Protocol:

ID-076A202

Official Title:

A multi-center, open-label, randomized, study to assess the onset of platelet aggregation inhibition after a single subcutaneous injection of ACT-246475 in adults with acute myocardial infarction

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ACT-246475

Coronary artery disease

Protocol ID-076A202

A multi-center, open-label, randomized, study to assess the onset of platelet aggregation inhibition after a single subcutaneous injection of ACT-246475 in adults with acute myocardial infarction

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SPONSOR CONTRIBUTORS TO THE PROTOCOL

Clinical Trial Scientist	[redacted]
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CONTRACT RESEARCH ORGANIZATIONS INFORMATION

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

SIGNATURE PAGE FOR IDORSIA PHARMACEUTICALS LTD

Hereinafter called sponsor

Study title

A multi-center, open-label, randomized, study to assess the onset of platelet aggregation inhibition after a single subcutaneous injection of ACT-246475 in adults with acute myocardial infarction

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	Name	Date	Signature
[redacted]			

INVESTIGATOR SIGNATURE PAGE

Study title

A multi-center, open-label, randomized, study to assess the onset of platelet aggregation inhibition after a single subcutaneous injection of ACT-246475 in adults with acute myocardial infarction

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	Country	Site number	Town	Date	Signature
[redacted]					

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LIST OF ABBREVIATIONS AND ACRONYMS

ACS	Acute coronary syndrome
ADP	Adenosine diphosphate
AE	Adverse event
AESI	Adverse event of specific interest
AMI	Acute myocardial infarction
CAD	Coronary artery disease
CFR	Code of Federal Regulations (US)
CI	Confidence interval
C_{max}	Maximum plasma concentration
CRA	Clinical Research Associate
CRO	Contract Research Organization
CSR	Clinical study report
CV	Coefficient of variation
CYP	Cytochrome P450
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EOS	End-of-Study
ESC	European Society of Cardiology
FAS	Full analysis set
GCP	Good Clinical Practice
i.v.	Intravenous
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IPA	Inhibition of platelet aggregation
IRB	Institutional Review Board
ISEC	Independent Safety Event Committee
ISF	Investigator Site File
LTA	Light transmission aggregometry
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	Modified Full analysis set
MI	Myocardial infarction

MRP2	Multidrug resistance protein 2
MTD	Maximum tolerated dose
NSTEMI	Non-ST-segment elevation myocardial infarction
OATP	Organic anion-transporting polypeptide
P-AM	Active metabolite of prasugrel
PCI	Percutaneous coronary intervention
PD	Pharmacodynamic(s)
PI	Principal Investigator
PK	Pharmacokinetic(s)
PPS	Per-protocol analysis set
PRU	$P2Y_{12}$ reaction units
RSI	Reference safety information
s.c.	Subcutaneous(ly)
s.l.	Sublingual
SAD	Single-ascending dose
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
SIV	Site initiation visit
ST	Stent thrombosis
STEMI	ST-segment elevation myocardial infarction
SUSAR	Suspected unexpected serious adverse reaction
$t_{½}$	Terminal half-life
TEAE	Treatment-emergent adverse event
TEAESI	Treatment-emergent adverse events of specific interest
TIMI	Thrombolysis in myocardial infarction
t_{max}	Time to reach maximum plasma concentration

NON-SUBSTANTIAL GLOBAL AMENDMENT 1

Amendment rationale

This amendment applies to global protocol ID-076A202 Version 1 dated 13 March 2018. The resulting amended global protocol is Version 2 dated 11 April 2018.

The reasons for this amendment are to provide the following clarification:

- The laboratory assessment "Activated Clotting Time" is a point-of-care test which cannot be performed centrally and will be performed at each site locally. In Section 7.2.5.1, it was indicated that all study-specific assessments will be performed centrally, this section is amended to clarify that the "Activated Clotting Time" will be performed locally.

Changes to the protocol

Two versions of the amended protocol will be prepared: 1) a clean version and 2) a Word comparison document, showing deletions and insertions in comparison to the previous protocol version.

Amended protocol sections

The sections of the protocol affected by this amendment are listed below. Where applicable, the same changes have also been made to the corresponding sections of the protocol synopsis:

7.2.5.1 Type of laboratory

7.2.5.2 Laboratory tests

PROTOCOL SYNOPSIS ID-076A202

TITLE	A multi-center, open-label, randomized study to assess the onset of platelet aggregation inhibition after a single subcutaneous injection of ACT-246475 in adults with acute myocardial infarction.
OBJECTIVES	**Primary objective** The primary objective of the study is to assess the inhibition of platelet aggregation (IPA) 30 minutes after a single subcutaneous (s.c.) injection of ACT-246475 in subjects with acute myocardial infarction (AMI) receiving conventional antithrombotic treatment (e.g., aspirin, oral $P2Y_{12}$ receptor antagonists, anticoagulants). **Other objectives** The other objectives of this study are: • To assess the pharmacokinetics (PK) of ACT-246475 in subjects with AMI. • To investigate safety and tolerability of ACT-246475.
DESIGN	This is a prospective, multi-center, open-label, randomized, parallel-group, Phase 2, exploratory study of a single s.c. administration of ACT-246475, at two different dose levels, in subjects with AMI (ST-segment elevation MI [STEMI] or non-STEMI [NSTEMI]) scheduled for invasive strategy. Approximately 42 adult subjects with confirmed diagnosis of AMI (STEMI or NSTEMI), and time from onset of symptoms of more than 30 min and less than 6 hours, will be randomized to receive ACT-246475 at the dose of either 8 mg or 16 mg, in a 1:1 ratio, injected s.c. in the thigh in addition to conventional standard-of-care treatment. Injection of ACT-246475 will be performed as soon as possible after randomization. The study comprises the following consecutive periods: **Screening period:** Starts when the subject gives informed consent (orally or in writing as described in Section 1.4.3) and ends with subject's randomization. **Treatment period:** Starts with subject's randomization and ends after the End-of-Study (EOS) assessments, approximately

	48 h after the administration of a single study treatment dose.
PLANNED DURATION	Approximately 4 months from first subject, first visit to last subject, last visit.
SITES / COUNTRIES	Approximately 3–8 sites in 1–2 countries are planned.
INCLUSION CRITERIA	1) Informed consent obtained prior to any study-mandated procedure. 2) Males aged from 18 to 85 and postmenopausal females aged up to 85 years. Postmenopausal is defined as 12 consecutive months with no menses without an alternative medical cause. 3) Onset of symptoms of AMI of more than 30 min and less than 6 hours prior to randomization. 4) Subjects presenting a type I AMI including STEMI or NSTEMI defined as follow: a) STEMI: new persistent ST-segment elevation ≥ 1 mm (1 mV) in two or more contiguous ECG leads, or b) NSTEMI: ECG changes compatible with myocardial ischemia without persistent ST-segment elevation and elevated troponin defined as a troponin T or I level ≥ 1.5 × the upper limit of normal. 5) Estimated body weight ≥ 40 kg (88 lbs).
EXCLUSION CRITERIA	**Conditions associated with the qualifying AMI:** 1) Cardiogenic shock or severe hemodynamic instability (e.g., Killip class 3–4). 2) Cardiopulmonary resuscitation. 3) Loading dose of any oral $P2Y_{12}$ receptor antagonist prior to randomization. **Bleeding risks:** 4) Active internal bleeding, or bleeding diathesis or conditions associated with high risk of bleeding (e.g., clotting disturbances, gastrointestinal bleed, hemoptysis). 5) Known clinically important anemia. 6) Oral anticoagulation therapy within 7 days prior to randomization. 7) Planned fibrinolytic therapy or any fibrinolytic therapy administered within 24 h prior to randomization.

	8) Known platelet disorders (e.g., thromboasthenia, thrombocytopenia, von Willebrand disease). **Conditions that may either put the subject at risk or influence the results of the study:** 9) End-stage renal failure requiring dialysis. 10) Any clinically significant findings on a physical exam, or laboratory tests that in the investigator's judgment would preclude safe or reliable participation of a subject in the study. 11) Concomitant diseases (e.g., advanced liver cirrhosis, mental illness, neurodegenerative disease, terminal malignancy…) or conditions (e.g., inability to communicate well with the investigator in the local language) that, in the opinion of the investigator, may put the subject at risk, prevent the subject from complying with study requirements or may be a confounder for the study interpretation. 12) Clinically relevant skin disease that prevents s.c. injection in the thigh, according to the investigator's judgment. 13) Known use of inhibitors of OATP1B1 or OATP1B3 (e.g., ritonavir, clarithromycin, erythromycin, cyclosporine, gemfibrozil) at screening. 14) Known hypersensitivity to ACT-246475, any of its excipients, or drugs of the $P2Y_{12}$ class. 15) Previous exposure to an investigational drug within 3 months prior to screening.
STUDY TREATMENTS	**Investigational treatment** 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) 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) in a volume of 0.8 mL, administered s.c. in the thigh at site by qualified personnel (e.g., nurse, physician).
CONCOMITANT THERAPY	**Allowed concomitant therapy** Standard treatment of AMI is allowed including anticoagulants

	and oral $P2Y_{12}$ receptor antagonists. When initiation of an oral $P2Y_{12}$ receptor antagonist is considered for a subject, it must be initiated after administration of ACT-246475. In absence of clinical data regarding administration of an irreversible $P2Y_{12}$ antagonist following the administration of ACT-246475, it is requested to use a reversible oral $P2Y_{12}$ receptor antagonist (e.g., ticagrelor). **Forbidden concomitant therapy** The following medications are prohibited from screening and up to the last PK blood collection: • Fibrinolytic therapy (e.g., streptokinase, alteplase…). • OATP1B1 and OATP1B3 inhibitors (e.g., atazanavir, ritonavir, lopinavir, simeprevir, clarithromycin, erythromycin, cyclosporine, eltrombopag, lapatinib, gemfibrozil, rifampin). • Glycoprotein IIb/IIIa inhibitors. • Oral irreversible $P2Y_{12}$ antagonists (clopidogrel or prasugrel). • Cangrelor.
ENDPOINTS	**Primary endpoint** The primary endpoint is the response to the treatment defined for each subject as a $P2Y_{12}$ reaction units value < 100 at the 30 min post-dose time point, as measured via VerifyNow®. This corresponds to an IPA induced by ADP > 80%. **Safety endpoints** The safety endpoints will be assessed up to EOS, i.e., over 48 hours post treatment administration: • Treatment-emergent adverse events (AEs)[1] and serious adverse events. • AE of specific interest (AESI): Hemorrhage. • Change in vital signs (systolic and diastolic arterial blood pressure and pulse rate) from baseline to all assessed time

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

	points during the study. • Change from baseline for clinical laboratory tests. • Treatment-emergent marked laboratory abnormalities. **Pharmacokinetic endpoints** PK endpoints include maximum plasma concentration (C_{max}) and time to reach C_{max} (t_{max}).
ASSESSMENTS	Refer to the schedule of assessments in Table 2.
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 study treatment. The Full analysis set (FAS) includes all randomized subjects who have been administered the study treatment. The modified FAS (mFAS) includes all subjects from the FAS who have an assessment of the primary endpoint. The Per-protocol set includes all subjects from FAS 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 analysis set (SAF) includes all subjects who received at least one dose of study treatment. The PK analysis set includes all subjects in the SAF who have at least one PK sample collected after administration of study treatment. **Main analysis** The primary analysis will be conducted using the mFAS and will consider the treatment actually received (which may differ from the assigned one). The analysis of the primary endpoint will be performed for each of the two treatment doses independently, i.e., considering 2 null hypotheses (proportion of patients achieving a response

is less or equal to 50%) at 0.025 type I error each.

The study will be declared positive with regard to the primary objective, if at least 1 of the 2 null hypotheses is rejected at 0.025 type I error level.

Subjects without primary endpoint assessment will be replaced.

A one-sided z-test will be computed and the 95% confidence interval of the proportion of responders will be provided.

Summary of response, in terms of number (%) of responding subjects, will be provided.

Sample size

The sample size is based on the study primary objective of assessing IPA 30 min after ACT-246475 administration, as assessed by the proportion of subjects achieving a response (i.e., $P2Y_{12}$ reaction units [PRU] < 100 at 30 min post study drug administration). The sample size should be sufficient to allow the rejection at least one of the null hypotheses.

The study should include 21 subjects evaluable for the primary pharmacodynamic endpoint in each arm considering:

- an overall two-sided type I error of 0.05, adjusted for multiplicity using the Bonferroni method for each of the 2 null hypotheses (testing each dose at an alpha level of 0.025),
- a power of 90%, and
- the following assumptions for the response rate under the null and alternative hypotheses as reported in the table below.

Proportion of responders under H_0	**Proportion of responders under H_1**	**Number of subjects *(total)***	**Number of subjects *(per arm)***
50%	85%	42	21

STUDY COMMITTEES	The Independent Safety Event Committee (ISEC) involved in the ID-076A201 study will also review safety data from this study. It consists of two independent clinical experts who will review safety data independently from the sponsor during the study. The ISEC 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 ISEC will be fully operational prior to enrollment of the first subject into the study. The ISEC will specifically focus on study-drug-related clinically relevant major bleeding events, according to the thrombolysis in myocardial infarction (TIMI) definition.

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]. In patients with suspected acute coronary syndrome (ACS), the median time to medical intervention in economically advanced countries, either in an ambulance or at the emergency department, is still between 2 and 4 h after onset of symptoms, with patient decision time contributing significantly to the pre-hospital delay in seeking care [Garofalo 2012, Tubaro 2011].

Patients experiencing an AMI have highly reactive platelets, which are insufficiently inhibited, even when they are receiving dual antiplatelet therapy with acetylsalicylic acid and clopidogrel [Gurbel 2003, Matetzky 2004, Wang 2010]. A recent observational study showed that the majority of patients presenting with ST-segment elevation MI (STEMI) due to coronary stent thrombosis and undergoing primary percutaneous coronary intervention (PCI), had high platelet reactivity whether they were on maintenance antiplatelet therapy while developing stent thrombosis or loaded with $P2Y_{12}$ inhibitor (clopidogrel, prasugrel or ticagrelor) shortly before immediate PCI [Godschalk 2017].

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 maximum potential for myocardial reperfusion and salvage in patients with STEMI is within the first 1 to 3 hours after symptom onset (so-called "golden time") [Savonitto 2017]. Hence, shortening the time to treatment with an antithrombotic agent could be of therapeutic benefit. The European Society of Cardiology (ESC) 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, Ibanez 2017].

ACT-246475, a subcutaneously (s.c.) administered $P2Y_{12}$ receptor antagonist is being developed for self-injection in patients with suspected AMI.

1.2 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 s.c. administration. Efficacy and safety studies with ACT-246475 in animal thrombosis models suggest its potential for an improved therapeutic window in clinical use, as compared with currently available oral agents.

In healthy adults, ACT-246475 has been determined to be safe and tolerated up to a single, s.c. dose of 32 mg in two single-ascending dose (SAD) studies (AC-076-101 and AC-076-102).

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

1.2.1 Nonclinical data

The binding of ACT-246475 to the receptor is fully reversible, with an equilibrium dissociation constant (Kd) of 1.5 nM. In human platelet-rich plasma, ACT-246475 inhibited adenosine diphosphate (ADP)-induced platelet aggregation with an inhibitor concentration causing 50% inhibition (IC_{50}) of 8.7 ng/mL (14 nM).

ACT-246475 dose-dependently blocked thrombus formation in two species, namely 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 similar antithrombotic effect, blood loss was 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 may explain, at least in part, the reduction in bleeding with ACT-246475 as compared with that observed with ticagrelor.

[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; therefore, CYP induction is not expected upon dosing of ACT-246475.

ACT-246475 has a poor cellular permeability and is a substrate of organic anion-transporting polypeptide (OATP)1B1, OATP1B3, and multidrug resistance protein 2 (MRP2) transport proteins. Concomitant administration of OATP1B inhibitors

or inducers is expected to modulate the pharmacokinetics (PK) of ACT-246475. The impact of MRP2 inhibition is unknown, as metabolism and active excretion of unchanged ACT-246475 in bile may both contribute to the clearance of ACT-246475 in the liver.

[redacted]

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

1.2.2 Effects in humans

Three clinical trials have been completed to date (AC-075-101, AC-076-101 and AC-076-102). Results of these studies are detailed in the IB [ACT-246475 IB] and summarized hereafter.

1.2.2.1 Study AC-075-101

This study consisted of oral administration of prodrug formulations and of ACT-246475 in healthy male subjects. Each dose and formulation was safe and well tolerated. The systemic exposure to the active moiety ACT-246475 was generally low. Accordingly, the inhibition of platelet aggregation (IPA) was also limited.

1.2.2.2 Study AC-076-101

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

[redacted]

1.2.2.3 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.

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) without 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 one AE each (headache; dizziness) after administration of ACT-246475.
- In the 8 mg dose group, there were 3 subjects with at least one 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 essentially 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. At the two highest doses administered, 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 one subject and headache, vomiting, dizziness, and dyspepsia in the other subject. Neither of the two subjects exposed to placebo reported AEs.

[redacted]

1.3 Purpose and rationale of the study

ACT-246475 is a potent, short-acting, reversible, and selective antagonist of the platelet $P2Y_{12}$ receptor to be administered subcutaneously. 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 complementary to study ID-076A201, which is being conducted in patients with stable coronary artery disease (CAD) to assess the PD, PK, tolerability and safety of a single s.c. injection of ACT-246475. AMI may be associated with sympathetic activation and subsequent peripheral vasoconstriction which might affect the uptake of ACT-246475 after s.c. administration and consequently its onset of action. This study will generate complementary data to assess whether the onset of action of ACT-246475 is affected in a population of patients with AMI. The impact of the 2 different doses on the PD and PK of ACT-246475 when administered on top of standard of care for AMI (e.g., antiplatelet and anticoagulant therapies) will be assessed in this study. The two doses will be the same as the ones evaluated in study ID-076A201.

1.4 Summary of known and potential risks and benefits

1.4.1 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 a nonclinical study, ACT-246475 was found to have less risk of bleeds compared to ticagrelor [Rey 2017]. This may be related to a different mechanism of action than that of ticagrelor: in contrast with ticagrelor, ACT-246475 had no effect on vascular tone and has no interference with the adenosine pathway. In addition, ACT-246475 exhibits competitive inhibition of the $P2Y_{12}$ receptor whereas inhibition by ticagrelor is non-competitive. More importantly, the risk of bleeds associated with the use of $P2Y_{12}$ receptor antagonists increases with the duration of treatment [Wilson 2017]. As ACT-246475 has a short duration of action and will be used as a single dose administration, bleeding risk exposure is expected to be minimal in this study.

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

In studies AC-076-101 and AC-076-102, s.c. administration of ACT-246475 has been determined to be safe and well tolerated at different dose levels ranging from 1 mg to 32 mg, and no particular safety concern was identified.

This study will be the first ACT-246475 study enrolling patients during an acute MI event. Accordingly, the Independent Safety Event Committee (ISEC) involved in the ID-076A201 study (subjects with stable CAD) is planned to review the data from this study [Section 3.3]. This committee will have overall responsibility for safeguarding the interests of subjects by monitoring safety data (with specific focus on bleeding events) and making appropriate recommendations based on the reported data, thus ensuring that the study is being conducted to the highest scientific and ethical standards.

1.4.2 Interference with oral $P2Y_{12}$ receptor antagonists

Co-administration of the oral, irreversible $P2Y_{12}$ receptor antagonists clopidogrel and prasugrel during infusion of cangrelor is prohibited given the potential lack of clopidogrel- / prasugrel-mediated IPA [Kengrexal® SmPC]. Mechanistically, this is due to the short half-life of the active metabolites of clopidogrel and prasugrel that, while still in the circulation, cannot bind to the receptor which is pre-occupied by cangrelor. Instead, if administered immediately after stopping the cangrelor infusion, clopidogrel and prasugrel both exhibit their expected PD effects [Steinhubl 2008, Schneider 2014, Judge 2016, Rollini 2016].

In vitro studies have been conducted to assess the PD interaction potential of ACT-246475 with ticagrelor and the active metabolite of prasugrel (P-AM) [B-16.064]. Here, additive effects were determined when ACT-246475 was added to platelets pre-bound to ticagrelor or P-AM. Instead, if P-AM was added to platelets pre-bound to ACT-246475 the inhibitory effects of P-AM on platelet aggregation were reduced.

Because of the current ESC guidelines [Valgimigli 2018] recommending administration of a loading dose of oral $P2Y_{12}$ receptor antagonist as early as possible after diagnosis of an AMI, it is expected that many subjects participating in the study will receive an oral $P2Y_{12}$ antagonist.

In the absence of clinical data regarding administration of the irreversible $P2Y_{12}$ antagonists clopidogrel or prasugrel following administration of ACT-246475, if oral treatment with a $P2Y_{12}$ receptor antagonist is to be initiated in subjects participating in this study, a reversible $P2Y_{12}$ receptor antagonist (e.g., ticagrelor) must be used.

1.4.3 Inclusion of vulnerable subjects

Eligible subjects present with AMI (STEMI or non-STEMI [NSTEMI]), which is a life-threatening condition, and therefore, fulfill ICH-GCP definition of vulnerable subjects ("persons in emergency situations").

The main ethical risk is that subject's written informed consent has to be quickly obtained so that the study treatment can be initiated as soon as possible. In this study, the following process will be used (or any similar process compliant with local regulation and that will be approved by the Ethics Committee):

- Recruitment and randomization, in hospital settings, can be performed by emergency medical services personnel (according to local regulations).
- Preliminary consent may be first obtained verbally followed by a signed one as soon as possible (depending on subject's medical condition).
- All efforts will be made to obtain the signed version of the informed consent form (ICF) prior to study treatment administration.
- If subject's condition does not allow obtaining a signed ICF prior to study treatment administration, subject's consent will be obtained orally in the presence of an impartial witness. The impartial witness will sign the ICF before any study-specific procedure is performed and the subject's signature of the ICF will be obtained as soon as possible and no later than at time of discharge.

The medical personnel obtaining the preliminary consent, will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study,
- Ensure each patient is notified that they are free to discontinue from the study at any time,
- Ensure that each patient is given the opportunity to ask questions.

1.4.4 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.

Latest ESC guidelines [Valgimigli 2018] recommend administration of a $P2Y_{12}$ receptor antagonist as close as possible to diagnosis of AMI. All study subjects will receive active study drug (ACT-246475) so that none of the subjects are deprived of a potentially beneficial drug.

ACT-246475 will be administered on top of standard of care. Its PD profile with fast onset of platelet inhibition, related to its administration via s.c. route, will allow bridging

to current oral $P2Y_{12}$ receptor antagonists which in the context of an AMI may have a delayed onset of action [see also Section 1.4.5].

The volume of blood collected for study purposes is estimated to be up to 55 mL over a period of approximately 2 days. This amount represents less than 2.0% of total blood volume for a subject with body weight ≥ 40 kg. This is in compliance with the recommendations for maximum blood collection for research purposes from several Independent Ethics Committees / Institutional Review Boards (IECs/IRBs), and is considered to represent a minimal risk for the subjects.

1.4.5 Potential benefits

ESC guidelines recommend pre-treatment with a $P2Y_{12}$ receptor antagonist in patients in whom coronary anatomy is known and the decision to proceed to PCI is made, as well as in patients with STEMI [Valgimigli 2018]. In the ATLANTIC study, early oral administration of a $P2Y_{12}$ receptor antagonist (ticagrelor) in the ambulance compared with administration in-hospital did not improve pre-PCI coronary reperfusion. This finding was considered related to the short interval between administration of study drug and PCI which may have blunted the drug effect and also to the delayed absorption and onset of action as observed with orally administered $P2Y_{12}$ receptor antagonists in patients with ACS [Montalescot 2014, Alexopoulos 2012, Parodi 2013]. [redacted] uch a fast PD effect of ACT-246475 can fill a gap of current oral antiplatelet therapies.

1.4.6 Overall benefit risk assessment

Overall, due to the favorable safety profile of ACT-246475, as well as its use on top of standard of care and earlier than other antithrombotic agents, the benefit-risk ratio for subjects to participate in this study is expected to be favorable.

It is the investigator's responsibility to monitor the benefit-risk 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 believes that continuation would be detrimental to the subject's wellbeing.

2 STUDY OBJECTIVES

2.1 Primary objective

The primary objective of the study is to assess the IPA 30 minutes after a single s.c. injection of ACT-246475 in subjects with AMI receiving conventional antithrombotic treatment (e.g., aspirin, oral $P2Y_{12}$ receptor antagonists, anticoagulants).

2.2 Other objectives

The other objectives of this study are:

- To assess the PK of ACT-246475 in subjects with AMI.
- To investigate safety and tolerability of ACT-246475.

3 OVERALL STUDY DESIGN AND PLAN

3.1 Study design

This is a prospective, multi-center, open-label, randomized, parallel-group, Phase 2, exploratory study of a single s.c. administration of ACT-246475, at two different dose levels, in subjects with AMI (STEMI or NSTEMI) scheduled for invasive strategy.

Approximately 42 adult subjects with confirmed diagnosis of AMI (STEMI or NSTEMI) and time from onset of symptoms of more than 30 min and less than 6 hours will be randomized to receive ACT-246475 either at the dose of 8 mg or 16 mg, in a 1:1 ratio injected s.c. into the thigh in addition to conventional standard-of-care treatment. Injection of ACT-246475 will be performed as soon as possible after randomization.

Subjects randomized who have not received ACT-246475 or who do not perform the 30-minute time point VerifyNow® assessment will be replaced.

The study will be conducted at approximately 3–8 sites in 2–3 countries (planned).

3.1.1 Study periods

The study is conducted during the hospitalization of the subject for AMI and the subjects will remain hospitalized during the entire study duration. The study comprises the following consecutive periods:

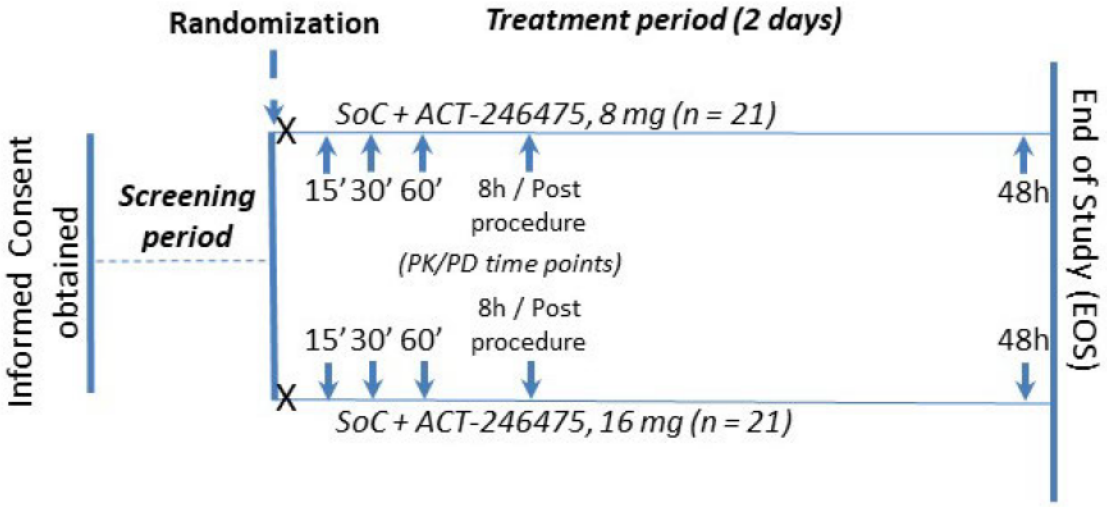
Screening period: Starts when the subject gives informed consent (orally or in writing, as described in Section 1.4.3) and ends with subject's randomization.

Treatment period: Starts with subject's randomization and ends after the End-of-Study (EOS) assessments, approximately 48 h after the administration of a single study treatment dose.

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

The overall study design is depicted in Figure 1.

Figure 1 Study design



EOS: End-of-Study; PD: pharmacodynamic; PK: pharmacokinetic; SoC: standard of care; X: administration of ACT-246475 (h0).

3.1.2 Study duration

The study starts with the first act of recruitment (i.e., informed consent provided by the first subject) and ends with the completion of the last subject's EOS assessments.

The overall duration of participation in the study (including screening period) of a subject will be approximately 2 days.

3.2 Study design rationale

The duration of the treatment period is justified by the primary objective, which is to characterize the onset of IPA after a single s.c. injection of ACT-246475 at two different doses in subjects with AMI.

The choice of the same two doses (i.e., 8 and 16 mg) as in the ongoing ID-076A201 study (see Section 5.1.1 for detailed rationale on dose selection), will provide supportive information for the selection of the dose to be tested in the Phase 3 pivotal study.

The IPA analysis will be performed with the VerifyNow® method. Results from VerifyNow® are well correlated with those obtained with the light transmission aggregometry (LTA) method [Varenhorst 2009, Gremmel 2015]. The VerifyNow® method has been preferred as it is more standardized than the LTA method and it is the method used for primary PD analysis in the ongoing ID-076A201 study in subjects with stable CAD. In addition, the volume of blood required per sample is higher for LTA (6 mL) than for the VerifyNow® method (3 mL). Accordingly, using the VerifyNow®

method will reduce the amount of blood collected for study purposes in a population with acute ischemic event.

The trial is conducted open-label to allow the investigator to adapt the standard AMI treatments to an individual subject's needs (e.g., antiplatelet and anticoagulant treatment). In addition, the primary endpoint being a pharmacological readout ($P2Y_{12}$ reaction units [PRU] value at 30 min) with no room for data interpretation, the open-label design is fully justified. Because of the limited sample size and the absence of a placebo group, the presentation of the safety data will be purely descriptive.

3.3 Study committees

The ISEC involved in the ID-076A201 study will review safety data from this study. It consists of two independent clinical experts who will review safety data independently from the sponsor during the study. The ISEC 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 ISEC will be fully operational prior to enrollment of the first subject into the study.

The ISEC will specifically focus on clinically relevant major bleeding events, according to the thrombolysis in myocardial infarction (TIMI) definition [Mehran 2011].

The ISEC will be governed by a specific charter and recommendations made by the ISEC will be documented and archived in the trial master file.

4 SUBJECT POPULATION

4.1 Subject population description

This study will enroll adult male subjects aged 18 to 85 years and postmenopausal female subjects aged up to 85 years, with confirmed STEMI or NSTEMI and onset of symptoms from 30 min to 6 hours prior to randomization.

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

In the acute phase of an MI, absorption of oral $P2Y_{12}$ receptor antagonists can be delayed [Alexopoulos 2012, Parodi 2013, Montalescot 2014]. Subjects experiencing an AMI may also have sympathetic over-stimulation and consequently impaired peripheral vascular circulation which may have an impact on uptake of s.c. drugs [Bonello 2015].

The population of this study is expected to reflect the general population of patients with AMI (STEMI and NSTEMI). It has been selected as it is close to the target population for Phase 3 (subjects who will self-inject ACT-246475 when they experience symptoms

suggestive of an AMI). The results from this study together with the ones from the ID-076A201 study will support the selection of the ACT-246475 dose to be used in the Phase 3 study.

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) Informed consent obtained prior to any study-mandated procedure.
2) Males aged from 18 to 85 years and postmenopausal females aged up to 85 years. Postmenopausal is defined as 12 consecutive months with no menses without an alternative medical cause.
3) Onset of AMI symptoms of more than 30 min and less than 6 hours prior to randomization.
4) Patients presenting a type I AMI including STEMI or NSTEMI defined as follow:
   a) STEMI: new persistent ST-segment elevation ≥ 1 mm (1 mV) in two or more contiguous ECG leads, or
   b) NSTEMI: ECG changes compatible with myocardial ischemia without persistent ST-segment elevation and elevated troponin defined as a troponin T or I level ≥ 1.5 × the upper limit of normal.
5) Estimated body weight ≥ 40 kg (88 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 the qualifying AMI:

1) Cardiogenic shock or severe hemodynamic instability (e.g., Killip class 3–4).
2) Cardiopulmonary resuscitation.
3) Loading dose of any oral $P2Y_{12}$ receptor antagonist prior to randomization.

Bleeding risks:

4) Active internal bleeding, or bleeding diathesis or conditions associated with high risk of bleeding (e.g., clotting disturbances, gastrointestinal bleed, hemoptysis).
5) Known clinically important anemia.
6) Oral anticoagulation therapy within 7 days prior to randomization
7) Planned fibrinolytic therapy or any fibrinolytic therapy administered within 24 h prior to randomization.
8) Known platelet disorders (e.g., thromboasthenia, thrombocytopenia, von Willebrand disease).

Conditions that may either put the subject at risk or influence the results of the study:

9) End-stage renal failure requiring dialysis.
10) Any clinically significant findings on a physical exam, or laboratory tests that in the investigator's judgment would preclude safe or reliable participation of a subject in the study.
11) Concomitant diseases (e.g., advanced liver cirrhosis, mental illness, neurodegenerative disease, terminal malignancy…) or conditions (e.g., inability to communicate well with the investigator in the local language) that, in the opinion of the investigator, may put the subject at risk, prevent the subject from complying with study requirements or may be a confounder for the study interpretation.
12) Clinically relevant skin disease that prevents s.c. injection in the thigh, according to the investigator's judgment.
13) Known use of inhibitors of OATP1B1 or OATP1B3 (e.g., ritonavir, clarithromycin, erythromycin, cyclosporine, gemfibrozil) at screening.
14) Known hypersensitivity to ACT-246475, any of its excipients, or drugs of the $P2Y_{12}$ class.
15) Previous exposure to an investigational drug within 3 months prior to screening.

5 TREATMENTS

5.1 Study treatment

5.1.1 Investigational treatment (ACT-246475): Description and rationale

Study treatment for s.c. administration will be available as sealed glass vials in one strength: 20 mg. The vials contain 22 mg of lyophilized ACT-246475A (hydrochloride salt of ACT-246475) to be reconstituted with 1 mL of water for injection (preparation of study treatment is detailed in Section 5.1.4). The s.c. formulation contains mannitol as 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 will be administered in the thigh.

ACT-246475 doses of 8 mg or 16 mg will be administered during this study. These doses are identical to those tested in subjects with stable CAD (Study ID-076A201). The doses of ACT-246475 have been selected based on data from the AC-076-102 SAD study to meet the following criteria:

- The low dose (8 mg) is the minimum dose achieving at least 85% IPA for 3 h on average, corresponding 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 85% or more in less than 5% of the subjects at 8 h. This corresponds to the maximum time accepted to limit interference with invasive and/or pharmacological standard of care of AMI.

Both doses achieved a mean %IPA ≥ 90% at 30 min

5.1.2 Study treatment supply

Manufacture, labeling, packaging, and supply of study treatment will be conducted according to Good Manufacturing 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) 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 pre-defined minimum number of study treatments has 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 control 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 printout will be made available to the Clinical Research Associate (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 and has been verified and reconciled by sponsor personnel or the deputy, and written permission for destruction has been obtained from 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

After having verified that the subject meets all inclusion criteria and none of the exclusion criteria, the subject will be randomized to receive 8 or 16 mg of ACT-246475.

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

The sites will be provided with sealed envelopes containing the randomization number and corresponding treatment allocation. At randomization, for each subject, one envelope will be opened, in a sequential order.

5.1.3.2 Study treatment dispensing

A treatment kit consists of 1 vial of 20 mg ACT-246475. All treatment kits are identical.

After randomization, the site will take one kit per subject and prepare the study drug according to the randomization group allocated and the instructions described in

Section 5.1.4. 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 taken 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 (including kit number) 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 ACT-246475 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, an additional dilution of the stock solution will be performed with 1 mL of NaCl 0.9% to obtain the required concentration for injection [Table 1].

The reconstituted ACT-246475 solution will be injected as a s.c. single dose in the anterior mid-thigh 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 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 s.c. 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	8 mg	1 mL	1 mL	10 mg/mL	0.8 mL
ACT-246475	16 mg	1 mL	Not applicable	20 mg/mL	0.8 mL

5.1.5 Blinding

Not applicable.

5.1.6 Unblinding

Not applicable.

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 electronic case report form (eCRF), verified and reconciled by the CRA during the routine site visits and at the end of the study. The study treatment accountability in the eCRF will include at least the following information for each study treatment unit (i.e., vial) administered 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. Any deviation from 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 giving informed consent.

A therapy that is study-concomitant is any treatment that is ongoing or initiated after providing informed consent, or initiated up to EOS.

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

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

Previous therapies related to treatment and prevention of CAD will be recorded in the eCRF if discontinued less than 1 month (≤ 30 days) prior to providing informed consent. Previous therapies related to treatment of the study-qualifying AMI will be recorded in the eCRF.

The generic name, start/end dates of administration (as well as whether it was ongoing at administration of study treatment and/or EOS), route, dose, and indication will be recorded in the eCRF. In addition, for oral $P2Y_{12}$ receptor antagonists, the time of each administration during the study will be recorded in the eCRF.

5.2.3 Allowed concomitant therapy

Standard treatment of AMI is allowed including anticoagulants and oral $P2Y_{12}$ receptor antagonists.

When initiation of an oral $P2Y_{12}$ receptor antagonist is considered for a subject [see also Section 1.4.2], it must be initiated after administration of ACT-246475. In absence of clinical data regarding administration of an irreversible $P2Y_{12}$ antagonist following the administration of ACT-246475, it is requested to use a reversible oral $P2Y_{12}$ receptor antagonist (e.g., ticagrelor).

5.2.4 Forbidden concomitant therapy

The following medications are prohibited from screening and up to the last PK blood collection:

- Fibrinolytic therapy (e.g., streptokinase, alteplase…).
- OATP1B1 and OATP1B3 inhibitors (e.g., atazanavir, ritonavir, lopinavir, simeprevir, clarithromycin, erythromycin, cyclosporine, eltrombopag, lapatinib, gemfibrozil, rifampin)
- Glycoprotein IIb/IIIa inhibitors.
- Irreversible oral $P2Y_{12}$ antagonists (clopidogrel or prasugrel)
- 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 response to the treatment defined for each subject as a PRU value < 100 at the 30 min post-dose time point, as measured via VerifyNow®. This corresponds to an IPA induced by ADP > 80% [Gaglia 2011, Gremmel 2009, Varenhorst 2009].

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

- PD profile over time based on absolute PRU values at 15, 30 and 60 min post-dose,
- PRU status (value < 100) at the 60 min post-dose time point.

6.2.2 Pharmacokinetic endpoints

- Plasma concentrations of ACT-246475 will be determined at 15 min, 30 min, 1 h, and 8 h post-dose.
- C_{max}.
- t_{max}.

6.3 Safety endpoints

The safety endpoints will be assessed up to end of study, i.e., over 48 h post treatment administration:

- Treatment-emergent AEs[2] and SAEs.
- AE of specific interest (AESI): Hemorrhage.
- Change in vital signs (systolic and diastolic arterial blood pressure and pulse rate) from baseline to all assessed time points during the study.
- Change from baseline to for clinical laboratory tests.
- Treatment-emergent marked laboratory abnormalities.

7 VISIT SCHEDULE AND STUDY ASSESSMENTS

7.1 Study visits

The study is performed during a subject's hospital stay related to the qualifying AMI. This is considered to be a single visit, and assessments are listed in Table 2.

7.1.1 Screening/re-screening

Screening starts when the subject has provided informed consent. The date on which the first screening assessment is performed corresponds to the date of the study 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 will be included in the study are considered as vulnerable and a specific consenting process is detailed in Section 1.4.3.

Subjects who have provided informed consent will be allocated a 7-digit subject identification number which will consist of: firsts 4 digits corresponding to the site identification number and lasts 3 digits corresponding to the sequential order of recruitment of the subjects from the site.

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

Re-screening is not permitted in this study.

7.1.2 Unscheduled visits

Not applicable as the study is conducted over a single visit.

However, unscheduled assessments may be performed at any time during the study based on the judgment of the investigator and the results of these assessments will be recorded in the eCRF.

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

Table 2 Visit and assessment schedule

PERIOD	SCREENING	TREATMENT PERIOD					
Visit	**Visit 1**						
Time point	**Pre-dose**	**0 min**	**15 min ±5 min**	**30 min ±5 min**	**60 min ±5 min**	**8 h / Post-procedure[1]**	**EOS 48 h ±2 h**
Informed consent	X						
Eligibility	X						
Demographics and Medical history (including TIMI risk score and Killip class of MI)	X						
Physical examination	X						
Body weight and height (estimated)	X						
Previous/concomitant therapy	X	X					X
Vital signs (BP and PR)	X			X	X		X
PK blood sampling			X	X	X	X[1]	
VerifyNow®	X		X	X	X		
Laboratory tests	X						X
hsTnT	X						
s.c. injection of ACT-246475		X					
AEs/SAEs	X	X					X

(S)AE: (serious) adverse event; BP: blood pressure; EOS: End-of-Study; hsTnT: high sensitivity troponin T; MI: myocardial infarction; PCI: percutaneous coronary intervention; PK: pharmacokinetic; PR: pulse rate; s.c.: subcutaneous; TIMI: thrombolysis in myocardial infarction.

1. The 8 h PK post-dose time point is flexible. If the subject gets an invasive procedure (PCI/angiography) within 8 h of study drug administration, the blood sample is to be collected at the end of the procedure. If no invasive procedure is performed within 8 h of study drug administration, the blood sample is to be collected approximately 8 h after study drug administration.

7.2 Study assessments

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

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

Calibration certificates / evidence of equipment maintenance for the below-listed equipment used to perform study assessments must be available prior to the 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® devices.

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 providing informed consent will be recorded on the medical history eCRF form. Where possible, diagnoses and not symptoms will be recorded.

Characteristics of the qualifying MI are of specific interest and will be captured on a dedicated eCRF form. They include:

- STEMI/NSTEMI, Date/time of symptom onset, TIMI risk score [Appendix 1], Killip class [Appendix 2].
- Procedures performed because of the qualifying MI (e.g., angiography, PCI).

The following events are of specific interest for this study and must be reported in the Medical History form:

- MI (prior to the qualifying MI).
- Stroke and transient ischemic attack.
- PCI or coronary artery bypass graft.
- Peripheral vascular surgery.

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

- Baseline demographics and physical characteristics (i.e., age, race/ethnicity, sex).
- 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 Pharmacokinetic assessments

7.2.3.1.1 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 ethylene diamine tetra-acetic 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 2.

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

7.2.3.1.2 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.

7.2.3.2 Pharmacodynamic assessments

7.2.3.2.1 Procedures for blood sampling

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

When applicable, the blood samples for PD assessments are to be preferably collected first, followed by blood samples for PK then blood samples for safety assessments. 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.

One blood sample will be drawn into 3 mL vacuum tubes for each VerifyNow® assay. Collection tubes will contain phenylalanine-proline-arginine-chloromethylketone (PPACK) as an anticoagulant. The platelet aggregation assays must be performed within 1 h of blood collection. 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 eCRF.

Detailed handling instructions for PD samples are provided in the laboratory manual.

7.2.3.2.2 Bioanalysis

ADP-induced platelet aggregation will be evaluated by using VerifyNow® method.

The 3 mL 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 instructions. The VerifyNow® system reports platelet aggregation as PRU.

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

- The VerifyNow® $P2Y_{12}$ 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 IPA. When available, the use of VerifyNow® $P2Y_{12}$ test is preferred.
- 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® $P2Y_{12}$ test is not available.

7.2.4 Safety assessments

The definitions, reporting, and follow-up of AEs and SAEs 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 AMI.

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 eCRF. Clinically relevant findings that are present prior to providing informed consent, must be recorded on the Medical History eCRF form. Physical examination findings made after providing informed consent that meet the definition of an AE [Section 9.1.1] must be recorded on the AE form of the eCRF.

7.2.4.2 Vital signs

Systolic and diastolic blood pressure and pulse rate will be measured in subjects in supine or sitting position. 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

If height and weight cannot be measured due to subject's condition, it is acceptable to use information provided by the subject or to take it from subject's medical chart if available.

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 except for Activated Clotting Time which is a point-of-care test and will be performed locally.

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 missing central laboratory results.

If the 48 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 (pre-defined) 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 providing informed consent must be recorded on the Medical History form of the eCRF. Any clinically relevant laboratory abnormalities detected after providing 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

Hematology

- Hemoglobin (g/L)
- Hematocrit (L/L)
- Erythrocyte count (10^{12}/L)
- Leukocyte count with differential counts (10^9/L)
- Platelet count (10^9/L)

Coagulation tests (test performed locally)

- Activated clotting time (sec)

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)
- Sodium, potassium, chloride, calcium (mmol/L)
- Albumin (g/L)

Cardiac enzymes

- High sensitivity troponin T

8 STUDY COMPLETION AND POST-STUDY TREATMENT/MEDICAL CARE

8.1 Study completion

A subject who has received study treatment and completed the EOS assessments 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 eCRF 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 sponsor for any reason, including premature termination or suspension of the study.

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 eCRF, if known.

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 health authorities, 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 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 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.

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 provision 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.

9.1.2 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 the AMI qualifying for entry in the study.
- 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 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).

9.1.3 Definition of suspected unexpected serious adverse reaction

The expectedness of an SAE is determined by the sponsor in the reference safety information (RSI) section provided in the most recent version of the IB [ACT-246475 IB]. Any SAE that is assessed as related and unexpected against the RSI is known as a suspected unexpected serious adverse reaction (SUSAR).

9.1.4 Definition of treatment-emergent adverse event

A treatment-emergent AE (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.

9.1.5 Intensity of adverse events

The intensity of clinical AEs is graded on a three-point scale (mild, moderate, severe) 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. 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 [see Section 9.3.2].

9.1.6 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.

9.1.7 Relationship to protocol-mandated procedure

An AE/SAE is defined as related to protocol-mandated procedure if it appears to have a reasonable possibility of a causal relationship to either the study design or to a protocol-mandated procedure (e.g., discontinuation of a subject's previous treatment leading to exacerbation of underlying disease). The determination of the likelihood that a protocol-mandated procedure caused the AE/SAE will be provided by the investigator.

9.2 Time period and frequency for AE/SAE assessment and follow-up

The occurrence of an AE/SAE may come to the attention of study personnel at any time during study. During the study, the investigator will inquire about the occurrence of AE/SAEs.

The clinical course of AEs/SAEs will be followed according to local standard medical practices.

9.2.1 Follow-up of adverse events

AEs still ongoing at the EOS must be followed up until they are no longer considered clinically relevant or until stabilization.

9.2.2 Follow-up of serious adverse events

SAEs still ongoing at the EOS must be followed up until resolution or stabilization, or until the event outcome is provided.

9.3 Reporting procedures

9.3.1 Reporting of adverse events

All AEs with an onset date after a subject has provided informed consent and up to the EOS must be recorded on specific AE forms of the eCRF.

Information to be collected in an AE form in the eCRF includes date and time of onset, action taken with the study treatment, outcome of AE, date of resolution (if applicable)

and Principal Investigator's (PI) assessment of intensity, and relationship to study treatment, study design or protocol mandated procedures.

If intensity of an AE changes during the study, only the worse intensity will be reported in the eCRF.

Follow-up information on an ongoing AE obtained after the subject's EOS will not be collected in the eCRF.

9.3.2 Additional reporting procedures for serious adverse events

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 occurring after a subject has provided informed consent and up to the EOS must be recorded on an SAE form, regardless of the investigator-attributed causal relationship with study treatment or study-mandated procedures.

The SAE forms must be sent to the sponsor's Global Drug Safety department (see contact details 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 h 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.

Follow-up information on an ongoing SAE obtained after a subject's EOS must be reported to the sponsor's Global Drug Safety department, but is not recorded in the eCRF.

New SAEs occurring after the EOS must be reported to the sponsor's Global Drug Safety department within 24 h 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.

9.3.3 Additional reporting procedures for suspected unexpected serious adverse reactions

Any SUSAR [see definition in Section 9.1.3] will be reported by the sponsor to concerned health authorities (including the EudraVigilance database if the study is conducted in Europe), IECs/IRBs and investigators.

9.4 Reporting of study treatment overdose, misuse, abuse and errors

Study treatment overdose (defined as higher than the dose of 16 mg), and study treatment errors will be reported as an AE when associated with signs or symptoms.

In addition, study treatment errors must be documented in the study drug log of the eCRF.

Misuse and abuse of the study treatment will be reported as an AE.

9.5 Study safety monitoring

Study safety information (AEs, SAEs, laboratory values, 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). The sponsor may request additional data pertaining to the diagnostic work-up of an AE or SAE (e.g., ECGs, medical imaging, local laboratory values) for the purpose of monitoring safety. Such additional data may be shared with external experts from the independent safety event committee [see Section 3.3].

10 STATISTICAL METHODS

All statistical analyses will be conducted by sponsor or by designated CROs supervised by 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 statistical plan described hereafter will be described and justified in the SAP or in the clinical study report (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 study treatment.

10.1.3 Full analysis set

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

For analyses performed on the FAS subjects will be evaluated according to the actual treatment they received, which may differ from the randomly assigned treatment.

10.1.4 Modified Full analysis set

The modified FAS (mFAS) includes all subjects from the FAS who have an assessment of the primary endpoint, i.e., PRU measured 30 minutes after study drug administration.

10.1.5 Per-protocol analysis set

The Per-protocol analysis 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 and will be specified in the SAP.

10.1.6 Safety set

The safety analysis set (SAF) includes all subjects who received at least one dose of study treatment.

Subjects will be evaluated according to the actual treatment they received, which may differ from the randomly assigned treatment.

10.1.7 Other analysis sets

10.1.7.1 Pharmacokinetic analysis set

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

10.1.8 Usage of the analysis sets

The analysis of PD endpoints will be performed on the mFAS while sensitivity analyses will be conducted using same endpoints as specified in Section 10.3 on the FAS and PPS.

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

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

Table 3 describes the analysis sets used for the analysis of each data set.

Table 3 Usage of analysis datasets

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

Note: 1: 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. RND: Randomized set; FAS: Full analysis set; mFAS: modified Full analysis set; PD: pharmacodynamic; PK: pharmacokinetic; PPS: Per-protocol set; SAF: 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 last value collected prior to randomization.

10.2.1 Primary efficacy variable(s)

Not applicable.

10.2.2 Key secondary efficacy variables

Not applicable.

10.2.3 Pharmacokinetic and pharmacodynamic variables

10.2.3.1 Pharmacokinetic variables

PK parameters will be derived using non-compartmental methods:

- C_{max} and t_{max} will be listed by dose group and subject and will be summarized by dose group.
- C_{max} and t_{max}* will be summarized with arithmetic mean, geometric mean, minimum, median, maximum, standard deviation (SD), standard error (SE), coefficient of variation (CV; %), and 95% confidence interval (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} values will be summarized by mean and SD of the logarithms.

10.2.3.2 Pharmacodynamic variables

The PD variables are (as measured by VerifyNow®):

- the absolute PRU value,
- the percentage of inhibition of platelet aggregation (if $P2Y_{12}$ test has been used).

10.2.4 Safety variables

10.2.4.1 Adverse events

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

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

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

10.2.4.2 Adverse event of specific interest: Hemorrhage

An AE of specific interest (AESI) hemorrhage is any AE with a preferred term (PT) belonging to the standardised MedDRA query "Haemorrhage (Excl. laboratory terms)".

TEAEs of specific interest (TEAESIs) are those AESIs with onset date/time ≥ date/time of first study treatment administration and ≤ 48 h after date/time of last study treatment administration.

10.2.4.3 Laboratory data

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

EOS laboratory test refers to the laboratory test performed at the 48 h post-dose time point.

For each continuous laboratory variable, the following will be summarized:

- Absolute value at each time point,
- Absolute change from baseline to each measured time point,
- Treatment-emergent marked laboratory abnormalities (i.e., samples date/time ≥ date/time of first study treatment administration and ≤ 48 h after date/time of last study treatment administration).

For categorical laboratory variables, the proportion of subjects by category at each time point will be summarized.

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

10.2.4.4 Vital signs

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

10.3 Description of statistical analyses

All analyses will be conducted by treatment group, i.e., ACT-246475 8 mg and ACT-246475 16 mg.

10.3.1 Overall testing strategy

The study is intended to assess the IPA 30 min after a single s.c. injection of ACT-246475.

It will be declared to be positive with regard to the primary objective if for at least one of the two tested doses of ACT-246475, the corresponding null hypotheses is rejected at the 0.025 alpha level.

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., more than 10% missing values at a given time point.

10.3.2 Analysis of efficacy variable(s)

Not applicable.

10.3.3 Analysis of the pharmacodynamic variables

All analyses of PD variables will be performed using the mFAS as primary analysis set, and based on the actually administered treatment, which may differ from the one assigned through the randomization process.

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

10.3.3.1 Hypotheses and statistical model

The primary objective is to assess IPA 30 min after a single s.c. injection of ACT-246475 in subjects with AMI receiving conventional antithrombotic treatment (e.g., aspirin, oral $P2Y_{12}$ receptor antagonists, anticoagulants).

In order to achieve this objective, the testing strategy will be to test the treatment effect (using the proportion p of responders, i.e., achieving PRU < 100) for each of the two treatment arms considering the following hypotheses:

H_{0HD}: $p_{HD} \leq 50\%$ vs H_{1HD}: $p_{HD} \geq 85\%$

H_{0LD}: $p_{LD} \leq 50\%$ vs H_{1LD}: $p_{LD} \geq 85\%$

where LD is the lower ACT-246475 dose (8 mg), and HD the higher ACT-246475 dose (16 mg).

Each of the two null hypotheses will be tested by a two-sided z-test at a significance level (alpha) of 0.025, which is an overall level of 0.05 for the study level and adjusted for multiplicity using Bonferroni method.

10.3.3.2 Handling of missing data

Subjects for whom the determination of the response is not possible, i.e., who have not received ACT-246475 or with a missing 30 min post-study drug administration assessment, will be replaced; no imputation will be considered.

10.3.3.3 Main analysis

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

It will consider the treatment actually received (which may differ from the assigned one).

The analysis of the primary endpoint will be performed for each of the two doses independently, i.e., considering 2 null hypotheses (proportion of patients achieving a response is less than or equal to 50%) at 0.025 type I error each [see Section 10.3.3.1].

The study will be declared positive with regard to the primary objective, if at least 1 of the 2 null hypotheses is rejected at 0.025 type I error level.

A one-sided z-test will be computed and the 95% CI of the proportion of responders will be provided.

Summary of response, in terms of number (%) of responding subjects, will be provided.

IPA as measured by VerifyNow® will also be summarized as a continuous variable.

Those summaries will also be provided considering the available PD assessment time points (15 min and 60 min post-dose).

10.3.3.4 Supportive/sensitivity analyses

Assuming relevant number of subjects in each STEMI/NSTEMI subgroup, the consistency across STEMI and NSTEMI subgroups will be assessed by testing the interaction effect of STEMI/NSTEMI with treatment dose on the primary endpoint analysis.

A logistic regression analysis of the PD response will be performed using subject, ACT-246475 dose (8 mg, and 16 mg), ST-segment elevation (STEMI vs NSTEMI), age (continuous), gender (male, female) as covariates.

Further analyses will be described in the SAP as necessary.

10.3.4 Analysis of the pharmacokinetic variables

Plasma concentrations per time point will be listed by dose group and subject, and summarized by time point and dose group using arithmetic and geometric mean, minimum, median, maximum, SD, SE, and two-sided 95% CI of the means and CV in %.

10.3.5 Analysis of the safety variable(s)

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

All safety analyses will be performed using the SAF, based on the actually administered treatment, which may differ from the one assigned through the randomization process.

10.3.5.1 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,
- TEAESIs,
- TEAEs related to study treatment,
- Occurrence of treatment-emergent non-serious AEs,
- Treatment-emergent SAEs,
- Occurrence of treatment-emergent SAEs,
- Treatment-emergent SAEs related to study treatment,
- TEAEs with fatal outcome,
- TEAEs related to study treatment with fatal outcome,

Additionally, summaries will be reported for TEAEs and for TEAESIs by event onset, i.e., peri- and during PCI.

10.3.5.2 Laboratory data

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

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

The absolute change from baseline to last value in the treatment period 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.

10.3.5.3 Vital signs and weight

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.

10.3.5.4 Safety monitoring of major bleeding and death

For the purpose of supporting the ISEC review, regular safety data review will be performed. This safety monitoring will report a summary of AEs, focusing on major bleeding events according to TIMI definition, and death.

10.4 Interim analyses

No formal interim analysis is planned.

This study includes regular safety monitoring, with a report submitted to the ISEC [see Section 10.3.5.4].

10.5 Sample size

The computation of the sample size was performed using East 6.0 software (version 6.4.0.1, 30 August 2016) from Cytel Inc.

The sample size is based on the study primary objective of assessing IPA 30 min after ACT-246475 administration, as assessed by the proportion of subjects achieving a response (i.e., PRU < 100 at 30 min post study drug administration). The sample size should be sufficient to allow the rejection at least one of the null hypotheses.

The study should include 21 subjects evaluable for the primary PD endpoint in each arm considering:

- an overall two-sided type I error of 0.05, adjusted for multiplicity using the Bonferroni method for each of the 2 null hypotheses (testing each dose at an alpha level of 0.025),
- a power of 90%, and
- the following assumptions for the response rate under the null and alternative hypotheses as reported in the table below.

Table 4 Assumptions for the response rate under the null and alternative hypotheses and sample size

Proportion of responders under H_0	Proportion of responders under H_1	Number of subjects *(total)*	Number of subjects *(per arm)*
50%	85%	42	21

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 eCRF derived from source documents must be consistent with the source documents.

eCRF data will be captured via electronic data capture. 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 eCRF.

For each subject screened (i.e., who provided informed consent), regardless of study treatment administration, an eCRF 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 eCRF.

11.2 Maintenance of data confidentiality

The investigator/delegate must ensure that data confidentiality is maintained. On eCRFs or other documents (e.g., documents attached to SAE forms) submitted to 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

eCRFs will be used for all subjects. The investigator(s) will have access to the site eCRF data until the database is locked. Thereafter, they will have read-only access. The eCRF 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/delegated 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 eCRF. 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 eCRF, or simply a data correction in the eCRF. The investigator/delegate must, on request, provide 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 event of health authority 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 lock.

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

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

After the database has been declared complete and accurate, the database will be locked. Any changes to the database after that time may only be made as described in the appropriate sponsor Quality System documents. After database lock, the investigator will receive the eCRFs of the subjects of his/her site (including all data changes made) on electronic media.

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 (according to local regulation) 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 sponsor/delegate. A study physician must always be involved in the consent process.

As much as possible, the subject and/or legally designated representative and authorized site personnel listed on the Delegation of Authority form supplied by 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. As the study is recruiting vulnerable subjects in an emergency situation who may not be able to sign the consent form at the start of the study, a specific process has been implemented and is described in Section 1.4.3.

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, if applicable, time when the subject was first introduced to the study, the date and, if applicable, time of consent, who participated in the consent discussion, who consented the subject, and any additional person present during the consent process (e.g., subject's family member[s]), and the information that a copy of the signed ICF was given to the subject / legally designated representative.

If the site intends to recruit subjects who are considered vulnerable (e.g., subject cannot read or write, 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.

Study subjects will be reimbursed for the study-related expenses (e.g., travel costs, meals, hotel), and may be offered financial compensation for their participation in the study only to the extent permitted by applicable local regulations.

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 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 data and records are accurate, legible, contemporaneous, original (or certified copy), attributable, complete, consistent, enduring, and available when needed.

These records are to be classified into two 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 sponsor to store these documents outside the site, so that they can be retrieved in the event 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, sponsor must be notified in advance.

If the site uses 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 eCRF during monitoring visits.

If the site uses 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 with 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 eCRF.

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 was 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 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 eCRFs 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 eCRFs 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 eCRF is completed after subject's visit, 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 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 content 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 sponsor.

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

12.10 Audit

Sponsor's Quality Assurance 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 sponsor's requirements (e.g., standard operating procedures) will also be verified. Prior to initiating this audit, the investigator will be contacted by 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

Health Authorities and/or IEC/IRB 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 Health Authority 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 publicly 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 (or PI for single-center studies).

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 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 sponsor and will be determined by mutual agreement.

Any study-related publication written independently by investigators must be submitted to sponsor for review at least 30 days prior to submission for publication or presentation at a congress. Upon review, 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

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14 APPENDICES

Appendix 1 TIMI risk score

TIMI risk score will be calculated for each patient by site and the calculated score will be recorded in the eCRF. Calculation will be according to the following characteristics:

The TIMI risk score for STEMI [Morrow 2000] (total score between 0 and 14):

- Age
  - < 65: 0 points
  - 65–74: 2 points
  - ≥ 75: 3 points
- At least one of the following Medical History: 1 point
  - Diabetes mellitus
  - Hypertension
  - Angina pectoris
- Systolic blood pressure at screening < 100 mmHg: 3 points
- Pulse rate at screening > 100 bpm: 2 points
- Killip class at screening II–IV: 2 points
- Weight at screening < 67 kg: 1 point
- Time from symptom onset to first dose of fibrinolytic > 4 hours: 1 point
- Anterior MI or left bundle branch block: 1 point

The TIMI risk score for NSTEMI [Antman 2000] (total score between 0 and 7):

- Age ≥ 65: 1 point
- At least 3 risk factors for CAD: 1 point
  - Family history of CAD
  - Hypertension
  - Hypercholesterolemia
  - Diabetes
  - Current smoker
- Known Coronary Stenosis ≥ 50%: 1 point
- Presence of ≥ 0.5 mm ST segment deviation on admission ECG: 1 point
- Severe angina (≥ 2 episodes in last 24 hrs): 1 point
- At least one elevated serum cardiac markers: 1 point
  - Creatine kinase MB
  - Cardiac-specific troponin level
- Use of aspirin in the last 7 days: 1 point

Appendix 2 Killip class for MIs

Killip classification will be assessed as:

- Killip class I: Absence of rales over the lung fields and absence of an S3
- Killip class II: Rales over 50% or less of the lung fields or the presence of an S3
- Killip class III: Rales over more than 50% of the lung fields
- Killip class IV: Cardiogenic shock: signs include hypotension (systolic pressure of 90 mmHg or less) and evidence of peripheral vasoconstriction such as oliguria, cyanosis and diaphoresis.