Statistical Analysis Plan: ID-076A201

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

ClinicalTrials.gov Identifier: NCT03384966

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STATISTICAL ANALYSIS PLAN

FOR CLINICAL STUDY REPORT

A MULTI-CENTER, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED STUDY TO ASSESS THE PHARMACODYNAMICS, PHARMACOKINETICS, TOLERABILITY, AND SAFETY OF A SINGLE SUBCUTANEOUS INJECTION OF ACT-246475 IN ADULTS WITH STABLE CORONARY ARTERY DISEASE

Purpose of Analysis	Clinical Study Report
Investigational Drug	ACT-246475
Protocol Number	ID-076A201
Idorsia Document Number	D-18.247
Document Status/Version Number	Final Version 3
Date	16 October 2018
Author	[redacted], Statistician*
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Reviewer	[redacted]

* Requires approval with signature

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LIST OF ABBREVIATIONS AND ACRONYMS

AE	Adverse event
AESI	Adverse events of special interest
ATC	Anatomical Therapeutic Chemical
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve from time zero to 24 h time point
BMI	Body mass index
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CI	Confidence interval
C_{max}	Maximum observed plasma concentration
DAPT	Dual anti-platelet therapy
eCRF	Electronic Case Report Form
EOS	End-of-Study
FAS	Full analysis set
FPA	Final platelet aggregation
HLGT	High level group term
INN	International Nonproprietary Name
IPA	Inhibition of platelet aggregation
LTA	Light transmission platelet aggregometry
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MPA	Maximum platelet aggregation
PCI	Percutaneous coronary intervention
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PPS	Per-protocol set
PRU	$P2Y_{12}$ reaction units
QTcB	QT corrected with Bazett's formula

QTcF	QT corrected with Fridericia's formula
RND	Randomized analysis set
s.c.	Subcutaneous
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SCR	Screened analysis set
SD	Standard deviation
SMG	Standardised Medical Dictionary for Regulatory Activities Query
SOC	System organ class
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TIA	Transient ischemic attack
t_{max}	Time to reach maximum observed plasma concentration
WHO	World Health Organization

1 INTRODUCTION

This statistical analysis plan (SAP) describes in detail the analyses and data presentation for the ID-076A201 final clinical study report.

The following study documents were used when writing this SAP.

Table 1 Study documents

Document	Date, Version
Study protocol	31 August 2017, Version 1
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

2 STUDY DESIGN AND FLOW

2.1 Study design

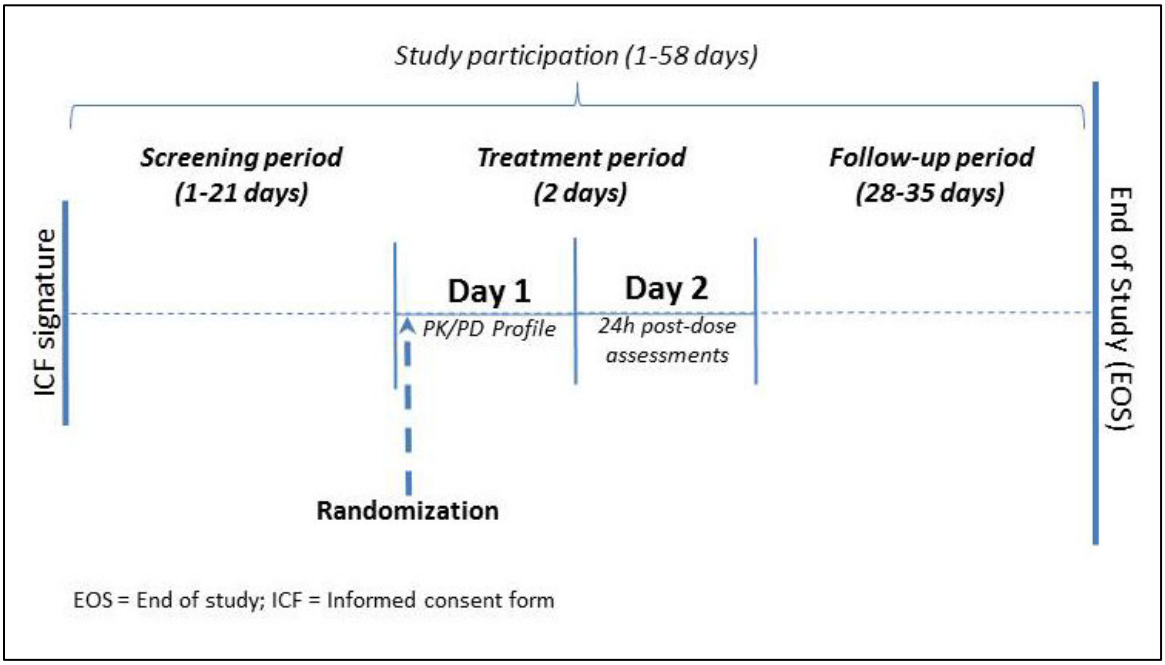
This is a prospective, multi-national, multi-center, double-blind, randomized, placebo-controlled, parallel-group, Phase 2, exploratory study of a single subcutaneous (s.c.) administration of ACT-246475, at 2 different dose levels, in subjects with stable coronary artery disease (CAD) receiving conventional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

Approximately 324 adult subjects with stable CAD will be randomized into 1 of the 8 combinations of the treatment, dose, and injection site using a 2:2:2:2:1:1:1:1 ratio [see protocol section 3.1.1]. Study subject randomization will be stratified based on baseline platelet reactivity value categorized either as high reactivity ($P2Y_{12}$ reaction units [PRU] > 250), medium reactivity (150 ≤ PRU ≤ 250), and low reactivity (PRU < 150).

Each subject will receive a single s.c. administration of either 8 mg ACT-246475, 16 mg ACT-246475 or matching placebo, either in the thigh or in the abdomen. Double blinding is applied to the treatment (ACT-246475 vs placebo), while the dose (8 vs 16 mg) is single blinded (subject blinded), and the injection site (thigh vs abdomen) is not blinded.

The study design is shown in Figure 1.

Figure 1 Study design



2.2 Study visit and assessment schedule

Please refer to the protocol section 7.

2.3 Overview of analysis periods

The study has 3 periods with regard to study drug administration:

1. *Baseline period*: from signature of informed consent to last moment prior to study drug administration.
2. *On treatment period*: from study drug administration and up to end of 48 hours (2 days) after study drug administration [see Section 10.1 for more details].
3. *Safety follow-up*: from the 49th hour for assessments with date/time, or from the third day for assessments with date only, after study drug administration and up to the end of the study.

3 OBJECTIVES

3.1 Primary objective(s)

The primary objective of the study is to characterize the inhibition of platelet aggregation (IPA) relative to placebo after a single s.c. injection of ACT-246475 either in the thigh or

in the abdomen at 2 different doses in subjects with stable CAD receiving conventional background oral antiplatelet therapy (e.g., acetylsalicylic acid, $P2Y_{12}$ receptor antagonists).

3.2 Secondary objectives

Not applicable.

3.3 Other objectives

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

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

4 ANALYSIS SETS

4.1 Definitions of analysis sets

Unless not relevant, i.e., for the Screened analysis set (SCR), or otherwise specified, summary statistics will be provided according to assigned treatment [as described in Section 8.1.1], which may differ from the treatment administered.

4.1.1 Screened analysis set

The 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.

To adhere to the intention-to-treat principle as much as possible:

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

If a subject is unblinded during the study, he/she will be included in the FAS.

4.1.4 Per-protocol analysis set

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

Criteria for sufficient compliance include exposure to treatment, availability of primary PD endpoint assessments and absence of protocol deviations that have an impact on the 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.

4.1.5 Safety analysis set

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

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

4.1.6 Pharmacokinetic analysis set

The PK analysis set includes all subjects from the SAF who have at least one plasma concentration measurement after administration of study treatment.

Subjects in the PK set will be evaluated according to the actual treatment they received, which may differ from the randomly assigned 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 were prepared using the SCR, unless otherwise specified.

Table 2 Analysis datasets usage

	Analysis sets					
Analyses	**SCR**	**RND**	**FAS**	**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	(x)	X	
Main (primary) PD endpoints			X	(x)		
Other PD endpoints			X			
Safety endpoints					X	
PK endpoints						X

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

The decision to perform a sensitivity analysis will be taken prior to any data unblinding, i.e., prior to database lock, during a blind data review.

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.

In addition to the treatment groups reporting as indicated in the sections below, summaries will report results for the *Total ACT-246475* group, which combines subjects from the two ACT-246475 dose groups.

5.1 Subject disposition

5.1.1 Screening failures

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

Summary of subjects by screening status (failure vs randomized), by country and by center will be provided using planned randomization groups instead of using the study treatment arm label, as described in Section 8.1.1.

The number (%) of subject by reasons for screening failures will be tabulated and listed.

5.1.2 Study completion/discontinuation

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

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

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, overall and important, will be summarized for the entire study and by study period (Screening, on study treatment, and safety follow-up).

This will be repeated by country and site.

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, he/she will be counted only once in summaries for this category/sub-category.

A listing will present the subjects for whom the randomization code was broken at site or sponsor office. It contains the date of unblinding and the reason for unblinding.

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 treatment group and overall.

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

If some subjects were administered incorrect study treatment (i.e., assigned treatment is not the received one), the subject disposition summary will also be provided by the actual treatment received.

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

5.4 Subject characteristics

In addition to the treatment groups to report as indicated in below sections, summaries will report results for the *Total ACT-246475* group, which combines subjects from the two ACT-246475 dose groups.

5.4.1 Demographics

The following demographic characteristics are collected on the 'Demographics', and 'Body Weight and Height' electronic Case Report Form (eCRF) pages.

- Age (years)
- Sex category: *Male and Female*
- Race group: *American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Other, Not applicable*
- Ethnic category: *Hispanic or Latino, Not Hispanic or Latino, and Unknown*
- Body weight (kg)
- Height (cm)
- Country of the site (assigned in the eCRF based on the list of sites)

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

The analysis described in this section will be replicated by gender using the FAS.

5.4.2 Baseline disease characteristics

Not applicable.

5.4.3 Other baseline characteristics

Other baseline characteristics, collected during Screening include childbearing potential status at Screening and contraceptive methods.

These are defined as collected on the eCRF ('Demographics' and 'Contraceptive Methods' forms respectively) and no derivation is required.

Subjects with childbearing potential at Screening, and contraceptive methods, will be listed.

5.4.4 Previous and concomitant medical history

For all the 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).

In addition to medical history, specific medical history events or intervention dates related to the following, are collected as predefined categories:

- Myocardial infarction (MI)
- Stroke
- Transient ischemic attack (TIA)
- Percutaneous coronary intervention (PCI)
- Coronary artery bypass graft (CABG)
- Peripheral vascular surgery

For those specific medical history variables, the incidence of subjects by category and sub-category, as defined below, will be summarized (frequency counts and percentages).

CAD-related conditions: MI, PCI, and CABG

Other medical conditions: Stroke, and TIA

Risk factors: diabetes mellitus, chronic kidney disease, hypertension, and dyslipidemia

Note that dyslipidemia is not predefined in the eCRF and will have to be retrieved from medical and concomitant medical history using the MedDRA SMQ *"Dyslipidaemia"*.

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

Diabetes mellitus is any medical history observation with MedDRA PT belonging to MedDRA high level group term (HLGT) "*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 MedDRA SMQ "*Chronic kidney disease*", existing prior to, and ongoing on day of, informed consent signature.

5.4.5 Previous and concomitant therapies

In this study, only medications are to be collected.

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 with Anatomical Therapeutic Chemical (ATC) code included in the following list, and administered on the day of start 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.

Ticlopidine, although listed in the table above, it is not expected to be used and therefore not included in categories of anti-platelet aggregation therapies defined below. However, all anti-platelet aggregation therapies will be listed.

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 ATC code corresponding 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 $P2Y_{12}$ antagonist
   Study-treatment concomitant medications at baseline (based on ingredient list)
   Do not include aspirin/acetylsalicylic acid **or** clopidogrel **or** prasugrel **or** ticagrelor
2. Aspirin/acetylsalicylic acid monotherapy
   Study-treatment concomitant medications at baseline (based on ingredient list)
   Include aspirin/acetylsalicylic acid **and** do not include clopidogrel **or** prasugrel **or** ticagrelor
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)
4. Dual anti-platelet therapy (DAPT): aspirin/acetylsalicylic acid and clopidogrel

Study-treatment concomitant medications at baseline (based on ingredient list)
Include aspirin/acetylsalicylic acid **and** clopidogrel

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

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

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

5.4.6 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 (administered vs not administered) will be provided.

In addition to the initial analysis set defined in the protocol (i.e., the FAS), this analysis will also be provided using the SAF.

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

6.8.1.1 Variable

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

The primary PD variable is the platelet reactivity as measured by VerifyNow® at each time point [see tables of assessments in the protocol: table 2 and table 3].

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

IF maximum of (PRU_{30m}, PRU_{1h}, PRU_{2h}, PRU_{4h}) < 100

AND (no more than 1 intermediate value (PRU_{1h} or PRU_{2h}) missing)

THEN PD response = YES

ELSE PD response = NO

Where PRU_{30m}, PRU_{1h}, PRU_{2h}, and PRU_{4h} refer to PRU measured by VerifyNow® at 30 minutes, 1, 2 and 4 hours after study drug administration. Time is based on planned time point and not on the actual collection time.

Supportive primary PD endpoint estimands

To assess robustness of results, two additional PD endpoints (estimands) will be defined for sensitivity analysis. The first endpoint, noted PD response#, will be based on the same

algorithm as described above but using the actual collection time to define the following time windows:

Table 4 Time windows definitions

Collection time point (nominal) (time post study drug administration)	Time from PRU_{30m} (assessment of response, i.e., PRU < 100)	Time windows (~ 5% margin) (min. from study drug administration)
15 minutes	-	14 to 16
30 minutes	0	28 to 32
1 hour	30 minutes	57 to 63
2 hours	1.5 hours	114 to 126
*3.5 hours**	*3 hours*	*199 to 221*
4 hours	3.5 hours	228 to 252
8 hours	7.5 hours	456 to 504
24 hours	23.5 hours	1368 to 1512

* no blood sample is taken at that time point, therefore no PRU value reported.
PRU, $P2Y_{12}$ reaction units.

The second endpoint, in the event of frequently missing PRU_{1h} or PRU_{2h} values, ≥ 10% missing values overall, noted PD response*, will consider only the 30 minutes and 4 hours post study drug administration time points:

IF maximum of (PRU_{30m}, PRU_{4h}) < 100
AND none of those values is missing
THEN PD response = YES*
ELSE PD response = NO*

6.8.1.2 Analysis

The analyses described in this section consider the primary endpoint, i.e., PD response. Sensitivity analysis of the other estimands are described in the sensitivity analyses section.

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

The study is designed to demonstrate that at least one dose of ACT-246475 enables a large proportion (a target of 85%) of the randomized subjects to achieve a clinically meaningful level of IPA, defined as a PRU < 100.

Hypotheses and statistical model

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

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

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

$$H_{p0_{HD}}: p_{placebo} = p_{HD} \quad \text{vs} \quad H_{p1_{HD}}: p_{placebo} \neq p_{HD}$$

$$H_{p0_{LD}}: p_{placebo} = p_{LD} \quad \text{vs} \quad H_{p1_{LD}}: p_{placebo} \neq p_{LD}$$

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

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

$$H_0: P_{responders} = 0.70 \quad \text{vs} \quad H_1: P_{responders} = 0.85.$$

Main analysis

The first set of null hypotheses ($H_{p0_{HD}}$ and $H_{p0_{LD}}$) will be tested each using a 2-sided z-test at an overall significance level (alpha) of 0.025, corresponding to an overall alpha level of 0.05 adjusted for multiplicity using the Bonferroni method.

Each of the second null hypotheses (H_{0HD} and H_{0LD}) will be tested by a 1-sided z-test at an overall significance level (alpha) of 0.05 adjusted for multiplicity using the Bonferroni method, i.e., 0.025 for each comparison.

The estimated proportion of responders and the corresponding 95% CI will be provided overall and by injection site, for each treatment arm.

A logistic regression analysis of the PD response will be performed to test for treatment effect (8 mg, 16 mg, and placebo) using the following covariates: injection site (abdomen, thigh), PRU level at randomization (stratification levels), age (continuous), sex (male, female), and assessment time (minutes) as continuous.

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

(treatment × injection site) as an interaction term to assess consistency of treatment effect across injection sites.

IPA as measured by VerifyNow® will also be summarized at each time point as a continuous parameter.

The evolution of PRU values over time will be described using box-and-whisker plots, visualizing mean, median, interquartile ranges, SD, and outliers.

Assuming a treatment × injection site interaction, summary and graphical analyses described above will be repeated by site injection sub-group.

6.8.1.3 Supportive/sensitivity analyses

The same analysis as described in the main analysis section will be performed on the additional PD response endpoints: PD response[#] and PD response[*].

The main analysis will be repeated on the PPS, if the size of the PPS is less than 10% compared to the size of the FAS.

6.8.1.4 Subgroup analyses

The consistency of treatment effect across the following subgroups, as defined in protocol section 10.3.2.4, will be assessed by repeating the main analysis on primary PD endpoint, assuming there are enough subjects, i.e., ≥ 20 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

6.8.2.1 Variables

Endpoints

Other PD endpoints include the following:

- **Extent of aggregation:** maximum platelet aggregation (MAP; %), final platelet aggregation (FPA; at 6 minutes, %) as measured by light transmission platelet aggregometry (LTA).

- **Absolute PRU values (for VerifyNow®) at each measured time point.**
- % of subjects at 8 h after study treatment injection with PRU value < 100 or < 0.95 × PRU baseline value if PRU baseline < 100 (i.e., platelet aggregation status 8 hours after study drug administration).

The following exploratory endpoints will also be considered in the PD analysis:

- IPA (noted IPA-V) as measured by VerifyNow®, data for this endpoint will be available only for some centers.

A supportive PD endpoint is defined in the protocol statistical section for LTA-PD response. However, the exact definition of the endpoint is not provided. Therefore, the following definition will be considered for defining LTA-PD response: an IPA-M of at least 50% starting 30 minutes after injection, lasting at least 3 hours, and not exceeding the 8th hour after study drug administration for subjects with value above.

Variables

The variable of *extent of aggregation* (MPA) is used as reported in the eCRF, and is expressed as a percentage.

The *absolute PRU* variable is the actual PRU value as reported by VerifyNow®, at each time point [see protocol table 2 and table 3], and is expressed as a number without unit (the higher the number, the less IPA).

The *subject platelet aggregation status 8 hours after study drug administration* variable is defined as binary with value determined as per the following algorithm:

$$IF\ (PRU_{baseline} \geq 100\ AND\ PRU_{8h} < 100)\ OR\ (PRU_{baseline} < 100\ AND\ PRU_{8h} < 0.95 \times PRU_{baseline})$$
$$THEN\ status = YES$$
$$ELSE\ status = NO$$

The variable of the *IPA by VerifyNow®* (IPA-V) is the value reported in the eCRF, and is expressed as a percentage. All analyses conducted on this variable will exclude missing values.

The LTA-PD response variable is defined as:

$$IF\ minimum\ of\ (IPA\text{-}M_{30m},\ IPA\text{-}M_{4h}) \geq 50\%$$
$$AND\ none\ is\ missing$$
$$THEN\ LTA\text{-}PD\ response = YES$$
$$ELSE\ LTA\text{-}PD\ response = NO$$

The variable *IPA-M at time t* (noted IPA-M_t) is expressed as a percentage, and defined as:

$$IPA\text{-}M_t = (1 - MPA_t / MPA_{baseline}) \times 100.$$

Where MPA_t is MPA at time t after study drug administration, and $MPA_{baseline}$ is the latest MPA value reported up to randomization.

MPA and FPA are measured twice at each point, for the analysis, the average of the two assessments will be used for each time point.

6.8.2.2 Analyses

Summary statistics will be provided for all secondary PD endpoints variables, by time point, and individual data will be listed.

The variables' extent of aggregation, absolute PRU, IPA, and FPA will be analyzed similarly to the longitudinal analysis described for the primary PD endpoint in Section 6.8.1.2, and will use the same factors.

A logistics regression model will be used to assess the treatment effect relative to placebo of each ACT-246475 dose on subject platelet aggregation status 8 hours after study drug administration. The factor considered in addition to the treatment group, will include injection site (abdomen, thigh), PRU level at randomization (stratification levels), age (continuous), and sex (male, female) as fixed factors. The model will also include (treatment × injection site) as an interaction term to assess consistency of treatment effect across injection sites.

Proportion of subject by platelet aggregation status 8 hours after study drug administration will be plotted as bar charts. Additional graphs will be provided by injection site.

6.8.2.3 Supportive/sensitivity analyses

Not applicable.

6.8.2.4 Subgroup analyses

Descriptive summaries will be provided for each secondary PD endpoints using the same sub-groups as defined in Section 6.8.2.4.

Descriptive statistics will also be provided for secondary PD endpoints by injection site sub-group.

6.8.3 Handling of missing data

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, however they will be counted as non-responders in the sensitivity analysis.

No other imputations are planned.

6.9 Analysis of pharmacokinetic variables

The PK variables will be summarized and listed using the PK set.

The plasma PK parameters of ACT-246475 will be derived by non-compartmental analysis of the plasma concentration-time profiles. PK endpoints include: maximum observed plasma concentration (C_{max}), time to reach C_{max} (t_{max}), and the area under the plasma concentration-time curve from time zero to 24 h time point ($AUC_{0\text{-}24h}$; study drug administration to 24 h time point post administration).

Log-transformed value of C_{max} and $AUC_{0–24h}$, will be used in the analysis.

The PK parameters (linear and log-transformed ones) will be summarized by dose group using descriptive statistics, i.e., arithmetic mean, SD, geometric mean, minimum, median, maximum, standard error, and 2-sided 95% CI of the means and coefficient of variation in %. Graphical representation of PK results over time (scheduled time point) will be provided using box-whisker plots. For t_{max}, the geometric mean and its 95% CI will not be calculated.

PK variables summary will be provided by dose, injection site, PRU category used for stratification, and by gender.

7 SAFETY VARIABLES AND ANALYSES

7.1 Overview of safety analyses including subgroup analyses

For categorical variable, 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.

In addition to the treatment groups indicated in below sections, summaries will report results for the *Total ACT-246475* group.

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 eCRF module 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.

AEs for which time of onset is missing will still be counted as treatment emergent if onset date is ≥ date of study drug administration and is ≤ date of study treatment administration +2 days.

7.2.1.3 Treatment-emergent adverse events related to study treatment

TEAEs related to study drugs are those TEAEs which have been reported as related to study treatment by the investigator, or for which this relationship is unknown (i.e., missing).

7.2.1.4 Treatment-emergent adverse events by intensity

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

For AEs with multiple intensities reported, the worst reported severity will be considered. If the intensity is missing, the AE will be considered as severe.

7.2.1.5 Non-treatment emergent adverse events

Non-treatment emergent AEs are those AEs with onset date/time ≥ date/time of study drug administration +48 h, or ≥ date of study treatment administration +2 days if the onset time is missing.

7.2.1.6 Serious adverse events

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

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

Post study drug administration SAEs not qualifying as TESAEs, are non-treatment emergent SAEs.

7.2.1.7 Adverse events leading to death

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

TEAEs leading to death are TEAEs with fatal outcome.

Non-TEAEs with fatal outcome and onset post-study drug administration are non--treatment emergent AEs leading to death.

7.2.1.8 Adverse events leading to study treatment discontinuation

Not applicable.

7.2.1.9 Other adverse events categories

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

For each AESI, the events will be classified as treatment-emergent AESIs if event onset date/time ≥ date/time of study drug administration and ≤ 48 h after date/time of study treatment administration.

Similarly, each event not classified as treatment-emergent AESIs, and with onset being post-study treatment administration will be classified as non-treatment emergent AESIs.

7.2.2 Analysis

For all the AE variables described in Section 7.2.1, the incidence of subjects with the event will be summarized (frequency counts and percentages) by SOC and/or PT as describe in Table 5.

Table 5 Reporting of AEs categories by event onset

Adverse events	**Onset during**	
	Treatment period (treatment-emergent)	**Safety follow-up period** (non-treatment emergent)
Any AEs	SOC+PT, PT only	PT only
All AEs related to study treatment	SOC+PT, PT only	PT only
AEs related to study treatment	SOC+PT, PT only	PT only
AEs related to study treatment by intensity	SOC+PT	-
SAEs	SOC+PT, PT only	PT only
AEs leading to death	SOC+PT, PT only	PT only
AEs belonging to SMQ "*Haemorrhage (excl. lab)*"	PT only	PT only
AEs belonging to HLGT "*Administration site reaction*"	PT only	-

-, not applicable; AE, adverse event; HLGT, high level group term; PT, preferred term; SAE, serious adverse event; SMQ, Standardised MedDRA Query; SOC, system organ class.

For TEAEs by intensity, the incidence of subjects with events will be summarized (frequency counts and percentages) 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.

Specific 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 SAEs, and non-serious AEs.

7.3 Death

Death is considered to have occurred if a primary cause of death is identified in the eCRF '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 on treatment deaths (within 2 days from study drug administration).

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

7.4 Laboratory tests

7.4.1 Measurements

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, 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 on the day of study drug administration or after, and up to the first 48 hours (2 days) after study administration, and that were not present at baseline.

Shift tables of on-treatment value vs baseline, for selected laboratory variables, may be provided according to results.

For each variable, the severity is based on the position of the value against reference ranges (central laboratory) and additional thresholds for significance [see Appendix C] and the worst abnormality is considered in each direction separately (lowest and highest).

7.4.2 Analysis

Descriptive summary statistics by analysis visit and 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, urinalysis) and by parameter. Data are displayed in SI units as provided by the central laboratory.

Urine pregnancy test results will be listed.

Treatment-emergent laboratory abnormalities are summarized by laboratory category, variable and severity over the on-treatment period.

For each lab 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.

7.5 Electrocardiography analysis

The analysis will be performed on the following variables:

- Treatment-emergent ECG abnormalities (i.e., with onset from time of study drug administration and up to 48 hours after and, not present at baseline),
- Absolute change from baseline to each time point in ECG variables: HR, and the intervals PQ/PR, QRS, QT, RR, QT corrected with Bazett's formula (QTcB) and QT corrected with Fridericia's formula (QTcF).

The absolute value and absolute change from baseline to each time point will be summarized.

Incidence of subjects with at least one marked abnormality across all ECG variables and by ECG variable will be provided overall (worst value), and for each of the three time points: pre-dose, at 1 hour and at 24 hours post study administration.

ECG marked abnormalities are defined for QT, QTcF and QTcB (msec), for the different cases:

1. Value > 450 ms for men,
2. Value > 470 ms for women,
3. Value > 500 ms regardless of gender,
4. Absolute change from baseline > 30 ms regardless of gender,
5. Absolute change from baseline > 60 ms regardless of gender

In addition, the treatment-emergent ECG findings, i.e., findings related to an ECG assessment occurring during on-treatment period and absent at baseline, are tabulated by

overall interpretation (normal, abnormal), by category (e.g., rhythm, ST segment) and treatment group.

7.6 Vital signs and body weight

7.6.1 Blood pressure and pulse 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 the value at each visit, in SI units, for all variables and the changes from baseline (continuous and categorical) as well as the abnormality grade/flag is produced and includes all visits. The values not included in the analyses are flagged.

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

The evolution of systolic and diastolic blood pressures values over time will be provided graphically by visit using box-and-whisker plots visualizing mean, median, interquartile ranges, SD, and outliers.

The number and percentage of subjects with at least one marked abnormality for blood pressure is provided by visit / 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 9.3 or higher.

8.1 General rules for data presentations

General rules for data presentations as described here 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 8 *randomization groups* corresponding to the combination of the four study treatment groups (i.e., ACT-246475 8 mg, ACT-246475 16 mg, and their matching placebos) and two injection sites (thigh and abdomen).

The main purpose of this randomization strategy was to balance treatment as well as site of injection assignment. For the analysis, the study treatment arms will consist of the treatment arms: *Placebo*, *ACT-246475 8 mg*, and *ACT-246475 16 mg*. The placebo treatment arm combines the two placebo dose-matching groups.

All analyses, unless stated otherwise, will be reported by those 3 treatment arms, and in this order.

In all Tables, Figures and Listings, treatment groups will be labeled using treatment label [last column of Table 6].

Table 6 Randomization groups and treatment group labels

Randomization groups		Treatment groups (labels for outputs)
Treatment	**Injection site**	
ACT-246475 8 mg	Thigh	ACT-246475 8 mg
ACT-246475 8 mg	Abdomen	
ACT-246475 16 mg	Thigh	ACT-246475 16 mg
ACT-246475 16 mg	Abdomen	
Placebo matching ACT-246475 8 mg	Thigh	Placebo
Placebo matching ACT-246475 8 mg	Abdomen	
Placebo matching ACT-246475 16 mg	Thigh	
Placebo matching ACT-246475 16 mg	Abdomen	

Some analyses may require displaying some of the following groups: *Screened failure* subjects group, *Total randomized* (i.e., any subject who has been assigned a study treatment), *Total ACT-246475* group (i.e., subjects randomized to either ACT-246475 8 or 16 mg arms), and *Total* (i.e., all subjects screened).

The order of the treatment group in the statistical report, would then be: Screened failures, ACT-246475 8 mg, ACT-246475 16 mg, Total randomized, Total ACT-246475, and Total.

8.1.2 Descriptive statistics

Descriptive statistics will be provided by treatment group (and all pooled groups for study subjects analyses) depending on the nature of the criteria:

Quantitative:

Number of observed values, number of missing 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 continuous variables, it is displayed after the number of non-missing observations, for categorical variables after the last category (no percentage reported).

Listings are grouped by treatment arm (same order as in tables headers, if applicable, screening failures are listed last), subject identification number and assessment date as applicable.

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 on-treatment period is defined as the period starting from study drug administration up to 48th hour post administration. However, some assessments will not have the exact time, only the day. In this case it will be assumed that the 48 hours on-treatment period corresponds to the day of study drug administration and to the two following days (1st, 2nd and 3rd day of the on-treatment period).

This results in an over-estimated duration of the on-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 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.

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

It is the date/time recorded in the 'Study Treatment Administration' eCRF page.

10.2.5 Definition of end of study treatment

Not applicable (study treatment is injected only once).

10.2.6 Definition of End-of-Study

EOS is defined as the day of the 30-day safety follow-up telephone call.

For randomized subjects who never received the study treatment, EOS date is defined as the earliest date amongst the following dates, as reported in the "Study Discontinuation" eCRF 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 in the Study Discontinuation eCRF 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 used in the analysis is the last reported one.

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

For subjects with multiple baseline assessment (multiple screening attempts), the last values are displayed and included in any analysis, while prior ones will only be presented in listings.

10.5 Coding dictionaries

The most recent version of MedDRA dictionary implemented in Idorsia at time of database closure will be used for coding medical history, and AEs. The version will be displayed in statistical outputs footnotes.

Similarly, the most recent version of the WHO Drug Reference Listing dictionary based on WHO Anatomical Therapeutic Chemical (ATC) classification system implemented in Idorsia at time of database closure will be used for coding of previous and concomitant therapies reported in this trial.

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 recorded on the 'Medical History' and 'Specific Medical History' eCRF pages.

Medical history are those procedures or diagnoses for which

1. The end date of the procedure or diagnosis is not missing and is earlier to the study treatment administration date.

   OR

2 The end date of the procedure or diagnosis is missing and Question 'Ongoing at Informed Consent signature?' in the 'Medical History' eCRF page is answered as 'No'

If neither applies, all other 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 or equal to study start date.

Study concomitant medications are defined as any medication that is ongoing after informed consent signature date, 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 a start date before date of study treatment administration and is either ongoing at end of study or has a stop date after the study treatment administration date.

Study treatment concomitant medications (a subset of study concomitant medications) are any medications that are either ongoing at study drug administration or initiated within a 2-day period from study treatment administration, i.e., on the day and the following day of study drug administration.

If no end date is available for a medication, it is considered ongoing, and is therefore both a *study concomitant medication* and a *study treatment concomitant medication*.

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 pharmacodynamic variable

The protocol section 10.2.4.2 describes the following PD variable: *% of subjects at 8 h after study treatment injection with PRU value < 100 or > 1.05 × baseline value.*

The intent of this variable was to estimate the proportion of subjects still with a low value of platelet aggregation 8 hours after administration of study drug. This is assuming that a baseline platelet aggregation ($PRU_{baseline}$) value ≥ 100.

As some subjects may have a $PRU_{baseline}$ value < 100, and a PRU_{8h} < 100, it is not sensible to consider those subjects in the group of subjects with still significantly low platelet aggregation after study drug administration. Unless the PRU_{8h} is lower than $PRU_{baseline}$.

For this purpose, and to be consistent with the intent of assessing back to normal/baseline value, the definition of this variable should be modified to: *% of subjects at 8 h after study treatment injection with PRU value < 100 or* ***< 0.95*** *× baseline value*.

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

Not applicable.

11.4 Additional analyses as compared to the study protocol

Not applicable.

12 LIST OF TABLES, LISTINGS AND FIGURES

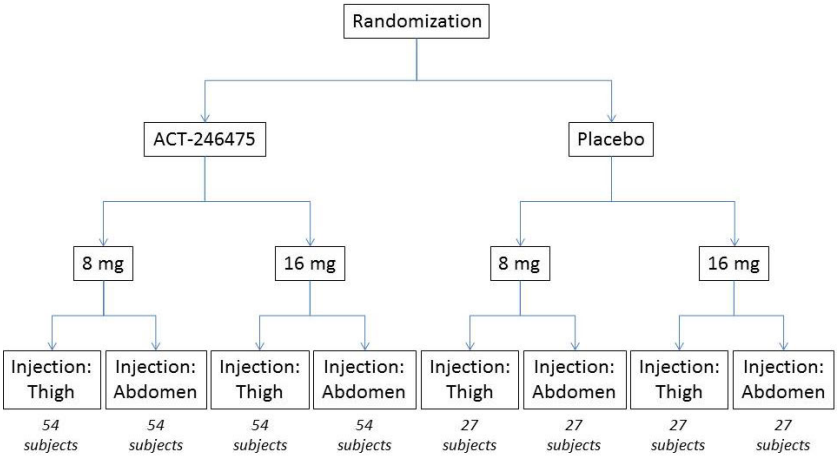
For the complete list of tables, listings and figures, please refer to the *SAP Appendix - List of statistical outputs* document.

13 APPENDICES

Appendix A Protocol synopsis

PROTOCOL SYNOPSIS ID-076A201

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

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

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

	Conditions that may prevent subject from complying with study requirements or may be a confounder for the study interpretation: 8. Pregnant or breastfeeding women. 9. Uncontrolled hypertension according to investigator's judgment. 10. Known and documented moderate or severe hepatic impairment. 11. End-stage renal failure requiring dialysis. 12. Any clinically significant findings on a physical exam, or laboratory tests prior to screening that in the investigator's judgment would preclude safe or reliable participation of a subject in the study. 13. Concomitant diseases (e.g., advanced liver cirrhosis, mental illness, neurodegenerative disease, terminal malignancy, etc.) or conditions (e.g., inability to communicate well with the investigator in the local language) that, in the opinion of the investigator, may prevent subject from complying with study requirements or may be a confounder for the study interpretation. 14. Veins unsuitable for intravenous puncture on either arm (e.g., difficult to locate, access, or puncture) according to the investigator's judgment. 15. Clinically relevant skin disease that prevents s.c. injection in the thigh or abdomen, according to the investigator's judgment. 16. Use of inhibitors of organic anion-transporting polypeptide (OATP)1B1 or OATP1B3 at screening (Visit 1). 17. Known hypersensitivity to ACT-246475, any of its excipients, or drugs of the P2Y12 class. 18. Previous exposure to investigational drug within 3 months prior to screening.
STUDY TREATMENTS	**Investigational treatment and matching placebo** Study treatment for s.c. administration will be available as sealed glass vials in 1 strength: 20 mg. The vials contain 22 mg of lyophilized ACT-246475A (hydrochloride salt of ACT-246475) or matching placebo to be reconstituted with 1 mL of water for injection. Further dilution with 1 mL NaCl 0.9% will be

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

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

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

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

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

Appendix B Protocol deviation list

[redacted]

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

Table below provides the reason considered for excluding subjects from analysis set.

Table 7 Definition of exclusions from analysis sets

Analysis set	Reason for exclusion from analysis set	Programming conditions
Screened analysis set	Informed consent not initially obtained for the study	DV.DVREFID = IPD1D1
Randomized analysis set	Subject does not have a randomization number	Not in DS.RANDNO
Full analysis set	Subject did not get study treatment	EX.EXDOSE not >0
Safety set	Subject did not get study treatment	EX.EXDOSE not >0
Per-protocol set	Previous exposure to investigational drug	DV.DVREFID = IPD2A6
	Subject with platelet disorders at Screening	DV.DVREFID = IPD2A9
	Initiation or change in dose of oral P2Y12 during study	DV.DVREFID = IPD2D1
	Incorrect administration of study drug	DV.DVREFID = IPD2E1 or IPD3C1
	Deviation from study drug preparation instructions	DV.DVREFID = IPD2E2
	Incorrect blood sampling for platelet assays	DV.DVREFID = IPD2F2
	Background oral antiplatelet therapy not stable for 1 month prior to randomization	DV.DVREFID = IPD2A1
	Subject does not have stable coronary artery disease	DV.DVREFID = IPD2A3
	At least one post-dose VerifyNow® blood sample not evaluable (excluding the 24 h post dose)	at least one missing LB.LBSTRESN where LB.LBTESTCD= "P2Y12RU" and LB.LBTPT in (15 MIN POST-DOSE, 30 MIN POST-DOSE, 1 HOUR POST-DOSE, 2 HOURS POST-DOSE, 4 HOURS POST-DOSE, 8 HOURS POST-DOSE)
	Subject taking OATP1B1 and/or OATP1B3 inhibitor (systemic route) at Screening	DV.DVREFID = IPD2A7
PK analysis set	Subject has no plasma concentration measurement after administration of study treatment	all PC.PCSTRESC = « » when PC.PCTPT not PRE-DOSE

ICF, informed consent form; OATP, organic anion transporting polypeptide; PK, pharmacokinetic(s).

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 the table below. The 'lower limit' and 'upper limit' refer to the earliest and latest possible dates, respectively.

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

Table 8 Handling of missing/incomplete date and time

Type of date	Date is incomplete	Date is missing
AE/CM resolution date	The upper limit.	No replacement, the AE/medication is considered as ongoing in the analysis.

Type of date	Date is incomplete	Date is missing
AE/CM onset date	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.	Whichever is the earlier of the date of resolution and the <study treatment> start date.

AE, adverse event; CM, concomitant medication.

Appendix E Document history

Version	Effective Date	Reason
1.0	27 May 2018	New document
2.0	3 October 2018	Update following dry-run 1 review
3.0	16 October 2018	Update following dry-run 2 review