AstraZeneca

Statistical Analysis Plan

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A Randomised, Double-Blind, Placebo-Controlled, International, Multicentre, Phase III Study to Investigate the Efficacy and Safety of Ticagrelor and ASA Compared with ASA in the Prevention of Stroke and Death in Patients with Acute Ischaemic Stroke or Transient Ischaemic Attack

[THALES – Acute Stroke or Transient IscHaemic Attack Treated with TicAgreLor and ASA for PrEvention of Stroke and Death]

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Study Statistician

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Global Product Statistician

[redacted] Date

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse event
AIS	Acute ischaemic stroke
ASA	Acetylsalicylic acid
BMI	Body mass index
DAE	Premature permanent discontinuation of IP due to adverse event
DMC	Data monitoring committee
FAS	Full analysis set
GUSTO	Bleeding scale: Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries
HR	Hazard ratio
IP	Investigational product
mRS	Modified Rankin scale
NIHSS	National Institute of Health Stroke Scale
SAE	Serious adverse event
TIA	Transient ischaemic attack

AMENDMENT HISTORY

Date	Brief description of change
09 February 2017	First version published
14 December 2017	1.3 Decimal places added to the significance level
	3.2 Clarification that ischaemic strokes will include strokes classified as "Undetermined" added
	4.1 Reference to the Integrated Quality and Risk Management Plan added
	4.2.1 Decimal places added to the significance level
	4.2.1 Sensitivity analysis updated
	4.2.3 AEs with outcome death added to the safety variables that will be summarised
	5 Decimal places added to significance levels
	5 Critical value added
11 June 2018	1.3 Number of events decreased from 770 to 764, significance level increased from 4.760% to 4.988%, and critical value increased from 0.867 to 0.868, based on updates to the Interim Analysis section
	4.2.1 Significance level updated to 4.988%
	4.2.2 Significance level updated to 4.988%
	4.2.4 Clarifications added regarding the analysis of patients with ipsilateral atherosclerotic stenosis
	5 The p-value at the interim decreased from 0.00762 to 0.001 and Lan-DeMets changed to the Haybittle-Peto procedure. Based on this update, the number of events at the interim have decreased from 462 to 458, the critical value at the interim has decreased from 0.780 to 0.735, and the significance level at the final analysis has increased from 4.760% to 4.988%
	5 A futility analysis has been added
27 May 2019	Signature pages. New study statistician ([redacted]) and global product statistician ([redacted])
	1.2 Number of patients decreased from 13000 to 11000 based on updated study assumptions. Timing of interim analysis changed from 60% to 70% of the primary events
	1.3 Assumed hazard ratio decreased from 0.805 to 0.775 and power increased from 85% to 90%. Based on these changes, the number of events has decreased from 764 to 647, the number of patients has decreased from 13000 to 11000, the significance level has increased from 4.988% to 4.996%, and the critical value has decreased from 0.868 to 0.857

Date	Brief description of change
	3 Rules for handling of data when Visit 3 has occurred outside of the visit window added
	3.3 Clarification regarding patients who never received any dose of IP added
	4.2.1 Significance level updated to 4.996%
	4.2.1 Sensitivity analysis 'on treatment' added
	4.2.1 Rule for handling of data when Visit 4 has been performed outside of the visit window added
	4.2.1.1 Time from index event to loading dose added to subgroup variables
	4.2.2 Significance level updated to 4.996%
	4.2.3 Analyses 'on treatment' added
	4.2.4 Clarification that strokes need to occur prior to or at the date of mRS measurement to be classified as non-disabling/disabling added
	5 Timing of interim analysis changed from 60% to 70% of the primary events. The number of events at the interim has decreased from 458 to 453, the critical value at the interim has decreased from 0.735 to 0.734, and the significance level at the final analysis has increased from 4.988% to 4.996%. The futility limit has decreased from 0.956 to 0.933
09 December 2019	2.1 Definition of safety analysis set and actual treatment added
	3.2 Clarification added to censoring rules in the event of last clinical event assessment occurring later than the date of death
	4.2.4 Added statement that ipsilateral atherosclerotic stenosis ≥30% is the main category
	4.2.4 Added peripheral arterial occlusive disease to definition of atherosclerosis in any vascular bed

1 STUDY DETAILS

1.1 Study objectives

1.1.1 Primary objective

- To demonstrate superior efficacy of ticagrelor and ASA compared with placebo and ASA in AIS/TIA patients in the prevention of the composite of stroke and death at 30 days

1.1.2 Secondary objectives

- To demonstrate superior efficacy of ticagrelor and ASA compared with placebo and ASA in AIS/TIA patients in the prevention of ischaemic stroke at 30 days
- To demonstrate superior efficacy of ticagrelor and ASA compared with placebo and ASA in AIS/TIA patients in reducing overall disability at 30 days

1.1.3 Safety objective

- To assess the safety of ticagrelor and ASA compared with that of placebo and ASA in AIS/TIA patients, in particular with respect to major bleeding events

1.1.4 Exploratory objectives

- To assess the efficacy of ticagrelor and ASA compared with placebo and ASA in AIS/TIA patients with ipsilateral atherosclerotic stenosis in the prevention of stroke and death at 30 days
- To assess the efficacy of ticagrelor and ASA compared with placebo and ASA in AIS/TIA patients in reducing disabling strokes at 30 days
- To describe health-related quality of life in AIS/TIA patients after treating with ticagrelor and ASA or placebo and ASA for 30 days

1.2 Study design

This is a randomised, placebo-controlled, double-blind, parallel-group, international, multicentre Phase III study to test the hypothesis that ticagrelor and acetylsalicylic acid (ASA) is superior to ASA in preventing stroke and death in patients with acute cerebral ischaemia. Patients with acute ischaemic stroke (AIS) or transient ischaemic attack (TIA) before randomisation and who fulfil all of the eligibility criteria will be randomised within 24 hours of symptom onset in a 1:1 ratio to ticagrelor or placebo, with all patients receiving ASA. The study includes 4 visits: on Day 1 (enrolment/randomisation; Visit 1), on Day 5 to 9 (Visit 2), on Day 30 to 34 (end of treatment period; Visit 3), and on Day 60 to 64 (end of study; Visit 4).

A loading dose of 180 mg ticagrelor or placebo will be given on Day 1 as soon as possible after randomisation. Thereafter, patients will receive either ticagrelor 90 mg twice daily or placebo twice daily. All patients should be treated with open-label ASA.

Approximately 11000 patients will be randomised at approximately 450 study sites. The study is event-driven and the final number of randomised patients will be determined based on blind data review. A data monitoring committee (DMC) will conduct an interim analysis for efficacy after approximately 70% of the primary events have been collected.

1.3 Number of subjects

At least 647 primary endpoint events are needed to provide 90% power assuming a hazard ratio (HR) of 0.775 in favour of ticagrelor at the significance level of 4.996%, adjusted for the planned efficacy interim analysis (647 events corresponding to a critical value of 0.857). Based on data from the SOCRATES study, a primary endpoint rate of 6.7% in the placebo group is assumed at 30 days following randomisation. Hence, randomising approximately 11000 patients to ticagrelor or placebo in a 1:1 ratio is expected to yield the 647 events needed. The study is event-driven and the final number of randomised patients will be determined based on blind data review.

2 ANALYSIS SETS

2.1 Definition of analysis sets

All variables, including safety variables, will be analysed using the full analysis set (FAS). All patients who have been randomised to investigational product (IP) will be included in the FAS irrespective of their protocol adherence and continued participation in the study. Patients will be analysed according to their randomised IP irrespective of whether the event occurred before or following discontinuation of IP.

Although the study objectives will be analysed based on the FAS and randomised treatment, a safety analysis set and actual treatment group will be included in the Analysis Data Model datasets. The safety analysis set will include all patients who have received at least 1 dose of randomised IP. Actual treatment will be the treatment actually given irrespective of randomisation. If a patient has received both ticagrelor and placebo, actual treatment group will be the treatment group the patient was randomised to.

2.2 Violations and deviations

Important protocol deviations will be identified prior to database lock, and will include, but not be limited to:

- Patients who were randomised but did not meet eligibility criteria

- Patients who received prohibited concomitant medication
- Patients who received the wrong IP at any time during the study
- Patients who were randomised but took no IP

Protocol deviations will not imply exclusion from any analyses.

3 PRIMARY AND SECONDARY VARIABLES

3.1 Primary variable

The primary variable is the time from randomisation to first subsequent stroke or death. Patients who have not experienced either of these events will be censored at Visit 3, Day 34, or the date of last event assessment, whichever occurs earlier. If Visit 3 has occurred within the visit window, Day 30 to 34, events will be included up to the date of Visit 3 (inclusive). If Visit 3 has occurred outside of the visit window (or is missing), it will be replaced by Day 34 for event inclusion and censoring.

Time will be calculated as the number of days plus one between the date of randomisation and the date of the first occurrence of the event, or, if no event has occurred, the date of censoring.

3.2 Secondary variables

The secondary variables, presented in the hierarchical order in which they will be tested, are:

1 Time from randomisation to first subsequent ischaemic stroke (including strokes classified as "Undetermined")
2 mRS score >1 at Visit 3

For the time-to-event variable, patients who have not experienced the event will be censored at Visit 3, Day 34, or the date of last event assessment, whichever occurs earlier. If Visit 3 has occurred outside of the visit window (or is missing), see Section 3.1. Furthermore, if the last clinical event assessment has occurred later than the date of death, the date of death will be used as the date of last clinical event assessment (applicable for all time-to-event variables not including death).

The mRS score for patients who have died prior to Visit 3 will by definition be 6. No other imputation for missing data will be made. However, if Visit 3 has occurred prior to Day 30 and the patient has died prior to or at Day 34, the mRS score will be 6.

3.3 Safety variables

The safety variables are:

- Time from randomisation to first bleeding event that fulfils SAE criteria and is categorised as GUSTO Severe
- Time from randomisation to first intracranial haemorrhage or fatal bleeding event
- Time from randomisation to first bleeding event that fulfils SAE criteria and is categorised as GUSTO Moderate/Severe
- Time from randomisation to premature permanent discontinuation of IP due to bleeding
- Occurrence of SAE
- Occurrence of DAE

For the time-to-event variables, patients who have not experienced the event will be censored at Visit 3, Day 34, or the date of last event assessment, whichever occurs earlier; or, for the time from randomisation to discontinuation due to bleeding variable only, the day of the last dose of IP, if earlier. Patients who never received any dose of IP will be censored at Day 1 for the discontinuation due to bleeding variable. If Visit 3 has occurred outside the visit window (or is missing), see Section 3.1.

3.4 Exploratory variables

The exploratory variables are:

- Time from randomisation to first subsequent stroke or death in patients with ipsilateral atherosclerotic stenosis
- mRS score >2 at Visit 3 in patients with subsequent stroke
- EQ-5D-5L profile

For the time-to-event variable, patients who have not experienced the event will be censored at Visit 3, Day 34, or the date of last event assessment, whichever occurs earlier. If Visit 3 has occurred outside the visit window (or is missing), see Section 3.1.

The mRS score for patients who have died prior to Visit 3 will by definition be 6. If Visit 3 has occurred prior to Day 30 and the patient has died prior to or at Day 34, the mRS score will be 6. Furthermore, for the disabling stroke variable (mRS score >2 at Visit 3 in patients with subsequent stroke), the stroke must have occurred prior to or at the date of the mRS measurement.

4 ANALYSIS METHODS

4.1 General principles

All analyses will be based on the intent-to-treat principle, using the FAS. In time-to-event analyses, the treatment groups will be compared using a Cox proportional hazards model with a factor for treatment group, using the Efron method for ties. P-values and 95% confidence

intervals for the HR will be based on the Wald statistic. In summary tables of these analyses, in addition to HR with confidence intervals and p-values, presentations will include the number and percentage of patients with events and Kaplan-Meier estimates of the event rate per treatment group. Kaplan-Meier estimates of the cumulative proportion of patients with events will be calculated and plotted, with the number of patients at risk indicated below the plot at specific time points. If the total number of events is less than 15, only the number and percentage of patients with events will be presented, but no Kaplan-Meier estimates, HRs, confidence intervals, or p-values.

No multiplicity adjustment will be made to confidence intervals as they will be interpreted descriptively and used as a measure of precision. The primary variable and the secondary variables will be included in a confirmatory testing procedure.

Continuous variables will be summarised by treatment group 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.

For a description of the critical to quality factors, and processes to ensure the quality of study conduct and the validity of study results, see the Integrated Quality and Risk Management Plan.

4.2 Analysis methods

4.2.1 Analysis of the primary variable

For the primary variable, time from randomisation to first subsequent stroke or death, the null hypothesis of no treatment effect, H0: HR (ticagrelor divided by placebo) = 1, versus the alternative hypothesis, H1: HR ≠1, will be tested at the 4.996% 2-sided significance level.

In the summary table of the primary analysis, separate analyses of each of the components (stroke, death) will also be presented.

If there are patients lost to follow-up in the ticagrelor group, a sensitivity ("tipping point") analysis may be performed by adding events to the ticagrelor group (at the time of censoring) until a non-significant result is obtained.

A sensitivity analysis 'on treatment' will be performed, including events from the date of the first dose of IP up to the date of the last dose of IP + 7 days (inclusive). Event-free patients will be censored at the date of the last dose of IP + 7 days or the date of last event assessment, whichever occurs earlier. Patients who never received any dose of IP will be censored at Day 1.

As an explorative analysis, primary events up to the end of the follow-up period will be analysed by repeating the primary analysis with event-free patients censored at Visit 4 (or Day 64) instead of Visit 3 (or Day 34). If Visit 4 has occurred within the visit window, Day 60 to 64, events will be included up to the date of Visit 4 (inclusive). If Visit 4 has occurred outside of the visit window (or is missing), it will be replaced by Day 64 for event inclusion and censoring.

4.2.1.1 Subgroup analyses of the primary variable

Subgroup analyses of the primary variable will be performed to evaluate variation of treatment effect. Tests for interaction between treatment and each subgroup variable will be performed in Cox proportional hazards models with factors for treatment, subgroup variable, and the interaction between treatment and subgroup variable if at least 15 events have occurred in each subgroup category.

The subgroup categories will be examined in Cox proportional hazards models with a factor for treatment group. Kaplan-Meier estimates, HRs, and 95% confidence intervals will be reported if at least 15 events have occurred within the subgroup category. The following subgroup variables and categories will be assessed:

- Age (<65, 65-75, >75 years)
- Sex (Male, Female)
- Race (White, Black, Asian, Other)
- Weight (<70, ≥70 kg)
- BMI (<30, ≥30 kg/m^2)
- Geographic region (Asia and Australia, Europe, North America, Central and South America)
- Diagnosis of index event (Stroke NIHSS score ≤3, Stroke NIHSS score >3, TIA)
- Time from index event to randomisation (<12, ≥12 hours)
- Time from index event to loading dose (<12, ≥12 hours)
- Diabetes mellitus (Yes, No)
- Hypertension (Yes, No)
- Prior ischaemic stroke or TIA (Yes, No)
- Prior ischaemic heart disease [defined as any of coronary artery bypass grafting, myocardial infarction, percutaneous coronary intervention, or coronary artery disease] (Yes, No)
- Prior ASA (Yes, No)
- Prior statin treatment (Yes, No)
- Smoking status (Current, Former, Never)

The effect of age, weight, BMI, time from index event to randomisation, and time from index event to loading dose may also be further analysed using continuous measurements.

4.2.2 Analysis of the secondary variables

The secondary variables will be included in the confirmatory testing procedure. Only if the treatment effect on the primary variable is significant at the 4.996% level will the secondary variables be tested in a confirmatory sense in the hierarchical order specified in Section 3.2. The hypothesis testing will continue at the 4.996% significance level until the first statistically non-significant treatment difference ($p \geq 0.04996$) is observed.

The time from randomisation to first subsequent ischaemic stroke will be analysed in the same manner as the primary variable. The proportion of patients with mRS score >1 at Visit 3 will be analysed using a logistic regression model with treatment group, history of stroke, and baseline NIHSS score as explanatory variables. A sensitivity analysis will be performed where missing mRS scores will be imputed as >1.

4.2.3 Analysis of the safety variables

The time-to-event safety variables will be analysed in the same manner as the primary variable, but will not be included in the confirmatory testing procedure. Sensitivity analyses 'on treatment' will be performed (see Section 4.2.1). Subgroup analyses, as specified in Section 4.2.1.1, will be performed for GUSTO Severe bleeding events. Furthermore, the analysis of GUSTO Severe bleeding events will be repeated with event-free patients censored at Visit 4 (or Day 64) instead of Visit 3 (or Day 34).

SAEs, DAEs, and AEs with outcome death summarised by system organ class and preferred term using the Medical Dictionary for Regulatory Activities, will be presented by treatment group using descriptive statistics.

4.2.4 Analysis of the exploratory variables

The time from randomisation to first subsequent stroke or death in patients with ipsilateral atherosclerotic stenosis will be analysed in the same manner as the primary variable. Analyses in four categories will be performed:

- Patients with ipsilateral atherosclerotic stenosis ≥50% (extracranial and intracranial combined and separately)
- Patients with ipsilateral atherosclerotic stenosis ≥30% (extracranial and intracranial combined and separately) [main category for reporting]
- Patients with atherosclerosis in any vascular bed (including cerebrovascular atherosclerosis or medical history of coronary artery bypass grafting, myocardial infarction, percutaneous coronary intervention, coronary artery disease, or peripheral arterial occlusive disease)

- Patients with ipsilateral stenosis who undergo carotid endarterectomy/intervention

The proportion of patients with subsequent stroke and mRS score >2 at Visit 3 will be analysed using a logistic regression model with treatment group, history of stroke, and baseline NIHSS score as explanatory variables. Additional analyses of disabling stroke will be performed by varying the threshold for the mRS score (>1 and >3), and by utilising the 3 categories no stroke, non-disabling stroke (mRS score ≤2), disabling stroke (mRS score >2). Strokes need to occur prior to or at the date of the mRS measurement to be classified as non-disabling/disabling.

EQ-5D-5L data will be presented by treatment group using descriptive statistics.

5 INTERIM ANALYSES

One interim analysis will be performed by the DMC following the accrual of 70% of the planned primary events (453). The efficacy stopping boundary at the interim is a 2-sided p-value <0.001 for the primary endpoint (corresponding to a critical value of 0.734). The interim p-value is small enough for the final analysis, based on the accrual of all events, to be conducted at a significance level of 4.996%, with the family-wise error rate controlled at 5.00%. This boundary was estimated in East V6.4 (copyright 1994-2016, Cytel Inc) using the Haybittle-Peto procedure.

If a recommendation to stop the study for efficacy is made at the interim, all subsequent testing of secondary efficacy variables will be done at a significance level of 0.1%.

The study may be stopped for futility if the observed HR for the primary endpoint is >0.933 (taking all available study information into account), corresponding to a predictive power of 5%.

The DMC will have access to the individual treatment codes and will be able to merge these with the collected study data while the study is ongoing. AstraZeneca will not be made aware of the treatment codes, and will have no knowledge of unblinded results, until after clean file and database lock have been declared. The DMC charter details roles, responsibilities, and procedures to ensure maintenance of the blinding and integrity of the study.

6 CHANGES OF ANALYSIS FROM PROTOCOL (NOT APPLICABLE)

7 REFERENCES (NOT APPLICABLE)

8 APPENDIX (NOT APPLICABLE)

SIGNATURE PAGE

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