Revised Clinical Study Protocol	
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A multicenter, single arm, open label, Phase IV study to evaluate safety and to describe the cumulative incidence of major cardiovascular events of Ticagrelor in Taiwanese patients with non ST-segment elevation myocardial infarction

Sponsor:

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AstraZeneca Research and Development site representative

[redacted] Date

[redacted]

The following Amendment(s) and Administrative Changes have been made to this protocol since the date of preparation:

Amendment No.	Date of Amendment	Local Amendment No:	Date of Local Amendment
1	13th November 2014		

Administrative Change No.	Date of Administrative Change	Local Administrative Change No.	Date of Local Administrative Change
1	22nd June 2015		

REVISED PROTOCOL SYNOPSIS

A multicenter, single arm, open label, Phase IV study to evaluate safety and to describe the cumulative incidence of major cardiovascular events of Ticagrelor in Taiwanese patients with non ST-segment elevation myocardial infarction

National Co-ordinating Investigator

[redacted]

Study centre(s) and number of subjects planned

This study will be conducted in approximately 15 investigational centres in Taiwan. It is expected that approximately 100 patients will be enrolled into study treatment.

Study period		Phase of development
Estimated date of first subject enrolled	Q1 2015	Phase IV
Estimated date of last subject completed	Q2 2017	

Objectives

Primary objective

To describe the safety and tolerability of Ticagrelor, by assessment of the bleeding events and other serious adverse events (SAEs) during 1year follow up in Taiwanese non ST-elevation MI (NSTEMI) patients.

To describe the efficacy of Ticagrelor, by cumulative incidence of major CV events (including CV death, MI and stroke) during 1 year follow up in Taiwanese NSTEMI patients.

Study design

This is a multicenter, single arm, open label, Phase IV study to evaluate safety and to describe the incidence of major CV events of ticagrelor in Taiwanese patients with NSTEMI.

Target subject population

Ticagrelor treated Taiwanese patients 20 years of age and over with non-ST elevation MI.

Investigational product, dosage and mode of administration

Ticagrelor 180mg loading dose taken orally, followed by 90mg bd

Comparator, dosage and mode of administration (Not applicable)

Duration of treatment

12 months.

Outcome variable(s):

Primary variables

- PLATO-defined fatal/life-threatening bleedings during 1year follow up in Taiwanese NSTEMI patients treated with ticagrelor.

- PLATO-defined major bleedings during 1year follow up in Taiwanese NSTEMI patients treated with ticagrelor.

- PLATO-defined major + minor bleedings during 1year follow up in Taiwanese NSTEMI patients treated with ticagrelor.

- Serious adverse events other than bleeding during 1year follow up in Taiwanese NSTEMI patients treated with ticagrelor.

- Major CV events (cardiovascular death, MI or stroke) during 1 year follow up in Taiwanese NSTEMI patients treated with Ticagrelor.

Statistical methods

The primary efficacy analysis will be based on the intent-to-treat principle using the full analysis set of investigator adjudicated events. The analysis set will include all patients who have taken at least one dose of study medication, regardless of protocol adherence or continued participation in the study. The cumulative incidence will be presented with K-M% with 95% CI.

Statistical methods will be descriptive. For continuous data, descriptive statistics will be presented as number of patients (n), mean, standard deviation (SD), median, minimum and maximum. For categorical data, the frequency and percentage of patients in each category will be presented. Counts that are zero will be displayed as “0”. Percentages will be based on non-missing data unless otherwise specified.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol

Abbreviation or special term	Explanation
ACS	Acute coronary syndrome
AE	Adverse event (see definition in Section 6.4.1)
ALT	Alanine aminotransferase
ARR	Absolute risk reduction
ASA	Acetylsalicylic acid
AST	Aspartate aminotransferase
A-V	Atrial-ventricular
AZ	AstraZeneca
bd	twice daily
CABG	Coronary artery bypass graft
CI	Confidence Interval
CK-MB	Creatinine kinase-MB
eCRF	Case Report Form (electronic)
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CV	Cardiovascular
CYP3A	Cytochrome P450 3A
DAE	Discontinuation of Investigational Product due to Adverse Event
ECG	Electrocardiogram
EC	Ethics Committee, synonymous with Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GI	Gastrointestinal
Hb	Haemoglobin
HR	Hazard ratio
ICH	International Conference on Harmonisation
IP	Investigational Product

Abbreviation or special term	Explanation
IP	Investigational Product
KM	Kaplan-Meier
LBBB	Left bundle branch block
LSLV	Last Subject Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MRI	Magnetic resonance imaging
NSAIDs	Non-steroidal anti-inflammatory drugs
NSTEMI	Non ST-segment elevation myocardial infarction
OAE	Other Significant Adverse Event (see definition in Section 11.2.1)
PGI2	Prostacyclins
PCI	Percutaneous coronary intervention
PI	Principal Investigator
PLATO	PLATelet inhibition and patient Outcomes
PRBC	Packed red blood cells
PTDV	Premature treatment discontinuation visit
RRR	Relative risk reduction
SAE	Serious adverse event (see definition in Section 6.4.2).
SUSAR	Suspected Unexpected Serious Adverse Reaction
TFDA	Taiwan Food and Drug Administration
TNT/TNI	Troponin T or I
ULN	Upper limit of normal range
WBDC	Web Based Data

1. INTRODUCTION

1.1 Background

Ticagrelor is a direct-acting, oral, reversibly binding $P2Y_{12}$ receptor antagonist approved for the reduction of thrombotic events in patients with acute coronary syndrome (ACS).

The PLATO (PLATelet inhibition and patient Outcomes) study was an 18,624 patient randomized, double-blind, parallel group, phase III, efficacy and safety study of ticagrelor compared with clopidogrel for prevention of vascular events in patients with Acute Coronary Syndromes (Wallentin 2009). Ticagrelor was superior to clopidogrel in the prevention of thrombotic events (relative risk reduction (RRR) 16%, absolute risk reduction (ARR) 1.9%) of the composite efficacy endpoint (cardiovascular (CV) death, myocardial infarction (MI) and stroke) over 12 months. The difference in treatments was driven by CV death and MI with no difference on strokes. Ticagrelor demonstrated a statistically significant RRR of 16% (ARR 1.1%) for MI and a 21% RRR (ARR 1.1%) for CV death. In PLATO, time to first PLATO-defined Major bleeding for ticagrelor did not differ significantly from that of clopidogrel. There were few fatal bleeding events in the study, 20 (0.3%) for ticagrelor and 23 (0.3%) for clopidogrel. When minor bleeding was included, combined PLATO-defined Major and Minor bleeding events were significantly higher on ticagrelor than on clopidogrel.

The PLATO study included 1,056 patients with acute coronary syndrome (ACS) in Asia, as follows:

Country	Number of patients enrolled
Taiwan	92
China	416
Hong Kong	16
Indonesia	62
Malaysia	56
Philippines	78
Singapore	64
South Korea	120
Thailand	152

Of 92 Taiwanese patients, 9 reported major bleeding events (3 patients randomised to ticagrelor, and 6 patients randomised to clopidogrel). The planned study will provide further safety profile of ticagrelor in Taiwanese ACS patients.

Further information regarding the background, pharmacological class, properties, and mechanism of action of ticagrelor can be found in the package insert for ticagrelor.

1.2 Research hypothesis

Ticagrelor is well tolerated, and effective in Taiwanese NSTEMI patients.

1.3 Rationale for conducting this study

Post-hoc analyses in subgroups of Asian and Taiwanese patients are shown (Table 1).

Table 1 Efficacy and bleeding in the overall PLATO cohort, Asia and Taiwan

	Ticagrelor		Clopidogrel		HR (95% CI)
	n	N with events (KM%)	n	N with events (KM%)	
Primary efficacy endpoint (composite of CV death, MI, stroke,)					
Overall	9333	864 (9.8)	9291	1014 (11.7)	0.84 (0.77-0.92)
Asian	533	67 (13.0)	523	79 (16.2)	0.82 (0.59-1.14)
Taiwan	46	7 (15.7)	46	5 (11.1)	1.41 (0.45-4.46)
Primary safety endpoint (PLATO-defined total major bleed)					
Overall	9235	961 (11.6)	9186	929 (11.2)	1.04 (0.95-1.13)
Asian	526	53 (10.9)	515	48 (10.8)	1.07 (0.73-1.59)
Taiwan	44	3 (7.2)	46	6 (15.9)	0.51 (0.13-2.05)
Fatal/life-threatening bleed					
Overall	9235	491 (5.8)	9186	480 (5.8)	1.03 (0.90-1.16)
Asian	526	33 (6.8)	515	29 (6.1)	1.10 (0.67-1.81)
Taiwan	44	2 (4.9)	46	5 (11.8)	0.40 (0.08-2.08)
Fatal bleed					
Overall	9235	20 (0.3)	9291	23 (0.3)	0.87 (0.48, 1.59)
Asian	526	2 (0.5)	515	2 (0.4)	0.97 (0.14, 6.87)
Taiwan	44	0 (0)	46	0 (0)	

KM: Kaplan-Meier, MI: myocardial infarction, CV: cardiovascular, HR: hazard ratio
Efficacy analyses performed on Full analysis set, safety analyses on Safety analysis set

The Taiwanese cohort had a much smaller sample size and a correspondingly wider confidence interval (CI) in all analyses compared with the overall study. The hazard ration (HR) for the comparison of ticagrelor to clopidogrel for the primary composite endpoint of CV death, MI, and stroke (HR 1.41 [95% CI 0.45, 4.46]; p=0.5534) was not statistically significant in the Taiwan cohort alone.

In the Taiwanese cohort, 'Total Major' bleeding was numerically less frequent in the ticagrelor patients (HR 0.51 [95% CI 0.13, 2.05]; p=0.3453). It is concluded that this result is consistent with PLATO overall, and that 'Total Major' bleeding in the Taiwanese cohort did not differ between the treatment groups.

On 11-May-2012, Ticagrelor was approved by the Taiwan Food and Drug Administration (TFDA); AstraZeneca (AZ) was required by TFDA on 22 July 2014 to conduct a post-approval study to describe the efficacy and safety profile of Ticagrelor in Taiwanese NSTEMI patients

1.4 Benefit/risk and ethical assessment

Ticagrelor is approved in more than 95 countries worldwide to prevent thrombotic events in patients with ACS. Current guidelines from the American Heart Association/American College of Cardiology, European Society of Cardiology and American College of Chest Physicians recommend ticagrelor and low maintenance dose acetylsalicylic acid (ASA) for treatment of ACS (Jneid 2012, Steg 2012, Hamm 2011, Vandvik 2012).

More than 53000 healthy subjects or patients have been exposed to ticagrelor in the completed phase I, II and III studies and the overall conclusion based on these studies is that ticagrelor has generally been well tolerated. In the PLATO study, ticagrelor reduced the primary efficacy composite endpoint of CV death/ MI/stroke by 16% (p=0.0003), MI by 16% (p=0.0045), CV death by 21% (p=0.0013) and all-cause mortality by 22% (nominal p value = 0.0003), as compared to clopidogrel. Despite greater inhibition of platelet aggregation with ticagrelor, the Total Major bleeding events with ticagrelor did not differ significantly from that of clopidogrel treatment (11.6% vs 11.2%, HR 1.04, [95% CI 0.95, 1.13]; p=0.4336). In addition, ticagrelor and clopidogrel did not differ significantly in fatal bleeding, or fatal/life-threatening bleeding. However, more non-CABG major bleeding, including non-procedural bleeding, was reported with ticagrelor treatment. Thus, ticagrelor prevents more major adverse cardiac events after ACS, most notably reducing CV mortality, compared with clopidogrel, without adding clinically important safety concerns.

2. STUDY OBJECTIVES

2.1 Primary objective

To describe the safety and tolerability of ticagrelor, by assessment of the bleeding events and other serious adverse events (SAEs) during 1 year follow up in Taiwanese non ST-elevation MI (NSTEMI) patients.

To describe the efficacy of Ticagrelor, by assessment of the incidence of major CV events (including CV death, MI and stroke) during 1 year follow up in Taiwanese NSTEMI patients treated with ticagrelor.

2.2 Secondary objective (Not applicable)

3. STUDY PLAN AND PROCEDURES

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca standard procedures.

3.1 Overall study design and flow chart

This is a multicenter, single arm, open label, Phase IV study to evaluate safety and to describe the incidence of major CV events of ticagrelor in Taiwanese patients with NSTEMI. The study design and plan are summarized in Figure 1 and Table 2.

Figure 1 Study flow chart

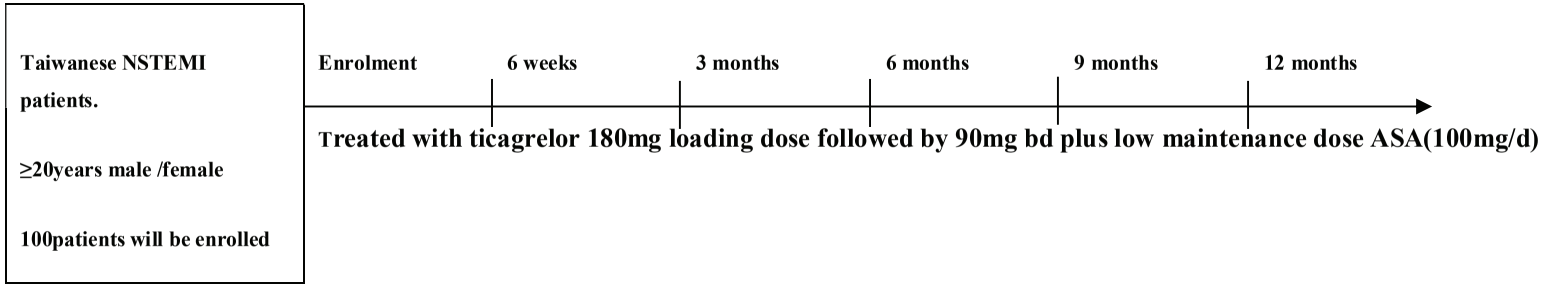

Table 2 Study Plan

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Premature Treatment Discontinuation Visit (PTDV)	Visit 6	Follow up visit 2weeks ± 3 days after Visit 6 For patients prematurely discontinuing study treatment[b]
	Enrollment	6 week ±1 week	3m ± 1week	6 m ± 1week	9 m ± 1week	Within 1week discontinuation of IP	12m ± 1week	
Informed consent	X							
Inclusion/exclusion criteria	X							
Demographics	X							
Relevant medical/surgical history including type of ACS	X							
Targeted physical examination including vital signs (pulse, blood pressure)	X	X				X	X	
Myocardial necrosis biomarkers[a]	X[d]							
12-lead ECG	X[d]							
Clinical chemistry & haematology[c]	X[d]	X				X	X	
Pregnancy test (urine) if applicable	X							

	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Premature Treatment Discontinuation Visit** (PTDV)	**Visit 6**	**Follow up visit 2weeks ± 3 days after Visit 6 For patients prematurely discontinuing study treatment[b]**
Concomitant medications	X	X	X	X	X	X	X	X
Major CV events, SAEs and Bleeding Events		X	X	X	X	X	X	X
Dispense investigational product	X	X	X	X	X			
AEs		X	X	X	X	X	X	X
Return investigational product		X	X	X	X	X	X	
Compliance/drug accountability		X	X	X	X	X	X	

a: Myocardial necrosis biomarkers measured for index event (local laboratory) and any subsequent suspected ACS or coronary revascularization procedure

b: the follow up visit can be done by telephone contact. For patients who complete 12 months of study treatment, the follow up visit is to be performed 2 weeks after visit 6. For patients discontinuing study treatment prematurely, the follow up visit procedures replace procedures for Visits 2-6

c: the clinical chemistry and hematology test can be added according to the investigator's discretion during each visit.

d: Myocardial necrosis biomarkers, 12-lead ECG and clinical chemistry and haematology already collected for the index event can be used for Visit 1.

3.1.1 Duration of Study

The anticipated duration of the study is approximately 24 months, including an anticipated enrolment period of 12 months and follow-up period of 12 months.

3.1.2 Enrolment

Male and female patients with NSTEMI, fulfilling all of the inclusion criteria (see Section 4.1) and none of the exclusion criteria (see Section 4.2) can be enrolled in this study.

Approximately 100 patients at approximately 8 study centres will be enrolled.

3.1.3 Protocol Visits

Patients will return approximately every 3 months as outlined in Figure 1 and Table 2, for assessment of events related to the objectives of the study including safety and incidence of major CV events. The Investigator/study centre personnel will record any bleeding events and other adverse event (AE)/SAEs, any suspected major CV event and use of medication including ticagrelor. An unscheduled visit may be conducted as a result of a follow-up phone contact.

3.1.4 Premature Treatment Discontinuation

Refer to Section 5.3.

3.2 Rationale for study design, doses and control groups

3.2.1 Rationale for study design

This is a multicenter, single arm, open label, Phase IV study to evaluate safety and to describe the incidence of major CV events of ticagrelor in a Taiwanese NSTEMI population in order to provide widely applicable results.

3.2.2 Patients and Choice of endpoints

The target population will be Taiwanese patients with NSTEMI to provide safety data in this patient type.

Similar to the PLATO study, PLATO defined bleeding endpoints are used. To describe the incidence of major CV events, the composite of CV death/MI/stroke is used in this study. Events will be locally adjudicated by the clinic investigator. Other non-hemorrhagic SAEs will also be recorded.

3.2.3 Dose regimens

Ticagrelor dose will be consistent with prescribing information in Taiwan: 180 mg loading dose followed by maintenance dose of 90 mg twice daily (bd). Loading dose of ticagrelor should be given regardless if the patient has received previous loading dose of clopidogrel, and regardless if the patient had ongoing clopidogrel treatment prior to the index event. Patients who have received loading dose with ticagrelor or have ongoing treatment with maintenance dose of ticagrelor should not receive a second loading dose, unless judged

necessary in the opinion of the investigator. Patients currently treated with prasugrel may not be included in the study. Patients are expected to receive concomitant low maintenance dose ASA, 100 mg daily.

3.2.4 Limitations of the study

The results of the phase IV study will be descriptive, and due to the small population of this study, there can be no formal statistical comparison to the data from the comparison of ticagrelor to clopidogrel in the PLATO study. However, the Kaplan-Meier% with 95% CI for the both studies will be presented.

4. SUBJECT SELECTION CRITERIA

Investigator(s) should keep a record, the subject screening log, of subjects who entered pre-study screening.

Each subject should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

4.1 Inclusion criteria

For inclusion in the study, subjects should fulfil the following criteria:

1. Provision of informed consent prior to any study specific procedures

2. Female or male aged at least 20 years

3. A patient who is considered as ethnic Taiwanese

4. Index event of non-ST elevation MI. The patient should be hospitalised for chest pain and potential ACS and be documented by cardiac ischaemic symptoms[a] of ≥10 minutes duration at rest[b] and:

   Positive biomarker evidence of myocardial necrosis: Either

   – Troponin T or I (TNT/TNI) greater than the laboratory upper normal limit on at least one occasion in association with the index clinical event (ie, any elevated troponin level)

   or

   – CK-MB, preferably CK-MB mass, greater than the laboratory upper normal limit on at least one occasion in association with the index clinical event

Patients should be enrolled as quickly as possible after presentation in order to maximize potential clinical benefits but at least within 24 hours after onset of symptoms. Patients may have been preloaded with clopidogrel or ticagrelor, as the dosing time of dual antiplatelet

treatment should follow the current requirement of critical care to ACS, that is to treat with dual anti-platelet agents in emergency room when indicated.

Definition of terms

a. Cardiac ischaemic symptoms: chest pain or discomfort or equivalent (eg, neck or jaw symptoms, dyspnoea believed to represent an angina pectoris equivalent) believed due to impaired coronary flow secondary to atherosclerotic disease. If symptoms are found not to be due to atherosclerosis related myocardial ischaemia before enrollment then the patient should not be enrolled (eg, pericarditis, myocarditis, normal coronary arteries by angiography).

b. At rest: started spontaneously or with exercise but did not resolve with rest.

c. Laboratory MI local decision limit: this is the value that is considered abnormal. For institutions that report an intermediate or indeterminate range for troponin I or T, these values are considered abnormal for this study

4.2 Exclusion criteria

Subjects should not enter the study if any of the following exclusion criteria are fulfilled:

1. ST-elevation MI, defined by:

   – Persistent ST segment elevation ≥1mm (0.1mV) in 2 or more contiguous leads

   or

   – New or presumed new left bundle branch block (LBBB)

2. Ongoing treatment with prasugrel

3. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site)

4. Previous enrolment in the present study

5. Participation in another clinical study with an investigational product during the last 1 month.

6. Contraindication or other reason that ticagrelor should not be administered (eg, hypersensitivity, active bleeding, moderate or severe liver disease, history of previous intracranial bleed, gastrointestinal (GI) bleed within past 6 months, major surgery within 30 days)

7. With coagulation disorder

8. With uric acid nephropathy

9. Index event is an acute complication of PCI

10. Patient has planned for an urgent coronary artery bypass graft (CABG) within 7 days from the enrolment

11. Oral anticoagulation therapy within 30 days prior to enrolment or cannot be stopped (ie, patient requires chronic therapy)

12. Fibrinolytic therapy in the 24 hours prior to enrolment, or planned fibrinolytic treatment following enrolment (eg, for ST elevation MI or pulmonary embolism)

13. Nonselective non-steroidal anti-inflammatory drugs (NSAIDs) and prostacyclins (PGI2) therapy that cannot be stopped

14. History of intolerance or allergy to ASA or ticagrelor

15. Increased risk of bradycardic events (eg, no pacemaker and known sick sinus syndrome, second degree A-V block, third degree A-V block or previous documented syncope suspected to be due to bradycardia).

16. Patient requires dialysis

17. Platelet count less than $100X10^9/L$

18. Haemoglobin (Hb) level less than 100g/L

19. Recent (within 30 days of dosing) blood donation

20. Women of child-bearing potential (ie, those who are not chemically or surgically sterilised or who are not post-menopausal) who are not willing to use a medically accepted method of contraception that is considered reliable in the judgment of the investigator OR women who are pregnant OR women who are breast-feeding

21. Concomitant oral or intravenous therapy (see examples below) with strong cytochrome P450 3A (CYP3A) inhibitors, CYP3A substrates with narrow therapeutic indices, or strong CYP3A inducers within 14 days of study treatment or cannot be stopped for the course of the study

    - Strong inhibitors: ketoconazole, itraconazole, voriconazole, telithromycin, clarithromycin, nefazadone, ritonavir, saquinavir, nelfinavir, indinavir, atanazavir, over 1 litre daily of grapefruit juice.

    - Substrates with narrow therapeutic index: cyclosporine, quinidine.

    - Strong inducers: rifampin/rifampicin, phenytoin, carbamazepine.

22. Any other condition which in the opinion of the investigator, may either put the patient at risk or influence the result of the study (eg, cardiogenic shock or severe haemodynamic instability, active cancer, risk for non-compliance, risk for being lost to follow up)

Procedures for withdrawal of incorrectly enrolled subjects see Section 5.3.

5. STUDY CONDUCT

5.1 Restrictions during the study

There are no specific dietary or activity restrictions other than those typical for this patient population.

Patients should not donate blood or bone marrow at any time during the study period.

Restrictions regarding concomitant medications are described in Section 5.6

5.2 Subject enrolment

The Investigator will:

1. Obtain signed informed consent (ICF) from the potential subject or their guardian/legal representative before any study specific procedures are performed. If ICF is not signed by the subject himself/herself, the subject should sign the ICF after his/her capability recovers.

2. Assign potential subject a unique enrolment number, beginning with 'E#'.

3. Determine subject eligibility. See Sections 4.1 and 4.2

If a subject withdraws from participation in the study, then his/her enrolment code cannot be reused.

5.2.1 Procedures for randomisation (Not applicable)

5.3 Procedures for handling subjects incorrectly enrolled

Subjects who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be enrolled. There can be no exceptions to this rule.

If a patient does not meet the selection criteria but is enrolled in error, a discussion should occur between the Study Physician and the Investigator regarding whether to continue or discontinue the patient from study medication. Consistent with Intent-To-Treat (ITT) principles, all enrolled patients should continue to be followed in the study (ie, attend protocol visits) and, unless treatment would be harmful, patients should continue to receive study medication.

In situations where an agreement cannot be reached, the patient should have their study medication stopped but will continue with study assessments. The Study Physician is to ensure all such decisions are appropriately documented.

5.4 Blinding and procedures for unblinding the study (Not applicable)

5.5 Treatments

5.5.1 Identity of investigational product(s)

Investigational product	Dosage form and strength	Manufacturer
Ticagrelor 90 mg	Plain, round, yellow, film-coated tablet, 90 mg	AstraZeneca

5.5.2 Doses and treatment regimens

Ticagrelor 180mg loading dose taken orally, followed by 90mg bd

5.5.3 Additional study drug (Not applicable)

5.5.4 Labelling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language.

The label will include the following information:

- Name of sponsor (AstraZeneca)
- Study drug dosage form, route of administration, and quantity of dosage units
- Storage conditions
- Study code
- Enrolment code
- Space for Subject Number to be written
- Directions for use
- Space for visit number to be written
- The name of the Investigator, where applicable (this may be pre-printed or to be added on the label when the investigational product / study drug is dispensed)

- The period of use eg, expiry date
- Keep out of reach of children
- For clinical trial use only

5.5.5 Storage

All study drugs should be kept in a secure place under appropriate storage conditions. The investigational product label on the pack specifies the appropriate storage.

5.6 Concomitant and post-study treatment(s)

In addition to the assigned study medication, all patients will take concomitant ASA, at a planned dose of 100 mg once daily, from enrolment through the end of the treatment period. If a patient develops an indication for higher dose ASA during the treatment period (e.g. acute coronary syndrome or percutaneous coronary intervention), higher dosing is allowed for the duration of that indication, after which the dose of ASA should be reduced to 100 mg once daily.

Other medication, which is considered necessary for the subject's safety and well being, may be given at the discretion of the investigator and recorded in the appropriate sections of the electronic Case Report Form (eCRF).

Investigators are reminded of the following potential drug-drug interactions.

5.6.1 Digoxin and other p-glycoprotein interactions

Ticagrelor modestly increases digoxin levels. Therefore digoxin levels should be monitored closely following initiation or discontinuation of ticagrelor. Other p-glycoprotein substrates may be expected to have similar changes in pharmacokinetics. Additional details can be found in the package insert for ticagrelor.

5.6.2 CYP450 interactions

5.6.2.1 CYP3A inhibitors

Strong inhibitors of CYP3A enzyme (eg, ketoconazole, itraconazole, voriconazole, telithromycin, clarithromycin [but not erythromycin or azithromycin], nefazadone, ritonavir, saquinavir, nelfinavir, indinavir, atazanavir, or over 1 litre daily of grapefruit juice) should not be co-administered with ticagrelor, as plasma levels of ticagrelor would be substantially increased.

5.6.2.2 CYP3A substrates or inducers

Concomitant therapy with simvastatin or lovastatin at doses higher than 40 mg daily is not permitted since administration with ticagrelor will result in higher serum concentrations and may put patients receiving more than 40 mg per day of simvastatin or lovastatin at increased risk of statin-related adverse effects. There are no restrictions to other statin therapies (ie,

doses of simvastatin or lovastatin ≤ 40 mg daily or any dose of any other statin is permitted). Investigators are advised to check lipid levels and adjust statin dosages per local practice.

Co-administration of ticagrelor with strong inducers of CYP3A also should be avoided (eg, rifampin/rifampicin, rifabutin, phenytoin, carbamazepine, phenobarbital).

5.6.3 Oral anticoagulants

Concomitant treatment with oral anticoagulants (ie, vitamin K antagonists, direct thrombin inhibitors, factor X inhibitors) is not recommended during the study. The investigator should carefully consider potential risks and benefits. Irrespective if study drug is stopped or not, the patient should remain in the study for evaluation.

5.6.4 Parental anticoagulants

Short-term treatment (ie, up to 7 days) with approved parenteral anticoagulants (eg. unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), bivalirudin, fondaparinux) is allowed. However, long-term treatment with LMWH or fondaparinux in outpatients (at venous thrombosis treatment or atrial fibrillation doses) in combination with study medication is not allowed. Concomitant treatment with venous thrombosis prophylaxis doses is allowed.

5.6.5 ADP receptor antagonists

Concomitant treatment with any other ADP receptor antagonists is not allowed in the study.

5.6.6 GPIIb/IIIa receptor antagonists

Short-term treatment (ie, up to 7 days) with GPIIb/IIIa antagonists is allowed during the study.

5.6.7 Dipyridamole and cilostazol

Concomitant treatment with dipyridamole or cilostazol is not permitted in the study.

5.6.8 Fibrinolytic treatment

If a patient is to be treated with fibrinolytic therapy, study medication should be stopped and restarted no earlier than 24 hours after completion of the fibrinolytic therapy and when the risk of bleeding is deemed low in the judgment of the investigator.

5.6.9 Non-steroidal anti-inflammatory drugs (NSAIDs)

Chronic treatment with non selective NSAID treatment or prostacyclin (PGI2) is not permitted. Short term treatment with NSAID or PGI2 up to 7 days is allowed.

5.7 Treatment compliance

The administration of all study drugs (including investigational products) should be recorded in the appropriate sections of the eCRF.

Patients will be asked to return all unused study medications and empty packages to the clinic at each visit. The patient's compliance will be assessed by the investigator and recorded in the eCRF. A pill count should be done at a patient level and recorded in the eCRF and a dispensing log by the study site personnel.

5.7.1 Accountability

The study drug provided for this study will be used only as directed in the study protocol.

The study site personnel will account for all study drugs dispensed to and returned from the subject.

Study site personnel will account for all study drugs received at the site, unused study drugs and for appropriate destruction. Certificates of delivery, destruction and return should be signed.

5.8 Discontinuation of investigational product

Subjects may be discontinued from investigational product (IP) in the following situations:

Adverse Event as judged by the investigator and/or AZ

Severe non-compliance to study protocol as judged by the investigator and/or AZ

Subjects should be discontinued from investigational product (IP) in the following situations:

Subject decision. The subject is at any time free to discontinue treatment, without prejudice to further treatment

Incorrectly enrolled patient in whom the inclusion/exclusion criteria violation would put the patient at undue risk (see Section 5.3)

Pregnancy

5.8.1 Procedures for discontinuation of a subject from investigational product

A subject that decides to discontinue investigational product will always be asked about the reason(s) and the presence of any adverse events. Adverse events will be followed up (See Sections 6.4.3 and 6.4.4); and all study drugs should be returned by the subject.

5.8.2 Temporary discontinuation from study medication

Surgery or procedures associated with major haemorrhage: It is recommended that cardiac surgery and major non-cardiac surgery that in the opinion of the investigator poses a risk for clinically major bleeding not be performed until at least 5 days after stopping study medication to avoid excessive bleeding. After surgery, study medications should be restarted when the risk of bleeding is deemed low in the judgment of the investigator.

Major bleeding: Study medication must be stopped immediately in case of a bleeding deemed to be clinically significant in the judgment of the investigator (eg, a significant fall in haemoglobin, need for transfusion, haemodynamically significant, or in a critical location such as intracranial, intraspinal, intraocular, or pericardial), but may be reinstated when the risk of bleeding is deemed low in the judgment of the Investigator and if not contraindicated. The study medication administration need not be stopped in case of a minor bleeding. All bleedings should be treated and followed up according to local clinical practice. Major bleeding events should be managed according to need with general support and blood.

Study medication should be restarted at the investigator's discretion to minimise the risk of thrombotic complications

Dyspnea: Evaluation of a patient who develops dyspnea should start with an assessment of timing relative to initiation of study drug, severity, and the presence of any signs or symptoms suggestive of cardiopulmonary disease. In patients with signs and symptoms suggestive of another cause of dyspnea (eg, heart failure exacerbation, chronic obstructive pulmonary disease flare), evaluation and treatment for those conditions should occur per local practice standards. Importantly, study drug should be continued in these patients without interruption.

> Also, in patients in whom the dyspnea begins soon after starting study drug and not associated with any signs or symptoms suggestive of significant cardiopulmonary disease, patients should **continue study drug without interruption** as the dyspnea typically resolves spontaneously while on treatment. The patient should be re-evaluated after several days. It is important to note that a drug holiday and subsequent rechallenge often results in recurrence of dyspnea.
>
> In patients with dyspnea likely due to study drug that proves intolerable, concomitant medications should be reviewed and, **when possible**, moderate CYP3A4 inhibitors (eg, diltiazem) changed to an alternative that is not a CYP3A4 inhibitor or discontinued.

5.8.3 Permanent premature discontinuation from study medication

Patients permanently discontinuing study medication should be given conventional therapy, if applicable. This medication(s) will be open label and obtained locally. All patients should always be asked to continue the regular visits as described below. **It is essential to collect as much data as possible for all patients throughout the study. Complete withdrawal from the study (withdrawal of consent) has a direct impact on the potential validity of all study data and should be avoided wherever possible**.

If the patient prematurely permanently discontinues study medication, there could be several different options for their continuation in the study as described below.

5.8.3.1 The patient agrees to undergo the premature treatment discontinuation visit and then continue in-person study visits

The patient agrees to undergo the Premature Treatment Discontinuation Visit (PTDV) and then continue in-person study visits every 3 months until 12 months after enrolment. This is the preferred option and patients who discontinue study medication will always be asked if they agree to this approach.

5.8.3.2 The patient unwilling to continue in-person study visits but agrees to undergo modified follow-up

If the patient agrees, the PTDV should be done. Subsequent visits through Visit 6 will be done as regular telephone contacts or by other means to ascertain whether any clinical endpoints or AEs have occurred and to inventory concomitant medications. Such a patient has not withdrawn his/her consent or withdrawn from the study.

5.8.3.3 The patient refuses any form of follow-up

If the patient refuses any form of follow-up, he/she officially withdraws from the study and withdraws consent. This approach should be avoided if possible.

5.9 Withdrawal from study

Subjects are at any time free to withdraw from study (investigational product and assessments), without prejudice to further treatment (withdrawal of consent). Such subjects will always be asked about the reason(s). If possible, they will be seen and assessed by an investigator; final visits should be 1 week after the discontinuation (See Table 2). Adverse events will be followed up by the investigator for as long as medically indicated, but without further recording in the eCRF); and all study drugs should be returned by the subject.

The Investigator should always ask the patient to allow contact 12 months after enrolment for a final follow-up to ascertain AEs even if participation in other visits is not agreed. At a minimum, permission to ascertain vital status should be obtained if at all possible. This agreement should be noted and signed by both the Investigator and the patient on the Informed consent form, as well as entered in the medical records. The reason for discontinuation and the date of discontinuation from the study must be documented in the eCRF.

Withdrawn subjects will not be replaced.

6. COLLECTION OF STUDY VARIABLES

The investigator will ensure that data are recorded in a timely fashion on the eCRF as specified in the study protocol and in accordance with the instructions provided. A copy of the eCRF data will be archived at the study centre.

6.1 Recording of data

The Rave Web Based Data Capture (WBDC) system will be used for data collection and query handling. The investigator will ensure that data are recorded on the eCRF as specified in the study protocol and in accordance with the instructions provided.

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement (CSA). The investigator will sign the completed eCRF. A copy of the completed eCRF will be archived at the study site.

6.2 Data collection at enrolment and follow-up

6.2.1 Enrolment procedures

Each patient will undergo enrolment procedures at Visit 1. The following data will be collected:

- Demographics (including sex, date of birth, confirmation of Taiwanese ethnicity)
- Relevant medical and surgical history
- Current concomitant medications
- Targeted physical examination including vital Signs (heart rate, blood pressure)
- Safety laboratory blood analyses (clinical chemistry and haematology)
- Urine pregnancy test (for females of child bearing potential)
- 12-lead ECG
- Myocardial necrosis biomarker

6.2.2 Follow-up procedures

Patients will have routine visits as outlined in Table 2. Any new suspected endpoint events, SAEs and current medications will be recorded. In order to determine whether or not clinical events meet the endpoint definition, it will be the responsibility of the Investigator to obtain all necessary source documents, including medical records from institutions where a hospitalisation may have occurred.

6.3 Efficacy

Suspected clinical efficacy endpoints will be collected in the eCRF. These events will be identified using standard questioning of the patient at each visit, or by information that the investigator may receive as part of standard medical practice. Safety endpoint events will be identified similarly.

For each suspected endpoint, the investigator will collect relevant additional source information where required, determine whether a safety or efficacy endpoint has occurred, and record their finding on the eCRF.

6.3.1 CV death

All deaths reported post-enrolment will be recorded and classified by the investigator as CV or non-CV.

6.3.2 MI

MI is diagnosed on the basis of elevation of myocardial necrosis biomarkers typical of acute MI with **at least 1 of the following:**

1. Recurrent cardiac ischaemic symptoms ≥20 minutes at rest

2. Development of new pathological Q waves on the ECG

3. New or presumed new ECG changes indicative of ischaemia in 2 or more contiguous leads (ST-segment elevation, ST-segment depression or T-wave inversion)

6.3.3 Stroke

A stroke is defined as a neurological deficit caused by an ischaemic or haemorrhagic central nervous system event with residual symptoms at least 24 hours after onset or leading to death.

Stroke will be further sub-classified as:

4. Ischaemic:

   Ischemic stroke is defined as an infarction of the central nervous system tissue that results from a thrombus or embolus impairing central nervous system perfusion (and not primarily due to haemorrhage) with residual signs or symptoms lasting at least 24 hours after onset or leading to death. Haemorrhage may be a consequence of ischemic stroke. In this situation, the stroke should be recorded as an ischemic stroke with hemorrhagic transformation rather than a hemorrhagic stroke event.

5. Haemorrhagic:

   Hemorrhagic stroke is defined as an acute episode of focal or global cerebral or spinal dysfunction with a documented cause of intracranial haemorrhage on imaging (eg, computed tomography (CT) scan or magnetic resonance imaging (MRI) scan) either in the cerebral parenchyma, or in the subdural, epidural or subarachnoid space with residual signs or symptoms at least 24 hours after onset or leading to death. Evidence of hemorrhagic stroke obtained from lumbar puncture, neurosurgery, or autopsy can also confirm the diagnosis.

6. Unknown/No imaging performed: if the type of stroke could not be determined by imaging or other means (from lumbar puncture, neurosurgery, or autopsy) but is judged to fulfill the stroke definition above, the stroke will be classified as ischaemic for purposes of the study.

6.4 Safety

The Principal Investigator (PI) is responsible for ensuring that all staff involved in the study is familiar with the content of this section.

6.4.1 Definition of adverse events

An adverse event (AE) is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product.

An undesirable medical condition can be symptoms, eg, nausea, chest pain, or signs, eg, tachycardia, enlarged liver, or the abnormal results of an investigation, eg, laboratory findings, electrocardiogram. In clinical studies an AE can include an undesirable medical condition occurring at any time after the patient has signed informed consent, including run-in or washout periods, even if no specific treatment has been administered.

The term AE is used to include both serious and non-serious AEs

6.4.2 Definitions of serious adverse event

A serious adverse event (SAE) is an AE, occurring at any study phase (ie, run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

Results in death

Is immediately life-threatening

Requires in-patient hospitalisation or prolongation of existing hospitalisation

Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions

Is a congenital abnormality/birth defect

Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

For further guidance on the definition of a SAE, see Appendix B to the Clinical Study Protocol.

6.4.3 Recording of adverse events

Time period for collection of adverse events

AE/SAEs will be recorded from the time of signature of informed consent throughout the treatment period, including the follow-up period, to last contact.

Follow-up of unresolved adverse events

Any AEs that are unresolved at the subject's last AE assessment in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Variables

The following variables will be collect for each AE;

- AE (verbatim)
- The date when the AE started and stopped
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product (yes or no)
- Action taken with regard to investigational product
- Outcome.

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)

- Causality assessment in relation to other medication

Description of AE

The following definitions for intensity rating are:

- mild (awareness of sign or symptom, but easily tolerated)
- moderate (discomfort sufficient to cause interference with normal activities)
- severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.4.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE.

Causality collection

The Investigator will assess causal relationship between Investigational Product and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

For SAEs causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix B to the Clinical Study Protocol.

Adverse Events based on signs and symptoms

All AEs spontaneously reported by the subject or reported in response to the open question from the study personnel: *'Have you had any health problems since the previous visit/you were last asked?'*, or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

Adverse Events based on examinations and tests

The results from protocol mandated laboratory tests and vital signs will be summarised in the clinical study report. Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

NB. Cases where a subject shows an AST **or** ALT ≥3xULN **and** total bilirubin ≥ 2xULN may need to be reported as SAEs, please refer to Appendix D 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions.

6.4.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **on the day** of initial receipt for fatal and life threatening events **and within five calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE immediately, or **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the WBDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the WBDC system is not available, then the Investigator or other study site personnel reports a SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the Investigator/study site personnel how to proceed.

6.4.5 Laboratory safety assessment

Blood samples for determination of clinical chemistry, haematology, and urinalysis will be taken at the times indicated in the Study Plan and Time Schedule (see Table 2).
The following laboratory variables will be measured:

- S-Creatinine
- S-Uric acid
- S-Alkaline phosphatase
- S-Aspartate aminotransferase (AST)
- S-Alanine aminotransferase (ALT)
- S-Total Bilirubin
  (Elevated values to be fractionated)
- B-Haemoglobin
- B-Platelets

NB. In case a subject shows an AST **or** ALT ≥3xULN **and** total bilirubin ≥ 2xULN please refer to Appendix D 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions.

For blood volume see Section 7.1.

6.4.6 Physical examination

A physical examination will be performed and include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen.

6.4.7 ECG (Not applicable)

6.4.8 Vital signs

6.4.8.1 Pulse and blood pressure

Supine blood pressure and pulse rate will be measured using non-invasive equipment after 10 minutes rest on a bed. For timings of assessments refer to the Study Plan and Time Schedule (see Table 2)

6.4.9 Other safety assessments

6.4.9.1 Bleeding events

For all bleeding events, the investigator will complete information on the eCRF specific to that bleeding event. Additionally, bleeding events will be reported as AE and SAEs if serious criteria are met. Fatal/life-threatening and other major bleeding events are key components of primary endpoint (Wallentin 2009).

Fatal/life-threatening bleeding events are defined by 1 or more of the following criteria:

- Fatal

- Intracranial
- Intrapericardial bleed with cardiac tamponade
- Hypovolemic shock or severe hypotension due to bleeding and requiring pressors or surgery
- Clinically overt or apparent bleeding associated with a decrease in Hb of more than 50 g/L
- Transfusion of 4 or more units [whole blood or packed red blood cells (PRBCs)] for bleeding.

Major other bleeding events are defined by 1 or more of the following criteria:

- Significantly disabling (eg, intraocular with permanent vision loss)
- Clinically overt or apparent bleeding associated with a decrease in Hb of 30 g/L to 50 g/L
- Transfusion of 2-3 units (whole blood or PRBCs) for bleeding.

Minor bleed is an event requiring medical intervention to stop or treat bleeding (eg, epistaxis requiring visit to medical facility for packing.

Minimal bleeds are events not requiring intervention or treatment (eg, bruising, bleeding gums, oozing from injection sites, etc).

6.4.9.1.1 Bleeding associated with procedures

Bleeding associated with procedures should be reported as an AE/SAE if exceeding normal bleeding for the specific procedure.

6.4.9.1.2 Management of bleeding

There is currently no antidote to ticagrelor and treatment of bleeding should therefore be symptomatic and handled according to the clinical routines at the investigational centre.

6.5 Patient reported outcomes (PRO) (Not applicable)

6.6 Pharmacokinetics (Not applicable)

6.7 Pharmacodynamics (Not applicable)

6.8 Pharmacogenetics (Not applicable)

6.9 Health economics (Not applicable)

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

The total volume of blood that will be drawn from each subject in this study is as follows:

Table 3 Volume of blood to be drawn from each subject

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry	5	3	15
	Haematology	2	3	6
Eligibility	Myocardial biomarker	5	1	5
Total				26

7.2 Handling, storage and destruction of biological samples

The samples will be used up or disposed of after analyses.

7.3 Labelling and shipment of biohazard samples

The Investigator ensures that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (material containing or suspected contain infectious substances that do not met Catergory A criteria), see Appendix C 'IATA 6.2 Guidance Document'.

Any samples identified as Infectious Category A material are not shipped and no further samples will be taken from the patient unless agreed with AstraZeneca and appropriate labelling, shipment and containment provisions are approved.

7.4 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

The Principal Investigator at each centre keeps full traceability of collected biological samples from the subjects while in storage at the centre until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

AstraZeneca keeps oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

7.5 Withdrawal of informed consent for donated biological samples

If a subject withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

The Principal Investigator:

Ensures subjects' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca

Ensures that biological samples from that subject, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented

Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed, the action documented and the signed document returned to the study site

Ensures that the subject and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the central laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice (GCP), applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

8.2 Subject data protection

The Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

8.3 Ethics and regulatory review

An Ethics Committee (EC) should approve the final study protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the subjects. The investigator will ensure the distribution of these documents to the applicable Ethics Committee, and to the study site staff.

The opinion of the Ethics Committee should be given in writing. The investigator should submit the written approval to AstraZeneca before enrolment of any subject into the study.

The Ethics Committee should approve all advertising used to recruit subjects for the study.

AstraZeneca should approve any modifications to the Informed Consent Form that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the Ethics Committee annually.

Before enrolment of any subject into the study, the final study protocol, including the final version of the Informed Consent Form, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca will provide Regulatory Authorities, Ethics Committees and Principal Investigators with safety updates/reports according to local requirements, including Suspected Unexpected Serious Adverse Reactions (SUSARs), where relevant.

8.4 Informed consent

The Principal Investigator(s) at each centre will:

Ensure each subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study

Ensure each subject is notified that they are free to discontinue from the study at any time

Ensure that each subject is given the opportunity to ask questions and allowed time to consider the information provided

Ensure each subject provides signed and dated informed consent before conducting any procedure specifically for the study

Ensure the original, signed Informed Consent Form(s) is/are stored in the Investigator's Study File

Ensure a copy of the signed Informed Consent Form is given to the subject

Ensure that any incentives for subjects who participate in the study as well as any provisions for subjects harmed as a consequence of study participation are described in the informed consent form that is approved by an Ethics Committee.

8.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the National Principal Investigator and AstraZeneca.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol (Revised Clinical Study Protocol).

The amendment is to be approved by the relevant Ethics Committee and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each Investigator(s). For distribution to Ethics Committee see Section 8.3.

If a protocol amendment requires a change to a centre's Informed Consent Form, AstraZeneca and the centre's Ethics Committee are to approve the revised Informed Consent Form before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each Ethics Committee.

8.6 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an Ethics Committee may perform audits or inspections at the centre, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements. The investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the centre.

9. STUDY MANAGEMENT BY ASTRAZENECA

9.1 Pre-study activities

Before the first subject is entered into the study, it is necessary for a representative of AstraZeneca to visit the investigational study site to:

Determine the adequacy of the facilities

Determine availability of appropriate subjects for the study

Discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence, and the responsibilities of AstraZeneca or its representatives. This will be documented in a Clinical Study Agreement between AstraZeneca and the investigator.

9.2 Training of study site personnel

Before the first subject is entered into the study, an AstraZeneca representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study specific procedures and the WBDC system(s) utilised.

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff).

9.3 Monitoring of the study

During the study, an AstraZeneca representative will have regular contacts with the study site, including visits to:

Provide information and support to the investigator(s)

Confirm that facilities remain acceptable

Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed

Perform source data verification (a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating subjects. This will require direct access to all original records for each subject (eg, clinic charts)

Ensure withdrawal of informed consent to the use of the subject's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the subject.

The AstraZeneca representative will be available between visits if the investigator(s) or other staffs at the centre need information and advice about the study conduct.

9.3.1 Source data

Location of source data can be found in the Clinical Study Agreement.

9.4 Study agreements

The Principal Investigator at each/the centre should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of subjects and in all other respects, not relating to study conduct or treatment of subjects, the terms of the Clinical Study Agreement shall prevail.

Agreements between AstraZeneca and the Principal Investigator should be in place before any study-related procedures can take place, or subjects are enrolled.

9.4.1 Archiving of study documents

The Investigator follows the principles outlined in the Clinical Study Agreement (CSA).

9.5 Study timetable and end of study

The end of the study is defined as 'the last visit of the last subject undergoing the study'.

The study is expected to start in Q1 2015 and to end by Q2 2017.

The study may be terminated at individual centres if the study procedures are not being performed according to GCP, or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with ticagrelor.

10. DATA MANAGEMENT BY ASTRAZENECA

Data management will be performed by Cognizant, AstraZeneca Data Management Centre staff.

Data will be entered in the WBDC system at the study site. Trained personnel at study site will be responsible for entering data on the observations, tests and assessments specified in the CSP, into the WBDC system according to the eCRF instructions. The eCRF Instruction will guide the study site in performing data entry. Data entered in the WBDC system will be

immediately saved to a central database and changes tracked to provide an audit trail. The data will then be Source Data Verified, reviewed/queried and updated as needed.

The data collected through third party sources will be obtained and reconciled against study data.

Adverse events and medical/surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the AstraZeneca Drug Dictionary. The Medical Coding Team at the AstraZeneca Data Management Centre will perform all coding.

Data queries will be raised for inconsistent, impossible or missing data. All entries to the study database will be available in an audit trail.

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

When all data have been coded, validated, electronically signed and locked, clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked.

Data associated with biological samples will be transferred to laboratories internal or external to AstraZeneca.

The Investigator ensures the accuracy, completeness and timeliness of the data recorded and of the provision of answers to data queries. The Investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

11. EVALUATION AND CALCULATION OF VARIABLES BY ASTRAZENECA

11.1 Calculation or derivation of efficacy variable(s)

Efficacy assessment will describe the incidence of major CV events (composite of CV death, MI, stroke), analyzed according to locally adjudicated PLATO definitions.

11.2 Calculation or derivation of safety variable(s)

The safety assessment will describe total major bleeding events (including the subsets of fatal and fatal/ life threatening events), combined major and minor bleeding events. Bleeding events will be analyzed according to locally adjudicated PLATO bleeding definitions. AEs and other SAEs other than bleeding will also be evaluated. Summaries will be presented using descriptive statistics.

Primary variables

- PLATO-defined fatal/life-threatening bleedings during 1year follow up in Taiwanese ACS patients treated with ticagrelor.

- PLATO-defined major bleedings during 1year follow up in Taiwanese ACS patients treated with ticagrelor.

- PLATO-defined major + minor bleedings during 1year follow up in Taiwanese ACS patients treated with ticagrelor.

- Serious adverse events other than bleeding during 1year follow up in Taiwanese ACS patients treated with ticagrelor.

11.2.1 Other significant adverse events (OAE)

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and DAEs. Based on the expert's judgement, significant adverse events of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered OAEs and reported as such in the Clinical Study Report. A similar review of laboratory/vital signs data will be performed for identification of OAEs.

Examples of these are marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment.

11.3 Calculation or derivation of patient reported outcome variables (Not applicable)

11.4 Calculation or derivation of pharmacokinetic variables (Not applicable)

11.5 Calculation or derivation of pharmacodynamic variable(s) (Not applicable)

11.6 Calculation or derivation of pharmacogenetic variables (Not applicable)

11.7 Calculation or derivation of health economic variables (Not applicable)

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION BY ASTRAZENECA

12.1 Description of analysis sets

12.1.1 Full analysis set

All patients who have taken at least one dose of investigational product.

The analyses of efficacy variables will use the full analysis set.

12.1.2 Safety analysis set

All subjects who received at least one dose of investigational product, and for whom any post-dose data are available will be included in the safety analysis set.

The analyses of all safety variables will use the safety analysis set.

12.2 Methods of statistical analyses

12.2.1 Primary objective-primary efficacy endpoint

The primary efficacy endpoint is the cumulative incidence of major CV events (including CV death, MI and stroke) during 1 year follow up in Taiwanese NSTEMI patients. The primary analysis will be presented with K-M% and with 95% CI. Patients who fail to record any event in the primary composite efficacy endpoint will be censored at the time of study closure (ie. date of End of Treatment Visit) or at the time of last available information, if earlier.

No statistical comparison can be performed to the results of PLATO, due to the small population of this study.

12.2.2 Primary objective-primary safety endpoint

Statistical methods will be descriptive. For continuous data, descriptive statistics will be presented as number of patients (n), mean, standard deviation (SD), median, minimum and maximum. For categorical data, the frequency and percentage of patients in each category will be presented. Counts that are zero will be displayed as “0”. Percentages will be based on non-missing data unless otherwise specified.

Patients will be censored at 7 days after their last dose of ticagrelor. Patients who withdraw consent to participate in the study will be included up to the date of their study termination.

12.3 Determination of sample size

This is a regulatory commitment study to investigate the safety profile and to describe the cumulative incidence of major cardiovascular events of ticagrelor including fatal/life-threatening bleeding among Taiwanese NSTEMI patients within 1 year of follow up. If the fatal/life-threatening bleeding rate is 5% then 100 patients would allow to **describe the safety profile** estimated with a precision of +/-4.3%, with a 95%CI.

12.4 Data monitoring committee (Not applicable)

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and AstraZeneca contacts

The Principal Investigator is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and is to be reported as such, see Section 6.4.4**

In the case of a medical emergency the investigator may contact the Study Delivery Team Leader. If the Study Delivery Team Leader is not available, contact the Study Delivery Team Physician at the AstraZeneca Research and Development.

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[redacted]	[redacted]	[redacted]

13.2 Overdose

An overdose of ticagrelor is defined as intake of 4 or more ticagrelor tablets (360 mg)/day.

In the event of an overdose of ticagrelor, the investigator must ascertain the time and extent of the overdose regardless of severity. The investigator should determine the causative circumstance and whether haemorrhagic or toxic complications have occurred or are likely to do so. Depending on these facts it must be decided whether the patient should be hospitalised for observation or not.

Bleeding is one of the most likely pharmacological effects of excessive ticagrelor dosing, and appropriate supportive measures such as volume replacement, local haemostatic measures, and decompression or drainage may be required depending on the extent of bleeding or volume of blood lost. Patients with overdose-related bleeding should be cautioned to avoid unnecessary activity, mechanical tissue stress, and minor trauma for at least 24 hours after the bleeding has stopped. For other symptoms that can be expected after an overdose of ticagrelor and additional information can be found in the package insert for ticagrelor.

An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.

An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an AstraZeneca study drug occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with SAE, standard reporting timelines apply, see Section 6.4.4. For other overdoses, reporting should be done within 30 days.

13.3 Pregnancy

All outcomes of pregnancy should be reported to AstraZeneca.

13.3.1 Maternal exposure

If a subject becomes pregnant during the course of the study investigational product should be discontinued immediately.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the subject was discontinued from the study.

If any pregnancy occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 days for SAEs, see Section 6.4.4 and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the eCRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy.

13.3.2 Paternal exposure

There are no restrictions against fathering a child when treated with ticagrelor. If paternal exposure pregnancy occurs in the course of the study, then investigators or other site personnel should inform appropriate AstraZeneca representatives immediately or no later than 24 hours as described in the maternal exposure Section 13.3.1.

14. LIST OF REFERENCES

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