Protocol: ID-076A201

A Multi-center, Double-blind, Randomized, Placebo-controlled Study to Assess the Pharmacodynamics, Pharmacokinetics, Tolerability, and Safety of a Single Subcutaneous Injection of ACT-246475 in Adults With Stable Coronary Artery Disease

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ACT-246475

Coronary artery disease

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CONTRACT RESEARCH ORGANIZATIONS' INFORMATION

Some activities will be delegated to Contract Research Organizations (CROs). A list of site-specific contact details can be found in the Investigator Site File.

SIGNATURE PAGE FOR IDORSIA PHARMACEUTICALS LTD

Hereinafter called the sponsor

Study title

A multi-center, double-blind, randomized, placebo-controlled study to assess the pharmacodynamics, pharmacokinetics, tolerability, and safety of a single subcutaneous injection of ACT-246475 in adults with stable coronary artery disease

I approve the terms and conditions relating to this study as defined in this protocol. I confirm that the information contained in this protocol is consistent with the current risk-benefit evaluation of ACT-246475, and with the ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki and the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines.

Title	[redacted]
Clinical Trial Physician	

INVESTIGATOR SIGNATURE PAGE

Study title

A multi-center, double-blind, randomized, placebo-controlled study to assess the pharmacodynamics, pharmacokinetics, tolerability, and safety of a single subcutaneous injection of ACT-246475 in adults with stable coronary artery disease

I agree to the terms and conditions relating to this study as defined in this protocol and any other protocol-related documents. I fully understand that any changes instituted by the investigator(s) without previous agreement with the sponsor would constitute a protocol deviation, including any ancillary studies or procedures performed on study subjects (other than those procedures necessary for the wellbeing of the subjects).

I agree to conduct this study in accordance with the Declaration of Helsinki principles, International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, and applicable regulations and laws.

Principal Investigator

[redacted]

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LIST OF ABBREVIATIONS AND ACRONYMS

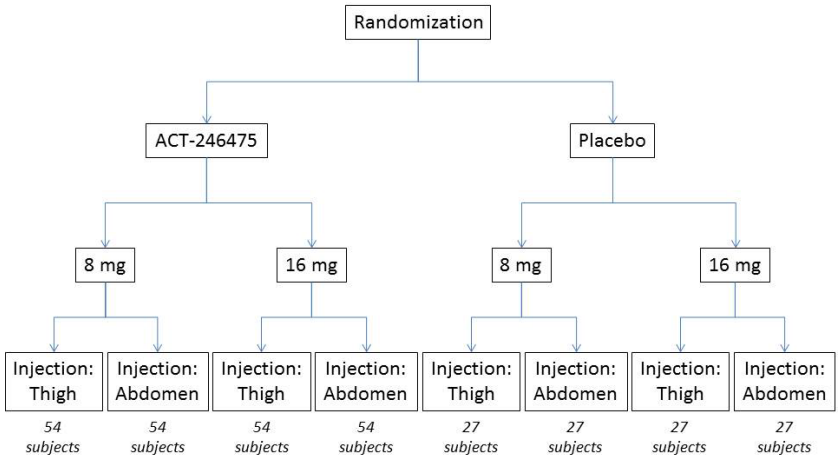
ACS	Acute coronary syndrome
ADP	Adenosine diphosphate
AE	Adverse event
AMI	Acute myocardial infarction
AUC	Area under the plasma concentration-time curve
$AUC_{0–24h}$	Area under the plasma concentration-time curve from time zero to 24 h time point
BP	Blood pressure
CAD	Coronary artery disease
CFR	Code of Federal Regulations (US)
CI	Confidence interval
C_{max}	Maximum plasma concentration
CRA	Clinical research associate
CRF	(Electronic) case report form
CRO	Contract Research Organization
CSR	Clinical study report
CTT	Clinical trial team
CV	Coefficient of variation
CYP	Cytochrome P450
DAPT	Dual antiplatelet therapy
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
eGFR	Estimated glomerular filtration rate
EOS	End-of-Study
FAS	Full analysis set
g	Gravitational constant
GCP	Good Clinical Practice
HA	Health authority
i.v.	Intravenous(ly)
IB	Investigator’s Brochure

ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
INR	International normalized ratio
IPA	Inhibition of platelet aggregation
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
LTA	Light transmission aggregometry
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MTD	Maximum tolerated dose
OATP	Organic anion-transporting polypeptide
PCI	Percutaneous coronary intervention
PD	Pharmacodynamic(s)
PI	Principal Investigator
PK	Pharmacokinetic(s)
PPACK	Phenylalanine-proline-arginine-chloromethyl ketone
PPS	Per-protocol set
PRP	Platelet-rich plasma
PRU	$P2Y_{12}$ reaction units
QA	(Sponsor) Quality Assurance
QS	(Sponsor) Quality System
QTcB	QT corrected with Bazett's formula
QTcF	QT corrected with Fridericia's formula
RND	Randomized analysis set
RSI	Reference safety information
s.c.	Subcutaneous
s.l.	Sublingual
SAD	Single-ascending dose
SAE	Serious adverse event

SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
SIV	Site initiation visit
SmPC	Summary of Product Characteristics
SS	Safety set
STEMI	ST-segment elevation myocardial infarction
SUSAR	Suspected unexpected serious adverse reaction
$t_{½}$	Terminal half-life
TEAE	Treatment-emergent adverse event
TIA	Transient ischemic attack
t_{max}	Time to reach maximum plasma concentration
TMF	Trial Master File

PROTOCOL SYNOPSIS ID-076A201

TITLE	A multi-center, double-blind, randomized, placebo-controlled study to assess the pharmacodynamics, pharmacokinetics, tolerability, and safety of a single subcutaneous injection of ACT-246475 in adults with stable coronary artery disease.
OBJECTIVES	**Primary objective(s)** The primary objective of the study is to characterize inhibition of platelet aggregation (IPA) relatively to placebo after a single subcutaneous (s.c.) injection of ACT-246475 either in the thigh or in the abdomen at 2 different doses in subjects with stable coronary artery disease (CAD) receiving conventional background oral antiplatelet therapy (e.g., acetylsalicylic acid, $P2Y_{12}$ receptor antagonists). **Other objectives** The other objectives of this study are described in Section 2.2.
DESIGN	This is a prospective, multi-national, multi-center, double-blind, randomized, placebo-controlled, parallel-group, Phase 2, exploratory study of a single s.c. administration of ACT-246475, at 2 different dose levels, in subjects with stable CAD receiving conventional background therapy (e.g., acetylsalicylic acid, $P2Y_{12}$ receptor antagonists, etc.). Approximately 324 adult subjects with stable CAD will be randomized into 1 of the 8 combinations of the treatment, dose, and injection site using a 2:2:2:2:1:1:1:1 ratio:

	 Each subject will receive a single s.c. administration of either 8 mg ACT-246475, 16 mg ACT-246475 or matching placebo, either in the thigh or in the abdomen. Double-blinding will apply to treatment (ACT-246475 vs placebo). The dose (8 mg vs 16 mg) will be single blinded (subject blinded). The injection site (thigh vs abdomen) will not be blinded. Treatment group allocation will be stratified based on baseline platelet reactivity value (expressed as $P2Y_{12}$ reaction units [PRU]) measured on Day 1 by the VerifyNow® assay before ACT-246475 injection considering the 3 following categories: high reactivity (PRU > 250), medium reactivity (150 ≤ PRU ≤ 250), and low reactivity (PRU < 150). The study comprises the following consecutive periods: **Screening period:** Lasts 1 to 21 days; starts with the signature of the informed consent form and ends on Day −1. **Treatment period:** Lasts 2 days: Day 1 and Day 2. **Follow-up period:** Lasts 28 to 35 days. Starts on Day 3 and ends with the safety follow-up telephone call.
PLANNED DURATION	Approximately 7 months from first subject, first visit to last subject, last visit.

SITE(S) / COUNTRY(IES)	Approximately 20 sites in 5–10 countries are planned.
INCLUSION CRITERIA	1. Signed informed consent prior to any study-mandated procedure. 2. Male and female subjects aged from 18–85 years, inclusive. 3. For women of childbearing potential: Negative urine pregnancy test at Visit 1 and at Visit 2 before randomization. 4. Stable CAD defined by the presence of any of the following conditions: a. History of CAD with coronary artery stenosis on coronary angiogram ≥ 50%. b. Previously documented myocardial infarction occurring more than 3 months prior to randomization. 5. Antiplatelet background therapy stable for at least 1 month prior to randomization. 6. Body weight ≥ 40.0 kg (88.2 lbs).
EXCLUSION CRITERIA	**Conditions associated with atherosclerosis:** 1. Acute coronary syndrome, percutaneous coronary intervention or any intervention for peripheral artery disease within 3 months prior to randomization. 2. Acute ischemic stroke or transient ischemic attack within 3 months prior to randomization. **Mitigation of bleeding risks:** 3. Active internal bleeding, or medical history of recent (< 1 month) bleeding disorders or conditions associated with high risk of bleeding (e.g., clotting disturbances, gastrointestinal bleed, hemoptysis). 4. Hemoglobin ≤ 10 g/dL at screening. 5. Loss of at least 250 mL of blood within 3 months of screening. 6. Use of anticoagulants (oral, parenteral) or fibrinolytic therapy within 24 h prior to screening (Visit 1). 7. Known platelet disorders (e.g., thrombasthenia, thrombocytopenia, von Willebrand disease).

	Conditions that may prevent subject from complying with study requirements or may be a confounder for the study interpretation: 8. Pregnant or breastfeeding women. 9. Uncontrolled hypertension according to investigator's judgment. 10. Known and documented moderate or severe hepatic impairment. 11. End-stage renal failure requiring dialysis. 12. Any clinically significant findings on a physical exam, or laboratory tests prior to screening that in the investigator's judgment would preclude safe or reliable participation of a subject in the study. 13. Concomitant diseases (e.g., advanced liver cirrhosis, mental illness, neurodegenerative disease, terminal malignancy, etc.) or conditions (e.g., inability to communicate well with the investigator in the local language) that, in the opinion of the investigator, may prevent subject from complying with study requirements or may be a confounder for the study interpretation. 14. Veins unsuitable for intravenous puncture on either arm (e.g., difficult to locate, access, or puncture) according to the investigator's judgment. 15. Clinically relevant skin disease that prevents s.c. injection in the thigh or abdomen, according to the investigator's judgment. 16. Use of inhibitors of organic anion-transporting polypeptide (OATP)1B1 or OATP1B3 at screening (Visit 1). 17. Known hypersensitivity to ACT-246475, any of its excipients, or drugs of the P2Y12 class. 18. Previous exposure to investigational drug within 3 months prior to screening.
STUDY TREATMENTS	**Investigational treatment and matching placebo** Study treatment for s.c. administration will be available as sealed glass vials in 1 strength: 20 mg. The vials contain 22 mg of lyophilized ACT-246475A (hydrochloride salt of ACT-246475) or matching placebo to be reconstituted with

	1 mL of water for injection. Further dilution with 1 mL NaCl 0.9% will be performed for preparation of the dose of 8 mg. The s.c. formulation contains mannitol as an inactive ingredient. Study treatment will be given as a single dose of ACT-246475 (8 or 16 mg) or of matching placebo in a volume of 0.8 mL, administered s.c. at site by qualified personnel (e.g., nurse, physician). The investigational treatment and its matching placebo are indistinguishable, and all treatment kits will be packaged in the same way.
CONCOMITANT THERAPY	**Allowed concomitant therapy** Unless medically necessary, subjects will continue their standard treatment(s) (including oral $P2Y_{12}$ receptor antagonists and acetylsalicylic acid) as prescribed (treatments and doses), from Visit 1 (screening) and up to the last PK or PD blood sample collection (whichever is latest). **Forbidden concomitant therapy** The following medications are prohibited from screening and up to last pharmacokinetic (PK) or pharmacodynamic (PD) blood collection (whichever is latest): • Fibrinolytic therapy (e.g., streptokinase, alteplase, etc.) • Anticoagulants (e.g., Coumadin, warfarin, anti Xa inhibitors, dabigatran, heparin) • OATP1B1 and OATP1B3 inhibitors (e.g., cyclosporine, eltrombopag, lapatinib, lopinavir, rifampin, ritonavir) Initiation of any of the following medications is prohibited from screening up to last PK or PD blood collection (whichever is latest): • Oral $P2Y_{12}$ receptor antagonists (e.g., clopidogrel, prasugrel, ticagrelor) • Cangrelor

ENDPOINTS	**Primary efficacy endpoint(s)** Not applicable **Pharmacodynamic endpoints** The primary PD endpoint is the PD response that is defined for each subject as a PRU < 100 starting 30 minutes after injection and lasting for at least 3 hours, as measured via the VerifyNow® assay. This corresponds to inhibition of adenosine diphosphate-induced platelet aggregation (IPA) > 80%. **Safety endpoints** The safety endpoints will be assessed up to End-of-Study: • Treatment-emergent adverse events (AEs) and serious AEs (SAEs). • All AEs and SAEs. • Change in vital signs (systolic and diastolic arterial blood pressure and pulse rate) from baseline to all assessed time points during the study. • Treatment-emergent ECG abnormalities. • Change from baseline to each measured time point in ECG variables: heart rate and the intervals: PQ/PR, QRS, QT, RR, QT corrected with Bazett's formula, QT corrected with Fridericia's formula. • Change from baseline to each measured time point for clinical laboratory tests. • Treatment-emergent marked laboratory abnormalities. **Pharmacokinetic endpoints** PK endpoints are described in Section 6.2.2.
ASSESSMENTS	Refer to the schedule of assessments in Table 2 and Table 3.
STATISTICAL METHODOLOGY	**Analysis sets** The Screened analysis set includes all subjects who are screened and have a subject identification number. The Randomized analysis set includes all subjects who have been assigned to a double blind study treatment. The Full analysis set (FAS) includes all randomized subjects

	who have been administered the study treatment. The Per-protocol set includes all FAS subjects who complied with protocol sufficiently to allow adequate estimation of the treatment effects (criteria for sufficient compliance will be detailed in the statistical analysis plan). The Safety set includes all subjects who received at least 1 dose of study treatment. The PK analysis set includes all Safety set subjects who have at least 1 PK sample collected after administration of study treatment. **Primary analysis** The analysis of the primary endpoint will be performed on the FAS comparing each active treatment dose to placebo using a 2-sided z-test at type I error level of 0.025 (corresponding to an overall level of 0.05 adjusted for multiplicity through Bonferroni method). For each active treatment arm for which comparison to placebo is statistically significant, the hypothesis that a proportion of patients achieving a response is greater than 70% will be tested at a 0.025 type I error level. The study will be declared positive with regard to the primary objective arm if, for at least 1 of the 2 active treatment arms, the 2 above-described tests are sequentially rejected. Additionally, longitudinal analysis of the treatment effect, from start of treatment up to 8 h after injection, on platelet reactivity as measured by VerifyNow®, i.e., PRU value, will be performed using a mixed model with PRU as dependent variable, subject as random factor, and treatment (8 mg, 16 mg, and placebo), injection site (abdomen, thigh), PRU level at randomization (stratification levels), age (continuous), gender (male, female), and assessment time (continuous) as fixed factors. The model will also include (treatment × injection site) as an interaction term to assess consistency of treatment effect across injection sites. A logistic regression analysis of the PD response will be performed using the same factors as covariates.

	Summary of PD response, in terms of number (%) of subjects, will be provided. IPA as measured by VerifyNow® will also be summarized as a continuous variable. **Supportive/sensitivity analyses** Consistency across the following subgroups will be assessed by repeating the primary endpoint analysis, assuming relevant number of subjects: • Age: < 55 vs ≥ 55 years • Body mass index: < 25.0 vs (≥ 25.0 and < 30.0) vs ≥ 30.0 kg/m^2 • Sex: male vs female • Diabetes mellitus at baseline: yes vs no • Chronic kidney disease: yes vs no Additional analyses of the supportive PD endpoint (light transmission aggregometry-based PD response) will be conducted using the same approach as described for the primary PD analysis. **Sample size** The primary objective is to assess the effectiveness of ACT-246475 to allow subjects to achieve a predefined PD response; therefore, the sample size provided is sufficient to sequentially demonstrate that at least 1 of the 2 ACT-246475 doses has a higher response rate than placebo and that this response rate is greater than 70%. The sample size required for demonstrating a difference to placebo, based on an overall type I error of 0.05 (2-sided), adjusted for multiplicity using a Bonferroni method to 0.025 for each comparison, a power of 90%, a response rate of 50% under H_0 (placebo) and 75% under H_1 is 96 per arm. The sample size required to demonstrate that the response rate is different from 70% is based on a 2-sided type I error of 0.025, a power of 90%; and the assumptions of a response rate of 70% under H_0 and 85% under H_1 is 98 per arm. The study should include at least 98 subjects in each treatment arm, and assuming a rate of drop-out or non-evaluable data of

	about 10%, 108 subjects should be included in each arm, giving a total of 324 subjects enrolled in the study.
STUDY COMMITTEES	A Safety Event Committee will consist of 2 independent clinical experts who will review unblinded safety data independently from the sponsor during the study. The Safety Event Committee has overall responsibility for safeguarding the interests of subjects by monitoring safety data obtained in the study and making appropriate recommendations based on the reported data. The Safety Event Committee will be fully operational prior to enrollment of the first subject into the study. The Safety Event Committee will specifically focus on study-drug-related clinically relevant major bleeding events, according to the Thrombolysis in Myocardial Infarction definition, that occur within the first 3 days after dosing.

PROTOCOL

1 BACKGROUND

1.1 Pre-hospital treatment of acute myocardial infarction

Despite marked improvement of in-hospital management of patients with acute myocardial infarction (AMI) in the past decades, there is still a medical need for an earlier treatment option to reduce high platelet reactivity, once a secondary event occurs [Nabel 2012]. The median time to medical intervention in economically advanced countries, either in an ambulance or at the emergency department, is still 2–4 hours after onset of symptoms, with patient decision time contributing significantly to the pre-hospital time delay [Garofalo 2012, Tubaro 2011].

Patients experiencing an AMI have highly reactive platelets, which are insufficiently inhibited even when they are receiving dual antiplatelet therapy (DAPT) with acetylsalicylic acid and clopidogrel [Gurbel 2003; Matetzky 2004; Wang 2010].

The earlier one intervenes on the ongoing platelet-rich thrombus responsible for AMI, the higher the chance to avoid early death and irreversible myocardial damage. The first 1–3 hours after symptom onset ('golden time') hold the maximum potential for myocardial reperfusion and salvage in patients with ST-segment elevation myocardial infarction (STEMI) [Savonitto 2017]. Hence, shortening the time to treatment could be of therapeutic benefit. The European Society of Cardiology guidelines recommend ticagrelor and prasugrel as a first-line antiplatelet therapy on top of acetylsalicylic acid in AMI; however, evidence of their benefit in the pre-hospital setting is lacking [Beygui 2015].

ACT-246475 is being developed for self-injection in patients with suspected AMI.

1.2 Role of adenosine diphosphate-induced platelet activation ($P2Y_{12}$ receptor)

When vascular integrity is compromised, signals are generated that cause circulating platelets to adhere to the vessel wall, become activated, and aggregate, forming a plug that seals off the site of injury to prevent blood loss. Autopsy studies demonstrated that the same processes occur upon rupture of an atherosclerotic plaque and can lead to uncontrolled platelet thrombus formation and vessel occlusion [Davies 1986]. Inhibition of platelet activation and aggregation is recognized as an effective strategy for prevention of atherothrombotic events in patients with atherosclerotic disease in the coronary, peripheral, and cerebrovascular circulation [Davì 2007, Michelson 2010].

The adenosine diphosphate (ADP) receptor $P2Y_{12}$ plays a critical role in platelet activation and aggregation [Andre 2003, Dorsam 2004]. Platelet activation is initially

triggered by the interaction of surface glycoproteins with components of the subendothelial matrix or ruptured atherosclerotic plaque and is amplified by the release of soluble mediators, which also recruit new platelets. One of the most important soluble mediators is ADP, which is an agonist at two G protein-coupled receptors, $P2Y_1$ and $P2Y_{12}$. Both $P2Y_1$ and $P2Y_{12}$ participate in the activation of integrin glycoprotein IIb/IIIa, which binds fibrinogen, creating the cross-linked aggregates that form the thrombus. Whereas $P2Y_1$ is important for the initial activation at low levels of ADP, it appears that $P2Y_{12}$ is required to amplify and sustain the responses leading to stable thrombus formation.

The $P2Y_{12}$ receptor is a validated target for treatment and secondary prevention of major adverse vascular events in patients with AMI, and early initiation of DAPT with acetylsalicylic acid and a $P2Y_{12}$ receptor antagonist is recommended [O'Gara 2013, Amsterdam 2014]. The efficacy of clopidogrel, the most widely used $P2Y_{12}$ receptor antagonist, is limited by its slow onset of action and variable platelet inhibition. The newer, irreversible $P2Y_{12}$ receptor antagonist prasugrel achieves more pronounced inhibition of platelet aggregation (IPA) and shows superior efficacy compared with clopidogrel, but the reduced risk of ischemic events is accompanied by an increased risk of bleeding [Wiviott 2007]. The need to reduce bleeding risk is illustrated by post-hoc analyses of several anti-platelet clinical studies [Eikelboom 2006, Amlani 2010]. These analyses revealed that there is a strong association between major bleeding and mortality in AMI patients.

$P2Y_{12}$ receptor antagonists from the thienopyridine class, such as clopidogrel and prasugrel, are prodrugs converted to active metabolites that irreversibly bind and inactivate the $P2Y_{12}$ receptor for the lifespan of the platelet. It was initially thought that antagonists that bind reversibly to the receptor, such as ticagrelor, are less likely to cause bleeding than those that cause irreversible blockade, possibly because receptors remain responsive to high local concentrations of ADP [van Giezen 2009, Becker 2010]. In the PLATO trial, ticagrelor demonstrated a significant reduction in the risk of death from vascular causes / myocardial infarction (MI) / stroke, without a significant increase in PLATO-defined major bleeding compared to clopidogrel [Wallentin 2009]. However, ticagrelor still significantly increased major bleeding not associated with coronary artery bypass surgery [Wallentin 2009, Husted 2011]. Therefore, novel principles of $P2Y_{12}$ antagonism are needed with the potential to improve efficacy without adversely affecting safety.

Some of the bleeding associated with current $P2Y_{12}$ receptor antagonists may be due to off-target effects. In a study comparing clopidogrel and prasugrel with genetic ablation of the $P2Y_{12}$ receptor in mice, the thienopyridines caused excess bleeding and had adverse effects on vascular tone [Andre 2011]. In-house nonclinical studies indicate that ticagrelor, but not ACT-246475, inhibits vasoconstriction in isolated vessels

[ACT-246475 IB]. After vessel injury, vasoconstriction is essential to achieve hemostasis and subsequent wound sealing. Therefore, a highly selective $P2Y_{12}$ receptor antagonist has the potential to provide an improved therapeutic window compared with current $P2Y_{12}$ receptor antagonists.

1.3 Study treatment (ACT-246475)

ACT-246475 is a new, potent, reversible, and highly selective $P2Y_{12}$ receptor antagonist with rapid onset and a short duration of action, suitable for subcutaneous (s.c.) administration. Efficacy and safety studies with ACT-246475 in animal thrombosis models suggest the potential for an improved therapeutic window in clinical use, compared with currently available oral agents.

ACT-246475 is considered as a promising new agent for secondary prevention of major adverse cardiovascular events in patients with suspected AMI, including those undergoing percutaneous coronary intervention (PCI).

1.3.1 Nonclinical data

ACT-246475 is a potent and selective $P2Y_{12}$ receptor antagonist. The binding of ACT-246475 to the receptor is fully reversible, with an equilibrium dissociation constant of 1.5 nM. In human platelet-rich plasma (PRP), ACT-246475 inhibited ADP-induced platelet aggregation with an inhibitor concentration causing 50% inhibition of 8.7 ng/mL (14 nM).

ACT-246475 dose-dependently blocked thrombus formation in 2 species, guinea pig and rat. In the rat $FeCl_3$ model, ACT-246475 was compared with ticagrelor, another reversible $P2Y_{12}$ receptor antagonist. ACT-246475 displayed an improved safety window with respect to bleeding risk, based on surgical blood loss assessed at antithrombotic doses. For a given antithrombotic effect, blood loss was up to 2.6-fold less with ACT-246475 than with ticagrelor. In mechanistic studies using rat isolated femoral arteries, ticagrelor, but not ACT-246475, caused relaxation of precontracted arteries and inhibited vasoconstriction induced by electrical field stimulation or phenylephrine (α_1-adrenoceptor-mediated). The absence of effect on vascular tone explains, at least in part, the reduction in bleeding with ACT-246475.

[redacted]

ACT-246475 has low potential for drug-drug interaction with co-medications dependent on cytochrome P450 (CYP) metabolism. ACT-246475 is not an activator of the human pregnane X receptor and CYP induction is, therefore, not expected upon dosing of ACT-246475.

[redacted]

[redacted]

Detailed information regarding nonclinical data is available in the Investigator's Brochure (IB) [ACT-246475 IB].

1.3.2 Effects in humans

Two clinical trials have been completed to date (AC-075-101, AC-076-101). Another trial is clinically completed with preliminary data available (AC-076-102). Results of these studies are detailed in the IB [ACT-246475 IB] and summarized hereafter.

1.3.2.1 Study AC-075-101

This study consisted of 2 parts:

In Part I, the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of single, ascending, oral doses (5, 20, 80, 320, and 1000 mg) of the prodrug ACT-281959 were assessed in 40 healthy, male subjects (n = 6/2 on active/placebo per dose level).

In Part II, the safety, tolerability and PK of single, oral doses of prodrug formulations I and II (70 mg) and ACT-246475 (50 mg) were determined in 9 healthy, male subjects applying a 3-way crossover, open-label design.

Each dose and formulation was safe and well tolerated. The systemic exposure to the active moiety ACT-246475 was generally low. Accordingly, the IPA was also limited.

1.3.2.2 Study AC-076-101

This was a randomized, double-blind, placebo-controlled, single-ascending dose (SAD) study to investigate the safety, tolerability, PK and PD of ACT-246475 after s.c. administration to healthy male subjects. [redacted]

[redacted]

1.3.2.3 Study AC-076-102

This was a randomized, double-blind, placebo-controlled, SAD study to investigate the safety, tolerability, PK, and PD of ACT–246475 after s.c. (Part A) and sublingual (s.l.; Part B) administration to healthy male subjects.

This study has been clinically completed and the database locked. The clinical study report (CSR) is not yet available.

In Part A, there were a total of 48 subjects exposed (6 subjects receiving active treatment and 2 subjects receiving placebo per dose level).

ACT–246475 has been determined to be safe and tolerated at each s.c. dose level ranging from 1 mg to 32 mg.

The overall AE incidence was 12.5% (6 of 48 subjects exposed) with no indication of dose dependency. There were 5 of 36 subjects with AEs after administration of ACT-246475 (13.9%) vs 1 of 12 after placebo (8.3%). Each AE after administration of ACT–246475 was mild and transient.

- In the 2 mg dose group, 2 subjects reported 1 AE each (headache; dizziness) after administration of ACT–246475.
- In the 8 mg dose group, there were 3 subjects with at least 1 AE after administration of ACT–246475 (rhinorrhea; headache; dizziness, nausea and hyperhidrosis).
- One subject reported 3 AEs after administration of placebo (catheter site erythema, nausea, and headache).
- In the other dose groups (1 mg, 4 mg, 16 mg, and 32 mg), no AEs were reported.

There were no deaths, SAEs, bleeding events, or AEs leading to discontinuation of the study. No clinically relevant changes in laboratory variables, vital signs, ECG variables, body weight, physical examination, or vigilance tests were observed.

Peak plasma concentrations were reached within approximately 30–45 min and $t_{½}$ ranged from 1.3–9.2 h. Exposure increased in a dose-proportional manner.

At each dose level, peak IPA was achieved within approximately 15–30 min post-dosing. Peak %IPA exceeded 85% at doses ≥ 4 mg. The duration of PD effects was dose dependent. Mean %IPA ≥ 85% was sustained for approximately 6 h and 12 h post-administration of 16 mg or 32 mg ACT–246475, respectively.

In Part B, there were a total of 8 subjects exposed (6/2 on active/placebo). ACT-246475 has been determined to be safe and tolerated after a single s.l. dose of 20 mg. Two subjects reported AEs after s.l. administration of ACT–246475: lightheadedness in 1 subject and headache, vomiting, dizziness, and dyspepsia in the other subject. Neither of the 2 subjects exposed to placebo reported AEs.

[redacted]

1.4 Purpose and rationale of the study

ACT-246475 is a potent, short-acting, reversible, and selective antagonist of the platelet $P2Y_{12}$ receptor, which is a validated target for the treatment and prevention of arterial thrombosis. ACT-246475 has shown a favorable PK/PD and safety profile in animal models, confirmed in studies conducted in healthy subjects. This Phase 2 study is conducted in subjects with atherosclerotic disease to generate data which are critical for dose selection in future clinical trials in the target AMI population. The impact of 2 different doses and 2 different sites of injection (abdomen vs thigh) on the PD, PK, safety and tolerability of ACT-246475 will be assessed.

1.5 Summary of known and potential risks and benefits

1.5.1 Potential risks related to study treatment administration

The main risks known to be associated with any $P2Y_{12}$ receptor antagonist are related to an increased risk of bleeding events [Eikelboom 2006, Wiviott 2007, Amlani 2010].

In nonclinical studies, ACT-246475 was found to have lower risk of bleeding compared to ticagrelor [Section 1.3.1]. This may be related to a different mechanism of action than that of ticagrelor: in contrast with ticagrelor, ACT-246475 has no interference with the adenosine pathway and ACT-246475 exhibits competitive inhibition of the $P2Y_{12}$ receptor whereas inhibition by ticagrelor is non-competitive. More importantly, the risk of bleeding associated with the use of $P2Y_{12}$ receptor antagonists increases with the

duration of treatment. As ACT-246475 has a short duration of action and is used as a single-dose administration, bleeding risk exposure is expected to be minimal in this study. The risks of bleeding are mitigated by exclusion of subjects who have active internal bleeding (exclusion criterion #3) or who are at high risk of bleeding: subjects with a history of recent bleeding disorder (exclusion criterion #3), subjects taking anticoagulants as background therapy (exclusion criterion #6), and subjects with known platelet disorders (exclusion criterion #7).

In this study, the highest dose planned to be used is 16 mg, which is 2-fold lower than the highest dose administered in the AC-076-102 SAD study conducted in healthy subjects.

In the AC-076-102 SAD study, headache was the most commonly reported AE [see Section 1.3.2.3]. There were no deaths, SAEs, bleeding events or AEs leading to discontinuation. No clinically relevant changes in laboratory variables, vital signs, ECG variables, body weight, physical examination, or vigilance tests were observed. Accordingly, s.c. administration of ACT-246475 has been determined to be safe and tolerated at each dose level ranging from 1 mg to 32 mg and, therefore, no MTD in humans has been defined.

This study will be the first ACT-246475 study enrolling patients. Accordingly, an independent Safety Event Committee [Section 3.4] will have overall responsibility for safeguarding the interests of subjects by monitoring unblinded safety data (with specific focus on bleeding events occurring within 3 days of study treatment administration) and making appropriate recommendations based on the reported data, thus ensuring that the study is conducted to the highest scientific and ethical standards.

1.5.2 Potential risks associated with study-specific procedures

The risks associated with the study-specific procedures are restricted to the standard risks associated with any blood collection. Such procedures are routine practice in the selected sites and, therefore, the risks are considered minimal for the subjects. The volume of blood collected for study purposes will be approximately 120 mL over a period of up to 3 weeks, with a maximum of approximately 88 mL collected on a single day. To minimize the risks associated with the amount of blood collected, the minimum weight for a subject to be eligible has been set to 40 kg (inclusion criterion #6), and subjects with low hemoglobin at baseline (exclusion criterion #4) or significant recent blood loss (exclusion criterion #5) are excluded. For the subjects with a body weight between 40 and 50 kg (88.2 and 110 lbs), the assessments requiring blood collection have been reduced: Light transmission aggregometry (LTA) platelet aggregation tests (supportive assessment) will not be performed in order to minimize the blood volume collected in these low-weight subjects. For these subjects, the total volume of blood collected for study purposes will be approximately 85 mL over a period of up to 3 weeks, with a maximum of approximately 58 mL collected on a single day. Overall, the blood volume

collected for study purposes will not exceed a maximum of approximately 3.5% of total blood volume over the 3-week study period and 2.5% of total blood volume over a single day. This is in compliance with the recommendations for maximum blood collection for research purposes from several Independent Ethics Committees or Institutional Review Boards (IECs/IRBs), and is therefore considered to represent a minimal risk for the subjects.

1.5.3 Potential risk of unblinding

Some study activities may potentially lead to unintentional unblinding. Performing the platelet aggregation tests may provide information that allows guessing of the actual treatment received (ACT-246475 or placebo). In order to limit the risks of unblinding, some study-specific roles for site personnel are defined and source documents will be kept separately [see Section 3.3].

The clinical research associates (CRAs) are considered unblinded [see Section 5.1.5] as they will have access to platelet aggregation test results. They will be in contact with the investigator and other site personnel who must remain blinded to these data. The CRA will be instructed to not communicate or discuss any platelet aggregation results except with the platelet aggregation technician. Accordingly, the risks of potential bias related to interaction between the CRA and site personnel are considered negligible.

However, inadvertent access to potentially unblinding data (e.g., data gathered with VerifyNow® or LTA assays) may still happen. Because the primary endpoint is an objective PD endpoint, this is not considered critical for the study and for the reliability of the results.

1.5.4 Potential benefits

There is no expected direct health benefit for an individual subject participating in this study. However, this study is part of the development of a new treatment addressing an unmet medical need that may ultimately benefit the population of patients at high risk of AMI recurrence. On top of reimbursement of their study-related expenses, subjects participating to this study will get financial compensation for their time spent in the study in compliance with local regulations [see Section 12.4].

1.5.5 Overall benefit risk assessment

Overall, due to the favorable safety profile of ACT-246475 as well as the use of routine standard procedures, the risks for subjects participating in this study are considered minimal and medically acceptable.

It is the investigator's responsibility to monitor the risk-benefit ratio of study treatment administration, as well as the degree of distress caused by study procedures on an

individual subject level, and to discontinue the study for a subject if, on balance, he/she is of the opinion that continuation would be detrimental to the subject's well-being.

2 STUDY OBJECTIVES

2.1 Primary objective

The primary objective of the study is to characterize IPA relative to placebo after a single s.c. injection of ACT-246475 either in the thigh or in the abdomen at 2 different doses in subjects with stable coronary artery disease (CAD) receiving conventional background oral antiplatelet therapy (e.g., acetylsalicylic acid, $P2Y_{12}$ receptor antagonists).

2.2 Other objectives

The other objectives of this study, following a single s.c. administration of ACT-246475, are:

- To assess the PK of ACT-246475.
- To assess the impact of the injection site location (thigh vs abdomen) on the PK and PD of ACT-246475.
- To investigate the impact of concomitant drug use, age, sex, and other covariates on the PK and PD of ACT-246475.
- To investigate the safety and tolerability of ACT-246475.

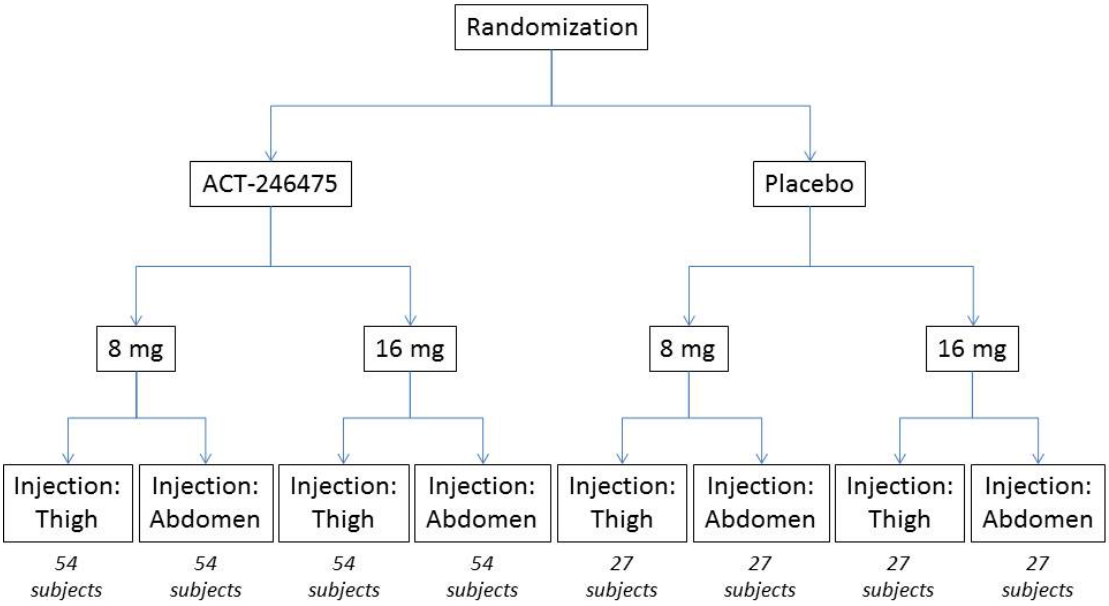
3 OVERALL STUDY DESIGN AND PLAN

3.1 Study design

This is a prospective, multi-national, multi-center, double-blind, randomized, placebo-controlled, parallel-group, Phase 2, exploratory study of a single s.c. administration of ACT-246475, at 2 different dose levels, in subjects with stable CAD receiving conventional background therapy (e.g., acetylsalicylic acid, $P2Y_{12}$ receptor antagonists, etc.).

Approximately 324 adult subjects with stable CAD will be randomized into 1 of the 8 combinations of the treatment, dose, and injection site using a 2:2:2:2:1:1:1:1 ratio as described in Figure 1.

Figure 1 Randomization scheme



Each subject will receive a single s.c. administration of either 8 mg ACT-246475, 16 mg ACT-246475 or matching placebo, either in the thigh or in the abdomen.

Treatment group allocation will be stratified based on baseline platelet reactivity value (expressed as $P2Y_{12}$ reaction units [PRU]) measured on Day 1 by the VerifyNow® assay before ACT-246475 injection, considering the 3 following categories: high reactivity (PRU > 250), medium reactivity (150 ≤ PRU ≤ 250), and low reactivity (PRU < 150).

No interim analysis is planned for this study.

The study will be conducted at approximately 20 sites and in 5–10 countries (recruitment will be competitive across sites). The list of sites including the name and title of the investigators who are responsible for conducting the trial, and the address and telephone numbers of the trial sites will be filed in the Trial Master File (TMF).

3.1.1 Study periods

The study comprises the following consecutive periods:

Screening period: Lasts 1–21 days; starts with the signature of the informed consent form (ICF) and ends on Day −1.

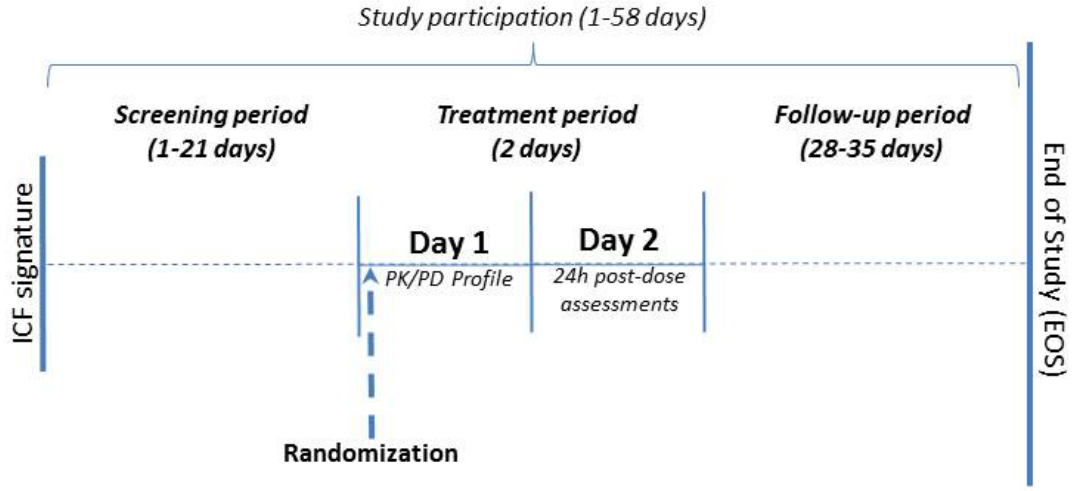
Treatment period: Lasts 2 days: Day 1 and Day 2.

Follow-up period: Lasts 28–35 days (i.e., 30–37 days after single administration of study drug). Starts on Day 3 and ends with the safety follow-up telephone call.

The visit schedule and protocol-mandated procedures will be performed according to the table of assessments [Table 2 and Table 3] and are described in Section 7.

The overall study design is depicted in Figure 2.

Figure 2 Study design



EOS = End of study; ICF = Informed consent form

3.1.2 Study duration

The study starts with the first act of recruitment (i.e., first ICF signed for the first subject) and ends with the last visit of the last subject.

The overall duration of participation in the study (including screening and follow-up periods) for a subject will be up to 58 days.

3.2 Study design rationale

The study design supports the different study objectives, i.e., assessing PD, PK, tolerability, and safety profiles of ACT-246475. The treatment period is justified by the primary objective, which is to characterize the IPA after a single s.c. injection of ACT-246475, either in the thigh or in the abdomen, at 2 different doses in subjects with stable CAD.

The use of 2 doses (i.e., 8 and 16 mg) will allow assessment of the dose/PK and dose/PD relationship in this patient population, which will enrich the results already obtained in a healthy subject population [see Section 5.1.1 for detailed rationale on dose selection].

The stratification by baseline PRU value is implemented in order to account for different levels of $P2Y_{12}$ inhibition at baseline. The boundaries have been selected to mimic the expected baseline level of $P2Y_{12}$ receptor inhibition depending on the type of background antiplatelet therapy [Gurbel 2009]: PRU < 150; 150 ≤ PRU ≤ 250; PRU > 250.

The primary PD analysis will be performed with the VerifyNow® method. Results from the VerifyNow® method are well correlated with those obtained with the LTA method [Varenhorst 2009, Gremmet 2015]. The VerifyNow® method has been preferred as it is more standardized than the LTA method; and therefore, less subject to variability in a multicenter study. In addition, the volume of blood required per sample is higher for LTA (6 mL) than for the VerifyNow® method (3 mL). Using the VerifyNow® method will allow assessment of more time points and, therefore, better characterization of the PD profile while requiring less blood withdrawn from the subjects. As LTA remains a reference method and to allow comparison with other trials, some LTA assessments will be performed at selected time points [Table 3].

The use of a double-blind placebo-controlled design is proposed to assess the safety of ACT-246475 compared with placebo and will support additional exploratory analyses. The double-blind design applies to the treatment allocation (i.e., ACT-246475 vs placebo). The knowledge of the dose (8 or 16 mg) and injection site is not expected to affect the primary objective (which is based on objective PD assessment) or the safety evaluation as the study is placebo-controlled. However, to reduce the risks of bias in safety reporting, the dose will be blinded to the subjects (single blind). The injection site will not be blinded in this study.

3.3 Site personnel and roles

3.3.1 Platelet aggregation technician

The technician(s) performing the platelet aggregation tests (VerifyNow® and LTA) will be considered unblinded to the treatment. They must not be involved in safety assessments and must not communicate with the results from the platelet aggregation tests to other study staff (only the stratification group will be communicated to the person in charge of randomization).

To maintain the blind, the results of the platelet aggregation tests will be entered in the case report form (CRF) only by the technician and will not be accessible to other site study staff. Up to unblinding of the study, the source documents for platelet aggregation assays will be kept in a separate location from the subjects' other source documents and will only be accessible to the platelet aggregation technician(s) and to the CRA.

3.4 Study committees

A Safety Event Committee will consist of 2 independent clinical experts who will review unblinded safety data independently from the sponsor during the study. The Safety Event Committee has overall responsibility for safeguarding the interests of subjects by monitoring safety data obtained in the study and making appropriate recommendations based on the reported data. The Safety Event Committee will be fully operational prior to enrollment of the first subject into the study.

The Safety Event Committee will specifically focus on study-drug-related clinically relevant major bleeding events, according to the Thrombolysis in Myocardial Infarction definition, that occur within the first 3 days after dosing.

The Safety Event Committee will be ruled by a specific charter and recommendations made by the Safety Event Committee will be documented and archived in the TMF.

4 SUBJECT POPULATION

4.1 Subject population description

This study will enroll adult male and female subjects aged 18–85 years (inclusive) with stable CAD, as defined by a history of CAD with coronary artery stenosis ≥ 50% on coronary angiogram or previously documented MI occurring more than 3 months before randomization.

Subjects with significant medical conditions (e.g., active internal bleeding, history of recent bleeding disorder, platelet disorders, subjects requiring dialysis) as well as subjects taking oral anticoagulants as background treatment are not eligible to enter the study.

Eligible subjects must be able and willing to give informed consent for participation in the clinical study.

4.2 Rationale for the selection of the study population

The population enrolled is expected to reflect the general population of patients with CAD.

Among these patients, those with prior MI are at higher risk of recurrent ischemic events [Fox 2008]. Such patients are treated with acetylsalicylic acid as life-long background therapy. In addition, the American College of Cardiology/American Heart Association and ESC guidelines for the management of patients with STEMI and non-STEMI recommend DAPT for the secondary prevention of recurrent ischemic events for up to 1 year after the acute coronary syndrome (ACS) event, a duration that may be shortened or extended in selected patients if required [Steg 2012; O'Gara 2013; Amsterdam 2014; Roffi 2016; Levine 2016]. The target population for this study will include patients with coronary artery stenosis and patients who have experienced an AMI more than 3 months

prior to randomization. Those patients being candidates for single or DAPT according to guidelines, it is therefore expected to collect sufficient PD and safety data of ACT-246475 on top of antiplatelet therapy including a $P2Y_{12}$ receptor antagonist.

Ticagrelor and prasugrel are both expected to already provide more than 80% of IPA in patients who are compliant with their treatment [Prasugrel® SmPC, Ticagrelor® SmPC]. It cannot be excluded that, despite treatment with a potent oral $P2Y_{12}$ receptor antagonist, some patients experiencing an MI still have high on-treatment platelet reactivity and may therefore benefit from ACT-246475.

4.3 Inclusion criteria

For inclusion in the study, all of the following inclusion criteria must be fulfilled. It is not permitted to waive any of the criteria for any subject:

1. Signed informed consent prior to any study-mandated procedure.
2. Male and female subjects aged from 18–85 years, inclusive.
3. For women of childbearing potential: Negative urine pregnancy test at Visit 1 and at Visit 2 before randomization.
4. Stable CAD defined by the presence of any of the following conditions:
   a. History of CAD with coronary artery stenosis on coronary angiogram ≥ 50%.
   b. Previously documented MI occurring more than 3 months prior to randomization.
5. Antiplatelet background therapy stable for at least 1 month prior to randomization.
6. Body weight ≥ 40.0 kg (88.2 lbs).

4.4 Exclusion criteria

Subjects must not fulfill any of the following exclusion criteria. It is not permitted to waive any of the criteria for any subject:

Conditions associated with atherosclerosis:

1. ACS, PCI or any intervention for peripheral artery disease within 3 months prior to randomization.
2. Acute ischemic stroke or transient ischemic attack (TIA) within 3 months prior to randomization.

Mitigation of bleeding risks:

3. Active internal bleeding, or medical history of recent (< 1 month) bleeding disorders or conditions associated with high risk of bleeding (e.g., clotting disturbances, gastrointestinal bleed, hemoptysis).

4. Hemoglobin ≤ 10 g/dL at screening[a].
5. Loss of at least 250 mL of blood within 3 months of screening.
6. Use of anticoagulants (oral, parenteral) or fibrinolytic therapy within 24 h prior to screening (Visit 1).
7. Known platelet disorders (e.g., thrombasthenia, thrombocytopenia, von Willebrand disease).

Conditions that may prevent subject from complying with study requirements or may be a confounder for the study interpretation:

8. Pregnant or breastfeeding women.
9. Uncontrolled hypertension according to investigator's judgment.
10. Known and documented moderate or severe hepatic impairment.
11. End-stage renal failure requiring dialysis.
12. Any clinically significant findings on a physical exam, or laboratory tests prior to screening that in the investigator's judgment would preclude safe or reliable participation of a subject in the study.
13. Concomitant diseases (e.g., advanced liver cirrhosis, mental illness, neurodegenerative disease, terminal malignancy, etc.) or conditions (e.g., inability to communicate well with the investigator in the local language) that, in the opinion of the investigator, may prevent subject from complying with study requirements or may be a confounder for the study interpretation.
14. Veins unsuitable for i.v. puncture on either arm (e.g., difficult to locate, access, or puncture) according to the investigator's judgment.
15. Clinically relevant skin disease that prevents s.c. injection in the thigh or abdomen, according to the investigator's judgment.
16. Use of inhibitors of organic anion-transporting polypeptide (OATP)1B1 or OATP1B3 at screening (Visit 1).
17. Known hypersensitivity to ACT-246475, any of its excipients, or drugs of the $P2Y_{12}$ class.
18. Previous exposure to any investigational drug within 3 months prior to screening.

[a] If the results from the central laboratory for Visit 1 are available at time of randomization they must be used for assessment of eligibility. Otherwise, it is acceptable to assess this criterion based on local laboratory data from Visit 1 or more recent.

4.5 Criteria for women of childbearing potential

4.5.1 Definition of childbearing potential

A woman is considered to be of childbearing potential unless she meets at least 1 of the following criteria:

- Previous bilateral salpingectomy, bilateral salpingo-oophorectomy or hysterectomy,
- Postmenopausal (defined as 12 consecutive months with no menses without an alternative medical cause [International council for harmonization (ICH) M3 definition]),
- Premature ovarian failure (confirmed by a specialist), XY genotype, Turner syndrome, uterine agenesis.

The reason for not being of childbearing potential will be recorded in the CRF.

4.5.2 Acceptable methods of contraception

Women of childbearing potential [see definition in Section 4.5.1] must use one of the following methods of birth control from Screening up to at least 30 days after study treatment administration:

1. Diaphragm / female condom / cervical cap / partner's use of a condom.
2. Intra-uterine devices.
3. Oral or injectable contraceptive agents, implants, or transdermal contraceptive hormone patches. If a hormonal contraceptive is chosen, it must be taken for at least 1 month prior to randomization.
4. Sterilization method (tubal ligation / occlusion, or partner's vasectomy).
5. True abstinence from intercourse with a male partner only when this is in line with the preferred lifestyle of the subject.

Rhythm methods are not considered as acceptable methods of contraception for this study.

The methods of birth control used (including non-pharmacological methods) must be recorded in the CRF.

5 TREATMENTS

5.1 Study treatment

5.1.1 Investigational treatment and matching placebo: Description and rationale

Study treatment for s.c. administration will be available as sealed glass vials in 1 strength: 20 mg. The vials contain 22 mg of lyophilized ACT-246475A (hydrochloride salt of

ACT-246475) or matching placebo to be reconstituted with 1 mL of water for injection. The s.c. formulation contains mannitol as an inactive ingredient.

Study treatment will be given as a single dose, administered s.c. at site by qualified personnel (e.g., nurse, physician).

ACT-246475 at 2 different doses (8 and 16 mg) and placebo will be administered during this study. The ACT-246475 doses have been selected based on data from the SAD AC-076-102 study and on modeling to meet the following criteria:

- The low dose (8 mg) is the minimal dose achieving at least 85% IPA for 3 h which corresponds to a time period during which complete suppression of platelet reactivity is needed before specific in-hospital management of ACS [Montalescot 2014].
- The high dose (16 mg) provides IPA of at least 85% in no more than 5% of the subjects at 8 h. This corresponds to the maximal time accepted to limit interference with invasive and/or pharmacological standard of care of AMI.

These 2 doses are considered distinct enough to allow further modeling of the optimal phase 3 dose based on study data.

Note: onset of action of ACT-246475 is not dose-dependent and therefore did not account for dose selection.

5.1.2 Study treatment supply

Manufacture, labeling, packaging, and supply of study treatment will be conducted according to Good Manufacturing Practice, Good Clinical Practice (GCP), and any local or national regulatory requirements.

All study treatment supplies are to be used only in accordance with this protocol, and not for any other purpose.

5.1.2.1 Study treatment packaging and labeling

Study treatment (ACT-246475 and matching placebo) will be provided in sealed glass vials as a lyophilizate to be reconstituted by a pharmacist or an authorized person as per local regulation.

Study treatment will be labeled to comply with the applicable laws and regulations of the countries in which the study sites are located.

5.1.2.2 Study treatment distribution and storage

The investigator is responsible for safe and proper handling and storage of the study treatment at the investigational site and for ensuring that the study treatment is administered only to subjects enrolled in the study and in accordance with the protocol.

5.1.2.2.1 Study treatment distribution

The study centers will be supplied with study treatment according to the centers' needs, depending on the rate of subject enrollment. Each center will have an individual stock of study treatment, which will be re-supplied continuously as soon as a predefined minimum number of study treatments have been reached.

5.1.2.2.2 Study treatment storage

Study treatment must be kept in a locked room or a locked cupboard in a restricted access room, which can be accessed only by the pharmacist, the investigator, or another duly designated person as specified on the delegation of authority form.

[redacted]

A temperature log must be maintained and temperature check will have to occur at least on a weekly basis at the site. The sponsor/delegate will provide a temperature log; however, the use of the log is not mandatory if the site has an acceptable means of recording the temperature. Any temperature recording system routinely used at the site will be acceptable as long as all required information is included and certification of calibration is provided. If the temperature is captured electronically, a print-out will be made available to the CRA during each on-site visit.

If a deviation from the approved temperature range is identified by the study center, the deviation must be reported to the CRA, preferably in writing and with supporting documentation (e.g., copy of the temperature log showing data for all excursion days). The CRA will immediately contact the sponsor for further advice. The affected study treatment must not be used (e.g., it will be segregated physically at the study center) until confirmation from the sponsor is obtained that its use is safe. If the temperature deviation is outside of the acceptable limit, the study treatment will be kept segregated at the study center and returned to the sponsor following internal study treatment return processes. New study treatment supplies will be provided to the study center.

Temperature deviations correspondence must be kept in the Investigator Site File (ISF).

5.1.2.3 Study treatment return and destruction

On an ongoing basis and/or on termination of the study, the CRA will collect used and unused treatment kits, which will be returned to the warehouse. In certain circumstances, used and unused study treatment containers may be destroyed at the site once study treatment accountability is finalized, has been verified and reconciled by sponsor personnel or the deputy, and written permission for destruction has been obtained from the sponsor. Further details are provided in the study treatment handling manual.

5.1.3 Study treatment assignment and dispensing

5.1.3.1 Study treatment assignment

At Visit 2, after having verified that the subject meets all inclusion criteria and none of the exclusion criteria, and after performing the pre-dose VerifyNow® assessments, the platelet aggregation technician will provide the PRU stratification group to the person who will randomize the subject using the Interactive Response Technology (IRT) system. The IRT will assign a randomization number to the subject and will assign the treatment kit number as well as the dose and injection site, which matches the treatment arm assigned by the randomization list to the randomization number.

The randomization list will be generated by an independent Contract Research Organization (CRO).

5.1.3.2 Study treatment dispensing

The IRT will allocate one treatment kit (1 vial) per subject at randomization. In the event of deviation from study treatment preparation instructions [Section 5.1.4] (e.g., breach of sterility conditions, incorrect dose), a new kit will be requested via the dispensing module of the IRT and preparation steps will be started again. The protocol-mandated study treatment dispensing procedures may not be altered without prior written approval from the sponsor. An accurate record of the date and amount of study treatment dispensed to each subject must be available for inspection at any time.

5.1.4 Study treatment preparation and administration

Detailed information about the study treatment preparation and stability of the solutions is provided within the study treatment handling manual.

The preparation of the study treatment must be done under aseptic conditions by a pharmacist or an authorized person according to local regulation.

The sealed glass vials containing the study treatment will be reconstituted with 1 mL of water for injection. The resulting stock solutions will be at a concentration of 20 mg/mL ACT-246475. For subjects randomized to receive the 8 mg dose of ACT-246475 or its matching placebo, dilution of the stock solution will be performed with 1 mL of NaCl 0.9% to obtain the required concentration for injection [Table 1]. For all doses, the total volume administered will be 0.8 mL (i.e., concentration of the solutions adapted).

The reconstituted ACT-246475 solution will be injected as s.c. single dose in the anterior mid-thigh skin or abdomen skin through [redacted] needle. The injected volume will be 0.8 mL for all subjects [redacted].

The protocol-mandated study treatment administration procedures may not be altered without prior written approval from the sponsor. An accurate record of the date and amount of study treatment administered to each subject must be available for inspection at any time.

[redacted]

In Table 1, the preparation of doses of the study treatment is described; detailed instructions are given in the study treatment handling manual.

The date and start time of preparation of the injection solution as well as the procedure must be recorded on source documents.

Table 1 Preparation of study treatment for subcutaneous administration

Study treatment	Dose	Volume of water for injection	Volume of NaCl 0.9%	Stock solution concentration	Aliquot of stock solution to be administered
ACT-246475 or placebo	8 mg	1 mL	1 mL	10 mg/mL	0.8 mL
ACT-246475 or placebo	16 mg	1 mL	-	20 mg/mL	0.8 mL

5.1.5 Blinding

This study will be performed in a double-blind fashion. The investigator, study personnel, subjects, sponsor personnel, and CRO personnel involved in the conduct of the study will remain blinded to the study treatment (ACT-246475 or placebo).

The dose (8 mg or 16 mg) will be blinded only for the subject. The injection site (thigh or abdomen) will not be blinded.

Sponsor staff responsible for clinical trial supply distribution will be partially unblinded at depot level to ensure adequate study oversight, but will remain blinded to subject randomization and subject treatment.

Sponsor staff responsible for suspected unexpected serious adverse reaction (SUSAR) management may be unblinded to some subject treatment allocations. These persons will be clearly identified, their unblinding will be documented in the TMF and they will not take part in any Clinical Trial Team (CTT) meetings after study set-up has been completed.

The CRAs and the site technician performing the platelet aggregation assays will have access to the platelet aggregation test results (VerifyNow® and LTA) and will, therefore, be considered unblinded (they will not have access to the randomization list).

The randomization list will be kept strictly confidential and accessible only to authorized persons, sponsor quality assurance (QA), and the PK analytical laboratory who are not involved in the conduct of the study, as long as the blinding needs to be maintained until final data analysis.

The investigational treatment and its matching placebo are indistinguishable, and all treatment kits will be packaged in the same way.

5.1.6 Unblinding

5.1.6.1 Unblinding for final analyses

Full randomization information will be made available for data analysis only after database closure, in accordance with the sponsor quality system (QS) documents.

5.1.6.2 Unblinding for interim analyses

Not applicable.

5.1.6.3 Unblinding for suspected unexpected serious adverse reactions

If a SUSAR occurs for a subject participating in the study, the sponsor's Global Drug Safety department or a representative will request the unblinding of the treatment assignment. The treatment assignment will not be communicated to site personnel or to the sponsor CTT. Unblinded SUSAR information will be provided to respective HA and IECs or IRBs only. SUSARs will be reported to investigators in a blinded fashion.

5.1.6.4 Emergency procedure for unblinding

The investigator, study personnel, and sponsor personnel must remain blinded to the subject's treatment assignment. The identity of the study treatment may be revealed only if the subject experiences a medical event, the management of which would require knowledge of the blinded treatment assignment. In this case, the investigator will receive the unblinded treatment assignment through the IRT. In these situations, the decision to unblind will reside solely with the investigator. Whenever it is possible, and if it does not interfere with (or does not delay) any decision in the best interest of the subject, the investigator will be invited to discuss the intended unblinding with sponsor personnel.

The occurrence of any unblinding during the study must be clearly justified and explained by the investigator. In all cases, sponsor personnel must be informed as soon as possible before or after the unblinding.

The circumstances leading to unblinding must be documented in the ISF and CRF.

5.1.7 Study treatment accountability and compliance with study treatment

5.1.7.1 Study treatment accountability

The inventory of study treatment dispensed and returned (i.e., study-treatment accountability) must be performed by site personnel. It is to be recorded by site personnel on the study-treatment dispensing and accountability log and in the CRF, verified and reconciled by the CRA during the routine site visits and at the end of the study. The study treatment accountability in the CRF will include at least the following information for each study treatment unit (i.e., vial) dispensed to the subject:

- Dispensed vial number
- Date vial dispensed

All study treatment supplies, including partially used or empty vials, must be retained at the site for review and reconciliation by the CRA.

5.1.7.2 Study treatment compliance

Study treatment compliance is based on administration of the study treatment as allocated by IRT. Any deviation from the randomization allocation will be reported as a protocol deviation.

5.1.8 Study treatment dose adjustments and interruptions

Study treatment dose adjustments are not permitted.

Study treatment interruptions are not applicable for this single-dose study.

5.1.9 Premature discontinuation of study treatment

Not applicable (single-dose study).

5.1.10 Study-specific criteria for interruption / premature discontinuation of study treatment

Not applicable (single-dose study).

5.2 Previous and concomitant therapy

5.2.1 Definitions

A previous therapy is any treatment for which the end date is prior to signing of informed consent.

A therapy that is study concomitant is any treatment that is ongoing or initiated after signing of informed consent, or initiated up to 30 days after study treatment administration.

A therapy that is study treatment concomitant is any treatment that is either ongoing at the start of study treatment or is initiated up to 48 hours after study treatment administration.

5.2.2 Reporting of previous/concomitant therapy in the case report form

The use of all study concomitant therapy (including contraceptives and traditional and alternative medicines, e.g., plant-, animal-, or mineral-based medicines) will be recorded in the CRF.

Previous therapies related to subject's underlying CAD will be recorded in the CRF if discontinued less than 1 month (≤ 30 days) prior to signing of the informed consent.

The generic name, start/end dates of administration (as well as whether it was ongoing at start of treatment and/or End-of-Study [EOS]), route, dose, and indication will be recorded in the CRF.

5.2.3 Allowed concomitant therapy

Unless medically necessary, subjects will continue their standard treatment(s) (including oral $P2Y_{12}$ receptor antagonists and acetylsalicylic acid) as prescribed (treatments and doses), from Visit 1 (screening) and up to the last PK or PD blood sample collection (whichever is latest).

5.2.4 Forbidden concomitant therapy

The following medications are prohibited from screening and up to last PK or PD blood collection (whichever is latest):

- Fibrinolytic therapy (e.g., streptokinase, alteplase, etc.)
- Anticoagulants (e.g., Coumadin, warfarin, anti Xa inhibitors, dabigatran, heparin)
- OATP1B1 and OATP1B3 inhibitors (e.g., cyclosporine, eltrombopag, lapatinib, lopinavir, rifampin, ritonavir)

Initiation of any of the following medications is prohibited from screening up to last PK or PD blood collection (whichever is latest):

- Oral $P2Y_{12}$ receptor antagonists (e.g., clopidogrel, prasugrel, ticagrelor)
- Cangrelor

6 STUDY ENDPOINTS

6.1 Efficacy endpoints

Not applicable.

6.2 Pharmacokinetic and pharmacodynamic endpoints

6.2.1 Pharmacodynamic endpoints

The primary PD endpoint is the PD response that is defined for each subject as a PRU < 100 starting 30 min after injection and lasting for at least 3 h, as measured via the VerifyNow® assay. This corresponds to inhibition of ADP-induced platelet aggregation (IPA) > 80% [Gaglia 2011, Gremmel 2009, Varenhorst 2009].

6.2.2 Pharmacokinetic endpoints

The plasma PK parameters of ACT-246475 will be derived by non-compartmental analysis of the plasma concentration-time profiles. PK endpoints include:

- C_{max}.
- t_{max}.
- The AUC from time zero to 24 h time point ($AUC_{0–24h}$).

6.3 Safety endpoints

The safety endpoints will be assessed up to EOS:

- Treatment-emergent AEs[b] (TEAEs) and SAEs.
- All AEs and SAEs.
- Change in vital signs (systolic and diastolic arterial BP and pulse rate) from baseline to all assessed time points during the study.
- Treatment-emergent ECG abnormalities.
- Change from baseline to each measured time point in ECG variables: heart rate, and the intervals: PQ/PR, QRS, QT, RR, QT corrected with Bazett's formula (QTcB), QT corrected with Fridericia's formula (QTcF).
- Change from baseline to each measured time point for clinical laboratory tests.
- Treatment-emergent marked laboratory abnormalities.

7 VISIT SCHEDULE AND STUDY ASSESSMENTS

7.1 Study visits

The study visits are listed in Table 2. For all visits, the subjects must be seen on the designated day. A follow-up safety visit must be performed 30–37 days after the single administration of study treatment.

[b] A treatment-emergent AE is any AE temporally associated with the administration of study treatment (until 48 h after study treatment administration) whether or not considered by the investigator as related to study treatment.

7.1.1 Screening/re-screening

Screening starts with the signature of the informed consent. The date on which the first screening assessment is performed corresponds to the date of the Screening visit.

It is the responsibility of the investigator/delegate to obtain written informed consent from each subject participating in this study after adequate face-to-face explanation of the objectives, methods and potential hazards of the study. The subjects who agree to participate in the study and the investigator/delegate must sign the ICF prior to any study-related assessment or procedure.

Subjects who have signed informed consent when the enrollment target has been met may still be randomized.

It is permitted to re-screen subjects once, if the reason for non-eligibility was transient (e.g., abnormal laboratory test, insufficient washout period of a forbidden medication). All screening assessments must be repeated at the time of re-screening unless they were performed within 1 week (7 days) of re-screening.

Screening (and re-screening) will be performed through the IRT system which will provide a unique subject number.

7.1.2 Unscheduled visits

Unscheduled visits may be performed at any time during the study. Depending on the reason for the unscheduled visit (e.g., AE), appropriate assessments will be performed based on the judgment of the investigator and the results will be recorded in the CRF. After an unscheduled visit, the regular scheduled study visits must continue according to the planned visit and assessment schedule.

Table 2 Visit and assessment schedule

PERIOD	**SCREENING PERIOD**	**TREATMENT PERIOD**		**FOLLOW-UP PERIOD**
Visit	**Visit 1**	**Visit 2 (Randomization[c])**	**Visit 3**	**EOS Visit (Visit 4; Telephone call)**
Study Day	**Day –21 to Day –1**	**Day 1**	**Day 2**	**Study treatment administration + 30–37 days**
Informed consent	X			
Eligibility	X	X[f]		
Demographics and medical history	X			
Physical examination	X	X[a]	X	
Body weight and height	X			
Previous/concomitant therapy	X	X	X	X
Urine pregnancy test[g]	X	X		X
Vital signs (BP, Pulse rate)	X	X[b]	X[b]	
12-lead ECG		X[b]	X[b]	
Laboratory tests[e]	X	X[a, f]	X[h]	
PK blood sampling		X[b]	X[b]	
VerifyNow®	X	X[b, c]	X[b]	
LTA (for patients ≥ 50.0 kg only) [d]	X	X[b, c]		
s.c. injection (ACT-246475 or placebo)		X		
AEs/SAEs	X	X	X	X

a. Physical examination and laboratory tests do not need to be repeated if screening assessments were performed within 7 days of Visit 2 and are to be performed pre-dose.
b. Refer to Table 3 for detailed timing of assessments.
c. Randomization will be performed after the pre-dose blood sampling for VerifyNow® and LTA assessments on Day 1. The dose allocated (8 mg or 16 mg) must not be communicated to the subject.
d. No blood samples are to be collected for LTA assays for subjects with body weight < 50.0 kg (110 lbs), only VerifyNow® assays are performed for these subjects.

e. Laboratory assessments include chemistry, hematology, and INR.
f. If screening hemoglobin results are not available at time of randomization, it is acceptable to randomize a subject based on a local laboratory result if blood sample was collected during the screening period.
g. For women of childbearing potential only.
h. If the 24 h post-dose central laboratory sample is lost or cannot be analyzed for whatever reason, the investigator may collect an additional sample for repeat analysis, as deemed medically needed, unless a local laboratory sample was collected within the same time-window and these test results are available.

AE, Adverse event; BP, Blood pressure; ECG, Electrocardiogram; EOS, End-of-Study; INR, International normalized ratio; LTA, Light transmission aggregometry; PK, Pharmacokinetics; s.c., Subcutaneous; SAE, Serious adverse event.

Table 3 Time points of main study assessments

PERIOD	**TREATMENT PERIOD**								
Visit	**Visit 2 (Randomization[a])**								**Visit 3**
Study Day	**Day 1[b]**								**Day 2[b]**
Time point	**Pre-dose**	**0 min**	**15 min ±1 min**	**30 min ±2 min**	**1h ±3 min**	**2h ±6 min**	**4h ±12 min**	**8h ±24 min**	**24h ±2h**
Vital signs (BP, Pulse rate)	X			X	X	X	X	X	X
12-lead ECG	X				X[d]				X
PK Blood sampling	X		X	X	X	X	X	X	X
VerifyNow®	X[a]		X	X	X	X	X	X	X
LTA (for patients ≥ 50.0 kg only)[c]	X[a]			X	X	X		X	
s.c. injection (ACT-246475 or placebo)		X							

a. Randomization will be performed after pre-dose blood sampling for VerifyNow® and LTA assessments on Day 1. The dose allocated (8 mg or 16 mg) must not be communicated to the subject.
b. The following order of assessments is to be followed (as applicable): PK sample (to be collected at the protocol-defined time point), VerifyNow® sample, LTA sample.
c. No blood samples are to be collected for LTA assays for subjects with body weight < 50.0 kg (110 lbs), only VerifyNow® assays are performed for these subjects.
d. Time window for performing the post-dose ECG is ±30 min.

BP, Blood pressure; ECG, Electrocardiogram; EOS, End-of-Study; LTA, Light transmission aggregometry; PK, Pharmacokinetics; s.c., Subcutaneous.

7.2 Study assessments

The study assessments and their respective timing are listed in Table 2 and Table 3.

All study assessments will be performed by qualified study personnel: medical, nursing, or specialist technical personnel, and will be recorded in the CRF, unless otherwise specified. Study assessments performed during unscheduled visits will also be recorded in the CRF. It is recommended to perform physical examination and measure vital signs (BP and pulse rate) prior to the blood samplings.

At the PK/PD time points, the following order for blood sampling is to be applied:

1. Hematology and chemistry samples (if any).
2. PK sample (to be collected at the protocol-defined time point according to the time window defined in Table 3).
3. VerifyNow® sample.
4. LTA sample.

Calibration certificates / evidence of equipment maintenance for the below-listed equipment used to perform study assessments must be available prior to screening of the first subject. Calibration certificates of other equipment must be available as per local requirements:

- Temperature measurement devices for study treatment storage area and freezer used for PK samples storage.
- VerifyNow® and LTA devices.
- Centrifuges used for preparation of the platelets for LTA assay.

7.2.1 Demographics / baseline characteristics

Demographic and baseline characteristic data to be collected on all subjects, including age, sex, race, and ethnicity. Relevant medical history / current medical conditions (e.g., chronic and ongoing acute conditions, serious past conditions) present before signing informed consent will be recorded on the medical history CRF form. Where possible, diagnoses and not symptoms will be recorded.

Medical history of special interest will be captured on the specific Medical History CRF form and includes, when applicable, the date of the most recent event for:

- MI, stroke, and TIA.
- PCI or coronary artery bypass graft.
- Peripheral vascular surgery.

For subjects who failed screening, at least the following data will be recorded in the CRF if available:

- Baseline demographics and physical characteristics (i.e., age, race/ethnicity, body weight, height, sex).
- LTA and VerifyNow® assessment results.
- Central laboratory and central ECG results.
- Reason for screening failure.
- AEs and SAEs.

7.2.2 Efficacy assessments

Not applicable.

7.2.3 Pharmacokinetic and pharmacodynamic assessments

7.2.3.1 Pharmacodynamic assessments

7.2.3.1.1 Procedures for blood sampling

The different time points for PD blood samples collection are detailed in Table 2 and Table 3.

The blood samples for PD assessments are to be collected immediately after the blood samples for PK or laboratory assessments. If, for any reason, this is not possible, a 2 mL volume of blood needs to be discarded prior to collection of the PD blood samples.

PD blood samples will be collected by direct venipuncture or via an i.v. catheter placed in an antecubital or large forearm vein in the arm, using 18–21 gauge needles.

Blood will be drawn into 3-mL vacuum tubes: 2 samples for LTA assay and one sample for VerifyNow® assay. Collection tubes for both LTA and VerifyNow® assays will contain phenylalanine-proline-arginine-chloromethyl ketone (PPACK) as an anticoagulant. The centrifugation step should be performed within 1 h after sampling. The platelet aggregation assays must be performed preferably within 1 h of blood collection and not exceeding 2 h. The date and the exact actual clock time of collection of each blood sample (including the unscheduled ones, if any) will be entered in the CRF.

Detailed handling instructions for PD samples (LTA and VerifyNow® samples) are provided in the laboratory manual.

7.2.3.1.2 Bioanalysis

ADP-induced platelet aggregation will be evaluated by 2 different assays, VerifyNow® and LTA, both measuring platelet-induced aggregation as an increase in light transmittance [Michelson 2009].

All PD measurements will be performed at the site by trained staff using validated procedures. Detailed instructions for the analysis of the PD samples (LTA and VerifyNow®) are provided in the laboratory manual.

7.2.3.1.2.1 VerifyNow® Assay

The blood sample will be inserted into the calibrated VerifyNow® system. Platelet-induced aggregation is measured with ADP as the agonist. The assay will be run according to the manufacturer's instructions. The VerifyNow® system will provide the results as PRU, corresponding to the extent of ADP-mediated aggregation measured in the ADP channel.

The VerifyNow® system will be used with 2 different tests depending on local availability:

- The VerifyNow® P2Y12 test reports platelet aggregation as PRU. In addition, a second channel with an internal standard consisting of thrombin receptor agonists is used for calculation of the percent of platelet aggregation inhibition. The VerifyNow® P2Y12 test is only available in Europe.
- The VerifyNow® PRU test does not have an internal standard and only reports platelet aggregation as PRU. It is globally available and will be used where the VerifyNow® P2Y12 test is not available.

7.2.3.1.2.2 Light transmission platelet aggregometry

The two 3 mL LTA blood samples will be centrifuged at 200 g for 7 min, the rotor should then come to a halt without brakes (brakes position 0 = switched off). This will allow for preparation of PRP. The assay will be performed with a light transmission aggregometer approved by the sponsor (e.g., Chrono-log 490, PAP-4, PAP-8, APACT), recording the aggregation after addition of 20 µM ADP as agonist for 6 min. The results are expressed as a percent change in light transmittance at maximum peak platelet aggregation and at final platelet aggregation after 6 min, calculated relative to the baseline signal of 0%. The measurements will be performed in duplicate.

7.2.3.2 Pharmacokinetic assessments

7.2.3.2.1 Procedures for blood sampling

Blood will be collected by direct venipuncture or via an i.v. catheter placed in an antecubital vein in the arm in a 4 mL Monovette® or equivalent tubes containing ethylenediaminetetraacetic acid (EDTA).

PK blood samples have to be processed within 30 min of collection. Instructions regarding sample collection, processing, labeling, and storage conditions are detailed in the laboratory manual.

The time points for PK assessment blood samples are described in Table 3.

The date and exact actual clock time of collection of each blood sample will be entered in the CRF.

7.2.3.2.2 Bioanalysis

The analysis of ACT-246475 in plasma will be performed using a validated liquid chromatography coupled to tandem mass spectrometry assay.

The foreseen lower limit of quantification is 1 ng/mL. Concentrations will be calculated by interpolation from a calibration curve. Quality control samples will be analyzed throughout the study. Their measured concentrations will be used to determine between-run and overall precision and accuracy of the analysis.

7.2.4 Safety assessments

The definitions, reporting, and follow-up of AEs, SAEs, and pregnancies are described in Section 9.

7.2.4.1 Physical examination

Physical examination will be performed according to site standard medical practice for subjects with stable CAD.

Other exams will be performed if indicated, based on medical history and/or symptoms.

Information for all physical examinations must be included in the source documentation at the study site. The observations will not be directly reported in the CRF. Clinically relevant findings that are present prior to signing of informed consent must be recorded on the Medical History CRF form. Physical examination findings made after signing of informed consent that meet the definition of an AE [Section 9.1.1] must be recorded on the AE form of the CRF.

7.2.4.2 Vital signs

Systolic and diastolic BP and pulse rate will be measured in subjects in supine or sitting position after at least 5 minutes of rest. It is recommended to use the same position and same arm for all measurements of the same subject.

7.2.4.3 Weight and height

Height and body weight will be measured in indoor clothing but without shoes.

7.2.4.4 ECG assessment

A standard 12-lead ECG will be performed with subject in the supine position, after a recommended 5-minute resting time.

Any clinically relevant ECG findings that are present prior to the administration of study treatment must be documented in the Medical History section of the CRF.

Any clinically relevant ECG finding which is found after the study treatment administration and was not present at Screening or worsened during the study must be reported as an AE as appropriate [see Section 9.1.1].

A central ECG service (see ECG manual for contact details) will be used for ECG evaluation.

Details about collection of ECG data, and the reporting of results and abnormalities, can be found in the ECG manual provided to the investigator.

7.2.5 Laboratory assessments

7.2.5.1 Type of laboratory

A central laboratory (see central laboratory manual for contact details) will be used for all protocol-mandated laboratory tests, including re-tests due to laboratory abnormalities and laboratory tests performed at unscheduled visits.

Exceptional circumstances that may require recording of local laboratory results of the variables described in Section 7.2.5.2 (with corresponding normal ranges) include hospitalization of the subject due to a medical emergency, and missing central laboratory results from a scheduled or unscheduled visit.

If the 24 h post-dose central laboratory sample is lost or cannot be analyzed for whatever reason, the investigator may collect an additional sample for repeat analysis, as deemed medically needed, unless a local laboratory sample was collected within the same time-window and these test results are available.

Central laboratory reports will be sent to the investigator. In the event of specific (predefined) laboratory abnormalities, the central laboratory will alert sponsor personnel and the concerned site personnel. Alert flags that will trigger such notifications are displayed in the laboratory manual.

All laboratory reports must be reviewed, signed and dated by the investigator or delegate within 10 working days of receipt and filed with the source documentation. The investigator/delegate must indicate on the laboratory report whether abnormal values are considered clinically relevant or not. Clinically relevant laboratory findings that are known at the time of signing of informed consent must be recorded on the Medical History form of the CRF. Any clinically relevant laboratory abnormalities detected after signing of informed consent must be reported as an AE or SAE as appropriate [see Section 9], and must be followed until the value returns to within the normal range or is stable, or until the change is no longer clinically relevant.

Details about the collection, sampling, storage, shipment procedures, and reporting of results and abnormal findings can be found in the laboratory manual.

7.2.5.2 Laboratory tests

7.2.5.2.1 Hematology

- Hemoglobin (g/L)
- Hematocrit (L/L)
- Erythrocyte count (10^9/L)
- Leukocyte count with differential counts (10^9/L)
- Platelet count (10^9/L)

7.2.5.2.2 Clinical chemistry

- Alanine aminotransferase (U/L)
- Aspartate aminotransferase (U/L)
- Alkaline phosphatase (U/L)
- Total and direct bilirubin (µmol/L)
- Creatinine (µmol/L)
- Creatinine clearance (eGFR) estimated with Cockcroft-Gault formula
- Blood urea nitrogen (mmol/L)
- Uric acid (µmol/L)
- Total cholesterol (mmol/L)
- Sodium, potassium, chloride, calcium (mmol/L)
- Albumin (g/L)

7.2.5.2.3 Coagulation tests

- International normalized ratio

7.2.5.2.4 Pregnancy test

- Urine pregnancy tests

8 STUDY COMPLETION AND POST-STUDY TREATMENT / MEDICAL CARE

8.1 Study completion

A subject who has received study treatment and completed the follow-up period is considered to have completed the study.

8.2 Premature withdrawal from study

Subjects may voluntarily withdraw from the study without justification for any reason at any time. Subjects are considered withdrawn if they state an intention to withdraw from further participation in all components of the study (i.e., withdrawal of consent), if they die, or are lost to follow-up. If a subject withdraws consent, no further data will be collected in the CRF from the date of withdrawal onward. The investigator may withdraw a subject from the study (without regard to the subject's consent) if, on balance, he/she believes that continued participation in the study would be contrary to the best interests of the subject. Withdrawal from the study may also result from a decision by the sponsor for any reason, including premature termination or suspension of the study.

Subjects are considered as lost to follow-up if all reasonable attempts by the investigator to communicate with the individual failed. The site must take preventive measures to avoid a subject being lost to follow-up (e.g., document different ways of contact such as telephone number, home address, email address, person to be contacted if the subject cannot be reached). If the subject cannot be reached, the site must make a reasonable effort to contact the subject, document all attempts, and enter the loss of follow-up information into the CRF. The following methods must be used: at least 3 telephone calls must be placed to the last available telephone number and one registered letter must be sent by post to the last available home address. Additional methods may be acceptable if they are compliant with local rules/regulations (e.g., a visit by site personnel to the subject's home), respecting the subject's right to privacy. If the subject is still unreachable after all contact attempts listed above, he/she will be considered to be lost to follow-up.

If premature withdrawal occurs for any reason, the reason (if known) for premature withdrawal from the study, along with who made the decision (subject, investigator, or sponsor personnel), must be recorded in the CRF, if known.

If, for whatever reason (except death or loss-to-follow-up), a subject is withdrawn from the study, the investigator should make efforts to schedule a last appointment / telephone call to assess the safety and wellbeing of the subject. Data obtained during this last appointment / telephone call will be recorded in the subject's medical records but it will not be collected in the CRF. The investigator must provide follow-up medical care for all

subjects who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care, as described in Section 8.4.

8.3 Premature termination or suspension of the study

The sponsor reserves the right to terminate the study at any time globally or locally. Investigators can terminate the participation of their site in the study at any time.

If a study is prematurely suspended or terminated, the sponsor/delegate will promptly inform the investigators, the IECs/IRBs, and HAs, as appropriate, and provide the reasons for the suspension or termination.

If the study is suspended or prematurely terminated for any reason, the investigator — in agreement with the sponsor — must promptly inform all enrolled subjects and ensure their appropriate treatment and follow-up, as described in Section 8.4. The sponsor/delegate may inform the investigator of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subjects' interests.

In addition, if the investigator suspends or terminates a study without prior agreement from the sponsor, the investigator must promptly inform sponsor personnel and the IEC/IRB, and provide both with a detailed written explanation of the termination or suspension.

If the IEC/IRB suspends or terminates its approval / favorable opinion of a study, the investigator must promptly notify sponsor personnel and provide a detailed written explanation of the termination or suspension.

8.4 Medical care of subjects after study completion / withdrawal from study

The subject's standard of care will not be affected by study participation. For this PK/PD and safety study, subjects will receive 1 single administration of study treatment on top of their standard of care.

9 SAFETY DEFINITIONS AND REPORTING REQUIREMENTS

9.1 Adverse events

9.1.1 Definition of adverse events

An AE is any untoward medical occurrence, i.e., any unfavorable and unintended sign, including an abnormal laboratory finding, symptom, or disease that occurs in a subject during the course of the study, whether or not considered by the investigator as related to study treatment.

A TEAE is any AE temporally associated with the use of study treatment until 48 h after study treatment administration whether or not considered by the investigator as related to

study treatment. The 48-h window for TEAEs has been defined to include at least 5 half-lives of ACT-246475.

AEs include:

- Exacerbation of a pre-existing disease.
- Increase in frequency or intensity of a pre-existing episodic disease or medical condition.
- Disease or medical condition detected or diagnosed during the course of the study even though it may have been present prior to the start of the study.
- Continuous persistent disease or symptoms present at study start that worsen following the signing of informed consent.
- Abnormal assessments, e.g., change on physical examination, ECG findings, if they represent a clinically significant finding that was not present at study start or worsened during the course of the study.
- Laboratory test abnormalities if they represent a clinically significant finding, symptomatic or not, which was not present at study start or worsened during the course of the study.

Overdose, misuse, abuse of the study treatment and study treatment errors will be reported as an AE.

9.1.2 Intensity of adverse events

The intensity of clinical AEs is graded on a 3-point scale (mild, moderate, severe) and is reported on specific AE pages of the CRF.

All changes in intensity of an AE during the study will be reported in the CRF.

The three categories of intensity are defined as follows:

- **Mild**

The event may be noticeable to the subject. It does not usually influence daily activities, and normally does not require intervention.

- **Moderate**

The event may make the subject uncomfortable. Performance of daily activities may be influenced, and intervention may be needed.

- **Severe**

The event may cause noticeable discomfort, and usually interferes with daily activities. The subject may not be able to continue in the study, and treatment or intervention is usually needed.

A mild, moderate, or severe AE may or may not be serious [see Section 9.2.1]. These terms are used to describe the intensity of a specific event. Medical judgment should be used on a case-by-case basis.

Seriousness, rather than intensity assessment, determines the regulatory reporting obligations.

9.1.3 Relationship to study treatment

Each AE must be assessed by the investigator as to whether or not there is a reasonable possibility of causal relationship to the study treatment, and reported as either related or unrelated. The determination of the likelihood that the study treatment caused the AE will be provided by the investigator.

9.1.4 Reporting of adverse events

All AEs with an onset date after signing of informed consent and up to 30 days after study treatment administration must be recorded on specific AE pages of the CRF.

9.1.5 Follow-up of adverse events

AEs still ongoing more than 30 days after study treatment administration must be followed up until they are no longer considered clinically relevant or until stabilization. The follow-up information obtained after the subject's EOS telephone call will not be collected by the sponsor.

9.2 Serious adverse events

9.2.1 Definitions of serious adverse events

An SAE is defined by the ICH guidelines as any AE fulfilling at least one of the following criteria:

- Fatal.
- Life-threatening: Refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death had it been more severe.
- Requiring in-patient hospitalization or prolongation of existing hospitalization.
- Resulting in persistent or significant disability or incapacity.
- Congenital anomaly or birth defect.

- Medically significant: Refers to important medical events that may not immediately result in death, be life-threatening, or require hospitalization but may be considered to be SAEs when, based upon appropriate medical judgment, they may jeopardize the subject, and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions above.

The following reasons for hospitalization are not considered as SAEs:

- Hospitalization for cosmetic elective surgery, or social and/or convenience reasons (including hospitalization related to protocol procedures).
- Hospitalization for pre-planned (i.e., planned prior to signing informed consent) surgery or standard monitoring of a pre-existing disease or medical condition that did not worsen, e.g., hospitalization for coronary angiography in a subject with stable angina pectoris.

However, complications that occur during hospitalization are AEs or SAEs (e.g., if a complication prolongs hospitalization).

9.2.2 Reporting of serious adverse events

All SAEs occurring after signing of informed consent up to 30 days after study treatment administration must be reported on AE pages in the CRF and on a SAE form, regardless of the investigator-attributed causal relationship with study treatment or study-mandated procedures.

An SAE is defined as related to protocol-mandated procedures if it appears to have a reasonable possibility of a causal relationship to either the study design or to protocol-mandated procedures (e.g., discontinuation of a subject's previous treatment during a washout period leading to exacerbation of underlying disease).

All SAEs must be reported by the investigator to the sponsor's Global Drug Safety department within 24 hours of the investigator's first knowledge of the event.

All SAEs must be recorded on a SAE form, irrespective of the study treatment received by the subject, and whether or not this event is considered by the investigator to be related to study treatment.

The SAE forms must be sent to the sponsor's Global Drug Safety department (contact details are provided on the SAE form). The investigator must complete the SAE form in English, and must assess the event's causal relationship to the study treatment.

Any relevant information from source documents regarding the SAE, e.g., hospital notes or discharge summaries, etc., must be summarized on the SAE form.

Follow-up information about a previously reported SAE must also be reported within 24 hours of receiving it. The sponsor's Global Drug Safety personnel may contact the investigator to obtain further information.

If the subject is hospitalized in a hospital other than the study site, it is the investigator's responsibility to contact this hospital to obtain all SAE-relevant information and documentation.

The expectedness of an adverse reaction is determined by the sponsor in the reference safety information (RSI) section provided in the most recent version of the IB. Any SAE that is assessed as related and unexpected against the RSI is known as a SUSAR and must be reported by the sponsor/delegate to concerned HAs (including the EudraVigilance database if the study is conducted in Europe), IECs/IRBs and investigators.

9.2.3 Follow-up of serious adverse events

SAEs still ongoing more than 30 days after study treatment administration must be followed up until resolution or stabilization, or until the event outcome is provided. The follow-up information obtained after the subject's EOS telephone call must be reported to the sponsor's Global Drug Safety department, but it is not recorded in the CRF.

9.2.4 After the 30-day follow-up period

New SAEs occurring after the 30-day follow-up period must be reported to the sponsor's Global Drug Safety department within 24 hours of the investigator's knowledge of the event, **only** if considered by the investigator to be causally related to previous exposure to the study treatment.

9.3 Pregnancy

If a woman becomes pregnant during study participation, the investigator must counsel the subject and discuss the risks of continuing with the pregnancy and the possible effects on the fetus.

9.3.1 Reporting of pregnancy

Any pregnancy occurring after study start (i.e., signing of informed consent) up to 30 days following study treatment administration must be reported within 24 hours of the investigator's knowledge of the event.

Pregnancies must be reported on the Pregnancy form, which is faxed to the sponsor's Global Drug Safety department (see contact details provided on the Pregnancy form), and on an AE page in the CRF.

9.3.2 Follow-up of pregnancy

Any pregnancies must be followed-up to their conclusion and the outcome must be reported to the sponsor's Global Drug Safety department.

Any AE associated with the pregnancy occurring during the follow-up period after study treatment administration must be reported on separate AE pages in the CRF. Any SAE occurring during the pregnancy must be reported on an SAE form as described in Section 9.3.1.

9.4 Study safety monitoring

Study safety information (AEs, SAEs, laboratory values, ECGs, vital signs, and study-specific examinations as required) is monitored and reviewed on a continuous basis by the sponsor's clinical team (in charge of ensuring subjects' safety as well as data quality). In addition, a Safety Event Committee is monitoring safety data [see Section 3.4].

10 STATISTICAL METHODS

All statistical analyses will be conducted by the sponsor or by designated CROs supervised by the sponsor.

A statistical analysis plan (SAP) will provide full details of the analyses, data displays, and algorithms to be used for data derivations.

Any deviation(s) from the original statistical plan described hereafter will be described and justified in the SAP or in the CSR, as appropriate.

10.1 Analysis sets

10.1.1 Screened analysis set

The Screened analysis set includes all subjects who are screened and have a subject identification number.

10.1.2 Randomized analysis set

The Randomized analysis set includes all subjects who have been assigned to a double-blind study treatment.

10.1.3 Full analysis set

The Full analysis set (FAS) includes all randomized subjects who have been administered the study treatment.

In order to adhere to the intention-to-treat principle as much as possible:

- Subjects are evaluated according to the study treatment they have been assigned to (which may be different from the study treatment they have received),
- All available data are included.

10.1.4 Per-protocol analysis set

The Per-protocol set (PPS) comprises all subjects from the FAS who complied with the protocol sufficiently to allow adequate estimation of the treatment effects. Criteria for sufficient compliance include exposure to treatment, availability of key endpoints measurements and absence of major protocol deviations that have an impact on the treatment effect.

The full list of criteria will be detailed in the SAP before making the full randomization information available.

10.1.5 Safety set

The Safety set (SS) includes all subjects who received study treatment. Subjects will be evaluated according to the actual treatment they received, which may differ from the randomly assigned treatment.

10.1.6 Pharmacokinetic analysis set

The PK analysis set includes all subjects in the SS who have at least one PK sample collected after administration of study treatment.

10.1.7 Usage of the analysis sets

The PD analysis will be performed on the FAS based on the study treatment as randomized. Sensitivity analyses will be conducted using same endpoints as specified in Section 10.3 on the PPS.

Safety analyses will be performed on the SS based on actual study treatment received.

Subject listings will be based on the SS, unless otherwise specified. Subject disposition will be described for the Screened analysis set.

Table 4 describes the analysis sets used for the analysis of each data set.

Table 4 Analysis datasets

Analysis	Screened set	RND	FAS	PPS	SS	PK set
Subject disposition	X					
Baseline and disease characteristics		(x)	X	(x)		
Previous and concomitant medication			X			
Study treatment exposure			X	(x)		
PD endpoints analyses			X	(x)		
Safety and tolerability analyses					X	
PK data analysis						X

Note: Selected safety parameters, X: main analysis, (x): Sensitivity analysis to be conducted only if > 10% difference of set size with set used for main analysis.
FAS, Full analysis set; PD, Pharmacodynamic; PK, Pharmacokinetic; PPS, Per-protocol set; RND, Randomized set; SS, Safety set.

10.2 Variables

The *absolute change from baseline to time T* is defined as the algebraic difference between the value observed at time T minus the value at baseline.

The *relative change from baseline to time T* is defined as the ratio of the absolute change from baseline to time T on the baseline value.

Unless specified otherwise, the *baseline value* is defined as the arithmetic mean of the last 2 values collected during the screening phase prior to randomization.

10.2.1 Primary efficacy variable(s)

Not applicable.

10.2.2 Key secondary efficacy variables

Not applicable.

10.2.3 Safety variables

10.2.3.1 Adverse events

An AE is defined as any event that is recorded on the AE CRF module regardless of the onset date.

TEAEs are those AEs with onset date/time ≥ date/time of first study treatment administration and ≤ 48 h after date/time of last study treatment administration.

The handling of missing or incomplete date/time of AEs and assessments will be described in the SAP.

10.2.3.2 Laboratory data

Laboratory analyses are based on data received from the central laboratory [see Section 7.2.5.2]. All transferred central laboratory data are taken into account regardless of whether they correspond to scheduled or unscheduled assessments.

Baseline laboratory test refers to the latest laboratory test performed prior to the first study treatment administration.

End-of-treatment laboratory test refers to the laboratory test performed on the day following the day of study treatment administration (Visit 3).

For each continuous laboratory parameter, the following variables will be summarized:

- Absolute value at each time point,
- Absolute change from baseline to each time point,
- Treatment-emergent marked laboratory abnormalities (i.e., up to 48 h after study treatment administration).

For categorical laboratory parameters, the following variables will be summarized:

- Proportion of subjects by categories at each time point.

Unless stated otherwise, no imputation for missing laboratory values will be performed.

10.2.3.3 ECG

ECG recording is performed at the time points described in Table 3.

- Treatment-emergent ECG abnormalities (i.e., up to 48 h after study treatment administration).
- Absolute change from baseline to each time point in ECG variables: HR, and the intervals: PQ/PR, QRS, QT, RR, QTcB, and QTcF.

10.2.3.4 Vital signs

- Absolute value in vital signs at each assessed time point during the study.
- Relative change from baseline to each measured time point in vital signs (systolic and diastolic arterial BP and pulse rate).

10.2.4 Pharmacokinetic and pharmacodynamic variables

10.2.4.1 Pharmacokinetic variables

Plasma concentrations per time point will be listed by treatment arm and subject, and summarized by time point and dose group using arithmetic and geometric mean,

minimum, median, maximum, standard deviation (SD), standard error (SE), and 2-sided 95% confidence interval (CI) of the means and coefficient of variation (CV) in %.

PK parameters will be derived using non-compartmental methods:

- C_{max}, t_{max}, and $AUC_{0–24h}$ will be listed by dose group and subject and will be summarized by dose group.
- C_{max}, t_{max}*, and $AUC_{0–24h}$ will be summarized with arithmetic mean, geometric mean, minimum, median, maximum, SD, SE, CV (%), and 95% CI of the arithmetic and geometric means.

  (* For t_{max} the geometric mean and its 95% CI will not be calculated).
- Log-transformed C_{max} and $AUC_{0–24h}$ values will be summarized with mean and SD of the logs.

10.2.4.2 Pharmacodynamic variables

The primary PD variable is the IPA as measured by VerifyNow® at each time point, as described in table of assessments [Table 2 and Table 3].

The primary PD endpoint is the *PD response* that is defined for each subject as a PRU < 100 starting 30 min after injection and lasting for at least 3 h, as measured via VerifyNow®.

Additional PD variables related to the main ones will also be considered at each time point:

- Extent of aggregation (measured through LTA).
- Absolute PRU values (for VerifyNow®).
- % of subjects at 8 h after study treatment injection with PRU value < 100 or > 1.05 × baseline value.

10.3 Description of statistical analyses

All analyses will be conducted by treatment arm on the FAS, i.e., ACT-246475 8 mg, ACT-246475 16 mg, and placebo.

10.3.1 Overall testing strategy

The study is intended to assess the effect of ACT-246475 on platelet aggregation.

The primary null hypotheses will be tested at a 0.025 alpha level for each comparison to placebo, and then, if the null hypothesis is rejected for at least 1 of the 2 active arms, it will be completed by testing in each active arm that the proportion of patients achieving a response is statistically greater than 70%.

The study will be declared to be positive with regard to the primary objective if, for at least 1 of the 2 active arms, the 2 null hypotheses are sequentially rejected at an adjusted alpha level of 0.025.

No imputation will be considered for handling missing values in the main analysis of PD. Imputations may be performed in sensitivity/exploratory analyses, if deemed necessary, e.g., if more than 10% missing values at a given time point.

10.3.2 Analysis of the primary pharmacodynamic variable

The study is designed to demonstrate that ACT-246475 treatment enables a large proportion (a target of 85%) of the enrolled subjects to achieve a clinically meaningful level of IPA, i.e., PRU < 100.

10.3.2.1 Hypotheses and statistical model

The primary goal is to determine that the proportion *p* of subjects receiving a dose of ACT-246475, who achieve the PD response as measured by VerifyNow®, is statistically greater than 70%.

In order to achieve this objective, the testing strategy will consider a sequential approach demonstrate a statistically significant difference between the control arm (placebo) and at least 1 of the active arms, then to confirm that the observed response rate (P_r) in the same active arm is statistically significantly greater than the predefined response rate.

The comparison of each of the 2 active treatment arms will be conducted vs placebo, with the following hypotheses:

H_{p0HD}: $p_{placebo} = p_{HD}$

vs

H_{p1HD}: $p_{placebo} \neq p_{HD}$

AND

H_{p0LD}: $p_{placebo} = p_{LD}$

vs

H_{p1LD}: $p_{placebo} \neq p_{LD}$

Where, $p_{placebo}$ is the proportion of responders in Placebo arm, p_{HD} is the proportion of responders in the ACT-246475 16 mg arm, and p_{LD} is the proportion of responders in the ACT-246475 8 mg arm.

The 2 null hypotheses will be tested for each dose by a 2-sided z-test at an overall significance level (alpha) of 0.05 adjusted for multiplicity using the Bonferroni method, i.e., 0.025 for each comparison.

Assuming that either $H_{p0HD,}$ or $H_{p0LD,}$ or both are rejected, then the following hypotheses will be tested for each of the active doses that were statistically significantly different from placebo:

H_0: $P_{responders} = 0.70$

vs

H_1: $P_{responders} > 0.70$

The null hypothesis will be tested for each dose by a 1-sided z-test at an overall significance level (alpha) of 0.05 adjusted for multiplicity using the Bonferroni method, i.e., 0.025 for each comparison.

10.3.2.2 Handling of missing data

Subjects for whom determination of the response is not possible will be counted as non-responders in the main analysis; no other imputation will be considered.

10.3.2.3 Main analysis

The primary statistical analysis will be performed on the FAS population for each dose level.

The first set of null hypotheses (H_{p0HD} and H_{p0LD}) will be tested for each dose by a 2-sided z-test at an overall significance level (alpha) of 0.05 adjusted for multiplicity using the Bonferroni method, i.e., 0.025 for each comparison.

The second null hypothesis (H_0) will be tested for each dose by a 1-sided z-test. The estimated proportion of responders in each arm and the corresponding 95% CI will be provided.

A longitudinal analysis of the treatment effect, from start of treatment up to 8 h after injection, on platelet reactivity as measured by VerifyNow®, i.e., PRU value, will be performed using a mixed model with PRU as the dependent variable, subject as a random factor, and treatment (8 mg, 16 mg, and placebo), injection site (abdomen, thigh), PRU level at randomization (stratification levels), age (continuous), gender (male, female), and assessment time (continuous) as fixed factors. The model will also include (treatment × injection site) as an interaction term to assess consistency of treatment effect across injection sites.

A logistic regression analysis of the PD response will be performed using the same factor as covariates.

Summary of PD response, in terms of number (%) of subjects, will be provided. IPA as measured by VerifyNow® will also be summarized as a continuous parameter.

10.3.2.4 Supportive/sensitivity analyses

The consistency across the following subgroups will be assessed by repeating the primary endpoint analysis, assuming there are a sufficient number of subjects:

1. Age: < 55 vs ≥ 55 years
2. Body mass index: < 25.0 vs (≥ 25.0 and < 30.0) vs ≥ 30.0 kg/m^2
3. Sex: male vs female
4. Diabetes mellitus at baseline: yes vs no
5. Chronic kidney disease: yes vs no

An additional analysis of the supportive PD endpoint (LTA-PD response) will be conducted using the same approach as described for the primary PD analysis.

Further analyses will be described in the SAP as necessary.

10.3.3 Analysis of key secondary efficacy variable(s)

Not applicable.

10.3.4 Analysis of the safety variables

Unless noted otherwise, the SS will be used for summaries and listings of safety data.

10.3.4.1 Adverse events

AEs coded using the most recent version of MedDRA, will be summarized (frequency counts and percentages) by system organ class and/or preferred term, and maximum intensity.

Summaries will be provided for the following data:

- TEAEs.
- TEAEs related to study treatment.
- Treatment-emergent non-serious AEs.
- Treatment-emergent SAEs.
- Treatment-emergent SAEs related to study treatment.
- TEAEs with fatal outcome.
- TEAEs related to study treatment with fatal outcome.

10.3.4.2 Laboratory data

Unless noted otherwise, summaries and listings will include unscheduled assessments reported by the central laboratory.

Descriptive summary statistics by scheduled visit will be provided for observed values and absolute changes from baseline in both hematology and blood chemistry laboratory variables.

The absolute change from baseline to each time point for hematology and blood chemistry variables will be summarized.

Number (%) of subjects with treatment-emergent marked laboratory abnormalities will be tabulated and all marked laboratory abnormalities will be listed.

10.3.4.3 Vital signs, weight and physical examination

Each summary and listing will include unscheduled assessments.

Absolute changes from baseline to last value on study treatment in vital signs will be summarized. The absolute values at each time point will also be summarized.

Physical examination abnormalities will be listed.

10.3.4.4 Electrocardiograms

Each ECG summary and listing will include unscheduled assessments.

The absolute change from baseline to each time point for ECG variables will be summarized. The absolute values at each time point will be summarized.

Number (%) of subjects having a marked ECG abnormality during the treatment period will be summarized.

All ECG values for subjects with at least one marked ECG abnormality will be listed.

10.4 Interim analyses

No interim analysis planned.

10.5 Sample size

The sample size is based on the primary PD endpoint, which is the proportion of subjects achieving a predefined PD response as measured by VerifyNow®. The computation of the sample size was performed using the East 6.0 software (version 6.4.0.1, 30 Aug. 2016) from Cytel.

This study includes 3 treatment arms, 2 active arms (ACT-246475 8 mg and 16 mg) and a placebo arm comprising the 2 dose-matching placebo groups.

The primary objective is to assess the effectiveness of ACT-246475 to allow subjects to achieve a predefined PD response, therefore the sample size will be provided in order to reach the necessary power to sequentially demonstrate that at least 1 of the 2 doses has a higher response rate than placebo and that this response rate is statistically significantly greater than the proportion of responders under H_0.

The sample size required for demonstrating a difference to placebo is based on an overall alpha of 0.05 (2-sided), adjusted for multiplicity using a Bonferroni method to 0.025 for each comparison, and a power of 0.9; the assumptions related to response rate under the null and alternative hypotheses are reported in the table below:

Proportion of responders under H_0 (placebo)	**Proportion of responders under H_1 (active)**	**Number of subjects *(total)***	**Number of subjects *(per arm)***
50%	75% *(odds ratio of 3)*	288	96

The sample size required to demonstrate that the achieved response rate is different from 70% is based on a 2-sided type I error (alpha) of 0.025, and a power of 0.9; the assumptions related to response rate under the null and alternative hypotheses, are reported in the table below:

Proportion of responders under H_0	**Proportion of responders under H_1**	**Number of subjects *(total for the 2 active arms)***	**Number of subjects *(per arm)***
70%	85%	196	98

Therefore the study should include at least 98 subjects evaluable for the primary PD endpoint in each treatment arm. Assuming a rate of drop-out or non-evaluable data of about 10%, each arm will include 108 subjects leading to a total for the study of 324 subjects.

11 DATA HANDLING

11.1 Data collection

The investigator/delegate is responsible for maintaining adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects.

Data reported in the CRF derived from source documents must be consistent with the source documents.

CRF data will be captured via electronic data capture (using the Rave system provided by Medidata Solutions, Inc., a web-based tool). The investigator and site personnel will be trained to enter and edit the data via a secure network, with secure access features (username, password, and identification — an electronic password system). A complete electronic audit trail will be maintained. The investigator/delegate will approve the data (i.e., confirm the accuracy of the data recorded) using an electronic signature (ref. to US 21 CFR Part 11).

Subject screening and randomization data will be completed for all subjects (i.e., eligible and non-eligible) through the IRT system and CRF.

For each subject screened (i.e., who signed an ICF), regardless of study treatment administration, a CRF must be completed and signed by the investigator/delegate. This also applies to those subjects who fail to complete the study. If a subject withdraws from the study, the reason must be noted on the CRF.

11.2 Maintenance of data confidentiality

The investigator/delegate must ensure that data confidentiality is maintained. On CRFs or other documents (e.g., documents attached to SAE forms / Pregnancy forms) submitted to the sponsor and any CROs, subjects must be identified only by number and never by their name or initials, date of birth, hospital numbers, or any other identifier. The investigator/delegate must keep a subject identification code list at the site, showing the screening/randomization number, the subject's name, date of birth, and address or any other locally accepted identifiers. Documents identifying the subjects (e.g., signed ICF) must not be sent to the sponsor, and must be kept in strict confidence by the investigator/delegate.

11.3 Database management and quality control

CRFs will be used for all subjects. The investigators will have access to the site CRF data until the database is closed. Thereafter, they will have read-only access. The CRF must be kept current to reflect subject status at any time point during the course of the study.

While entering the data, the investigator/delegate will be instantly alerted to data queries by validated programmed checks. Additional data review will be performed by sponsor/delegate personnel on an ongoing basis to look for unexpected patterns in data and for study monitoring. If discrepant data are detected, a query specifying the problem and requesting clarification will be issued and visible to the investigator/delegate via the CRF. All electronic queries visible in the system either require a data correction (when applicable) and a response from the investigator/delegate to clarify the queried data

directly in the CRF, or simply a data correction in the CRF. The investigator/delegate must, on request, supply the sponsor with any required background data from the study documentation or clinical records. This is particularly important when errors in data transcription are suspected. In the case of HA queries, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

This process will continue until database closure.

Laboratory samples and ECGs will be processed through a central vendor and the results will be electronically sent to the sponsor.

AEs are coded according to the latest MedDRA used by the sponsor.

After the database has been declared complete and accurate, the database will be closed. Any changes to the database after that time may only be made as described in the appropriate sponsor QS docs. After database closure, the investigator will receive the CRFs of the subjects of his/her site (including all data changes made) on electronic media or as a paper copy.

12 PROCEDURES AND GOOD CLINICAL PRACTICE

12.1 Ethics and Good Clinical Practice

Sponsor/delegate personnel and the investigators will ensure that the study is conducted in full compliance with this protocol, ICH-GCP Guidelines, the principles of the 'Declaration of Helsinki', and with the laws and regulations of the country in which the study is conducted.

12.2 Independent Ethics Committee / Institutional Review Board

The investigator will submit this protocol and any related document(s) provided to the subject (such as the ICF) to an IEC/IRB. Approval from the committee/board must be obtained before starting the study, and must be documented in a dated letter to the investigator, clearly identifying the study, the documents reviewed, and the date of approval.

Modifications made to the protocol or the ICF after receipt of the approval must also be submitted as amendments by the investigator to the IEC/IRB in accordance with local procedures and regulations.

A list of members participating in the IEC/IRB meetings must be provided, including the names, qualifications, and functions of these members. If that is not possible, the attempts made to obtain this information along with an explanation as to why it cannot be obtained or disclosed must be documented in the study documentation.

If a member of the study personnel was present during an IEC/IRB meeting, it must be clear that this person did not vote.

12.3 Informed consent

It is the responsibility of the investigator/delegate to obtain informed consent according to ICH-GCP and Declaration of Helsinki guidelines and local regulations from each individual participating in this study and/or legally designated representative. The investigator/delegate must explain to subjects that they are completely free to refuse to enter the study, or to voluntarily withdraw from the study at any time for any reason without having to provide any justification. Special attention shall be paid to the information needs of specific subject populations and of individual subjects, as well as to the methods used to give the information. Adequate time shall be given for the subject and/or legally designated representative to consider his or her decision to participate in the study and it shall be verified that the subject has understood the information (e.g., by asking the subject to explain what is going to happen).

The ICF will be provided in the country local language(s).

Site personnel authorized to participate in the consent process and/or to obtain consent from the subject and/or legally designated representative will be listed on the Delegation of Authority form supplied by the sponsor/delegate. A study physician must always be involved in the consent process.

The subject and/or legally designated representative and authorized site personnel listed on the Delegation of Authority form supplied by the sponsor/delegate must sign, personally date, and time (if the first study-mandated procedure is to be performed on the same day informed consent is obtained) the ICF before any study-related procedures (i.e., any procedures required by the protocol) begin.

A copy (or a second original) of the signed and dated ICF is given to the subject and/or legally designated representative; the original is filed in the site documentation. The informed consent process must be fully documented in the subject's medical records. This must include, at a minimum, the study reference, the subject number, the date and the information that a copy of the signed ICF was given to the subject/legally designated representative. Where applicable, this must also include the time and date when the subject was first introduced to the study, the time of consent, who participated in the consent discussion, who consented the subject and any additional person present during the consent process (e.g., the subject's family member[s])

If the site intends to recruit subjects who are considered vulnerable (e.g., subject cannot read or write, or does not speak or understand the ICF language), additional measures must be implemented in order to ensure subject's rights are respected and the consent

obtained is legally valid. The sponsor, the regulatory authorities (if applicable), and the IEC/IRB must be informed prior to the recruitment. The consent process (e.g., involvement of an impartial witness) must be fully described, submitted to, and approved by the IEC/IRB, according to procedures and before subjects are recruited.

12.4 Compensation to subjects and investigators

The sponsor provides insurance in order to indemnify (with both legal and financial coverage) the investigator/site against claims arising from the study, except for claims that arise from malpractice and/or negligence.

The compensation of the subject in the event of study-related injuries will comply with applicable regulations.

There is no direct health benefit for the subjects participating in the study. Accordingly, subjects may receive financial compensation for the time spent in the clinical trial in compliance with local regulation.

12.5 Protocol adherence/compliance

The investigator must conduct the study in compliance with the IEC/IRB and/or the regulatory authority-approved version of the protocol and must not implement any deviation/change from the protocol, except when deviation is necessary to eliminate an immediate hazard to the subject.

If a protocol deviation occurs, the investigator/delegate will inform the sponsor or its representative in a timely manner. The investigator/delegate must document and explain any deviation from the approved protocol. Deviations considered to be a violation of ICH-GCP must be reported to the IEC/IRB and regulatory authorities according to the sponsor or (overruling) local requirements.

All protocol deviations will be reported in the CSR. IECs/IRBs will be provided with listings of protocol deviations as per local requirements.

12.6 Protocol amendments

Any change to the protocol can only be made through a written protocol amendment. An amended protocol must be submitted to the IEC/IRB and regulatory authorities, in accordance with local regulations and procedures.

12.7 Essential documents and retention of documents

The investigator/delegate must maintain adequate records necessary for the reconstruction and evaluation of the study. A number of attributes are considered of universal importance to source data and the records that hold those data. These include that the source data and records are attributable, legible, contemporaneous, original

(or certified copy), accurate, and complete. Changes to source data and records must be traceable, must not obscure the original entry and must be explained if necessary (e.g., via an audit trail).

These records are to be classified into 2 different categories of documents: ISF and subjects' source documents.

These records must be kept by the investigator for as long as is necessary to comply with the sponsor's requirements (i.e., as specified in the clinical study agreement), and national and/or international regulations, whichever would be the longest period. If the investigator cannot guarantee this archiving requirement at the site for any or all of the documents, special arrangements, respecting the data confidentiality, must be made between the investigator and the sponsor to store these documents outside the site, so that they can be retrieved in case of a regulatory inspection. No study document should be destroyed without prior written approval from the sponsor. Should the investigator wish to assign the study records to another party, or move them to another location, the sponsor must be notified in advance.

If the site is using an electronic/computerized system to store subject medical records, it can be used for the purpose of the clinical study if it is validated (as per 21 CFR Part 11 or equivalent standard) and if the CRA has been provided personal and restricted access to study subjects only, to verify consistency between electronic source data and the CRF during monitoring visits.

If the site is using an electronic/computerized system to store subject medical records but it could not be confirmed that the system is validated or if the CRA could not be provided access to the system, the site is requested to print the complete set of source data needed for verification by the CRA. The printouts must be numbered, stapled together with a coversheet, signed and dated by the investigator/delegate to confirm that these certified copies are exact copies containing the same information as the original source data. The printouts will be considered as the official clinical study records and must be filed either with the subject's medical records or with the subject's CRF.

In order to verify that the process the site uses to prepare certified copies is reliable, the CRA must be able to observe this process and confirm that the comparison of the source documents and the certified copy did not reveal inconsistencies. The CRA does not need to verify this process for all data of all subjects but at least for some of them (e.g., first subject; regular check during the study of critical data like inclusion/exclusion criteria, endpoints for some subjects) as per the sponsor's instructions. If it were not possible for the CRA to observe this process, it would not be possible to rely on the site's certified copies and therefore the site cannot be selected for the clinical study.

12.8 Monitoring

Prior to study start, a site initiation visit (SIV) will be performed after the required essential study documents are approved by the sponsor or delegate. The study treatment will be shipped to the site upon approval of the required essential documents.

The principal investigator (PI) must ensure that all site personnel involved in the study are present during the SIV and will dedicate enough time to it.

The SIV must be completed before the site can start the screening of study subjects. Following the SIV, a copy of the completed initiation visit report and follow-up letter will be provided to the PI and filed in the ISF.

During the study, the CRA will contact and visit the site regularly and must be permitted, on request, to have access to study facilities and all source documents needed to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered in the CRFs and other protocol-related documents. Sponsor monitoring standards require full verification that informed consent has been provided, verification of adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of the main PD, safety, and tolerability endpoints. Additional checks of the consistency of the source data with the CRFs will be performed according to the study-specific monitoring guidelines. The frequency of the monitoring visits will be based on subject recruitment rate and critical data-collection times.

The PI must ensure that the CRF is completed after a subject's visit (site visit or telephone call), and that all requested subject files (e.g., ICFs, medical notes/charts, other documentation verifying the activities conducted for the study) are available for review by the CRA. The required site personnel must be available during monitoring visits and allow adequate time to meet with the CRA to discuss study-related issues.

The investigator agrees to cooperate with the CRA(s) to ensure that any issues detected in the course of these monitoring visits are resolved. If the subject is hospitalized or dies in a hospital other than the study site, the investigator is responsible for contacting that hospital in order to document the SAE, in accordance with local regulations.

A close-out visit will be performed for any initiated site when there are no more active subjects and all follow-up issues have been resolved. If a site does not enroll any subjects, the close-out visit may be performed prior to study database closure at the discretion of the sponsor.

12.9 Investigator Site File

Each site will be provided with an ISF at the latest during the SIV. It will contain all the essential documents that are required to be up-to-date and filed at site as per ICH-GCP section 8.

The ISF will include a table of contents listing the essential documents. All study-related documentation must be maintained in the ISF.

In some cases, exceptions can be discussed with the CRA regarding the filing of the study documents outside the ISF. It should be clearly documented where each document is filed. This note to file should be present in the specific tab of the document in the ISF.

The ISF must be stored in a secure and access-restricted area during and after the study. It must be kept by the site for as long as needed to comply with any applicable rules and regulations, ICH-GCP, as well as instructions from the sponsor. If the site needs to transfer the ISF to another location and/or if site facility can no longer store the ISF, the PI must immediately inform the sponsor.

If the PI will change, or if the site will relocate, the CRA must be notified as soon as possible.

12.10 Audit

The sponsor's QA representatives may audit the investigator site (during the study or after its completion). The purpose of this visit will be to determine the investigator's adherence to ICH-GCP, the protocol, and applicable regulations; adherence to the sponsor's requirements (e.g., standard operating procedures) will also be verified. Prior to initiating this audit, the investigator will be contacted by the sponsor/delegate to arrange a time for the audit.

The investigator and site personnel must cooperate with the auditor(s) and allow access to all study documentation (e.g., subject records) and facilities.

12.11 Inspections

HAs and/or IECs/IRBs may also conduct an inspection of this study (during the study or after its completion) at the site.

Should an inspection be announced by a HA and/or IEC/IRB, the investigator must immediately inform the sponsor (usually via the CRA) that such a request has been made.

The investigator and site personnel must cooperate with inspector(s) and allow access to all study documentation (e.g., subject records) and study facilities.

12.12 Reporting of study results and publication

The sponsor/delegate will post the key elements of this protocol and the summary of results within the required timelines on publically accessible databases (e.g., clinicaltrials.gov, EU database), as required by law and regulation.

Study results will be documented in a CSR that will be signed by sponsor representatives and the Coordinating Investigator.

In accordance with the Good Publication Practices and ethical practice, the results of the study will be submitted for publication in a peer-reviewed journal. Study results can be submitted for presentation at a congress before submission to a peer-reviewed journal.

The Coordinating Investigator and the Steering Committee, if any, will have the opportunity to review the analysis of the data and to discuss the interpretation of the study results with the sponsor personnel prior to submission to a peer-reviewed journal or presentation at a congress.

Authorship will be determined in accordance with the International Committee of Journal Editors criteria, and be based on:

- substantial contributions to the conception or design of the study, or the acquisition, analysis, or interpretation of data; and
- drafting of the publication or critical review for important intellectual content; and
- providing final approval of the version to be published; and
- agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

The list of authors of any publication of study results may include representatives of the sponsor and will be determined by mutual agreement.

Any study-related publication written independently by investigators must be submitted to the sponsor for review at least 30 days prior to submission for publication or presentation at a congress. Upon review, the sponsor may provide comments, and may also request alterations and/or deletions for the sole purpose of protecting its confidential information and/or patent rights. Neither the institution nor the investigator should permit publication during such a review period.

The sponsor's Policy on Scientific Publications can be found at:
https://www.idorsia.com/documents/com/policies-charters/policy-scientific-publications.pdf

13 REFERENCES

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