SYNOPSIS OF RESEARCH REPORT [redacted] (PROTOCOL BP25619)

COMPANY: NAME OF FINISHED PRODUCT: NAME OF ACTIVE SUBSTANCE(S):	(FOR NATIONAL AUTHORITY USE ONLY)

TITLE OF THE STUDY / REPORT No. / DATE OF REPORT	A Multi-Center, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of 2 Doses of RO4905417 (R1512) Administered to Patients with Non ST-Elevation Myocardial Infarction (NSTEMI) Undergoing Percutaneous Coronary Intervention (PCI) – Report No. [redacted] / September 2013
INVESTIGATORS / CENTERS AND COUNTRIES	The study was conducted in 4 countries at 66 sites (35 in the United States, 12 in Canada, 14 in Poland, and 5 in The Netherlands).
PUBLICATION (REFERENCE)	Tardif JC, Tanguay JF, Wright SS et al. Effects of the P-selectin antagonist inclacumab on myocardial damage after percutaneous coronary intervention for non-ST-segment elevation myocardial infarction: results of the SELECT-ACS trial. J Am Coll Cardiol 2013; 61:2048-2055.
CLINICAL PHASE	IIa
OBJECTIVES	The primary objective of the study was to evaluate the efficacy of RO4905417 in reducing procedural myocardial damage during PCI. The secondary objectives were: 1) To evaluate the changes in other cardiac and renal biomarkers; and 2) To evaluate the safety of RO4905417 by monitoring of adverse events and the incidence of major adverse cardiovascular events (MACEs) at 30 and 120 days after PCI after a single dose of study drug.
STUDY DESIGN	Study BP25619 was a multicenter phase IIa randomized, double-blind, placebo controlled efficacy and safety study of 2 doses of RO4905417 (5 mg/kg or 20 mg/kg) in patients with NSTEMI, who were scheduled to undergo PCI.
NUMBER OF SUBJECTS	The study planned to enroll 516 patients. The study randomized 544 patients: placebo n=183, RO4905417 5 mg/kg n=180, and RO4905417 20 mg/kg n=181.
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	The study recruited patients with a diagnosis of a qualifying NSTEMI event in a clinical setting consistent with myocardial ischemia, defined by abnormal levels of cardiac biomarkers troponin I or T or CK-MB mass with at least one determination > the 99th percentile or above the upper reference limit as specified by the local laboratory.
TRIAL DRUG / (BATCH) No.	The RO4905417 batch numbers used in this study were: [redacted], [redacted], [redacted], and [redacted].
DOSE / ROUTE / REGIMEN / DURATION	RO4905417/Placebo was administered as a single intravenous infusion completed at least 1h, and not more than 24h, before the planned PCI.
REFERENCE DRUG /	The placebo batch numbers used in this study were: [redacted].

(BATCH) No.	
CRITERIA FOR EVALUATION	
EFFICACY:	The primary endpoint was the change from baseline in troponin I at 16 and 24h post PCI in RO4905417 treatment groups as compared to placebo. The secondary endpoints of this study were: • Change from baseline in troponin I at 8h post PCI in RO4905417 treatment groups as compared to placebo; • Peak and AUC_{0-24h} for troponin I 24h post PCI in RO4905417 treatment group as compared to placebo; • Change from baseline in CK-MB at 8, 16 and 24h post PCI in RO4905417 treatment groups as compared to placebo; • Change from baseline at 120 days post PCI in GDF-15 in RO4905417 treatment group as compared to placebo; • Change from baseline in cystatin C at 24h and 30 days post PCI in RO4905417 treatment groups as compared to placebo.
PHARMACOKINETICS / PHARMACODYNAMICS:	Concentrations of RO4905417 were determined in plasma samples taken at 8h, 30 and 120 days post PCI by enzyme-linked immunosorbent assay (ELISA). Concentration of soluble P-selectin (sP-selectin) were determined in plasma samples taken at baseline, and 8h post PCI by ELISA.
SAFETY:	Safety assessments included: treatment emergent adverse events (TEAEs), laboratory tests, Human Anti-Human Antibody (HAHA) formation, vital signs, electrocardiograms (ECGs), monitoring of infection, and TEAEs occurring in the first 24h. The incidence of MACEs, bleeding and renal failure were also recorded.
STATISTICAL METHODS:	Baseline, efficacy and safety data were reported using descriptive statistics. Efficacy analyses were carried out primarily on the PP population using an Analyses of Covariance, with the exception of the AUC_{0-24h} endpoint, which used an Analysis of Variance (ANOVA). sP-selectin change from baseline at 8h was compared across groups using an ANOVA computed on the randomized Population. No statistical tests were used on safety parameters to assess treatment differences. Descriptive statistics were compiled using the Safety Population. Occurrence and time to MACEs, bleeding, and renal failure at 30 and 120 days was compared across groups using Chi-square and a log-rank tests, respectively, performed on the Safety Population.

METHODOLOGY

Screening was performed for up to 3 days prior to PCI. At Baseline (V1), eligible patients were randomized 1:1 to RO4905417 5 mg/kg, 20 mg/kg or matching placebo. Baseline assessments and procedures were performed. At V1.1, patients received a single infusion of the study drug prior to PCI (V1.2). Patients were assessed 8h (V1.3), 16h (V1.4), and 24h (V1.5) post PCI. Follow-up safety visits were conducted 30 days (V2) and 120 days (V3) post PCI.

EFFICACY RESULTS

RO4905417 at a dose of 5 mg/kg did not show any discernable effect versus placebo on the primary and secondary efficacy endpoints.

RO4905417 20 mg/kg treatment showed a consistent trend, although not of statistical significance, to limit the rise of troponin I and CK-MB post PCI. This trend was strongest in the ITT population. Moreover, the 20 mg/kg patient group with higher baseline sP-selectin concentrations showed a statistically significant lower rise in troponin I at 24h. No statistical significant difference was seen between RO4905417 20 mg/kg and placebo on the GDF-15 and cystatin C endpoints.

PHARMACOKINETIC RESULTS

The range of RO4905417 concentration data of 5 and 20 mg/kg largely overlapped those reported in healthy subjects receiving the same dose, though mean exposure data were on average slightly lower.

PHARMACODYNAMIC RESULTS

A statistically significant reduction in sP-selectin concentration (22%) at 8h was observed for RO4905417 20 mg/kg relative to placebo. No significant effect was seen with the 5 mg/kg dose.

SAFETY RESULTS

There were 6 deaths reported during the study (RO4905417 5 mg/kg n=4, RO4905417 20 mg/kg n=2), which were all considered unrelated to the study medication by the investigator.

The most common TEAEs were coronary artery bypass, chest pain, nausea, headache, and hypotension. The most frequently reported TESAEs were associated with “surgical and medical procedures” and “cardiac disorders”. No discernable difference in the nature of TEAEs was identified between the treatment groups; however, more TEAEs were reported in the RO4905417 5 mg/kg arm relative to the other two groups.

The occurrence of infections was relatively low and comparable across treatment arms. The most frequently reported TEAEs within the first 24 hours were procedure related. Overall, the nature of TEAEs seen within the first 24h was in keeping with that reported for the remainder of the study, and comparable across treatment groups.

The proportion of patients with at least one MACE was higher in the RO4905417 arms versus placebo at 30 and 120 days. A statistically significant difference between RO4905417 5 mg/kg and placebo was noted at 30 days. The occurrence of bleeding and renal failure was low, with no apparent dose response.

There was no specific pattern related to RO4905417 administration, or for dose-dependent changes over time in laboratory tests, HAHA formation, vital sign, and ECGs.

CONCLUSIONS

RO4905417 at doses of 5 or 20 mg/kg, when given prior to PCI, did not demonstrate any statistically significant effect on the rise of troponin I at 16 and 24h post PCI. However, although not of statistical significance, there was a consistent trend for RO4905417 at a dose of 20 mg/kg to limit the rise of troponin I and CK-MB levels post PCI. This trend was strongest in the ITT population. Moreover, patients treated with RO4905417 20 mg/kg with higher baseline sP-selectin concentrations showed a statistically significant lower rise in troponin I 24h post PCI.

RO4905417 was generally safe and well tolerated at both doses, when administered as a single intravenous infusion. The nature of the observed TEAEs were similar in the placebo and active treatment groups; however numerically more TEAEs were reported in the group receiving RO4905417 5 mg/kg than in the other two groups.

There was no apparent effect of RO4905417 on laboratory parameters, vital signs, ECGs, immunogenicity, occurrence of infections, bleeding, and renal failure.

The consistency of the results from this study suggest that the P-selectin antagonist RO4905417, at a dose of 20 mg/kg, has the potential to limit myocardial injury as evidenced by the release of cardiac necrosis biomarkers. Further clinical studies will be required to determine if this translates into a reduction of myocardial damage associated with PCI, and the clinical value (benefit or harm) of RO4905417 in patients presenting with myocardial infarction whether or not they undergo PCI.