THE MEDICINES COMPANY®

# CANGRELOR

# MAINTENANCE OF PLATELET INHIBITION WITH CANGRELOR AFTER DISCONTINUATION OF THIENOPYRIDINES IN PATIENTS UNDERGOING SURGERY: THE BRIDGE TRIAL

## PROTOCOL NO. TMC-CAN-08-02

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| Principal Coordinating Investigator: | Eric J. Topol, MD |
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| Indication studied: | Platelet inhibition in patients undergoing PCI |
| Developmental phase of study: | Phase II |
| First patient enrolled (Stage I): | 02 Jan 2009 |
| First patient enrolled (Stage II): | 14 Oct 2009 |
| Last patient completed: | 07 Jun 2011 |
| Release date of report: | FINAL 29 March 2013 |



*This trial was conducted in accordance with the ethical principles of Good Clinical Practice, according to the ICH Harmonised Tripartite Guideline.*

## 2. SYNOPSIS

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| **Name of Sponsor/Company:** The Medicines Company<br>**Name of Finished Product:** Cangrelor for Injection<br>**Name of Active Ingredient:** Cangrelor | Individual Study Table Referring to Part of the Dossier | *(For National Authority Use Only)* |

**Title of Study:** Maintenance of platelet inhiBition with cangreloR after dIscontinuation of thienopyriDines in patients undergoing surGEry: The BRIDGE trial (TMC-CAN-08-02).

**Principal Investigator:** Eric J. Topol, MD.

**Study Center(s):** Patients were enrolled at 35 study centers in 5 countries: Austria, the Czech Republic, the Netherlands, the United Kingdom (UK) and the United States (US).

**Publications (Reference):**

| **Study Period (Years):** | **Phase of development:** |
|---|---|
| Date first patient enrolled (Stage I): 02 Jan 2009<br>Date first patient enrolled (Stage II): 14 Oct 2009<br>Date last patient completed: 07 Jun 2011 | II |

**Objectives:**

The primary objective of this trial was to demonstrate that, after discontinuation of oral $P2Y_{12}$ inhibitors and compared to placebo, intravenous (IV) cangrelor provides effective and consistent $P2Y_{12}$ inhibition up to the time of surgery, without increasing surgical bleeding. Effective $P2Y_{12}$ inhibition is demonstrated by maintenance of platelet reactivity at levels known to be associated with a low risk of thrombotic events.

The trial was conducted in two stages. Stage I was dose-finding and Stage II was randomized, double-blind, placebo-controlled.

The primary objective of Stage I was to identify the dose of cangrelor that achieved a level of antiplatelet effect after discontinuation of oral $P2Y_{12}$ therapy equivalent to that expected to be maintained if oral $P2Y_{12}$ therapy had not been discontinued.

The primary efficacy objective of Stage II was to demonstrate that cangrelor (at a dose identified in Stage I) maintained levels of platelet reactivity below a threshold known to be associated with a low risk of thrombotic events (P2Y12 Reaction Unit <240) as measured by the Accumetrics Verify*Now*™ P2Y12 assay for the duration of the infusion, compared to placebo.

The main safety objective of the trial was to demonstrate that patients who received a cangrelor infusion before cardiac surgery had an acceptable safety profile and underwent surgery without excessive surgical bleeding.

**Methodology:**

**Stage I:** prospective, open-label, dose-finding, multi-center

**Stage II:** prospective, double-blind, randomized (1:1), multi-center

**Number of Patients (Planned and Analyzed):**

**Stage I (open-label, dose-finding)**

*Planned:* 5 to 20 patients (a maximum of 4 cohorts of 5 patients each)
*Randomized:* 11 patients total, 5 in Cohort I and 6 in Cohort II
*Analyzed:* 10 patients, 5 in Cohort I and 5 in Cohort II

**Stage II (double-blind, randomized)**

*Planned:* Up to 200 patients with up to 100 per arm (cangrelor vs placebo)
*Randomized:* 210 patients total, 106 in cangrelor arm and 104 in placebo arm
*Analyzed:* Intent-to-treat population: 183 patients total, 93 cangrelor and 90 placebo
Per protocol population: 147 patients total, 70 cangrelor and 77 placebo
Safety population: 207 patients total, 106 cangrelor and 101 placebo

**Diagnosis and Main Criteria for Inclusion:** Patients with Acute Coronary Syndrome (ACS) and/or patients with a stent that were at increased risk of thrombotic events due to discontinuation of an oral $P2Y_{12}$ inhibitor prior to cardiac surgery.

**Test Product, Dose and Mode of Administration, Batch Number(s):**

Cangrelor (Cangrelor for Injection) was supplied in 10 milliliter (mL)vials, each containing 50 milligram (mg) of cangrelor as the tetrasodium salt, plus mannitol (European Pharmacopoeia [PhEur]/United States Pharmacopeia [USP]) and sorbitol (PhEur/USP) as excipients.

**Stage I (open-label, dose-finding):** Cangrelor was administered as an intravenous infusion to cohorts of 5 patients in a stepwise fashion at predetermined doses (0.5 µg/kg/min, 0.75 µg/kg/min, 1.0 microgram(µg)/kilogram(kg)/minute(min) and 1.5 µg/kg/min) until the primary endpoint was met, or a dose of 2.0 µg/kg/min was reached.
Ben Venue Lot 1280162.

**Stage II (double-blind, randomized):** Cangrelor was administered as an intravenous infusion. The infusion dose of cangrelor was based on the results of the Stage I evaluation and determined to be 0.75 µg/kg/min. This dose was confirmed by the Data and Safety Monitoring Board (DSMB) following enrollment of the first 24 patients in Stage II.
Ben Venue Lots: 1280162, 1297930, 1297935, 1389571, 2070017, 2070018 and Baxter Lots: 905945, 906165, 906220, 907921.

**Duration of Treatment:** Study drug infusion was initiated immediately after randomization (within 72 hours of last dose of oral $P2Y_{12}$ inhibitor) and maintained throughout the pre-operative period for a minimum of 48 hours. Infusion durations of up to 7 days were allowed. Sites were instructed to discontinue the infusion 1 to 6 hours prior to surgical incision. Study drug was not administered during or after cardiac surgery.

**Reference Therapy, Dose and Mode of Administration, Batch Number(s):**

**Stage I (open-label, dose-finding):** No reference therapy was used in Stage I.

**Stage II (double-blind, randomized):** Matching placebo (Cangrelor Placebo for Injection) was supplied in 10 mL vials identical to that of the cangrelor test product, with each vial containing mannitol and sorbitol. Placebo was to be administered as an intravenous infusion, in the same manner as the cangrelor intravenous infusion.
Ben Venue Lots: 1389571 and 2070018 and Baxter Lots: 905945 and 907921.

**Criteria for Evaluation:**

***Primary Efficacy:***

**Stage I (open-label, dose-finding):** The primary efficacy endpoint for Stage I was maintenance of platelet inhibition during cangrelor infusion at levels above 60% in at least 80% of patient samples as reported by the Verify*Now*™ P2Y12 point of care assay (calculated using the internal reference BASE channel). This endpoint was selected as an approximation of the antiplatelet effect expected to be maintained if oral $P2Y_{12}$ inhibitors had not been discontinued.

**Stage II (double-blind, randomized):** The primary efficacy endpoint for Stage II was the percentage of patients with Platelet Reaction Units (PRU) <240, as determined by the Verify*Now*™ P2Y12 point of care assay, measured during study drug infusion pre-surgery. This endpoint was selected as it is considered by consensus of the Working Group on Platelet Reactivity to be the threshold for the level of platelet inhibition required to maintain a low risk of coronary thrombosis and cardiac ischemic events [Bonello et al, 2010].

***Secondary Efficacy:***

- Percentage of total patient samples with at least 60% platelet inhibition as determined by Verify*Now*™ P2Y12 point of care assay, measured during study drug infusion prior to surgery
- Percentage of total patient samples with PRU <240 as determined by Verify*Now*™ P2Y12 point of care assay measured during study drug infusion prior to surgery
- Percentage of patients with PRU <240 in their last on-treatment sample prior to surgery
- Percentage of patients in whom all PRU evaluations during study drug infusion prior to surgery were less than or equal to baseline PRU

***Additional Efficacy Analyses:***

- Time course of platelet reactivity during the bridging period
- Platelet reactivity by patient type and treatment
- Exploratory efficacy analysis for variations in patient characteristics
- Sensitivity Analysis of efficacy endpoints

***Primary Safety:***

The main safety endpoint was the absence of excessive coronary artery bypass graft (CABG)-related bleeding, defined as the occurrence of surgical re-exploration, 24-hour chest tube output of >1.5 liters (L), and/or packed red blood cell transfusions >4 units.

***Secondary Safety:***

- CABG-related bleeding, defined as the occurrence of one or more of the following during surgery, through hospital discharge:
- Fatal bleeding
- Perioperative intracranial bleeding within 48 hours
- Reoperation following closure of sternotomy for the purpose of controlling bleeding
- Transfusion of ≥5 units of whole blood or packed red blood cells within a 48-hour period. Cell saver products were not counted, and platelet transfusions were not included in the definition of major bleeding (though recorded and reported)
- Chest tube output ≥2 L within a 24-hour period
- Non-CABG (preoperative) bleeding (according to protocol defined GUSTO, TIMI and ACUITY bleeding criteria)
- All blood product transfusions up to 7 days after surgery or discharge, whichever was sooner

***Additional Bleeding Analyses:***

- Predictors of surgical bleeding and transfusion
- Predictors of non-CABG bleeding

***Additional Safety Observations:***

- Incidence of the combined ischemic endpoint of death, myocardial infarction (MI), stroke or need for ischemia-derived revascularization (IDR) within 30 days following surgery
- Incidence of the combined ischemic endpoint of death, MI, stroke or need for IDR from the time of randomization until discontinuation of study drug
- Incidence of adverse events (AEs) and serious adverse events (SAEs) up to 7 days post-surgery or discharge, whichever occurred first

**Statistical Methods:**

During Stage I, after each dose-specific cohort of open-label patients completed their treatment, an interim analysis was performed and results were reviewed by the Executive Committee. These data received medical review by the Sponsor to determine the dose of cangrelor for Stage II, based on the lowest dose providing a consistent level of platelet inhibition of >60% using the Verify*Now*™ P2Y12 assay.

For Stage II, a sample size of 106 (53 each arm) was calculated to provide 90% study power at a significance level of 0.05, based on the assumption that 30% of placebo-treated patients and at least 60% of cangrelor-treated patients would maintain platelet inhibition below PRU<240. The primary study endpoint was analyzed using a logistic regression model adjusted by expected days to surgery, determined at the time of randomization. Patient demographics, medical history, drug administration and surgical procedures were summarized by treatment group.

**Summary of Results:**

**Stage I (open-label, dose-finding):** The primary endpoint was met in Cohort II and a cangrelor infusion of 0.75 µg/kg/min was identified as the dose that provided consistent and effective platelet inhibition after discontinuation of oral $P2Y_{12}$ therapy to at least the extent expected to be maintained if oral $P2Y_{12}$ inhibitors had not been discontinued.

In Cohort I, a cangrelor dose of 0.5 µg/kg/min prior to surgery maintained platelet inhibition above 60% in only 76.5% (13/17) of patient samples. In Cohort II, the primary endpoint of maintenance of platelet inhibition above 60% in at least 80% of patient samples was met. Cangrelor at a dose of 0.75 µg/kg/min maintained platelet inhibition above 60% in 94.4% (17/18) of patient samples. When measuring platelet inhibition during infusion according to the Working Group on Platelet Reactivity consensus, 80% of patients in Cohort I and 100% of patients in Cohort II had all on-infusion samples <240 PRU during the cangrelor infusion. There were no safety-related concerns with cangrelor administration at this dose. A cangrelor dose of 0.75 µg/kg/min was selected for further evaluation in the randomized, double-blind phase (Stage II).

**Stage II (double-blind, randomized):**

***Efficacy:*** Cangrelor at an infusion dose of 0.75 µg/kg/min provides effective and consistent inhibition of platelet reactivity well below levels known to be consistent with less stent thrombosis (ST) and a reduction in thrombotic events. The primary efficacy endpoint was met with 98.8% of cangrelor-treated patients maintaining target levels of platelet inhibition (<240 PRU) for all time points measured over the bridging period compared to 19.0% of placebo patients (relative risk [RR], 5.2 [95% CI, 3.3-8.1] p <0.001).

For all secondary efficacy endpoints measured, compared to placebo, cangrelor demonstrated significantly better pharmacodynamic effects, well below threshold levels during infusion.

After discontinuation of the infusion (1 to 6 hours before surgery), platelet function prior to surgery was similar for cangrelor and placebo groups (p=0.212). This rapid return of platelet function is consistent with the short half-life of cangrelor (3 to 6 min).

***Safety*:** Compared to placebo, cangrelor does not increase surgical bleeding risk. There was no difference in the primary safety endpoint of protocol-defined excessive surgical bleeding for patients receiving cangrelor (11.8%) vs placebo (10.4%).

Additionally, other pre-specified markers of surgical bleeding were similar, including: bleeding consistent with BARC defined CABG-related bleeding (9.8% cangrelor vs 10.4% placebo); chest tube output at 4 hours (325.4 mL cangrelor vs 297.1 mL placebo) and 24 hours (830.4 mL cangrelor vs 805.2 mL placebo) and the number of patients receiving transfusions (25.5% cangrelor vs 32.3% placebo). Among those patients who received a transfusion there were no differences in the number of transfusions administered.

Cangrelor was associated with a numerical increase in non-CABG related bleeding occurring during the 5-day bridge period. There was a numerical increase in GUSTO mild and TIMI/ACUITY minor bleeding driven primarily by ecchymosis, oozing at the puncture site, and hematoma <5 centimeter (cm) located at the puncture site. These events are not known to be correlated with long term adverse clinical outcomes and the overall incidence of minor bleeding may have been increased in part by repeat venipuncture associated with the trial conduct. There was also a numerical increase in GUSTO moderate (2 events in cangrelor vs 1 event in placebo) and ACUITY major bleeding (3 events in cangrelor vs 1 event in placebo). Review of the electronic case report forms (eCRFs) for each of the three patients involved suggested that all of the events were associated with other interventional procedures, were not spontaneous bleeds.

Ischemic endpoints of death, MI, stroke and IDR were reported by the investigator. Ischemic endpoints were low in both treatment groups prior to surgery in Stage II, 2.8% (3/106) and 4.0% (4/101), in cangrelor and placebo patients, respectively. The number of deaths in the cangrelor group was numerically lower than in the placebo group during the pre-procedure period (1 event in cangrelor vs 3 in placebo). Post-procedure ischemic endpoints were low and similar between the groups (3 events in cangrelor vs one in placebo).

There were a similar number of patients with Adverse Events (AEs) and Serious Adverse Events (SAEs) between cangrelor- and placebo-treated patients: AEs: 58/106 (54.7%) vs 56/101 (55.4%); SAEs: 11/106 (10.4%) vs 9/101(8.9%). The incidence of dyspnea (including exertional dyspnea) was reported in 2.8% (3/106) of patients treated with cangrelor and in 0.9% (1/101) of patients who received placebo. All events of dyspnea were non-serious, mild in intensity, and recovered. The incidence of post-baseline clinically significant laboratory tests in hematology and serum chemistry was similar in both groups.

**Conclusions:**

During the bridge period, cangrelor, at a dose 0.75 µg/kg/min, demonstrated effective and consistent platelet $P2Y_{12}$ inhibition well below the threshold associated with less stent thrombosis (ST) and thrombotic events compared with placebo, without increasing surgical bleeding risk. The lack of increase in surgical bleeding observed with cangrelor is consistent with its rapid offset of effect after discontinuation of the infusion. In the cangrelor group a numerical increase in non-CABG bleeding prior to surgery was observed compared to placebo, but was not due to spontaneous bleeding did not compromise the use of cangrelor for bridging patients off oral $P2Y_{12}$ inhibitors.

In the contemporary management of patients taking oral $P2Y_{12}$ inhibitors who require surgery a dilemma exists – to discontinue therapy and risk thrombosis or to continue treatment and risk hemorrhage. The favorable benefit risk profile of cangrelor makes it a clinically important treatment alternative that allows physicians to minimize ischemic events without increasing the risk of surgical bleeding during the bridge period.

Date of the report: 29 March 2013