AstraZeneca

Statistical Analysis Plan

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A Multinational, Randomised, Double-Blind, Placebo-Controlled Trial to Evaluate the Effect of Ticagrelor twice daily on the Incidence of Cardiovascular Death, Myocardial Infarction or Stroke in Patients with Type 2 Diabetes Mellitus

[THEMIS - effect of Ticagrelor on Health outcomes in diabEtes Mellitus patients Intervention Study]

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Study Statistician [redacted] 2018-09-18
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Global Product Statistician [redacted]

18 SEPTEMBER 2018
Date

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
Adjudicated endpoint event	An event that fulfils study specific endpoint criteria as confirmed during adjudication by the independent CEC
AE	Adverse Event
ALI	Acute Limb Ischaemia
ASA	Acetylsalicylic acid
BARC	Bleeding Academic Research Consortium
bd	Twice daily dosing
CEC	Clinical Endpoint Committee
CSP	Clinical Study Protocol
CV	Cardiovascular
DAE	Discontinuation of study medication due to an Adverse Event.
DMC	Data Monitoring Committee
DVT	Deep Vein Thrombosis
eCRF	Electronic Case Report Form
EQ-5D	Euro Quality of Life – 5 dimensions
FAS	Full Analysis Set
HR	Hazard Ratio
ITT	Intention-to-treat
LTFU	Lost To Follow-Up
MedDRA	Medical dictionary for regulatory activities
MI	Myocardial infarction
PACD	Primary analysis censoring date
PEGASUS	Study acronym - PrEvention with TicaGrelor of SecondAry Thrombotic Events in High-RiSk Patients with Prior AcUte Coronary Syndrome
PLATO	A study of PLATelet inhibition and patient Outcomes
SAE	Serious Adverse Event
SCV	Study Closure Visit
T2DM	Type 2 Diabetes Mellitus

Abbreviation or special term	Explanation
TIMI	Thrombolysis In Myocardial Infarction

AMENDMENT HISTORY

Date	Brief description of change
31 January 2014	First version published
27 March 2017	Title changed to reflect the reduced dose in clinical study protocol amendment, by replacing "Ticagrelor 90 mg twice daily" with "Ticagrelor twice daily". 1.1.1 Changed "Ticagrelor 90 mg twice daily" to "Ticagrelor twice daily". 1.1.2 Changed secondary objectives to reflect clinical study protocol amendment, from prevention of the composite of all-cause death/MI/stroke, CV death, all-cause death (presented in hierarchical order) to prevention of CV death, MI, ischaemic stroke, all-cause death (presented in hierarchical order). 1.1.3 Changed exploratory objectives to reflect clinical study protocol amendment: Composite of all-cause death/MI/stroke and composite of irreversible harm added, while MI and ischaemic stroke are moved to secondary objectives. The analysis of the composite CV death, non-fatal MI, non-fatal stroke and major bleeding (TIMI major) removed. 1.1.3 The composite of arterial and venous thrombotic events fulfilling serious adverse event criteria added as an exploratory analysis. The analysis of prevention of coronary arterial revascularisation added. First paragraph in 1.2 changed to reflect clinical study protocol amendment, increasing from expected 17000 to 19000 to be randomised, 750 to 1385 primary endpoint events, 35 to 58 months maximal study duration of treatment, 15 to 29 months minimum follow-up, 24 to 40 months average follow-up and enrolment period increased from18 to 28 months. 1.3 Second paragraph changed to reflect clinical study protocol amendment, assumed HR changed from 0.80 to 0.84, from expected 750 to 1385 collected adjudicated events and changed power from 86 % to 90 %. 1.3 Third paragraph: changed timelines and number of patients due to clinical study protocol amendment. 2.1.2 Changed definition of safety analysis set according to clinical study protocol Amendment 3. 2.1.3 Changed from "at the time of enrolment" to "at time of randomisation visit" to reflect the time of collecting the information. 2.2 Changed section name from "Deviations" to "Violations and deviations" according to standards. 2.2 Study drug non compliance was eliminated from the protocol deviations. 2.2 Inserted information of how the analysis will be made when a patient is randomised more than once and for patients randomised on site 5730.

Date	Brief description of change
	3.2 Clarification added: for the analysis of all-cause death, the analysis will include collected vital status information known through public records and not be limited to adjudicated death events.
	3.2.2 Changed secondary efficacy variables, corresponding to changes made in section 1.1.2
	3.2.3 Changed exploratory efficacy variables, corresponding to changes made in section 1.1.3
	3.4 Changes made to reflect CSP amendment, to include ticagrelor 60 mg and ticagrelor 60 mg placebo as alternative doses.
	3.4 Definition of compliant removed (in earlier versions defined as 80% of planned study medication) and the sentence about that interruptions >1 week are reported (captured in the clinical study protocol).
	First paragraph of 4.1: eliminated sentence "If collected, these events will be included in listings and tables".
	4.1 The score statistic replaced by the Wald statistic for the calculation of p-values and confidence intervals for HR using the Cox proportional hazards model.
	4.1 Included minimum number of events requirement.
	4.1.1 A clarification made in the 4th paragraph: from "Thus, in the main analyses patients will be censored at the time of consent withdrawal" to "Thus, in the main analyses patients will be censored at the time when all elements of the endpoint were assessed for those patients who withdraw consent and for whom only vital status is known from public records".
	4.1.1 Changed censoring rule for analysis of discontinuation due to bleeding event, the same censoring rule as for time-to-event analysis of bleeding will be applied.
	4.1.3 Removed sentences "To examine this assumption, variables that may be related to censoring, e.g. the occurrence of SAEs, bleeding or certain AEs, will be explored. Frequencies will be calculated per treatment group and compared between patients censored prior to PACD, and those with complete follow-up. As discussed above patients censored prior to PACD are expected to almost exclusively be patients who have withdrawn consent. Note that any subjects withdrawing consent after a primary event will be included in the analysis of the primary endpoint."
	4.2.1.1 The sensitivity analysis of missing data has been modified to reflect amendment 3 of the clinical study protocol.
	4.2.1.1 Sensitivity analysis of the primary variable: on treatment, with investigator reported events, with REACH risk score, blood pressure, heart rate and pulse pressure has been added.
	4.2.1.1 A recurrent event analysis with the Wei-Lin-Weissfeld model and with the Lin-Wei-Yang-Ying model has been added.

Date	Brief description of change
	4.2.1.1 Sensitivity analyses to examine the dose-switch have been added, since the dose was reduced in the first amendment of the clinical study protocol.
	4.2.1.1 Changed definition of complete follow-up, that a patient have died of non-CV death will not imply that the patient have complete follow-up.
	4.2.1.2 Changed model for estimating the hazard ratio: from model with treatment, subgroup and interaction between treatment and subgroup as factors to only treatment as factor. Included minimum number of events requirement.
	4.2.1.2 The last paragraph about compliance analyses has been removed.
	4.2.1.2 The subgroups ASA use at any time during the study and lipid lowering drug use have been removed. History of PCI, stent implantation and type of stent have been combined, the categories for ASA dose have been changed from previous cut at 75 mg to 81 mg while the categories for HbA1c have been changed from a cut at 6.5 % to 7%. The '≥' symbol has been replaced by '>', and '<' has been replaced by '≤' for the categories of the subgroups BMI and creatinine clearance. The subgroups History of coronary arterial revascularisation, Duration of diabetes and History of any diabetes complications have been added. All subgroups that are based on medication or lab values are changed to "at baseline", except ASA that is changed to "at randomisation".
	Time since most recent PCI, time since most recent CABG history of poly-vascular disease and number of prior vascular beds added to the list of subgroups.
	First sentence in 4.2.3 changed number of secondary efficacy variables due to CSP amendment.
	4.2.6 Concomitant medications and protocol deviations removed from what will be presented for the safety analysis set since it will be presented for the full analysis set.
	Second paragraph in 4.2.6: 'results from physical examination' removed from since such results are not collected in the study.
	4.2.6.2 Exploration of concomitant antithrombotic therapy as potential risk factor eliminated. Analysis of the subgroup with a history of prior spontaneous bleeding removed (not collected).
	4.2.6.2 Sensitivity analyses of TIMI Major bleeding have been added.
	4.2.6.3 Changed definition of treatment period in order to conform with time to safety endpoint analyses.
	4.2.6.3 Added sensitivity analysis of reported AEs, SAEs and DAEs for patients randomised to ticagrelor 60 mg or ticagrelor 60 mg placebo.
	Second paragraph in 5: changes made to reflect CSP amendment, from 375 to 517 planned primary events, and changed from second to first order secondary efficacy variable for CV death.
	Section 6 Changes of analysis from protocol has been added.
	Three references added: Wei 1989, Lin 2000 and Wilson 2012, respectively.

Date	Brief description of change
17 September 2018	Signature page: new Global product statistician [redacted] Amendment history: Clarifying changes made in March 2017 in Section 1.1.3 Exploratory endpoints added to Section 1.1.3 and Section 3.2.3 Section 2.2 sensitivity analysis that included patients randomised at a specific site has been removed. Section 3.2.2: added clarification that strokes classified as "Unknown type of stroke/No imaging performed" will be included in the analysis of ischaemic stroke. 4.2.1.2 Subgroup analyses for each component of the primary efficacy variable added. Also, sentence added that analyses in a specific country subgroup may be done and reported separately. 4.2.1.2, Table 1: "History of PCI, Yes/No" inserted as a new subgroup characteristic in table and the "No" category therefore removed from the subgroup of stent types and the title of that subgroup characteristic clarified to "Type of stent". The category "No history of CABG" removed from subgroup "Time since most recent CABG", since already covered in subgroup "History of CABG Yes/No". The "No" category has also been removed from "ASA dose at baseline" and "Time since PCI", covered in "ASA use at randomisation" and "History of PCI", respectively. Creatinine clearance replaced by eGFR, name of subgroup characteristic corrected to better reflect the variable defining the subgroup. 4.2.2 Added sentence of repeating the subgroup analyses for the secondary efficacy variables. Section 6, changed from two to eight exploratory objectives.

1. STUDY DETAILS

1.1 Study objectives

1.1.1 Primary objective

The primary objective of the study is to compare the effect of long-term treatment with ticagrelor twice daily (bd) vs. placebo for the prevention of major cardiovascular (CV) events (composite of CV death, myocardial infarction [MI] or stroke) in patients with Type 2 Diabetes Mellitus (T2DM) at high risk for CV events, but without a medical history of previous MI or stroke.

The primary efficacy variable is time from randomisation to first occurrence of any event from the composite of CV death, MI or stroke (ischaemic, haemorrhagic or unknown aetiology).

1.1.2 Secondary objectives

The secondary objectives of the study (presented in hierarchical order) are to compare the effect of long-term treatment with ticagrelor vs. placebo for:

1. Prevention of CV death. The efficacy variable is time from randomisation to death of CV cause

2. Prevention of MI. The efficacy variable is time from randomisation to first occurrence of MI

3. Prevention of ischaemic stroke. The efficacy variable is time from randomisation to first occurrence of ischaemic stroke

4. Prevention of all-cause death. The efficacy variable is time from randomisation to death of any cause.

1.1.3 Exploratory objectives

Other objectives are to explore other long-term treatment effects of ticagrelor vs. placebo on:

- Prevention of the composite of all-cause death, MI or stroke. The efficacy variable is time from randomisation to first occurrence of any event from the composite of all-cause death, MI or stroke

- Prevention of stroke. The efficacy variable is time from randomisation to first occurrence of stroke

- Effect on irreversible harm events, the composite of all-cause mortality, MI, stroke, intracranial haemorrhage and fatal bleeding. The efficacy variable is time from

randomisation to first occurrence of any event from the composite of all-cause mortality, MI, stroke, intracranial haemorrhage and fatal bleeding

- Prevention of the composite of arterial and venous thrombotic events that fulfills any SAE criteria. The efficacy variable is time from randomisation to the first occurrence of any event from the composite of arterial and venous thrombotic events that fulfills any SAE criteria (not included in CSP, see section 6)

- Prevention of coronary arterial revascularisations. The efficacy variable is time from randomization to the first occurrence of any coronary arterial revascularisation (not included in CSP, see section 6)

- Prevention of the composite of acute limb ischaemia (ALI) and major amputation of vascular aetiology. The efficacy variable is time from randomisation to first occurrence of any event from the composite of ALI and major amputation of vascular aetiology (not included in CSP, see section 6)

- Prevention of the composite of urgent peripheral arterial revascularisation, venous thrombotic event (defined as deep vein thrombosis [DVT] or pulmonary embolism), ALI and major amputation of vascular aetiology. The efficacy variable is time from randomisation to first occurrence of any event from the composite of urgent peripheral arterial revascularisation, venous thrombotic event, ALI and major amputation of vascular aetiology (not included in CSP, see section 6)

- Prevention of the composite of all-cause mortality, MI, stroke, ALI and major amputation of vascular aetiology. The efficacy variable is time from randomisation to first occurrence of any event from the composite of all-cause mortality, MI, stroke, ALI and major amputation of vascular aetiology (not included in CSP, see section 6)

- Prevention of the composite of CV death, MI, stroke, ALI, major amputation of vascular aetiology and venous thrombotic event. The efficacy variable is time from randomisation to first occurrence of any event from the composite of CV death, MI, stroke, ALI, major amputation of vascular aetiology and venous thrombotic event (not included in CSP, see section 6)

- Prevention of the composite of CV death, MI, stroke, ALI, major amputation of vascular aetiology and urgent peripheral arterial revascularisation. The efficacy variable is time from randomisation to first occurrence of any event from the composite of CV death, MI, stroke, ALI, major amputation of vascular aetiology and urgent peripheral arterial revascularisation (not included in CSP, see section 6)

- Prevention of the composite of all-cause mortality, MI, stroke, ALI, major amputation of vascular aetiology, venous thrombotic event, urgent peripheral arterial revascularisation and coronary revascularisation. The efficacy variable is time from randomisation to first occurrence of any event from the composite of all-

cause mortality, MI, stroke, ALI, major amputation of vascular aetiology, venous thrombotic event, urgent peripheral arterial revascularisation and coronary revascularisation (not included in CSP, see section 6)

- Health care resource utilisation and utilities assessed by Euro Quality of Life-5 Dimensions (EQ-5D) questionnaire to support health technology assessment and health economic modelling.

1.1.4 Safety objectives

The overall safety objective of this study is to assess the safety and tolerability of long-term therapy with ticagrelor compared to placebo in patients with T2DM at high risk of CV events, with or without background low-dose aspirin therapy. Bleeding events will be analysed using the Thrombolysis in Myocardial Infarction Study Group (TIMI), PLATO (PLATelet inhibitation and patient Outcomes) and the Bleeding Academic Research Consortium (BARC) definitions. Specific focus will be on:

- Time to first TIMI Major bleeding event (primary safety objective)
- Time to first TIMI Major or Minor bleeding event
- Time to first PLATO Major bleeding event
- Time to permanent discontinuation of study medication due to any bleeding event.

Non-serious AEs of interest (i.e. dyspnoea, renal impairment, bradyarrhythmia, gout, and pneumonia), adverse events that leads to permanent discontinuation of study medication (DAEs) and all serious adverse events (SAEs) will be reviewed within the context of the earlier safety experience with the drug.

1.2 Study design

The study is event-driven and 19000 randomised patients are estimated to be required in order to collect 1385 adjudicated primary endpoint events. The anticipated maximal duration of treatment with study medication for an individual patient is 58 months. However, the actual duration of the study will be based on accrual of the pre-determined number of adjudicated primary endpoint events, and therefore the study may be shorter or longer than 58 months. The expected minimum follow-up period is 29 months and the expected average follow-up period is 40 months, based on an enrolment period of 28 months. A study closure plan will be developed that accounts for the patient recruitment pattern and the event rate to reach the predetermined number of adjudicated primary endpoint events (1385).

As safety is continuously monitored, the study may be terminated early if either a clear beneficial or harmful effect of the study treatment is detected during the Data Monitoring Committee (DMC) review.

1.3 Number of subjects

Based on clinical studies and epidemiological information, the event rate for the composite of CV death, MI or stroke has been estimated to be 2.5% annually in a population consisting of patients with T2DM at high risk for CV events without previous medical history of MI or stroke.

The final primary treatment comparison will be made at a significance level of 4.96% adjusted for the planned efficacy interim analysis. Assuming a true hazard ratio (HR) of 0.84 between ticagrelor and placebo, 1385 primary endpoint events will provide a power of 90%.

With an annual event rate of 2.5% in the placebo treatment group, 19000 patients, randomised in a 1:1 ratio, with an average follow-up period of 40 months, are estimated to provide the required number of primary events. The expected minimum follow-up period is 29 months, based on an enrolment period of 28 months.

The expected number of patients who will be lost-to-follow-up is negligible and hence not considered in the determination of samples size.

2. ANALYSIS SETS

2.1 Definition of analysis sets

2.1.1 Full analysis set (FAS)

All patients who have been randomised to study treatment will be included in the full analysis set (FAS) irrespective of their protocol adherence and continued participation in the study. Patients will be analysed according to their randomised study medication irrespective of whether the event occurred before or following discontinuation of study medication. Patients who withdraw consent to participate in the study will be included up to the date of their study termination except for vital status known through public records (for use in the analysis of all-cause death). All efficacy variables will be analysed using the FAS.

2.1.2 Safety analysis set

All patients who received at least 1 dose of randomised ticagrelor or placebo, will be included in the safety analysis set. Throughout the safety results sections, erroneously treated patients (e.g., those randomised to ticagrelor but actually given placebo) will be accounted for in the actual treatment group. A patient who in error has received both ticagrelor and placebo will be accounted for in the randomised treatment group.

2.1.3 Analysis set for U.S. Food and Drug Administration regulatory purposes

The primary analysis will be on the FAS in a subset of patients on acetylsalicylic acid (ASA) therapy at the day of randomisation visit.

2.2 Violations and deviations

Important protocol deviations will be summarised by treatment group and will include but not be limited to:

- Patients who were randomised but did not meet inclusion and exclusion criteria
- Patients who received prohibited concomitant medication
- Patients who received the wrong study medication at any time during the study
- Patients who were randomised but took no study medication.

Protocol deviations will be identified by programmed checks prior to database lock. However, as full analysis set (FAS) is the primary analysis set, protocol deviations will not imply exclusion from the analysis.

If one patient has been randomised more than once in the study, the patient will be analysed according to the first randomisation and all collected data will be reconciled at the discretion of the investigator.

Patients that were randomised at site 5730 will not be included in any analysis sets. AstraZeneca has reported the investigator to authorities for potential scientific misconduct and made the decision to exclude the patients from the analyses.

3. PRIMARY AND SECONDARY VARIABLES

3.1 Adjudication of clinical endpoint events

Clinical efficacy endpoint events and bleeding events will be evaluated by a Clinical Endpoint Committee (CEC) that is independent of the sponsor and investigators. Events will be identified using standard questioning of the patient at each visit, or by information the investigator may receive as part of standard medical practice. Safety endpoint events will be identified similarly. The investigator will complete endpoint event specific forms on the electronic case report form (eCRF) and compile additional source information into an 'Endpoint Package' which will be sent to the CEC for central adjudication.

3.2 Efficacy variables

The efficacy objectives will be evaluated using analysis of time from randomisation to first event, using only events positively adjudicated by the CEC (except for the analysis of all-cause death where also vital status known from public records will be used). Time will be calculated as the number of days plus one between the date of randomisation and date of the first occurrence of the event, or, if no event has occurred, the date of censoring (see Section 4.1.1).

When the first event is a MI or stroke, the time to the primary event will be the time to the MI or stroke, irrespective of whether or not the patient dies as a sequel of the event.

Deaths where cause of death is unknown will be accounted for as CV deaths in the efficacy analyses.

3.2.1 Primary efficacy variable

The primary efficacy variable is time from randomisation to first occurrence of any event from the composite of CV death, MI or stroke (ischaemic, haemorrhagic or unknown aetiology).

3.2.2 Secondary efficacy variables

Secondary efficacy variables are:

1. Time from randomisation to death of CV cause

2. Time from randomisation to first occurrence of MI

3. Time from randomisation to first occurrence of ischaemic stroke (including strokes classified as "Unknown type of stroke/No imaging performed")

4. Time from randomisation to death of any cause.

3.2.3 Exploratory efficacy variables

Other efficacy variables are:

- Time from randomisation to first occurrence of any event from the composite of all-cause death, MI or stroke

- Time from randomisation to first occurrence of stroke

- Time from randomisation to first occurrence of any event from the composite of all-cause mortality, MI, stroke, intracranial haemorrhage and fatal bleeding (irreversible harm events)

- Time from randomisation to the first occurrence of any event from the composite of arterial and venous thrombotic events that fulfils any SAE criteria

- Time from randomisation to first occurrence of coronary arterial revascularisation

- Time from randomisation to first occurrence of any event from the composite of ALI and major amputation of vascular aetiology

- Time from randomisation to first occurrence of any event from the composite of urgent peripheral arterial revascularisation, venous thrombotic event, ALI and major amputation of vascular aetiology

- Time from randomisation to first occurrence of any event from the composite of all-cause mortality, MI, stroke, ALI and major amputation of vascular aetiology

- Time from randomisation to first occurrence of any event from the composite of CV death, MI, stroke, ALI, major amputation of vascular aetiology and venous thrombotic event

- Time from randomisation to first occurrence of any event from the composite of CV death, MI, stroke, ALI, major amputation of vascular aetiology and urgent peripheral arterial revascularisation

- Time from randomisation to first occurrence of any event from the composite of all-cause mortality, MI, stroke, ALI, major amputation of vascular aetiology, venous thrombotic event, urgent peripheral arterial revascularisation and coronary revascularisation

- Health care resource utilisation and utilities assessed by EQ-5D questionnaire to support health technology assessment and health economic modelling.

3.3 Safety variables

3.3.1 Adverse events

AEs of interest (i.e., dyspnoea, renal impairment, bradyarrhythmia, gout, and pneumonia) and DAEs (Discontinuations of Study Medication due to Adverse Event) will be collected from randomisation throughout the study until and including the Study Closure Visit (SCV).

All SAEs will be recorded from the time of informed consent throughout the study until and including the SCV. Events adjudicated to the endpoint events non-fatal MI, primary ischaemic stroke or CV death, although qualifying as SAEs, will only be reported as primary endpoint events in the Clinical Study Report.

Section 6.4 in the Clinical Study Protocol (CSP) gives more detailed information on adverse event data collection.

3.3.2 Bleeding events

Bleeding events that are self-limited, and do not prompt medical evaluation or intervention, need not to be reported. For all bleeding events that are unexpected or of unanticipated quantity, the investigator will complete information on the eCRF specific to that bleeding event. In addition, for all reported bleeding events relevant information will be compiled and sent to the CEC for central adjudication according to the following bleeding definitions: TIMI, PLATO and BARC. Additional details can be found in the CEC Charter.

Additionally, all bleeding events (including haemorrhagic stroke) fulfilling the SAE criteria will be reported as SAEs by the sponsor to the health authorities. If the adjudication of a stroke event unveils a haemorrhagic stroke not yet reported as SAE, it will be reported as SAE to the health authorities. Further details can be found in Section 6.4.5 in the CSP.

Specific focus will be on the following bleeding variables, from time of randomisation:

- Time to first TIMI Major bleeding event (primary safety objective)
- Time to first TIMI Major or Minor bleeding event
- Time to first PLATO Major bleeding event
- Time to permanent discontinuation of study medication due to any bleeding event.

3.4 Treatment compliance

Patients will be asked to return all unused study medication and empty packages to the clinic at each visit. The number of dispensed and returned pills (determined by pill count) will be recorded in the eCRF. Based on the pill counts, the percentage treatment compliance will be calculated as the number of pills taken (dispensed minus returned) relative to the expected number of taken pills. The expected number of pills taken will be calculated as:

> (number of pills to be taken daily)×(number of days between visits – number of days of planned interruption)

The number of pills to be taken daily is 2, initially either 2 ticagrelor 90 mg or 2 ticagrelor 90 mg placebo, while after Clinical Study Protocol Amendment No 1, either 2 ticagrelor 60 mg or 2 ticagrelor 60 mg placebo.

4. ANALYSIS METHODS

4.1 General principles

Clinical events reported after database lock will not be included in the primary efficacy and safety analysis.

For time to event variables, treatments will be compared using a Cox proportional hazards model with a factor for treatment group, using the Efron method for ties. Censoring principles are described in Section 4.1.1. The p-values (calculated using the Wald test), HR and 95% confidence intervals for the HR will be reported. Summary tables of these analyses will also include the number of patients with an event and Kaplan-Meier estimates of the event rates per treatment group estimated at a time point determined on the basis of the available follow-up. Kaplan-Meier estimates of the cumulative proportion of patients with events will be estimated and plotted, with the number of patients at risk indicated below the plot at specific time points. If the total number of events in an endpoint or subgroup category is <15, only percentage of patients with events will be presented, but no Kaplan-Meier estimates, HRs, confidence intervals or p-values.

The primary and secondary efficacy variables will be included in a confirmatory testing procedure described in Section 4.2.3. No further multiplicity adjustment will be made to

confidence intervals or p-values. Analyses of efficacy or safety variables that are not part of the confirmatory analyses are considered exploratory and any p-value and confidence interval will be used as a measure of precision only.

In addition to specific analyses and presentations that are detailed in the following sections, results will be summarised using descriptive statistics, including the number of patients, mean, standard deviation, median and range as appropriate. For categorical variables counts and percentage per treatment group will be presented. Summaries of continuous variables will be based on non-missing observations. Percentage for categorical variables will be calculated based the total number of patients in the treatment group, i.e. the denominator includes the number of patients with missing values for the variable.

Demographic characteristics, qualifying risk factors and other specific medical and surgical history will be summarised for the FAS using descriptive statistics.

4.1.1 Censoring

The executive committee will monitor the accrual of the number of primary events and when appropriate predict and define a primary analysis censoring date (PACD) at which time the pre-defined target number of events for the primary composite endpoint are expected to have occurred.

The PACD will be the common date at which all patients who are event free for the given endpoint and have not withdrawn consent for participating in the study will be censored in efficacy time-to-event analyses. Events that occur after the PACD but before the SCV will also be collected and adjudicated. These events will be included in sensitivity analyses but not in the primary analysis. Events that occur after SCV will be described in text or tabulated descriptively.

Patients who have not had the event(s) in question will be censored at the earlier of (1) the PACD and (2) the last study contact when all components of the endpoint in question were assessed. In the analysis of CV death and composites including CV death censoring will occur at the earlier of (1), (2) and (3) the date of death from non-cardiovascular causes. For endpoints not including death, all deaths are censoring events.

Complete endpoint information will be pursued with every effort for all patients regardless of their study medication status, unless they exercise their right to withdraw consent. Patients who have a non-fatal event will continue study follow-up. For patients who withdraw consent and for whom only vital status (known to be alive at study closure, or date of death) may be obtained from public records, the occurrence of all components of the primary endpoint cannot be assessed. Thus, in the main analyses patients will be censored at the time when all elements of the endpoint were assessed for those patients who withdraw consent and for whom only vital status is known from public records. However, the determination of all-cause death will utilise all publicly known mortality data, even that extending beyond date of consent withdrawal. The vital status information will be included in the analysis of all-cause death as a single endpoint, and in sensitivity analysis and tabulations.

Similarly, complete information on the primary endpoint may not be obtained for patients who are lost to follow-up (LTFU). Any such patient will be censored in the analysis of the primary composite endpoint at the last contact where all elements of the endpoint were assessed. A patient will not be recorded as LTFU until the end of the study, after every allowable effort to get in contact has been made. Hence, it is anticipated that the number of patients LTFU will be limited.

In safety time-to-event analysis of bleeding and discontinuation of study drug due to bleeding, patients not having suffered any bleeding event in the given category will be censored at the earlier of SCV, 7 days after last dose of study drug, death, last contact or withdrawal of consent.

4.1.2 Premature permanent discontinuation of study medication

Discontinuation from study medication is not the same as withdrawal from the study. As described in Section 5.8.3 in the CSP there are several options for continuation in the study.

It is expected that complete information on the primary composite endpoint event (and as much as possible of the eCRF data for patients contacted by telephone) will be obtained for all patients who prematurely discontinue study medication, unless they refuse any form of follow-up and withdraw consent or are LTFU. Thus, event free patients who prematurely permanently discontinue study medication will in general not be censored before PACD in the primary ITT analysis.

4.1.3 Investigation of informative censoring

The time-to-event analysis (Cox regression) relies on the assumption of non-informative censoring.

Sensitivity analyses to assess possible effects of informative censoring on the primary endpoint event are described in Section 4.1.1 and Section 4.2.1.1.

4.2 Analysis methods

4.2.1 Primary efficacy variable

The primary efficacy variable, time from randomisation to the first occurrence of any event from the composite of CV death, MI and stroke, will be analysed using the methodology described in Section 4.1. The null hypothesis of no treatment effect,

H_0: HR(ticagrelor divided by placebo) = 1,

versus the alternative hypothesis,

H_1: HR $\neq$ 1,

will be tested at 4.96% two-sided significance level to account for the planned interim analyses with the overall type I error preserved at 5% (see Section 5).

4.2.1.1 Model checking and sensitivity analyses

The assumption of proportional hazards for the factor for treatment group will be assessed visually using log-cumulative hazard plots. The effect of any departures from proportional hazards will be discussed as part of the presentation of results of the analyses.

To assess possible effects of missing data, sensitivity analyses will be done as follows. The event rate in the placebo arm will be used to estimate the intensity of a Poisson process. Based on the missing follow-up time, i.e. the time from censoring to PACD, the expected number of events in the ticagrelor group that could have been observed if the patients had completed the study will be estimated from the Poisson process. The comparison of ticagrelor and placebo will be recalculated with these additional events. If the result is still significant with these additional events, the minimum intensity of the Poisson process that on average gives non-significant results when adding events to the ticagrelor group will be estimated using simulations.

Sensitivity analysis of the primary composite endpoint event will also include analysis

- Including vital status information from patients who have withdrawn consent, where deaths are assumed to be CV deaths
- Including events that occur after PACD but before SCV (i.e. patients who have not had the events will be censored at the earlier of the SCV date, last study contact when all components were assessed or date of death from non-CV causes)
- With a Wei-Lin-Weissfeld model for recurrent event analysis of the events in the primary composite endpoint (Wei 1989), where 3 are the maximum number of events
- With a Lin-Wei-Yang-Ying model for recurrent event analysis of the events in the primary composite endpoint (Lin 2000)
- On treatment, where patients who have not had a primary event will be censored 3, 7 and 30 days after last dose of study drug, respectively
- With events as reported by the investigator
- With treatment and Reduction of Atherothrombosis for Continued Health (REACH) risk score for secondary CV events as covariates in a Cox proportional hazards model (Wilson 2012)
- With treatment and a risk factor as explanatory variables in a Cox proportional hazards model, for the risk factors systolic blood pressure, diastolic blood pressure, pulse pressure and heart rate at baseline, respectively
- With treatment and duration of diabetes (continuous) as explanatory variables in a Cox proportional hazards model.

The proportion of patients with complete follow-up will be presented per treatment group. Patients for whom all components of the primary endpoint event have been ascertained on or after PACD are considered to have complete follow-up.

To explore the consistency between the treatment effect of ticagrelor 60 mg and the overall treatment effect of ticagrelor, a sensitivity analysis of the primary efficacy variable with a Cox proportional hazards model with time dependent covariates will be performed. In this model a factor for treatment group and a time dependent indicator of the dose of study drug for patients treated with ticagrelor are included as covariates. The model can be written:

$$h(t, x_1, x_2(t))=h_0(t)\exp\{\beta_1 \cdot x_1+\beta_2 \cdot x_2(t)\}$$

where $h_0(t)$ is the baseline hazard, β_1 is the coefficient for treatment group, x_1 is defined as 0 for placebo and 1 for ticagrelor, β_2 is the coefficient for the time dependent study drug dose variable for ticagrelor and $x_2(t)$ is equal to 1 if the patient is treated with ticagrelor 60 mg at time t and otherwise equal to 0. Thus, the hazard ratio of ticagrelor 60 mg versus placebo is $\exp\{\beta_1+\beta_2\}$.

Further sensitivity analysis of the consistency of treatment effect for the 60 mg dose compared to the overall treatment effect will be performed by assessing the effect in patients randomised to ticagrelor 60 mg compared to those randomised to ticagrelor 60 mg placebo.

Sensitivity analysis of the primary composite endpoint event will also include analysis on-treatment in patients randomised ticagrelor 60 mg or ticagrelor 60 mg placebo and in patients randomised to ticagrelor 90 mg or ticagrelor 90 mg placebo, respectively. The treatment effect of the randomised dose of ticagrelor versus the randomised dose of ticagrelor placebo will be estimated with a Cox proportional hazards model with treatment as the only explanatory variable. Events that occur up to and including 7 days after last randomised dose of study drug will be included in the analysis, and event free patients will be censored at the earlier of 7 days after last randomised dose of study drug, last contact, non-CV death, SCV or withdrawal of consent.

A landmark analysis of the primary composite endpoint to explore the consistency of treatment effect over treatment dose will be performed. In the analysis, the incidence of primary composite events when the patients are treated with ticagrelor 90 mg or ticagrelor 90 mg placebo, and when patients are treated with ticagrelor 60 mg or ticagrelor 60 mg placebo for patients who were event free up to the day of the first 60 mg dose are examined.

4.2.1.2 Exploratory analyses and subgroup analyses of the primary efficacy variable

Subgroup analyses on the primary efficacy variable, and its components, will be performed to evaluate variation of treatment effect. The subgroups in Table 1 will be examined in Cox regression models with a factor for treatment. Kaplan-Meier estimates, hazard ratios and 95% confidence intervals will be reported for each subgroup category if at least 15 events have occurred within the subgroup category. A test of interaction between treatment and each subgroup will be performed in a Cox proportional hazards model with factors for treatment,

subgroup and the interaction between treatment and subgroup for each subgroup where at least 15 events have occurred in each category.

Table 1 Characteristics and categories for subgroup analysis of the primary composite endpoint

Characteristic	Categories
Age (years)	< 65, 65-75, >75
Sex	Male, Female
Race	White, Black or African American, Asian, Other
BMI (kg/m^2)	≤ 30, >30
Geographic region	Asia and Australia, Europe and South Africa, North America, Central and South America
ASA use at randomisation	Yes, No
ASA dose at baseline (mg)	≤81, >81
HbA1c at baseline (%)	≤ 7 , > 7
eGFR (MDRD) at baseline ($mL/min/1.73\ m^2$)	≤ 60, > 60
Insulin use at baseline	Yes, No
History of Angina	Yes, No
Multivessel Coronary Artery Disease (>1 vessel)	Yes, No
History of PCI	Yes, No
Type of stent	PCI and any DES (including patients with both DES and BMS), PCI and BMS, PCI without stent implantation
History of CABG	Yes, No
History of Coronary Arterial Revascularisation	Yes, No
Statin use at baseline	Yes, No
PPI use at baseline	Yes, No
Current smoker	Yes, No
Duration of diabetes (years)	≤10, >10
History of any diabetes complications at baseline	Yes, No
Number of prior diabetes complications	0, 1, 2, 3-4
History of Peripheral Arterial Occlusive disease	Yes, No
History of Poly-vascular disease	Yes, No
Number of prior vascular beds	1, 2, 3
Time since most recent PCI (years)	<1, 1-3, >3

Characteristic	Categories
Time since most recent CABG (years)	≤5, >5

BMI = Body Mass Index, BMS = Bare metal stent, CABG = Coronary Artery Bypass, DES = Drug eluting stent, eGFR = estimated Glomerular Filtration Rate, HbA1c = Haemoglobin A1c, MDRD = Modification of Diet in Renal Disease, PCI = Percutaneous Coronary Intervention, PPI = Proton Pump Inhibitor. Baseline is defined as before or at the day of randomisation visit. Poly-vascular disease is defined as history of more than one vascular bed (out of the three possible vascular beds: coronary arterial disease, peripheral arterial occlusive disease, and carotid artery stenosis or cerebral revascularisation.

In addition to subgroup characteristics listed in Table 1, analyses in a specific country subgroup may be done and reported separately to meet requirements for regulatory submissions to local authorities.

4.2.2 Secondary efficacy variables

The secondary efficacy variables will be analysed using the methodology described in Section 4.1. The analyses in section 4.2.1.2 will be repeated for the secondary efficacy variables.

4.2.3 Confirmatory analysis

The analysis of the primary variable described in Section 4.2.1 and the four secondary efficacy variables listed in Section 3.2.2 will comprise the confirmatory analysis. In order to address the issue of multiple testing a hierarchical test sequence will be used. The sequence will start with the primary variable and then follow in the order specified in Section 3.2.2.

The testing at the interim analysis will be at the two-sided 0.1% significance level, while a two-sided 4.96% significance level will be used at the final analysis. In what follows the testing at the final analysis is described, while further detail about the testing at the interim analysis is provided in Section 5.

Only if the treatment effect on the primary efficacy variable is significant at the two-sided 4.96% significance level, will the secondary efficacy variables be tested in a confirmatory sense in the order given in Section 3.2.2. The hypothesis testing will continue at the two-sided 4.96% significance level until the first statistically non-significant treatment difference ($p \geq 0.0496$) is observed. Secondary efficacy variable will be tested in an exploratory manner if there has been at least one non-significant test earlier in the sequence.

4.2.4 Exploratory efficacy variables

Time to event variables will be analysed using the methodology described in Section 4.1.

4.2.5 Health Economics

The variables collected to support health economic evaluation are the EQ-5D questionnaire, administered every 6 months at on-site visits from Visits 2 throughout the study until SCV, and health care resource utilisation data for hospitalisations will be presented descriptively for the FAS per treatment. Further details and other health economic analyses will be specified in

a separate health economic analysis plan and presented in a separate report and are therefore not addressed in this SAP.

4.2.6 Analysis of safety data

All safety analyses will be based on the safety analysis set defined in Section 2.1.2.

Exposure to study drug, reasons and time to discontinuation of study drug, local laboratory data at baseline and vital signs will be summarised per treatment group using descriptive statistics.

4.2.6.1 Bleeding events

Bleeding events will be categorised on the basis of

- Category according to TIMI and PLATO definitions (as defined in the CEC charter), BARC bleeding profiles
- Provocation (ie, spontaneous, procedural and traumatic).

Bleeding events will be summarised by treatment group. The number of transfused blood units will be summarised per treatment group.

The total number of bleeding events, counting multiple events per patient, will be presented.

4.2.6.2 Time to event analysis of bleedings

Time to bleeding event variables will be analysed using the same methodology as for the efficacy variables as described in Section 4.1.

Explorative analysis of time to bleeding for selected subgroups will be performed for the main bleeding categorisations (TIMI major, TIMI major or minor, and PLATO major). Subgroups will be the groups defined for the efficacy analysis in Section 4.2.1.2.

Sensitivity analysis of TIMI major bleeding to address the consistency of the overall effect of ticagrelor on bleeding compared to the 60 mg dose will be performed with a Cox proportional hazards model with time dependent covariates, as described in Section 4.2.1.1 for the primary variable.

Furthermore, a sensitivity analysis of TIMI major bleeding on-treatment in patients randomised to ticagrelor 60 mg or ticagrelor 60 mg placebo and in patients randomised to ticagrelor 90 mg or ticagrelor 90 mg placebo will be performed. These analyses include events that occur up to and including 7 days after last randomised dose of study drug, and event free patients will be censored at the earlier of 7 days after last randomised dose of study drug, last contact, death, SCV or withdrawal of consent.

A landmark analysis of TIMI major bleeding to explore the consistency of treatment effect over treatment dose will be performed. In the analysis, the incidence of TIMI major bleedings

when the patients are treated with ticagrelor 90 mg or ticagrelor 90 mg placebo, and when patients are treated with ticagrelor 60 mg or ticagrelor 60 mg placebo for patients who were event free up to the day of the first 60 mg dose are examined.

4.2.6.3 SAE and non-serious AE of interest

Each AE will be assigned to on/off treatment period as

- Baseline period: The time before randomisation
- On treatment: The time from randomisation until 7 days after last dose study drug
- Off treatment: More than 7 days after last dose of study drug.

AEs will be assigned to the period where they start.

AEs of interest, DAEs as well as SAEs will be evaluated. Summaries, by system organ class and preferred term using MedDRA, will be presented by treatment group using descriptive statistics. All AEs relating to bleeding will be summarised separately. A subset of these summaries will be repeated for patients randomised to ticagrelor 60 mg or ticagrelor 60 mg placebo as a sensitivity analysis.

5. INTERIM ANALYSES

One efficacy interim analysis will be performed by the DMC. The DMC charter contains more information about the DMC procedures. A copy of the treatment codes will be made available to the statistician on the DMC. The Executive Committee and AstraZeneca will not be made aware of the treatment codes until after clean file and database lock are declared. Similarly, all summary output reviewed at each DMC meeting will be held in confidence by the DMC members until the end of the study when clean file and database lock are declared.

The interim analysis will be performed following the accrual and confirmation by adjudication of 517 primary events. The stopping boundary at the interim analysis is a two-sided p-value <0.001 for both primary endpoint event (CV death, MI, and stroke) and for CV death (the 1st secondary efficacy variable). The interim p-value is small enough for the final analysis to be conducted at a significance level of 4.96%, with the family wise error rate controlled at 5.00%. These boundaries were estimated using a Haybittle-Peto procedure (Haybittle 1971, Peto 1976).

If a recommendation to stop the study is made at the interim, all subsequent testing will be done at the same significance level as for the interim.

6. CHANGES OF ANALYSIS FROM PROTOCOL

Eight exploratory objectives have been added since these were considered to be of interest for scientific exchange.

7. REFERENCES

Wei 1989
Wei LJ, Lin DY and Weissfeld L. Regression Analysis of Multivariate Incomplete Failure Time Data by Modeling Marginal Distributions. Journal of the American Statistical Association 1989;84:1065-1073.

Lin 2000
Lin DY, Wei LJ, Yang I and Ying Z. Semiparametric regression for the mean and rate functions of recurrent events. J. R. Stat. Soc. B 2000:62:711-730.

Wilson 2012
Wilson PWF, D'Agostino Sr R, Bhatt DL, Eagle K, Pencina MJ, Smith SC, et al. An international Model to Predict Recurrent Cardiovascular Disease. The American Journal of Medicine 2012;125:695-703.

Haybittle 1971
Haybittle JL. Repeated assessment of results in clinical trials of cancer treatment. Brit J Radiology 1971;44:793-7.

Peto 1976
Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient: I. Introduction and design. Brit J Cancer 1976;34:585-612.