1. SYNOPSIS

Name of Sponsor/Company: Ablynx NV	Individual Study Table Referring to part of the Dossier	(for National Authority Use only)
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TITLE OF 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.

INVESTIGATOR(S) AND STUDY CENTER(S): 7 countries: Austria, Belgium, Czech Republic, Germany, Israel, Poland, and Switzerland

STUDY DATES: From: 01 September 2009 (first patient randomized)
To: 29 March 2012 (last patient 1 year Follow-Up)

This report presents the results up to end of study - 1 year Follow-Up visit.

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-0081 versus 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)

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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 PATIENTS:

Planned: 368 patients

Randomized: 380 patients (191 to ALX-0081 and 189 to ReoPro®)

DIAGNOSIS AND MAIN 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, DOSE, MODE OF ADMINISTRATION:

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).

REFERENCE THERAPY, DOSE, MODE OF ADMINISTRATION:

ReoPro® administration followed the package information and consisted of an i.v. bolus injection followed by continuous infusion over 12 hours. The dosage was a 0.25 mg/kg i.v. bolus administered 10-60 minutes prior to the PCI procedure followed by a continuous i.v. infusion of 0.125 µg/kg/min (to a maximum of 10 µg/min) for 12 hours.

Commercial ReoPro® from the investigational sites Pharmacies was used in this study.

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CRITERIA FOR EVALUATION:

Primary endpoints:

- Incidence and severity of bleeding classified by the following criteria within 30 days:
  - TIMI major bleeding events.
  - TIMI minor bleeding events.
  - 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 within 30 days.
- MACE (both within 30 days and up to the final follow-up visit at 1 year):
  - All cause mortality (including cardiovascular and non-cardiovascular).
  - Myocardial infarction.
  - Target vessel revascularization (TVR) (coronary artery bypass graft [CABG] or PCI as recorded through AE reporting).
- CVE, including stroke and transient ischemic attack (TIA) (both within 30 days and up to the final follow-up visit at 1 year).
- ALX-0081 pharmacokinetic (PK) parameters.
- Pharmacodynamic (PD) assessment through ristocetin cofactor activity [RICO] assay, von Willebrand factor [vWF] and Factor VIII (FVIII).
- Immunogenicity of ALX-0081 (development of antidrug antibodies [ADA])

Safety endpoints:

- AEs

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 (consisting of all randomized patients who received at least one dose of study medication, with

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treatment assignment designated according to randomized treatment) was used as the primary population for all baseline and demographic and primary and secondary endpoint tables and the safety population (consisting of all patients who received at least one dose of study medication, with treatment assignment designated according to actual treatment received) was used for all safety tables. All data were listed by randomized treatment.

All 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.

All safety parameters were summarized descriptively by treatment.

SUMMARY OF RESULTS AND CONCLUSIONS:

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. By TIMI classification, the number of major and minimal bleeds adjudicated was 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). 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.

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A higher percentage 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. One (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®.

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.

PK Assessment

After multiple IV bolus dosing, ALX-0081 reached a steady-state from at least 18 hours postdose (or 4th dosing) onwards.

Immunogenicity

10.9% of the subjects (17/156) developed treatment-emergent anti-drug antibodies. No neutralizing antibodies were detected.

No adverse events linked with the presence of ADA responses were reported in the study.

Safety

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

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Key safety outcomes observed were:

- The percentage of patients who reported at least one treatment emergent AE (TEAE) within 30 days of study administration was 62.4% (113 patients) in the ALX-0081 treatment group and 57.4% (105 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.
- 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.
- One (0.5%) patient in the ReoPro® treatment group and none in the ALX-0081 died during the study to Day 30. 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.
- 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.

CONCLUSIONS:

The results of this study did not provide evidence for a benefit of ALX-0081 treatment over ReoPro® in terms of reducing bleeding events in high risk PCI patients. ALX-0081 was well tolerated and there were no safety concerns raised for treatment with ALX-0081 in this study.

DATE OF REPORT: December 2016