Sponsor: Sanofi **Drug substance:** ALX-0081	**Study Identifiers:** NCT01020383, EudraCT 2009-012206-39 **Study code:** ALX-0081-2.1/09
Title of the study: A phase II randomized, open-label clinical trial in high risk percutaneous coronary intervention (PCI) patients receiving standard antithrombotic treatment plus either ALX-0081 or GPIIb/IIIa inhibitor (ReoPro®) over a period of 24 hours	
Study centers: Thirty-nine active sites (out of 48 approved sites) in 7 countries: Austria (4 sites), Belgium (5 sites), Czech Republic (4 sites), Germany (3 sites), Israel (7 sites), Poland (14 sites), and Switzerland (2 sites).	
Study period: Date first participant enrolled: 01/Sep/2009 Date last participant completed: 29/Mar/2012 Study Status: Completed	
Phase of development: II	
Objectives: Primary: To compare the safety, more specifically bleeding, of ALX-0081 versus the GPIIb/IIIa inhibitor ReoPro® in high risk PCI patients. Secondary: To compare the tolerability, biological and clinical effectiveness of ALX-0081versus ReoPro® in high risk PCI patients.	
Methodology: This was a multicenter, randomized and open-label Phase II study to compare the safety, tolerability, and biological and clinical effectiveness of ALX-0081 versus the GPIIb/IIIa inhibitor ReoPro® in high risk PCI patients. Patients who needed to undergo a PCI procedure were screened within 48 hours before the PCI. All patients received standard treatment with acetylsalicylic acid (ASA) plus clopidogrel and heparin. Eligible patients were randomly assigned to receive open-label study treatment with either ALX-0081 or ReoPro®. Patients were stratified according to PCI type (elective or ad-hoc) and stent type (bare metal stent or drug eluting stent). Angiography procedures were assessed by a central laboratory. All adverse events (AEs) were adjudicated by the Clinical Evaluation Committee (CEC) who determined which AEs were classified as major adverse cardiac events (MACE), cerebrovascular events (CVE) and/or Thrombolysis-In-Myocardial-Infarction (TIMI) bleeding events. In addition, a Data Safety Monitoring Board (DSMB) monitored the number of bleeding events and serious adverse events (SAEs) during the study in order to make recommendations on study termination in case of an excessive number of bleeding events.	
Number of participants: Planned: 368 Randomized: 380	
Diagnosis and criteria for inclusion: Male and female patients (aged ≥ 18 years old) who needed to undergo a PCI procedure within 48 hours were enrolled. Patients with unstable angina or Non ST Segment Elevation Myocardial Infarction (NSTEMI), or stable angina with at least two factors indicating a high risk PCI were eligible. Risk factors for PCI were defined as: ● Patient-related: diabetic patients, renal failure (glomerular filtration rate < 60), reduced left ventricular ejection fraction < 35%, age > 75 years, female gender, and/or ● Lesion/anatomy-related: SYNTAX score > 26, bifurcation lesions, multi-vessel disease, intracoronary thrombus.	

Test product

ALX-0081 was administered as an intravenous (i.v.) bolus injection 5-15 minutes prior to the PCI procedure and i.v. bolus injections were repeated every 6 hours until 18 hours post-PCI (four doses of ALX-0081 were given to each patient). The first dose of ALX-0081 was 6 mg, followed by three doses of 4 mg.

Duration of treatment:

The treatment period for all patients was 24 hours and patients were hospitalized until Day 3 with a follow-up visit on Day 7 (± 1 day) and Day 30 (± 3 days), and also at 6 months (± 7 days) and 1 year (± 7 days).

Criteria for evaluation:

Primary endpoints:

- Incidence and severity of bleeding classified by the following criteria within 30 days:

o TIMI major bleeding events.

o TIMI minor bleeding events.

o TIMI minimal bleeding events.

The primary variable was defined as the proportion of patients who experienced at least one CEC classified TIMI bleed (major, minor or minimal) which occurred on-study.

Secondary endpoints:

- Incidence of each of the three above mentioned bleeding event classifications taken separately.
- MACE:

o All cause mortality (including cardiovascular and non cardiovascular).

o Myocardial infarction.

o Target vessel revascularization (TVR) (coronary artery bypass graft [CABG] or PCI).

- CVE, including stroke and transient ischemic attack (TIA).
- ALX-0081 pharmacokinetic (PK) parameters. Please note that the PK results were analyzed separately and are reported in a PK Report.
- Pharmacodynamic (PD) assessment through ristocetin cofactor activity [RICO] assay, von Willebrand factor [vWF] and Factor VIII (FVIII).
- Immunogenicity of ALX-0081 (e.g. development of antidrug antibodies [ADA]). Please note that the ADA results were analyzed separately.

Statistical methods:

All statistical testing was performed at the 1-sided 5% significance level, with only the upper confidence limit being presented in the tables (as applicable). Unless otherwise stated, the Intention to Treat (ITT) population was used as the primary population for all baseline and demographic and primary and secondary endpoint tables and the safety population was used for all safety tables. All data were listed by randomized treatment. In addition, to assess the robustness of the results, the analyses of bleeding, MACE and CVE were also repeated in the per protocol (PP) population.

All the listings, tables and figures in this report were produced for the analyses performed after all patients had at least 30 days of follow-up data. The primary outcome of the study was the proportion of adjudicated TIMI major, minor and bleeding events requiring medical attention, defined as TIMI minimal bleeding events. These data were compared using the Cochran Mantel Haenszel method and allowed for the two stratification factors of stent type and PCI type. The analysis results included the relative risk, the 1-sided upper 95% confidence limit and the associated p-value. The Cochran Mantel Haenszel method was also repeated based on the rate of adjudicated MACE events observed in each of the treatment groups and the rate of adjudicated CVEs observed in each of the treatment groups.

In addition to the formal analysis of the total number of major, minor and minimal bleeds and combined grouping of MACEs and CVEs, the data were also summarized by the individual classification of the event (i.e. major, minor or minimal bleeds, all cause mortality, myocardial infarction, TVR [CABG or PCI]), stroke and TIA.

Summaries were also produced showing observed values and change from baseline values (where applicable) for the PD, laboratory and all other safety data. A DSMB monitored the safety data and reviewed the results of the interim analysis as specified in the DSMB Charter. In addition, all AEs were adjudicated by the CEC and classified as MACE, CVE, and/or TIMI bleeding (major, minor or minimal bleeds), or none of these events as detailed in the CEC charter.

Tables were presented using standard summary statistics to show the number of patients with the following MACEs and CVEs by treatment group. The table summarized all MACE and CVEs according to the CEC adjudication, using both the ITT and PP population.

All safety parameters were summarized descriptively by treatment. Tables of AEs by intensity and relationship to study drug were also provided. A summary of the number and percentage of patients by treatment who experienced a ‘drug interruption’ or ‘permanent withdrawal of drug’ was also presented.

Summary Results:

Efficacy:

The number of patients with CEC adjudicated bleeding events within 30 days was higher in the ALX-0081 treatment group (36 [19.9%] patients) than in the ReoPro® treatment group (28 [15.3%] patients), giving a relative risk of 1.30 and one-sided p-value of 0.877. The number of patients who experienced at least one bleeding related event within 30 days of study administration as assessed by the Investigator in the electronic case report form was quantitatively similar in both treatment groups: 59 (32.6%) patients in the ALX-0081 group and 63 (34.4%) patients in the ReoPro® group. By TIMI classification, the number of major and minimal bleeds adjudicated was quantitatively similar in both treatment groups (3 [1.7%] and 2 [1.1%] patients with major bleeds and 25 [13.8%] and 24 [13.1%] patients with minimal bleeds in the ALX-0081 and ReoPro® treatment groups, respectively). A quantitatively greater number of patients had minor bleeds in the ALX-0081 treatment group (8 [4.4%] patients) than in the ReoPro® treatment group (2 [1.1%] patients). Six (10.2%) patients in the ALX-0081 treatment group and 4 (6.3%) patients in the ReoPro® treatment group required blood transfusion, for a total of 16 units of blood in the ALX-0081 treatment group and 21 units of blood in the ReoPro® treatment group. Most of the bleeding events were of mild intensity in both treatment groups.

At the 1 year follow-up, the number of patients with CEC adjudicated bleeding events remained higher in the ALX-0081 treatment group (38 [21.0%] patients) than in the ReoPro® treatment group (29 [15.8%] patients), giving a relative risk that increased from 1.30 to 1.33.

The number of patients with CEC adjudicated MACEs was low. A higher number of patients in the ALX-0081 treatment group (10 [5.5%] patients) as compared to the ReoPro® treatment group (4 [2.2%] patients) experienced a CEC adjudicated MACE. Of those patients in the ALX-0081 treatment group, 9 (5.0%) had myocardial infarction and 5 (2.8%) had TVR (4 of these patients had both myocardial infarction and TVR). Of those with CEC adjudicated MACEs in the ReoPro® treatment group, 3 (1.6%) patients had myocardial infarction and 1 (0.5%) had TVR and an all cause mortality event. Only 1 (0.6%) patient experienced a CEC adjudicated CVE. This patient was in the ALX-0081 treatment group and the CVE was classified as stroke.

At 1 year of follow-up, the occurrence of additional MACEs in each treatment arm decreased the relative risk increase of MACE from 1.53 to 0.58 for ALX-0081 over ReoPro®.

In summary, it was not possible to conclude a statistically significant benefit for ALX-0081 with regard to clinical outcome as adjudicated by the CEC, including bleeding profile, MACE and CVE.

PD Assessment

As expected, an immediate drop in RICO activity was observed 5 to 10 minutes after the ALX-0081 bolus injection, whereas no inhibition of RICO activity was observed with the ReoPro® treatment. Clinically relevant RICO inhibition (< 20%) was maintained for 24 hours post-bolus of first dose administration in the ALX-0081 treatment group. This effect was accompanied by a mild and transient decrease in vWF antigen and FVIII activity in the ALX-0081 treatment group, as expected based on the pharmacology of ALX-0081.

Safety results:

There were no significant safety concerns raised for treatment with ALX-0081 in this study and the results seen were as would be expected for this patient population of high risk PCI patients. Key safety outcomes observed were:

- In the ALX-0081 treatment group, the mean (± SD) administered dose was 17.05 ± 3.05 mg, with a median dose of 18.0 mg (range 6.0 to 18.0 mg). In the ReoPro® treatment group, the mean (± SD) administered dose was 26.90 ± 4.25 mg, with a median dose of 27.20 mg (range 7.20 to 36.00 mg).
- The proportion of patients who reported at least one treatment emergent AE (TEAE) within 30 days of study administration was 113 (62.4%) patients in the ALX-0081 treatment group and 105 (57.4%) patients in the ReoPro® treatment group. The most common system organ class (SOC) evoked in the TEAEs were injury, poisoning and procedural complications in both treatment groups.
- At 30 days, the incidence of anemia was almost similar in both treatment groups: 6 (3.3%) patients in the ALX-0081 treatment group, and 5 (2.7%) in the ReoPro® treatment group) reported anemia as TEAE during the study to Day 30. Decreased hemoglobin was not reported as TEAE in any patient in the ALX-0081 treatment group, and was reported in 1 (0.5%) patient in the ReoPro® treatment group. Decreased hematocrit and decreased red blood cell count were not reported as TEAEs in any patient in the ALX-0081 treatment group, and were reported in 3 (1.6%) patients in the ReoPro® treatment group. No change in trends were objectivated at 1 year.
- The proportions of patients with TEAEs of each category of intensity (mild, moderate or severe) or relationship (related, possibly related or unlikely/not related) were similar in both treatment groups.
- Only 1 (0.5%) patient in the ReoPro® treatment group and none in the ALX-0081 died during the study to Day 30 due to AEs. Nine additional patients(5 in the ALX-0081 treatment group and 4 in the ReoPro® treatment group) died after Day 30 and before the 1 year follow-up. All of these events were considered to be unlikely/not related to the study drug, except for a PT of syncope for a patient in the ALX-0081 group which was possibly related.
- Within 30 days of study administration, serious TEAEs were reported in 24 (13.3%) patients in the ALX-0081 treatment group and 18 (9.8%) patients in the ReoPro® treatment group. The most common SOC evoked in the serious TEAEs were injury, poisoning and procedural complications in the ALX-0081 treatment group, and cardiac disorders in the ReoPro® treatment group.
- The number of patients with AEs leading to permanent withdrawal of the study drug was similar in both treatment groups (9 [5.0%] and 8 [4.4%] patients in the ALX-0081 and the ReoPro® treatment groups, respectively).
- The number of patients with AEs leading to study drug interruption were 1 [0.6%] and 5 [2.7%] patients in the ALX-0081 and the ReoPro® treatment groups, respectively.
- None of the changes in hematology or liver function parameters reported over the course of the study were of any clinical relevance. Mean creatinine levels increased over time whereas mean GFR slightly declined in both treatment groups. Both findings were expected in patients undergoing PCI and were most likely related to the contrast agent administration. No other remarkable findings or differences between treatment groups were observed regarding kidney function tests. A higher aPTT at baseline, which most likely corresponded with heparin treatment; followed by a decline in mean aPTT values over time back to the normal range was observed in both treatment groups. No other remarkable findings or differences between treatment groups were observed regarding coagulation factors.
- No remarkable findings or differences between the treatment groups were observed regarding physical examination or vital signs.

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