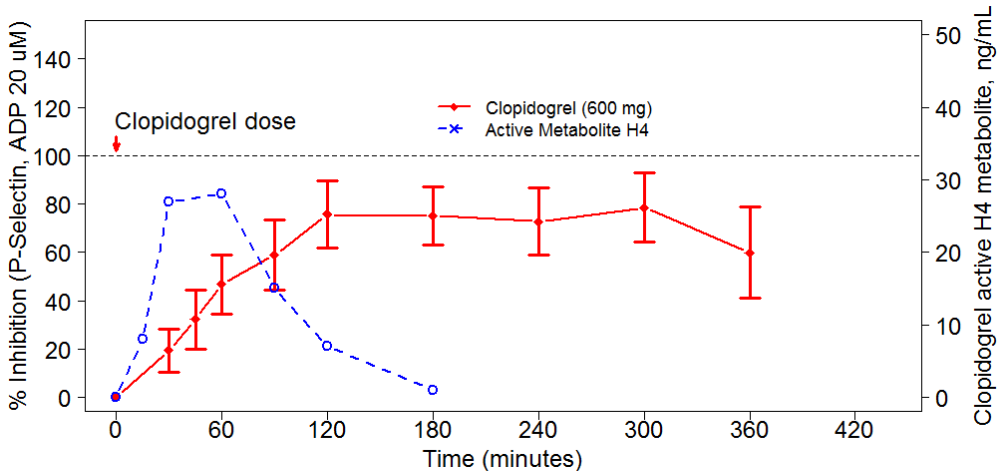


Figure 11. Average platelet inhibition-time course for a single 600 mg dose of clopidogrel administered at time 0 minutes. Percentage inhibition in P-Selectin expression to 20 µM ADP measured by Flow Cytometry was used. A representative plasma profile of the active metabolite H4 following administration of 600 mg clopidogrel in CYP2C19 extensive metabolizers (extracted from Study PKD11147; NDA 20839) is shown as a blue dotted line and repeated in Figures 12 and 13.

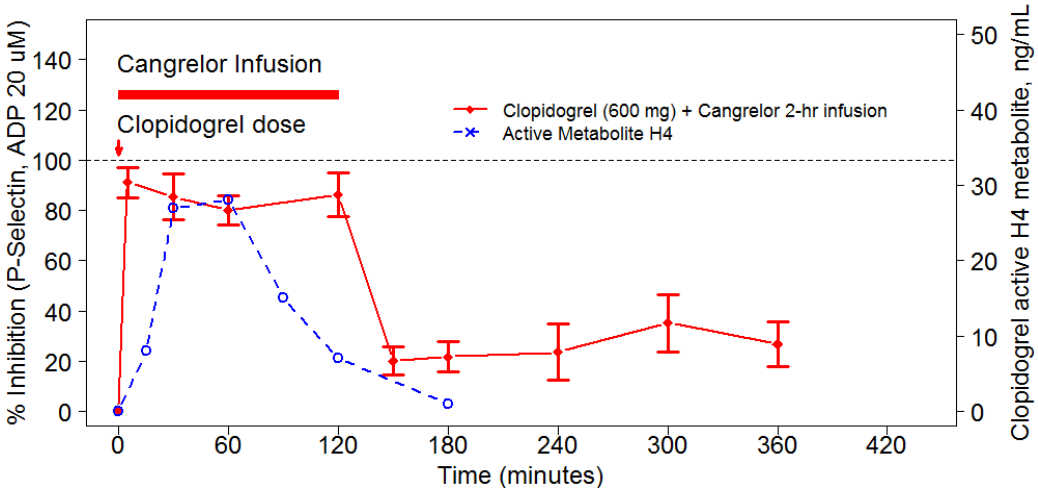


Figure 12 The antiplatelet effect of clopidogrel was attenuated when co-administered with cangrelor. Both clopidogrel 600 mg and cangrelor (30 µg/kg bolus + 2 hour of 4 µg/kg/min infusion) were administered at time 0 minutes. The red horizontal bar indicates cangrelor infusion duration. Clopidogrel's active metabolite H4 reaches its peak plasma levels during the cangrelor infusion when the platelet $P2Y_{12}$ recetptors are still ocuuplied by cangrelor. When cangrelor infusion was stopped at 120 minutes, most of H4 metabolite was already cleared from systemic circulation.

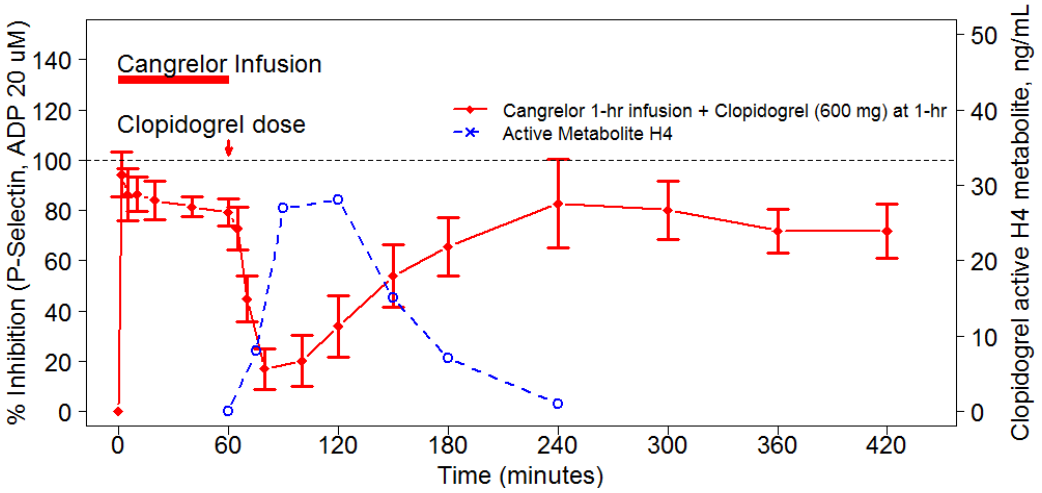


Figure 13 Administering the clopidogrel dose after stopping cangrelor infusion did not alter the expected PD effect from clopidogrel. The horizontal red bar indicates cangrelor infusion duration. Cangrelor 30 µg/kg bolus + 1 hour of 4 µg/kg/min infusion followed by clopidogrel 600 mg administered at time 60 minutes (shown by red arrow) were used in the study. Clopidogrel's active metabolite H4 reaches its peak plasma levels after the cangrelor infusion was stopped and therefore can bind with the available platelet $P2Y_{12}$ recetptors and exert its expected PD effects.

It is hypothesized that the attenuation of clopidogrel's PD effect when co-administered with cangrelor is because of the competition between clopidogrel's active metabolite H4 and cangrelor for the platelet $P2Y_{12}$ ADP-receptors. The active metabolite of clopidogrel has short plasma half-life (cleared from plasma in about 3 hours after oral clopidogrel dose) and can irreversibly bind to $P2Y_{12}$ receptors on the platelets if they are available. If this overlaps with cangrelor administration, both cangrelor and the active metabolite H4 will compete for the same receptors. This scenario is depicted in Figure 12 where cangrelor and clopidogrel are both administered at time zero minutes. The cangrelor infusion duration overlaps with the t_{max} of clopidogrel's active metabolite, which is reached 30-60 minutes after oral administration of clopidogrel, decreasing the ability of clopidogrel's active metabolite to irreversibly bind to $P2Y_{12}$ receptors. This translates to a decreased platelet inhibition compared to clopidogrel administered after stopping the cangrelor (with faster offset in PD effects) infusion (Figure 13). Such a phenomenon mediated by competitive inhibition at the same target site is observed when reversible agents are co-administered with irreversibly acting agents e.g., aspirin +

ibuprofen interaction through competitive inhibition of the acetylation site of cyclooxygenase in the platelet[4].

Other irreversible oral $P2Y_{12}$ inhibitors, such as prasugrel, may also show some attenuation in platelet inhibition if co-administered with cangrelor. However, the active metabolite of prasugrel has an elimination half-life of about 7 hours (range 2-15 hours) and the attenuation in platelet inhibition may be lesser that with clopidogrel upon co-administration.

These results suggest that administration of clopidogrel at the end of cangrelor infusion overcomes the loss of clopidogrel effect when compared to clopidogrel administration at the start of infusion. However, there still exists a temporary dip in the antiplatelet activity at the end of cangrelor infusion. In fact, applicant's transition strategy has only managed to shift the delay in the time to reach the maximum inhibition achieved with clopidogrel loading dose. Alternatively, a potential transition strategy that can be envisioned is to split the loading dose of clopidogrel and span the timing of administration to 'before' and 'after' stopping of cangrelor infusion. It should be noted that even with this strategy, the possibility of an overlap in PK and thus a potential for attenuation of the PD effects of the first dose of clopidogrel exists. However, this may result in lesser attenuation of the antiplatelet activity during transition and shorter time to reach the maximum platelet inhibition.

3.3.11.2 Transition to ticagrelor

The transition from cangrelor to ticagrelor was evaluated in study MDCO-CAN-12-03 in 12 patients with stable coronary artery disease who were taking aspirin 81 mg daily. Patients were administered cangrelor (30 µg/kg bolus followed by 4 µg/kg/min for 2 hours) and a 180 mg dose of ticagrelor 30 or 75 minutes after the start of cangrelor infusion (see Figure 14 below).

[4] FDA Information for Healthcare Professionals: Concomitant Use of Ibuprofen and Aspirin
http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm125222.htm

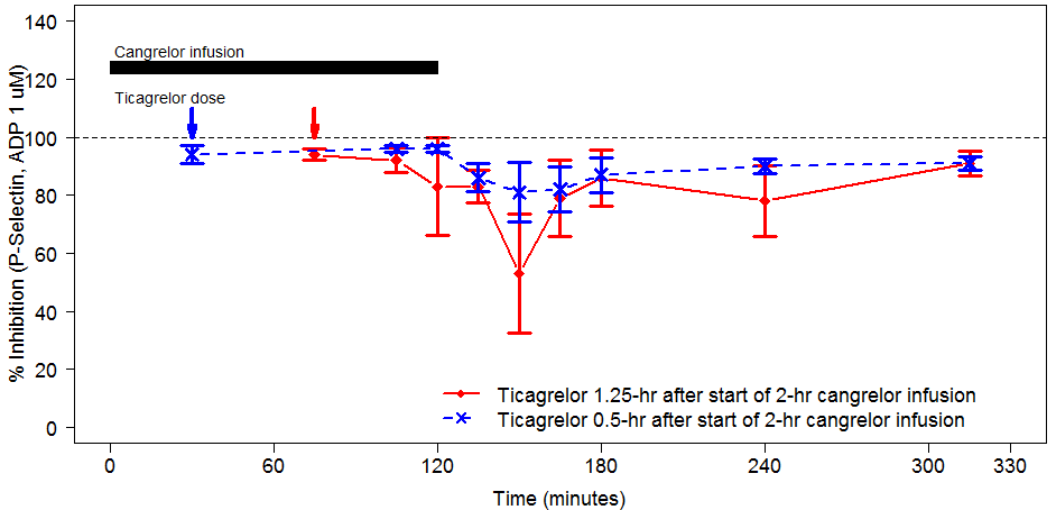


Figure 14. Transition from IV cangrelor to oral ticagrelor – Percentage inhibition in P-selectin expression to 1 µM ADP measured by Flow Cytometry for IV cangrelor (30 µg/kg bolus + 2 hours of 4 µg/kg/min infusion) and a 180 mg oral dose of ticagrelor adminsitered at 0.5 hours (blue dashed line with cross symbols) or at 1.25 hours (red solid line with diamond symbols) after the start of the infusion. The arrows indicate ticagrelor dose administration and the solid black bar indicate cangrelor infusion duration from time 0 minute to 120 minutes.

The inhibitory effect of cangrelor and ticagrelor was preserved when both products were co-administered and that patients can be transitioned to ticagrelor from cangrelor during infusion. Following discontinuation of the infusion, there was a decrease in platelet inhibition for about 30 minutes in treatment arms scenarios ranging from 96 % and 83 % inhibition at the end of the cangrelor infusion to 81% and 53 % inhibition. However, earlier administration of ticagrelor resulted in more consistent maintenance of antiplatelet activity after stopping of the cangrelor infusion for these two scenarios. This observation is in agreement with reported ticagrelor PK/PD that showed its maximum plasma concentrations at ~ 1.5 hours and elimination half-life of ~ 7 hours for ticagrelor (and ~ 9 hours for active metabolite) as well as peak platelet inhibition at approximately 1.5 to 2 hours after administration.

3.3.12 What is the transition strategy for switching from oral $P2Y_{12}$ inhibitors to IV cangrelor?

The transition from oral $P2Y_{12}$ inhibitors like clopidogrel or prasugrel to cangrelor was evaluated in study TMC-CAN-08-02 (BRIDGE) in patients awaiting CABG surgery. Shown in Figure 15 below are baseline and on-treatment *VerifyNow*^{TM} PRU assessments for subjects who were on oral $P2Y_{12}$ therapy and either stopped treatment or stopped treatment and switched to cangrelor.

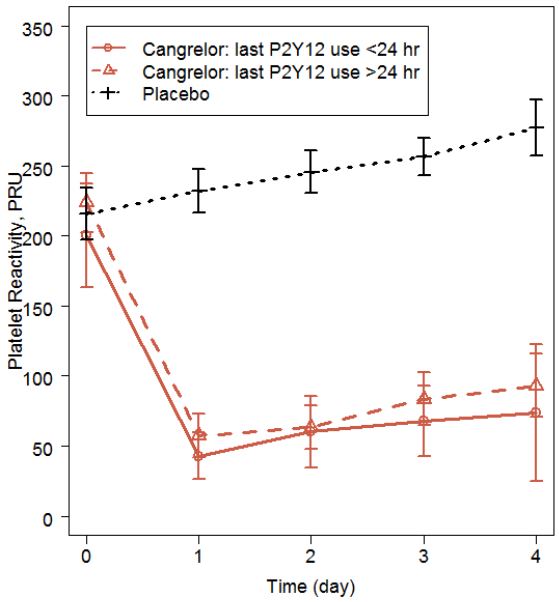


Figure 15. Platelet reactivity unit (PRU) values versus time for patients transitioning from oral $P2Y_{12}$ inhibitors to placebo (black, dotted line) or cangrelor whose last $P2Y_{12}$ use was within 24 hours (red, circles with solid line) or more than 24 hours (red, triangles with broken line) prior to baseline

The majority of patients in all treatment arms were transitioning from clopidogrel use (~ 99 % in placebo and ~ 92 % in cangrelor groups) while the remaining patients were transitioning from prasugrel. Most patients were on 75 mg clopidogrel (~ 84 % in placebo and ~ 70 % in cangrelor groups). The cangrelor patients were further divided into patients whose last oral $P2Y_{12}$ inhibitor dose was within 24 hours versus more than 24 hours. This division was chosen as patients whose last dose was within 24 hours represents a direct transition from clopidogrel to cangrelor. The PRU profiles for the cangrelor treatment arms overlap whether patients had received their last oral $P2Y_{12}$ inhibitor dose within 24 hours or more than 24 hours prior to initiation of cangrelor treatment. This observation supports that patients on an oral $P2Y_{12}$ inhibitor can be transitioned to cangrelor therapy without any significant changes in observed pharmacological effect.

3.4 Biopharmaceutics

3.4.1 What are the characteristics of the bioanalytical method(s) used in the clinical pharmacology studies?

The PK analyses focused on plasma concentrations of cangrelor and its primary circulating metabolite AR-C69712. The Phase I program used solid phase extraction (SPE)/column

switching high performance liquid chromatographic (HPLC) method (SC-100236), while the Phase II program used a semi-automated SPE/SPE/HPLC method (SC-101725) or its variants (FL05-TMC-TR005R1) with ultra-violet absorbance detection at 281 nm. In addition, there were additional LC-MS/MS methods for the estimation of cangrelor (BPM-1044-R1) and AR-C69712 (BTM-1075-R0) from human plasma (Table 4). All the assay methods were validated for use in the clinical studies.

Table 4 Reported bioanalytical assay linearity, accuracy and precision

Analytes/Parameters	Cangrelor*	AR-C69712**
LLOQ	5.0 ng/mL	0.5 ng/mL
Range	5.0-1000 ng/mL	0.5-500 ng/mL
QC Precision (inter-day % CV)	2.1-3.1	2.2-6.8
QC Accuracy (% range)	101.7-106.6	104.2-106.1

LC-MS/MS Methods: *BTM-1044-R1, **BTM-1075-R0

The analytes were stable for 3 freeze-thaw cycles and for up to a day at room temperature. The reported recovery of the analytes from human plasma was consistent and adequate. The reported accuracy and precision of the assays were within the acceptable limits (≤20 % at LOQ and ≤15% at all other QC levels) and the validation parameters are acceptable.

3.4.2 How is the final marketing image formulation bridged to the Phase III formulation?

The pivotal efficacy study CHAMPION-PHOENIX used the same IV formulation (cangrelor diluted in sterile normal saline) as the proposed marketing image formulation. Cangrelor for injection is provided in 10 mL vials, each containing 50 mg cangrelor as tetra-sodium salt and should be reconstituted with 5 mL sterile water for injection and further diluted with normal saline or 5% dextrose injection, before use.

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/s/

SREEDHARAN N SABARINATH
01/10/2014

JEFFRY FLORIAN
01/10/2014

YANING WANG
01/10/2014

RAJANIKANTH MADABUSHI
01/10/2014

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

Medicines Company has submitted [redacted] (b) (4) (cangrelor for injection), an intravenous, agent that is hypothesized to block ADP-induced platelet activation and aggregation. The applicant is seeking approval for the following two indications: (1) reduction of thrombotic events in patients with coronary artery disease undergoing percutaneous coronary intervention (PCI) and (2) to maintain $P2Y_{12}$ inhibition in acute coronary syndrome patients or patients with stents who are at increased risk for thrombotic events when oral $P2Y_{12}$ therapy is interrupted due to surgery. The primary evidence of efficacy in support of the first indication is CHAMPION-PHOENIX. Two other trials, CHAMPION-PCI and PLATFORM are indicated as supportive evidence for this indication. The applicant states that the BRIDGE trial supports second indication. The clinical pharmacology information on cangrelor and its metabolites were derived from 16 clinical studies including a radiolabelled ADME study, a DDI study and a PK study in renal impairment.

	Information		Information
NDA Number:	**204958**	**Brand Name:**	[redacted] (b) (4)
OCP Division:	**DCP1**	**Generic Name:**	**Cangrelor for injection**
Medical Division:	**DCRP**	**Drug Class:**	**$P2Y_{12}$ Platelet inhibitor**
OCP Reviewer	**Sreedharan Sabarinath**	**Indication(s):**	**(1) reduction of thrombotic events in patients with coronary artery disease undergoing percutaneous coronary intervention (PCI) and (2) to maintain P2Y12 inhibition in acute coronary syndrome patients or patients with stents who are at increased risk for thrombotic events when oral P2Y12 therapy is interrupted due to surgery**
OCP Team Leader:	**Rajanikanth Madabushi**	**Dosage Form:**	**Lyophilized powder for reconstitution**
Pharmacometrics Reviewer:	**Jeffrey Florian**	**Route of Administration:**	**intravenous**
Sponsor:	**The Medicines Company**	**Dosing Regimen:**	**PCI: 30µg/kg iv bolus plus 4µg/kg/min iv infusion for at least 2 hrs Bridge: 0.75 µg/kg/min until 1h prior to surgery**
Date of Submission	**04/30/2013**	**Priority Classification:**	**Standard**
Estimated Due Date of OCP Review	**December 2014**	**AC Meeting:**	**January 2014**
Medical Division Due Date	**December 2014**	**PDUFA Due Date:**	**04/30/2014**

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Mass balance:	**X**	**2**	**2**	SC-931-9017, SC-100199 – metabolic profile, excretion studies-radio-labeled
Blood/plasma ratio:	**X**	**1**	**1**	SE10009
Plasma protein binding:	**X**	**1**		
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**X**	**3**	**3**	SC-931-5014 – healthy males SC-931-5036 – healthy females SC-931-9064 – ex vivo ADP
multiple dose:	**X**	**1**	**1**	TMC-CAN-04-02 – bolus + infusion
Patients-				
single dose:	**X**	**2**	**2**	SC-931-5058 – UA/MI SC-931-5060 – UA/MI
multiple dose:	**X**	**1**	**1**	SC-931-5135 – STEMI
Dose proportionality -				
fasting / non-fasting single dose:	**X**			
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	**X**	**1**	**1**	SC-931-5037- ASA, Heparin and NTG on PK and PD of cangrelor
In-vivo effects of primary drug:				
In-vitro:	**X**	**3**	**3**	SC-102858 – CYP inhibition 300739180 - CYP induction 300736967 – CYP induction
Subpopulation studies -				
ethnicity:				
gender:	**X**			
pediatrics:				
geriatrics:				
renal impairment:	**X**			SC-931-5109
hepatic impairment:				
PD -				
In vitro	**X**	**2**	**2**	Platelet inhibition studies PR-30144-Washed platelets PR-30145 - healthy blood PR-30138 – ADP uptake PR-30139
Phase 2:	**X**	**2**	**2**	SC-931-5129 - Patients with PCI MDCO-CAN-12-03 – transition, cangrelor to ticagrelor
Phase 3:	**X**	**3**	**3**	TMC-CAN-05-02-S1 TMC-CAN-05-03-S1 Platelet sub-studies in CHAMPION P3 and BRIDGE - TMC-CAN-08-02 (stages 1 and 2)
PK/PD -				
Phase 1 and/or 2, proof of concept:	**X**			
Phase 3 clinical trial:	**X**			
Population Analyses -				
Data rich:	**X**	**1**	**1**	Pop-PK/PD report
Data sparse:	**X**	**1**		Pop-PK/PD report
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies			**22**	

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	Intravenous marketing formulation is the same as P3 formulation
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	Intravenous route of administration
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	Requested pediatric waiver
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

a
IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

: YES

No potential review issues are identified at this time.

Sreedharan Sabarinath 06/18/2013
Reviewing Clinical Pharmacologist Date

Rajanikanth Madabushi 06/18/2013
Team Leader/Supervisor Date

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/s/

SREEDHARAN N SABARINATH
06/18/2013

RAJANIKANTH MADABUSHI
06/18/2013

PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

NDA Number: 204958 **Applicant:** The Medicines Company **Letter Date:** 4/30/2013

Drug Name: Cangrelor for Injection **NDA Type:** 505 (b)(1) **Stamp Date:** 4/30/2013

The following are necessary to initiate a review of the NDA application:

	Content Parameter	Yes	No	Comments
1	Is the product quality microbiology information described in the NDA and organized in a manner to allow substantive review to begin? Is it legible, indexed, and/or paginated adequately?	X		Submission is in eCTD format
2	Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product?	X		See 3.2.P.3.3
3	Has the applicant submitted protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product?	X		See 3.2.P.3.5
4	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?	X		English versions are available when necessary
5	Has the applicant submitted preservative effectiveness studies (if applicable) and container-closure integrity studies?	X		See 3.2.P.2.5 and Report CC167.12
6	Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?	X		See 3.2.P.5.1
7	Has the applicant submitted the results of analytical method verification studies?	X		See 3.2.P.5.3
8	Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions?			N/A
9	If sterile, are extended post-constitution and/or post-dilution hold times in the draft labeling supported by microbiological data?	X		Testing is limited and may not support post reconstitution and dilution hold times. Further review will be required. See stability.summary.pdf, pg. 29 and 54.
10	Is this NDA fileable? If not, then describe why.	X		

Additional Comments:
(b) (4) is intended for IV administration only after reconstitution and dilution. (b) (4) is administered as a 30 ug/kg IV bolus followed by 4 ug/kg/minute IV infusion. Sterile Water for Injection is used for reconstitution; dilution is performed in Sodium Chloride Injection 0.9% USP or 5% Dextrose Injection USP. In some cases, IV administration may occur over a (b) (4) period. Reconstituted and diluted (b) (4) may be stored at USP Controlled Room Temperature for up to 24 hours. Any remaining unused portion in the vial is discarded.

A request will be made for the sponsor to submit microbiological data to demonstrate that the reconstituted and diluted product solution will not support microbial growth during the proposed storage and administration period.

Steven P. Donald CDER/OPS/NDMS	5/14/2013
Reviewing Microbiologist	Date
Stephen Langille CDER/OPS/NDMS	5/14/2013
Microbiology Secondary Reviewer/Team Leader	Date

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/s/

STEVEN P DONALD
06/04/2013

STEPHEN E LANGILLE
06/04/2013