Statistical Analysis Plan:

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

ClinicalTrials.gov Identifier:

NCT03487445

STATISTICAL ANALYSIS PLAN

FOR CLINICAL STUDY REPORT

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

Purpose of Analysis	Clinical Study Report
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LIST OF ABBREVIATIONS AND ACRONYMS

AE	Adverse event
AESI	Adverse event of special interest
AMI	Acute myocardial infarction
ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
CI	Confidence interval
C_{max}	Maximum plasma concentration
CRF	Case Report Form
DAPT	Dual antiplatelet therapy
EOS	End-of-Study
FAS	Full analysis set
INN	International Nonproprietary Name
IPA	Inhibition of platelet aggregation
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	Modified Full analysis set
NSTEMI	Non-ST-segment elevation myocardial infarction
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PPS	Per-protocol set
PRU	$P2Y_{12}$ reaction units
PT	Preferred Term
RND	Randomized analysis set
s.c.	Subcutaneous(ly)
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SCR	Screened analysis set
SD	Standard deviation
SMQ	Standardised Medical Dictionary for Regulatory Activities Query

SOC	System organ class
STEMI	ST-segment elevation myocardial infarction
TEAE	Treatment-emergent adverse event
TIMI	Thrombolysis in myocardial infarction
t_{max}	Time to reach maximum plasma concentration
WHO	World Health Organization

1 INTRODUCTION

This statistical analysis plan (SAP) describes in detail the analyses and data presentation for the ID-076A202 clinical study report.

The following study documents were used when writing this SAP.

Table 1 Study documents

Document	Date, Version
Study protocol	11 April 2018, Version 2
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

2 STUDY DESIGN AND FLOW

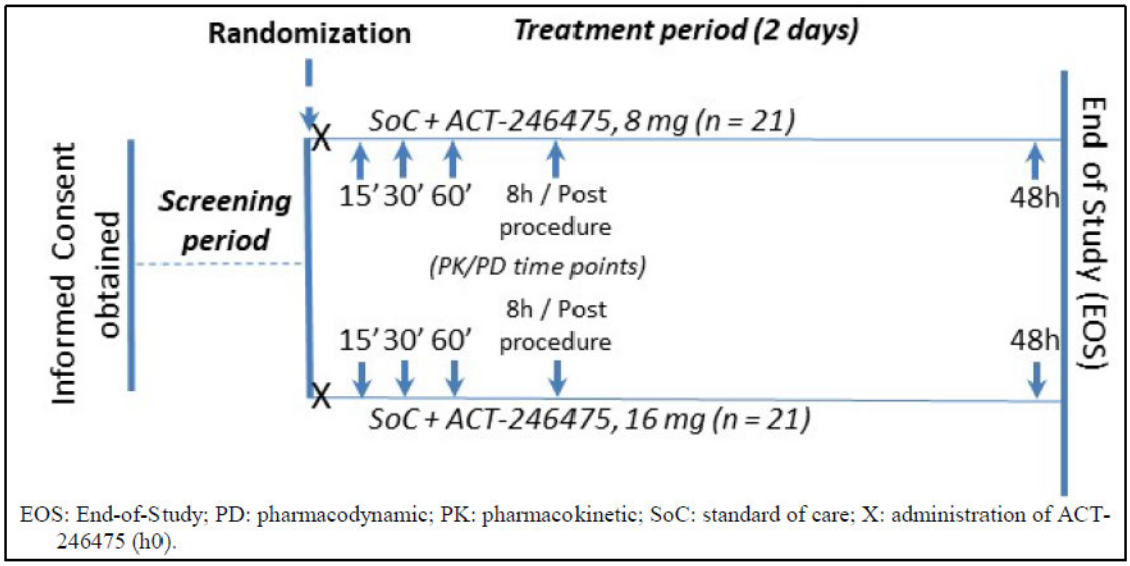
2.1 Study design

This is a prospective, multi-center, open-label, randomized, parallel-group, Phase 2, exploratory study of a single subcutaneous (s.c.) administration of ACT-246475, at two different dose levels, in subjects with acute myocardial infarction (AMI; ST-segment elevation myocardial infarction [STEMI] or non-STEMI [NSTEMI]) scheduled for invasive strategy.

Approximately 42 adult subjects with confirmed diagnosis of AMI (STEMI or NSTEMI), with a 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 or 16 mg, in a 1:1 ratio, injected s.c. in the thigh in addition to standard of care / conventional treatment. Injection of ACT-246475 will be performed as soon as possible after randomization.

The study design is shown 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).

2.2 Study visit and assessment schedule

Please refer to the protocol section 7.

2.3 Overview of analysis periods

The study has 2 periods:

1. *Screening period*: from signature of informed consent up to time of randomization.
2. *Treatment period*: from randomization and up to 48 hours (2 days) after the administration of the single dose of ACT-246475 [see Section 10.1 for more details].

3 OBJECTIVES

3.1 Primary objective(s)

The primary objective of the study is to assess the inhibition of adenosine diphosphate-induced platelet aggregation 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).

3.2 Secondary objectives

Not applicable.

3.3 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.

4 ANALYSIS SETS

4.1 Definitions of analysis sets

Unless not relevant, or otherwise specified, summary statistics will be provided by study treatment group (i.e., dose level) and combining all subjects [as described in Section 8.1.1].

4.1.1 Screened analysis set

The Screened analysis set (SCR) includes all subjects who provided informed consent and received a subject identification number.

4.1.2 Randomized analysis set

The Randomized analysis set (RND) includes all subjects from the SCR who have been assigned to a study treatment (i.e., have a randomization number).

4.1.3 Full analysis set

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

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

4.1.4 Modified Full analysis set

The modified FAS (mFAS) includes all subjects from the FAS who have an assessment of the primary endpoint, i.e., $P2Y_{12}$ reaction units (PRU) measured 30 minutes after study drug administration.

4.1.5 Per-protocol analysis set

The Per-protocol set (PPS) comprises all subjects from the mFAS who complied with the protocol sufficiently to allow adequate estimation of the study treatment effects.

Criteria for sufficient compliance include exposure to study treatment, availability of key endpoint measurements and absence of major protocol deviations that have an impact on the study treatment effect.

The full list of criteria (protocol deviations and other reasons for exclusion) will be established prior to clinical database lock and is detailed in Appendix B.

4.1.6 Safety analysis set

The Safety analysis set (SAF) includes all subjects from the SCR who received the study treatment (i.e., ACT-246475 8 or 16 mg).

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

4.1.7 Pharmacokinetic analysis set

The PK analysis set (PK set) includes all subjects from the SAF who have at least one PK sample (i.e., at least one plasma ACT-246475 concentration measurement) after administration of study treatment.

Subjects in the PK set will be evaluated according to the actual study treatment dose they received, which may differ from the randomly assigned study treatment.

4.2 Usage of the analysis sets

The analysis sets used for statistical analyses of specific variables are shown in Table 2. Subject data listings are to be prepared using the SCR, unless otherwise specified.

Table 2 Analysis datasets usage

	Analysis sets						
Analyses	**SCR**	**RND**	**FAS**	**mFAS**	**PPS**	**SAF**	**PK set**
Subject disposition	X						
Protocol deviations, Analysis sets	X						
Demographics characteristics		x	X		(x)		
Medical history and current medical conditions			X				
Previous and concomitant medications			X				
Study treatment exposure						X	
Main (primary) PD endpoints				X	(x)		
Other PD endpoints			X				
Safety and tolerability endpoints						X	
PK endpoints							X

Note: X: main analysis, x: analysis to be performed unless exact same set as for main analysis, (x): sensitivity analysis to be conducted only if > 10% difference of set size with set used for main analysis. FAS, Full analysis set; mFAS, modified Full analysis set; PD, pharmacodynamic; PK, pharmacokinetic(s); PPS, Per-protocol set; RND, Randomized analysis set; SAF, Safety analysis set; SCR, Screened analysis set.

5 STUDY SUBJECTS, VARIABLES AND ANALYSES

For categorical variables, the incidence of subjects by category will be summarized (frequency counts and percentages), while for continuous variables, summaries will use the following descriptive statistics, unless stated otherwise: arithmetic mean, standard deviation (SD), minimum, 1st quartile, median, 3rd quartile, and maximum.

5.1 Subject disposition

5.1.1 Screening failures

The standard definition of screening failure, as described in Section 10.2.7, will be used.

Summary of subjects by status; screened, randomized, and treated, by country and by center will be provided.

Reason for screening failure will be listed.

5.1.2 Study completion/discontinuation

The definition of study premature discontinuation as described in Section 10.2.8 will be used.

Summary of subjects by study completion status (completing study vs premature discontinuation), and distribution by reason for premature study discontinuation will be provided.

5.1.3 Study treatment completion/discontinuation

Not applicable.

5.2 Protocol deviations

Subjects with at least one protocol deviation, the overall and important deviations will be summarized for screening, and treatment period [see Section 2.3].

Subjects will be counted once in each summary, i.e., if a subject has more than 1 protocol deviation for a given category/sub-category/description, the subject will be counted only once in summaries for this category/sub-category/description.

Subjects' protocol deviations will be listed. This listing will include all deviation descriptions, identifiers and categories. Subjects without any protocol deviations are not included in this listing.

5.3 Inclusion in / exclusion from analysis sets

5.3.1 Subject disposition

A summary table will present an overview (frequency and percentage) of the recruitment for each country and site, by dose group and overall.

The subjects' disposition (frequency and percentage) will be summarized by dose group and overall for the defined analysis sets.

The reason for exclusion of subjects from each analysis set will be listed.

5.4 Subject characteristics

5.4.1 Demographics

The following demographic characteristics are collected in the study Case Report Form (CRF):

- Age (years)
- Sex category: *Male and Female*
- Race group: *Black or African American, American Indian or Alaska native, Native Hawaiian or other Pacific islander, Asian, White, Other, Not applicable*
- Ethnic category: *Hispanic or Latino, Not Hispanic or Latino, and Unknown*
- Body weight (kg) at screening
- Height (cm) at screening
- Country

In addition, the following variables at baseline are derived:

- Age group: *< 18 to < 65, ≥ 65 to < 85, and ≥ 85 years*
- Age group: *< 55 and ≥ 55 years*
- Body mass index (BMI; kg/m^2)
- BMI category: *< 25, ≥ 25 to < 30, and ≥ 30.0 kg/m^2*.

BMI at screening will be computed using the following formula: BMI (kg/m^2) = weight / $height^2$, with weight expressed in kilograms, and height in meters.

5.4.2 Baseline disease characteristics

Not applicable.

5.4.3 Other baseline characteristics

Not applicable.

5.4.4 Previous and concomitant medical history

For the two categories, previous and concomitant medical history, the incidence of subjects with the event will be summarized (frequency counts and percentages) by system organ class (SOC) and/or preferred term (PT).

5.4.5 Qualifying acute myocardial infarction characteristics

In addition to medical history, the characteristics of the qualifying AMI, are also collected, which includes:

- Onset date and time of AMI symptoms
- Diagnosis: STEMI (all, thrombolysis in myocardial infarction [TIMI] score < 3, TIMI score ≥ 3), NSTEMI (all, TIMI score < 5, TIMI score ≥ 5)
- Thrombolysis in myocardial infarction risk score: range from 0 to 14

- Killip class: I, II, III, IV
- Surgical, therapeutic or diagnostic procedures performed:
  - Percutaneous coronary intervention
  - Coronary angiography
  - Bare metal stent insertion
  - Drug eluting stent insertion
  - Bioresorbable vascular scaffold stent insertion
  - Other

For the categorical variables, the number of subjects by category will be summarized (frequency counts and percentages).

The time (in hours) since onset of AMI symptoms to study drug injection will be summarized using descriptive statistics.

Also, the frequency of diabetes mellitus, hypertension, dyslipidemia, and chronic kidney disease at baseline will be summarized (counts and percentages).

Diabetes mellitus is any medical history MedDRA PT belonging to MedDRA High Level Term "*Diabetes mellitus (incl. subtypes)*", existing prior to, and ongoing on day of, informed consent signature.

Chronic kidney disease is any medical history observation with MedDRA PT belonging to the Standardised MedDRA Query (SMQ) "*Chronic kidney disease*", existing prior to, and ongoing on day of, informed consent signature.

Hypertension is defined as any medical history observation with MedDRA PT belonging to the SMQ "*Hypertension*" of narrow terms, existing prior to, and ongoing on day of, informed consent signature.

Hypertension is defined as any medical history observation with MedDRA PT belonging to the SMQ "*Dyslipidaemia*" of narrow terms, existing prior to, and ongoing on day of, informed consent signature.

Pre-dosing troponin T will also be summarized by using descriptive statistics, by treatment group.

5.4.6 Previous and concomitant therapies

In this study, only medications are to be collected.

The handling of missing or incomplete date/time of previous/concomitant therapies is described in Appendix D.

The following categories [see Section 10.7 for definition] will be considered for analysis:

- Previous medications,
- Study concomitant medications,
- Study-treatment concomitant medications at baseline,
- Study-treatment concomitant medications.

Oral $P2Y_{12}$ receptor antagonists at baseline include any study-treatment concomitant medications at baseline included in the following list shown in Table 3, and administered on the day of administration of study medication:

Table 3 Oral $P2Y_{12}$ receptor antagonists

ATC code	Ingredient name
B01AC04	clopidogrel
B01AC05	ticlopidine
B01AC22	prasugrel
B01AC24	ticagrelor

ATC, Anatomical Therapeutic Chemical.

For study-treatment concomitant medications at baseline, study-treatment concomitant medications, and oral $P2Y_{12}$ receptor antagonists at baseline categories, the incidence of subjects with a medication will be summarized (frequency counts and percentages) by Anatomical Therapeutic Chemical (ATC) code corresponding to the INN.

All previous/concomitant medications will be listed.

The number and proportion of subjects with such a study-treatment concomitant medication at baseline will be summarized (frequency counts and percentages) by the following categories:

1. No aspirin/acetylsalicylic acid nor $P2Y_{12}$ receptor antagonist

   Study-treatment concomitant medications at baseline (based on ingredient list)
   Do not include aspirin/acetylsalicylic acid **or** carbasalate **or** clopidogrel **or** prasugrel **or** ticagrelor **or** ticlopidine

2. Aspirin/acetylsalicylic acid monotherapy

   Study-treatment concomitant medications at baseline (based on ingredient list)
   Include aspirin/acetylsalicylic acid **or** carbasalate, **and** do not include clopidogrel **or** prasugrel **or** ticagrelor **or** ticlopidine.

3. $P2Y_{12}$ receptor antagonist monotherapy at least one, and for each drug: clopidogrel, prasugrel, and ticagrelor.

   Study-treatment concomitant medications at baseline (based on ingredient list)
   Do not include aspirin/acetylsalicylic acid **or** carbasalate, **and** include clopidogrel **or** prasugrel **or** ticagrelor **or** ticlopidine.

4. Dual antiplatelet therapy (DAPT): aspirin/acetylsalicylic acid and clopidogrel.
   Study-treatment concomitant medications at baseline (based on ingredient list)
   Include aspirin/acetylsalicylic acid **or** carbasalate, **and** clopidogrel.

5. DAPT: aspirin/acetylsalicylic acid and ticagrelor.
   Study treatment concomitant medications at baseline (based on ingredient list)
   Include aspirin/acetylsalicylic acid **or** carbasalate, **and** ticagrelor.

6. DAPT: aspirin/acetylsalicylic acid and prasugrel.
   Study treatment concomitant medications at baseline (based on ingredient list)
   Include aspirin/acetylsalicylic acid **or** carbasalate, **and** prasugrel.

7. DAPT: any combination.
   Study treatment concomitant medications at baseline (based on ingredient list)
   Include aspirin/acetylsalicylic acid **or** carbasalate, **and** clopidogrel **or** prasugrel **or** ticagrelor **or** ticlopidine.

5.4.7 Other subject characteristics

Not applicable.

5.5 Study treatment exposure and compliance

5.5.1 Exposure

The number and percentage of subjects by study drug administration status will be provided.

5.5.2 Compliance with study treatment

Not applicable.

6 EFFICACY VARIABLES AND ANALYSES

6.1 Overview

Not applicable.

6.2 Primary endpoint analysis

Not applicable.

6.3 Key secondary endpoint analysis

Not applicable.

6.4 Other efficacy endpoint analysis

Not applicable.

6.5 Analysis of quality of life variables

Not applicable.

6.6 Analysis of pharmacoeconomic variables

Not applicable.

6.7 Analysis of epidemiological measures and risk-benefit evaluations

Not applicable.

6.8 Analysis of pharmacodynamic variables

For categorical variables, the incidence of subjects by category will be summarized by using frequency counts, percentages and the corresponding 95% confidence interval (CI) when relevant.

Continuous variables will be summarized using: arithmetic mean, SD, minimum, 1st quartile, median, 3rd quartile, maximum, and 95% CI of the mean when relevant.

6.8.1 Primary pharmacodynamic endpoint

The study is designed to demonstrate that a single injection of ACT-246475 enables a large proportion (a target of 85%) of subjects to achieve a clinically meaningful level of inhibition of platelet aggregation (IPA), i.e., PRU < 100 at 30 minutes after study drug injection.

6.8.1.1 Variable

The primary pharmacodynamic (PD) endpoint is the *PD response* that is defined for each subject as a PRU < 100 at 30 min after study drug injection, as measured via VerifyNow®.

The primary PD variable (PRU_{30m}) is the platelet reactivity as measured by VerifyNow® at 30 min after study drug injection [see the table of assessments in the protocol, table 2].

The analysis variable of the PD response is defined as follows for a given subject:

$$IF\ PRU_{30m} < 100$$

$$THEN\ PD\ response = YES$$

$$ELSE\ PD\ response = NO$$

PRU time is based on planned time point and not on the actual collection time.

Supportive primary PD endpoint

The following endpoint is not described in the protocol and has been added. The main purpose is to assess the effect of the two study treatment doses, when relaxing the time of a PRU < 100, i.e., considering as a response a PRU < 100 at 15, 30 or 60 min. post injection.

This endpoint is defined as per the following algorithm and will describe the subject's *PD response within the 1st hour*:

$$IF\ minimum\ of\ (PRU_{15m}, PRU_{30m}, PRU_{60m}) < 100$$
$$THEN\ PD\ response\ within\ 1^{st}\ hour = YES$$
$$ELSE\ PD\ response\ within\ 1^{st}\ hour = NO$$

Where PRU_{15m}, PRU_{30m}, and PRU_{60m} refer to PRU measured by VerifyNow® at 15, 30, and 60 minutes after study drug administration.

PRU time is based on planned time point and not on the actual collection time.

6.8.1.2 Analysis

The analyses described in this section consider the primary endpoint, i.e., PD response. Sensitivity analysis of the PD endpoints will be described in Section 6.8.1.3.

Unless stated otherwise, all analyses will be conducted on the mFAS.

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).

To achieve this objective, the testing strategy will be to test the study treatment effect (using the proportion p of responders, i.e., achieving PRU < 100 at 30 minutes post-injection) for each of the two doses, 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.

Main analysis

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

It will be based on the study treatment 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 protocol section 10.3.3.1].

The study will be declared positive for the primary objective, if at least 1 out 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.

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

6.8.1.3 Supportive/sensitivity analyses

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

Those summaries will be provided considering the available PD assessment time points (baseline, 15, 30, and 60 min post dose).

A mixed model to assess treatment effect at 30 min. from start of treatment injection on platelet reactivity as measured by VerifyNow®, i.e., PRU value, will be performed using subject as a random factor, and treatment (8 mg, and 16 mg), age (continuous), sex (male, female), and time from onset of symptoms to study treatment administration (continuous, hours), as fixed factors.

Assuming relevant number of subjects (i.e., ≥ 10 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 study treatment dose in the primary endpoint analysis. Logistic regression analysis of the PD response will be performed using ACT-246475 dose (8 mg vs 16 mg), ST-segment elevation (STEMI vs NSTEMI), age (continuous), and gender (male vs female) as covariates.

The same analysis as described in the main analysis section will be performed on the additional PD response within the 1st hour endpoint using the FAS.

The main analysis, on the PD response, and PD response within the 1st hour, will be repeated on the PPS if the PPS is at least 10% smaller than the mFAS.

6.8.1.4 Subgroup analyses

The protocol does not plan any analysis by subgroup, however the study treatment effect across the following subgroups will be explored by repeating the main analysis on primary PD endpoint, assuming there are enough subjects, i.e., ≥ 10 subjects by subgroup.

- Age: < 55 vs ≥ 55 years
- BMI: < 25.0 vs (≥ 25.0 and < 30.0) vs ≥ 30.0 kg/m^2
- Sex: male vs female
- Diabetes mellitus at baseline: yes vs no

- Chronic kidney disease: yes vs no

PTs to consider for identification of subjects with/without diabetes mellitus, or chronic kidney disease, are described in Section 5.4.4.

6.8.2 Other pharmacodynamic endpoints analysis

Unless stated otherwise, all analyses will be conducted on the FAS.

6.8.2.1 Variables

Endpoints

Other PD endpoints are the following:

- *PD profile over time* based on absolute PRU values at 15, 30 and 60 minutes post dose,
- *PRU_{60m} status*: PRU status (value < 100) at the 60 minutes post dose time point.

Variables

The *PD profile over time* variable will be based on actual PRU values reported at 15, 30 and 60 minutes after study drug injection.

The *PRU_{60m}* variable is the actual $P2Y_{12}$ reaction unit value as reported by VerifyNow®, at 60 min after study drug injection.

6.8.2.2 Analyses

Summary statistics will be provided for the PD endpoint variable *PRU_{60m} status*, and individual data will be listed. It will be analyzed similarly to the primary PD endpoint in Section 6.8.1.2, and will use the same factors.

A longitudinal analysis of the study treatment effect, on *PD profile over time* will be performed using a mixed model with PRU as the dependent variable, subject as a random factor, and study treatment (ACT-246475 8 mg, and ACT-246475 16 mg), PRU level at baseline, time from onset of symptoms to study treatment administration (continuous, hours), age (continuous), sex (male, female), and assessment time (15, 30 and 60 minutes) as fixed factors.

The proportion of subjects with PRU < 100 by assessment time (0 to 60 minutes) will be plotted as bar charts.

Descriptive statistics of PRU relative change from baseline at each time point will be provided, where change from baseline is defined as the ratio of ([PRU at time t – PRU pre-dose] / PRU pre-dose) expressed in percentage.

6.8.2.3 Supportive/sensitivity analyses

Not applicable.

6.8.2.4 Subgroup analyses

Descriptive summaries will be provided for each secondary PD endpoint, i.e., PD profile over time, and PRU_{60m} status, using the same sub-groups as defined in Section 6.8.1.4.

6.8.3 Handling of missing data

No imputations are planned.

Subjects for whom determination of the PD response is not possible will not be included in the computation of response rate for the main analysis.

The same approach will be considered for the exploratory endpoint PD response within the 1st hour.

6.9 Analysis of pharmacokinetic variables

The PK variables will be summarized and listed as provided using the PK set and will use the study treatment received.

The plasma PK parameters of ACT-246475 will be derived by non-compartmental analysis of the plasma concentration-time profiles. PK endpoints are: Maximum plasma concentration (C_{max}), and time to reach C_{max} (t_{max}).

Log-transformed value of C_{max} will be used in the analysis, while t_{max} will be used as is.

The PK parameters t_{max}, and $\log(C_{max})$ will be summarized by dose group using descriptive statistics, i.e., arithmetic mean, SD, geometric mean, minimum, median, maximum, standard error, and two-sided 95% CI of the means and coefficient of variation in %. Graphical representation of PK results over time will be provided using box-whisker plots.

Note that for t_{max}, the geometric mean and its 95% CI will not be calculated.

7 SAFETY VARIABLES AND ANALYSES

7.1 Overview of safety analyses including subgroup analyses

For categorical variables, the incidence of subjects by category will be summarized by using frequency counts, and percentages.

Continuous variables will be summarized using: arithmetic mean, SD, minimum, 1st quartile, median, 3rd quartile, and maximum.

No sub-group analyses are planned for safety data.

7.2 Adverse events

The handling of missing or incomplete date/time of adverse events (AEs) and assessments is described in Appendix D.

7.2.1 Variables

7.2.1.1 All adverse events

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

7.2.1.2 Treatment-emergent adverse events

Treatment-emergent AEs (TEAEs) are those AEs with onset date/time ≥ date/time of study drug administration and ≤ 48 h after date/time of study treatment administration.

An AE for which **time** of onset is missing will be counted as treatment-emergent if onset **date** is ≥ date of study drug administration and is ≤ date of study treatment administration +2 days. An AE with onset time missing, and end date and time are identical to study treatment start date and time, is not a treatment emergent AE.

7.2.1.3 Treatment-emergent adverse events related to study treatment

TEAEs related to study drug are those TEAEs which are reported as related to study treatment by the investigator.

7.2.1.4 Treatment-emergent adverse events by intensity

AE intensity is reported by the investigator using the following severity scale: mild, moderate, or severe.

For AEs with multiple intensities reported, the worst reported severity will be considered.

7.2.1.5 Serious adverse events

A serious AE (SAE) is an AE that has been reported as serious by the investigator in the CRF.

7.2.1.6 Adverse events leading to death

An AE will be considered as leading to death if the AE outcome is fatal.

7.2.1.7 Adverse events leading to study treatment discontinuation

Not applicable.

7.2.1.8 Other adverse event categories

Two AEs of special interest (AESIs) are defined, one will include any AE included in MedDRA SMQ “Haemorrhage (excl. lab)” of narrow terms, the other will include any AE included in the MedDRA high level group term "Administration site reaction"

AESIs will be summarized and listed.

7.2.2 Analysis

For all the AE variables described in Section 7.2.1, the incidence of subjects with TEAEs will be summarized (frequency counts and percentages) by SOC and/or PT.

For TEAEs by intensity, the incidence of subjects with events will be summarized (frequency counts and percentages) by SOC and/or PT and by maximum intensity (worst).

All AEs will be listed separately for subjects included in the SAF and for subjects not included in the SAF. SAEs will be flagged.

Listings will also be provided for SAEs and AESIs for the SAF only.

7.2.3 Analyses for key study data disclosure to regulatory authorities

The analyses described in Section 7.2.2 will also be performed on number of event occurrences, i.e., summarizing the total number of events, for SAEs, treatment-related SAE, and non-serious AEs.

7.3 Death

Death will be considered to have occurred if a primary cause of death is reported in the CRF 'Death' form.

The original terms used by the investigators to describe deaths (i.e., death cause) are assigned PTs for classification and tabulation using the latest implemented MedDRA version dictionary.

Death will be classified as on study deaths (from study start to End-of-Study [EOS]) and treatment-emergent deaths (within 2 days from study drug administration).

All deaths including cause of death will be listed, and flagged as per period of occurrence (screening and treatment periods).

7.4 Laboratory tests

7.4.1 Measurements

Except coagulation test (activated clotting time) performed locally and used for the analysis described in this section, only laboratory data received from the central laboratory [see protocol section 7.2.5.2] will be included in the analyses described in this section.

However, all laboratory data received from local laboratories will be included in the listings.

Treatment-emergent laboratory abnormalities are central laboratory abnormalities for which blood sample collection were collected at time of study drug administration or within the first 48 hours (2 days) after study administration, and that were not present at baseline.

Worst treatment-emergent marked laboratory abnormalities [see Appendix C] will be summarized by dose group.

7.4.2 Analysis

Descriptive summary statistics by visit and study treatment group will be provided for observed values and, when reported at baseline and post-baseline, absolute changes from baseline by category (hematology/coagulation, chemistry) and by parameter. Data will be displayed in SI units as provided by the central laboratory.

Treatment-emergent laboratory abnormalities will be summarized by laboratory category, variable and severity (marked laboratory abnormality).

Only subjects at risk, i.e., with no marked abnormality present prior to study drug start, will be included in these analyses.

For each laboratory category, a listing of the value at each time point, in SI units, for all variables and the changes from baseline (continuous and categorical), as well as the abnormality grade/flag will be produced and will include all visits. The values not considered in the analyses, i.e., local laboratories, will be flagged. A listing of subjects with at least 1 marked laboratory abnormality will also be provided.

7.5 Electrocardiography analysis

Not applicable.

7.6 Vital signs and body weight

7.6.1 Blood pressure and pulse rate analysis

This includes the systolic and diastolic blood pressures (sitting and/or supine), and pulse rate.

Systolic and diastolic blood pressures will be summarized regardless of the subject position at time of measure.

A listing of values, in SI units, for all variables and the changes from baseline (continuous and categorical) as well as the abnormality grade/flag will be produced and includes all time points. The values not included in the analyses will be flagged.

For each parameter at each time point over the course of the study, quantitative descriptive statistics for the value and the change from baseline will be presented by parameter, by time point and treatment group.

7.6.2 Body weight, and other vital sign analyses

Body weight values and assessment date will be listed.

7.7 Other safety variables and analyses

Not applicable.

8 GENERAL STATISTICAL METHODOLOGY

Data will be analyzed using SAS version 9.4 or higher.

8.1 General rules for data presentations

General rules for data presentations as described below are followed unless otherwise specified.

Data are listed and summarized by descriptive statistics (tables or figures) as described below.

8.1.1 Treatment groups

The study included the following 2 groups corresponding to the 2 study treatment groups (i.e., ACT-246475 8 mg and ACT-246475 16 mg). All analyses, unless stated otherwise, will be reported by those 2 treatment arms, and overall, in this order.

8.1.2 Descriptive statistics

Descriptive statistics will be provided by dose group and overall, depending on the nature of the criteria:

Quantitative:

Number of observed values, mean, SD, minimum and maximum, median, 1st and 3rd quartiles.

Qualitative:

Number of observed values, number of missing values, number and percentage of subjects per level/category.

Unless otherwise specified in the table shells, the percentage calculation will not consider missing values in denominators.

The number of missing values is displayed only if > 0. For categorical variables, those missing are displayed after the last category and no percentage is reported.

Listings are grouped by dose group (same order as in tables headers, if applicable, screening failures are listed last).

Raw data listings, if required, are based on datasets as received. All data collected are displayed, including unscheduled visits (if any).

8.2 Efficacy analyses

Not applicable.

9 INTERIM ANALYSES

Not applicable.

10 GENERAL DEFINITIONS AND DERIVATIONS

10.1 Analysis periods and visit windows

The treatment period is defined as the period starting from time of study drug administration up to 48 hours post administration. However, some assessments may only have the date reported and no time reported (either the time was not planned to be collected or is missing). In this case it will be assumed that the 48 hours treatment period corresponds to the day of study drug administration and to the two following days (1st, 2nd and 3rd day of the treatment period).

This may result in an over-estimated duration of the treatment period for those events that do not have assessment time.

10.2 Dates, times and days

10.2.1 Definition of study start

Study start day is the day of informed consent signature.

10.2.2 Baseline

Baseline is the last non-missing assessment performed or value measured before or on the day and time of study drug administration (i.e., prior to study treatment administration), unless otherwise defined in the specific analysis section.

Subjects without any data for a parameter before treatment administration will have a missing baseline (and therefore a missing change from baseline) value for this parameter.

If it is not possible to allocate an event/measure to the baseline period (missing date and/or time), it will be considered as being post-baseline.

10.2.3 Post-baseline assessment

Post-baseline assessment is any assessment performed after baseline and up to EOS.

10.2.4 Treatment start date/time

Treatment start date/time is the date/time recorded in the 'Study Treatment Administration' CRF page.

10.2.5 Definition of end of study treatment

Not applicable.

10.2.6 Definition of End-of-Study

EOS for a single subject is defined as the day when safety follow-up assessments are performed.

For randomized subjects who never received the study treatment, EOS date is defined as the earliest date amongst the following, as reported in the "Study Discontinuation" CRF page:

1. Date of last successful contact,
2. Date of subject decision,
3. Date of physician decision,
4. Date of subject death,
5. Date subject was informed of sponsor's decision.

10.2.7 Definition of screening failure

A subject is considered a screening failure if he/she was not randomized (i.e., has not been assigned a study drug).

10.2.8 Definition of premature study discontinuation

Subjects are considered to have prematurely discontinued the study if a reason for stopping the study is provided on the Study Discontinuation CRF page.

The date and the reason for study discontinuation are collected in the "Study Discontinuation" form (and in the "Death" form if the subject died).

10.3 Definition of reason for screening failure

For subjects who are considered a screening failure, the reason for screening failure is as reported in the CRF.

10.4 Convention for demography data considered for analysis when multiple values reported

For subjects with multiple baseline assessments, only the last values are included in any analysis, while all values will be presented in the listings and date of informed consent signature will remain the date of the first signature.

10.5 Coding dictionaries

The version of MedDRA used for coding medical history and AEs will be displayed in statistical output footnotes.

Similarly, the version of the WHO Drug Reference Listing dictionary based on the WHO ATC classification system used for coding of previous and concomitant therapies reported in this study will be displayed in statistical output footnotes.

10.6 Medical history and current (study concomitant) medical conditions

Medical history and current medical conditions, i.e., study concomitant medical conditions, at baseline include previous and/or concomitant procedures or diagnoses.

Medical procedures will be identified as medical history, i.e., ended prior to informed consent signature date, and as concomitant, for those ongoing at or after the signature date of the informed consent.

If none apply, procedures and diagnoses are considered *study concomitant medical conditions*.

10.7 Previous and concomitant medication

Previous medications are defined as any medication with a start date prior to study start date [see definition in Section 10.2.1] and with an end date (last administration) prior to study start date.

Study concomitant medications are defined as any medication that is ongoing on the date when informed consent is obtained, or initiated at any time between study start and up to EOS [see definition in Section 10.2.6].

Study-treatment concomitant medications at baseline (a subset of study-concomitant medications) are defined as any medication with "started prior to first study treatment administration" indicated as "yes" or with a start date before date of study treatment administration and is either ongoing at end of study or has an end date after the study treatment administration date.

Study-treatment concomitant medications (a subset of study-concomitant medications) are any *study-treatment concomitant medications at baseline* and any medications initiated within the 48-hour (2-day) period from study treatment administration.

If no end date is available for a medication, it is considered ongoing at EOS.

11 CHANGES OR CLARIFICATIONS TO ANALYSES PLANNED IN THE STUDY PROTOCOL

11.1 Changes to the analyses planned in the study protocol

11.1.1 Change in sensitivity analysis

The protocol indicated that the sensitivity analysis for the PD endpoints was to be conducted on the FAS. This will not be performed, as the main difference between the FAS and mFAS is the presence of a PRU measurement 30 minutes after study drug administration, a condition required to perform the analysis on the FAS as no imputation is planned for this endpoint.

11.1.2 Study drug exposure

The protocol specified that study drug exposure was to be analyzed on the FAS and the PPS (sensitivity analysis). This has been modified so that the analysis of study drug exposure is performed on the SAF, the definition of which is the same as the FAS but provides better consistency for safety data interpretation.

11.2 Changes in the conduct of the study / data collection

Not applicable.

11.3 Clarifications concerning endpoint definitions and related variables or statistical methods

Analysis set

The PPS definition has been modified to use the analysis set used for analysis of primary endpoint as a reference. Instead of using the FAS as the reference set to define the PPS, the mFAS is used and is more relevant as this analysis set is the one used for performing the analyses on the primary PD endpoint.

The protocol indicated that analysis of *demographics characteristics* would be performed on the RND only if there was a difference between the RND and the set used for the main analysis (FAS). The SAP now requires that this analysis is performed on the RND as well, regardless of the difference to the FAS, unless the RND includes exactly the same subjects, in which case the analysis on the RND is not needed.

11.4 Additional analyses as compared to the study protocol

Not applicable.

12 LIST OF TABLES, LISTINGS AND FIGURES

A complete list of tables, listings and figures is provided in the *SAP Appendix - List of statistical outputs* document.

13 APPENDICES

Appendix A Protocol synopsis

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 $\geq$ 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 $\geq 1.5 \times$ the upper limit of normal. 5) Estimated body weight $\geq$ 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.

[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.

	• 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 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.

Appendix B Protocol deviation list

[redacted]

The actual list of protocol deviations leading to exclusion from analysis set will be updated prior to study closure if required.

The table below provides the reasons considered for excluding subjects from analysis set.

Table 4 Definition of exclusions from analysis sets

Reason for exclusion from set	Reason	Programmable condition
Screened set	Informed consent not initially obtained for the study	no record in DS where DS.DSDECOD='INFORMED CONSENT OBTAINED' or DS.DSSTDTC='' when DS.DSDECOD='INFORMED CONSENT OBTAINED'
Randomized set	Not randomized	no DS.RANDNO
Full Analysis set	Subject did not get study treatment	EX.EXDOSE not >0
Modified FAS	30-minute post-dose VerifyNow® blood sample missing	missing LB.LBSTRESN where LB.LBTESTCD= P2Y12RU and LB.LBTPT= 30 MINUTE POST DOSE
Safety Set	Subject did not get study treatment	EX.EXDOSE not >0
Per Protocol set	Subject included without a type 1 MI	MH.MHLLT='Acute myocardial infarction type 2' (LLTCD=10079263) where MH.MHENRTPT='ONGOING' and MH.MHENTPT=' INFORMED CONSENT' or at least one record with IE.IETESTCD = INCL04
Per Protocol set	Onset of AMI symptoms more than 6 hours prior to randomization	at least one record with IE.IETESTCD = INCL03
Per Protocol set	Subject included with severe hemodynamic instability	at least one record with IE.IETESTCD = EXCL01
Per Protocol set	Subject received a loading dose of oral $P2Y_{12}$ receptor antagonist prior to randomization	at least one record with IE.IETESTCD = EXCL03
Per Protocol set	Subject with concomitant important anemia	at least one record with IE.IETESTCD = EXCL05

Per Protocol set	Subject with concomitant platelet disorders	at least one record with IE.IETESTCD = EXCL08
Per Protocol set	Subject with concomitant disease or condition that may have prevented subject from complaining with study requirements of may be a confounder of study interpretation.	at least one record with IE.IETESTCD in(EXCL12, EXCL14, EXCL15)
Per Protocol set	Incorrect administration of the study drug	DV.DVREFID = 02C01, 02C02
Per Protocol set	30-minute post-dose VerifyNow® blood sample collected outside of the protocol-defined window	DV.DVREFID = 03F03 or computed as need be
Per Protocol set	Issues with blood sample collection or processing for platelet aggregation assays	DV.DVREFID = 03F10, 03F08
Per Protocol set	Treatment with forbidden i.v. platelet inhibitors before assessment of the 30-minute time point.	DV.DVREFID = 04A02
PK set	Subject does not have at least one plasma concentration measurement after administration of study treatment	all PC.PCSTRESC = « » when PC.PCTPT not PRE-DOSE

AMI, acute myocardial infarction; i.v., intravenous; PK, pharmacokinetic set.

Appendix C Definitions of marked abnormalities

The definitions of marked laboratory abnormalities are described in Idorsia standard document [redacted]

Appendix D Handling of missing or incomplete date and/or time

This section describes some general principles to be followed in the case of missing or incomplete date/time.

Note that unless noted otherwise, the non-imputed date/time will be reported in listings.

An incomplete (missing day or month) or missing AE/concomitant therapy date will be imputed as described in Table 5. The 'lower limit' and 'upper limit' refer to the earliest and latest possible dates, respectively.

As an example: If the start date is MAR2017 (missing day), the lower limit is 01MAR2017 and the upper limit is 31MAR2017; If the start date is 2017 (missing day and month), the lower limit is 01JAN2017 and the upper limit is 31DEC2017.

Table 5 Handling of missing/incomplete date and time

Type of date	Date is incomplete	Date is missing
AE/CM end date	The upper limit.	No replacement, the AE/medication is considered as ongoing in the analysis.
AE/CM onset date	Unless, the event is flagged as *Started prior to first study treatment administration* on the CRF*, the below rule applies. If the (imputed) resolution date is on or after the start of the study treatment and if the start of the study treatment falls within the upper and lower limits (inclusive), the study treatment start date is used. If the resolution date is missing and the study treatment start date falls within the upper and lower limits (inclusive) the study treatment start date is used. In all the other cases the lower limit is used. If the event is flagged PRIOR TO FIRST DOSE*; the study treatment start date **–1 day** is used.	Whichever is the earlier of the date of resolution and the <study treatment> start date.

AE, adverse event; CM, concomitant medication; CRF, case report form.
Medical history dates will not be imputed. If separate reports need to be done for previous or concomitant medication, the flag on the CRF** will be used.
* Flag for concomitant medications: *Started prior to first study treatment administration* answered *Yes* on the CRF *Previous/Concomitant Medication* page,
** Flag for medical history: *Ongoing at Informed Consent signature* answered *Yes* on the CRF *Medical History* page.

Appendix E Document history

Version	Effective Date	Reason
Final 1	29 November 2018	New document