Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention (TWILIGHT)
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Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

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This supplement contains the following items:

1. Original protocol, final protocol, summary of changes.
2. Original statistical analysis plan, final statistical analysis plan, summary of changes.

Drug Substance	Ticagrelor and Aspirin
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TWILIGHT Study

Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention

Sponsor: **AstraZeneca**

Academic Research Organization (ARO): **The Office of Intervention Cardiovascular Research and Clinical Trials at Icahn School of Medicine at Mount Sinai**

CONFIDENTIAL

PROTOCOL SYNOPSIS

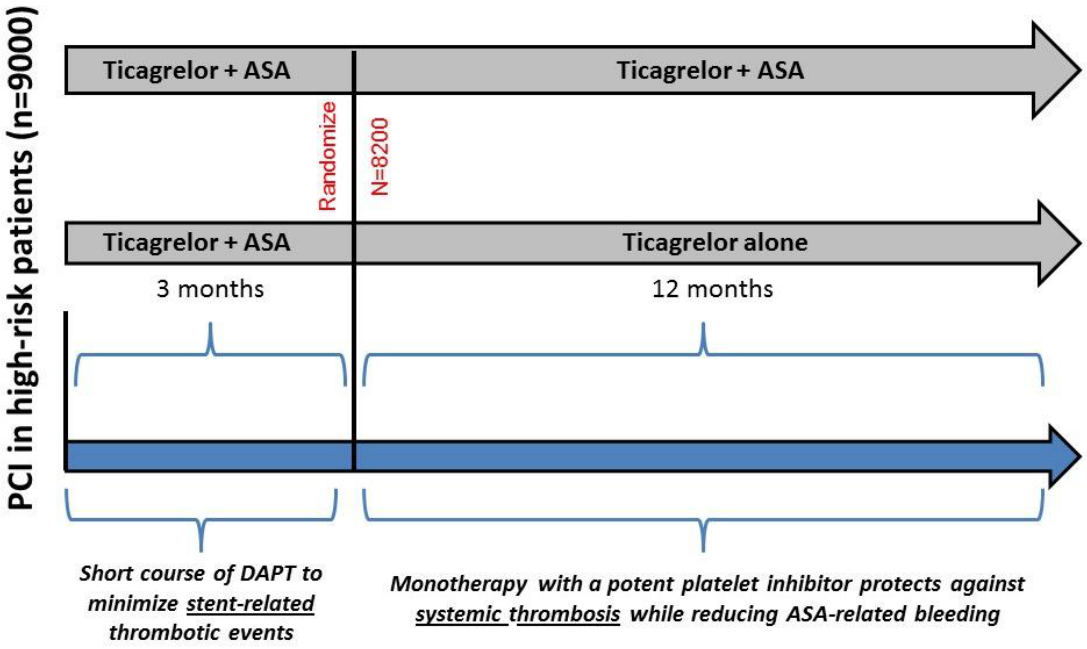
Title of Study	TWLIGHT Study - Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention
Primary Investigator:	Roxana Mehran, MD, FACC, FACP, FCCP, FESC, FAHA, FSCAI Professor of Medicine and Director of Interventional Cardiovascular Research and Clinical Trials Icahn School of Medicine at Mount Sinai
Study Centers:	Up to 100 sites in U.S., Canada, South America, and Europe
Study Design	Multicenter, prospective, blinded dual-arm study
Purposes	**Aim 1:** To determine the efficacy of ticagrelor alone versus ticagrelor plus aspirin in reducing clinically relevant bleeding among high-risk patients who had PCI with at least one drug-eluting stent. **Aim 2:** To determine the safety of ticagrelor versus ticagrelor plus aspirin in reducing ischemic adverse events at one year among high-risk patients undergoing PCI with at least one drug-eluting stent.
Enrollment and Patient Population	Up to 9000 high-risk patients who have undergone successful elective or urgent PCI with at least one locally approved drug eluting stent discharged on DAPT with aspirin and ticagrelor of at least 3 months intended duration.
Primary Objective	The primary objective of this study is to determine the impact of antiplatelet monotherapy with ticagrelor alone versus DAPT with ticagrelor plus aspirin for 12 months in reducing clinically relevant bleeding (efficacy) among high-risk patients undergoing PCI who have completed a 3-month course of aspirin plus ticagrelor.
Secondary Objectives	The secondary objective of this study is to determine the impact of antiplatelet monotherapy with ticagrelor alone versus DAPT with ticagrelor plus aspirin for 12 months in reducing major ischemic adverse events (safety) among high-risk patients undergoing PCI who have completed a 3-month course of aspirin plus ticagrelor.
Randomization	The eligibility for randomization for all enrolled subjects will be evaluated at the in-person 3-month study visit. Subjects with any of the following will not be randomized: • Refusal of randomization by subject or treating physician • Withdrawal of consent • Lost to follow-up

	• Death • Major bleeding (BARC Types 3b or 5) • Occurrence of an ischemic event after PCI such as myocardial infarction, definite or probable stent thrombosis, ischemic stroke, coronary revascularization with drug-eluting stent • No longer taking DAPT with aspirin and ticagrelor • Non physician-guided cessation of aspirin or ticagrelor of 5 days or greater. • Women of child bearing potential (as determined by hospital standard of care) • Renal failure requiring dialysis • Current indication for oral anticoagulation or high dose aspirin
Eligibility Criteria	High-risk patients who have undergone successful elective or urgent PCI with at least one locally approved drug eluting stent discharged on DAPT with aspirin and ticagrelor of at least 3 months intended duration will be eligible for the TWILIGHT study. Enrollment into the study will require meeting at least one clinical inclusion, one angiographic inclusion and none of the exclusion criteria. <u>Clinical Inclusion Criteria:</u> • Adult patients ≥ 65 years of age • Recent (≥3 days) presentation with acute coronary syndrome with clinical stabilization and decreasing cardiac enzymes • Established vascular disease defined as previous MI, documented PAD or CAD/PAD revascularization • Diabetes mellitus treated with medications (oral hypoglycemic, subcutaneous injection of insulin) • Chronic kidney disease defined as an estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73m^2 or creatinine clearance (CrCl) < 60 ml/min <u>Angiographic Inclusion Criteria:</u> • Multivessel coronary artery disease • Target lesion requiring total stent length >30 mm • SYNTAX score ≥23 • Bifurcation lesions with Medina X,X,1 classification requiring at least 2 stents • Left main (≥50%) or proximal LAD (≥70%) lesion • Calcified target lesion requiring atherectomy <u>Exclusion Criteria:</u> • Under 18 years of age

	• Contraindication to aspirin • Contraindication to ticagrelor • Planned surgery within 90 days • Planned coronary revascularization (surgical or percutaneous) within 90 days • Need for chronic oral anticoagulation • Prior stroke • Dialysis-dependent renal failure • Active bleeding or extreme-risk for major bleeding (e.g. active peptic ulcer disease, gastrointestinal pathology with a raised risk for bleeding, malignancies with a raised risk for bleeding) • Emergent or salvage PCI or STEMI presentation. • Liver cirrhosis • Life expectancy < 1 year • Unable or unwilling to provide informed consent • Women of child bearing potential (as determined by hospital standard of care) • Fibrinolytic therapy within 24 hours of index PCI • Concomitant therapy with a strong cytochrome P-450 3A inhibitor or inducer • Platelet count < 100,000 mm^3 • Requiring ongoing treatment with aspirin > 325 mg daily
Statistical Methods	
Primary Efficacy Analysis	The primary efficacy analysis will be performed on the ITT population. The primary objective is to determine if ticagrelor monotherapy is superior to ticagrelor plus aspirin for the primary efficacy endpoint (BARC Types 2, 3 or 5 bleeding). The null hypothesis for this analysis is that the HR for the experimental group (H_0) = 1. The alternative hypothesis is that the HR for the experimental group (H_A) ≠ 1. A test of superiority at the two-sided 0.05 level will be performed using a Cox proportional hazard model that includes treatment group as a covariate. A point estimate and two-sided 95% CI for the relative risk as measured by the hazard ratio will be calculated based on the Cox proportional hazards model. Event rates will be estimated at one year and Kaplan-Meier curves will be plotted for the time from randomization to the first occurrence of confirmed BARC Type 2, 3 or 5 bleeding by treatment group. This analysis will be repeated in the per protocol (PP) cohort to support the primary results.

Primary Safety Analysis	The primary safety analysis will be performed on the PP cohort. The primary objective is to determine if ticagrelor monotherapy is non-inferior to ticagrelor plus aspirin for the primary safety endpoint (cardiovascular death, non-fatal myocardial infarction, ischemic stroke or ischemia-driven revascularization). The null hypothesis for this analysis is that the HR for the experimental group (H_0) > 1.22. The alternative hypothesis is that the HR for the experimental group (H_A) ≤ 1.22. A test of non-inferiority at the two-sided 0.05 level will be performed using a Cox proportional hazard model that includes treatment group as a covariate. A point estimate and two-sided 95% CI for the relative risk as measured by the hazard ratio will be calculated based on the Cox proportional hazards model. Event rates will be estimated at one year and Kaplan-Meier curves will be plotted for the time from randomization to the first occurrence of confirmed cardiovascular death, non-fatal myocardial infarction, ischemic stroke or ischemia-driven revascularization by treatment group. If the upper limit of the 95% CI for the point estimate is less than or equal to 1.22 then the criteria for non-inferiority will be met.
Statistical Methods	Unless otherwise stated, all hypothesis tests will be performed using two-sided tests at the 5% significance level. Continuous variables will be summarized using descriptive statistics including means and standard deviations if normally distributed or median with interquartile ranges for skewed distributions. Discrete variables will be summarized using absolute and relative frequencies.
Sample Size Parameters	A cumulative bleeding rate of 4.5% is anticipated between time of randomization and 1 year. Assuming a 2% loss to follow-up and non-compliance / cross-over rate of 4%, the current trial will require 8200 subjects to detect a relative reduction in bleeding of 28% with ticagrelor monotherapy with 80% power and a Type I error of 0.05. It is anticipated that approximately 8% - 10% of enrolled subjects will not be eligible for randomization and therefore 9000 subjects will be enrolled at the time of PCI.

TWILIGHT DESIGN



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PROTOCOL SIGNATURE PAGE

I have read this clinical investigation plan and appendices and agree to adhere to the requirements. I will provide copies of this clinical investigation plan and all pertinent information to the trial personnel under my supervision. I will discuss this material with them and ensure they are fully informed regarding the device and the conduct of the trial.

I will conduct the trial in accordance with the clinical investigation plan, Good Clinical Practice guidelines, EN ISO 14155:2011 (Clinical Investigation of Medical Devices for Human Subjects - Good Clinical Practice), as well as local regulations. I also accept respective revisions to the clinical investigation plan approved by authorized personnel of the ARO and by regulatory authorities.

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_____
Investigator Name (print)

_____
Investigator Name (signature)

_____
Date

_____
Institution Name (print)

LIST OF ABBREVIATIONS

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

Abbreviation or special term	Explanation
AE	Adverse Event
ARO	Academic Research Organization
ASA	Acetylsalicylic Acid (Aspirin)
BMI	Body Mass Index
BMS	Bare Metal Stent
CAD	Coronary Artery Disease
CEC	Clinical Events Committee
CRF	Case Report Form
DAPT	Dual Antiplatelet Therapy
DES	Drug Eluting Stent
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
FDA	Food and Drug Administration (U.S.)
FFR	Fractional Flow Reserve
ICF	Informed Consent Form
IND	Investigational New Drug Application (FDA)
IRB	Institutional Review Board
ISS	Investigator Sponsored Study
ITT	Intention-to-Treat (analysis dataset)
IVUS	Intravascular Ultrasound
IXRS	Interactive Voice/Web Response System
LAD	Left Anterior Descending (Coronary Artery)
MI	Myocardial Infarction
NSAID	Non-Steroidal Anti-Inflammatory Drug
NSTEMI	Non ST Elevation Myocardial Infarction
$P2Y_{12}$	The $P2Y_{12}$ protein is found mainly but not exclusively on the surface of blood platelets, and is an important regulator in blood clotting.
PAD	Peripheral Artery Disease
PCI	Percutaneous Coronary Intervention
PP	Per Protocol (analysis dataset)
SAE	Serious Adverse Event
STEMI	ST Elevation Myocardial Infarction

The following abbreviations and special terms describe other clinical protocols or academic bodies.

Abbreviation or special term	**Explanation**
BARC	Bleeding Academic Research Consortium
EXCELLENT	*Trial Name:* Efficacy of Xience/Promus versus Cypher in Reducint Late Loss after Stenting
GUSTO	Trial Name: Global Utilization of Streptokinase and TPA for Occluded Arteries
OPTIMIZE	*Trial Name:* Optimized Duration of Clopidogrel Therapy following Treatment with the Endeavor Zotarolimus-Eluting Stent in the Real World Clinical Practice
PLATO	*Trial Name:* Platelet Inhibition and Patient Outcomes Trial
PRODIGY	*Trial Name:* Synergy between Stent and Drugs to Avoid Ischemic Recurrences after Percutaneous Coronary Intervention
SYNTAX	*Trial Name:* TAXUS Drug-Eluting Stent versus Coronary Artery Bypass Surgery for the Treatment of Narrowed Arteries
TIMI	*Trial Name:* Thrombolysis in Myocardial Infarction

1. INTRODUCTION

Pharmacologic platelet inhibition with aspirin and a $P2Y_{12}$ inhibitor is a requirement in all patients undergoing percutaneous coronary intervention (PCI) with stenting. Such dual antiplatelet therapy (DAPT) is recommended by international guidelines, with duration varying according to clinical presentation (i.e. acute coronary syndrome) or type of stent implanted during PCI (bare metal vs. drug eluting) (1-3).

While clopidogrel is the most widely used $P2Y_{12}$ inhibitor, its efficacy is hampered by substantial variability in platelet inhibition that may be attributable to clinical, genetic and procedural parameters (4-7). Moreover, although the novel thienopyridine prasugrel has a more potent and consistent effect on platelet inhibition (8, 9), bleeding risk is significantly higher compared to clopidogrel in acute coronary syndrome (ACS) patients following PCI (10). In contrast, ticagrelor, an oral, reversible, direct-acting inhibitor of the adenosine diphosphate $P2Y_{12}$ receptor (11) has proven faster, greater and more consistent $P2Y_{12}$ inhibition than either clopidogrel or prasugrel (12-14). In the landmark Study of Platelet Inhibition and Patient Outcomes (PLATO) trial, ticagrelor significantly reduced death from vascular causes, myocardial infarction, or stroke, without significantly increasing overall major bleeding in patients presenting with acute coronary syndromes (15).

Along with the advent of more potent antiplatelet pharmacotherapy, stent technology has also advanced in a concordant fashion with the introduction of safer and less thrombogenic platforms. These devices, compared to their older-generation counterparts, yield significant reductions in thrombotic events that are durable over the long term (16). As a consequence,

classical paradigms favoring a minimum of DAPT duration of 1 year, particularly in elective patients, are being challenged as PCI safety continues to evolve and improve. Randomized comparisons of different DAPT durations such as the OPTIMIZE and the PRODIGY trials suggest no increased risk for thrombotic events after only 3-6 months of DAPT in PCI patients treated primarily with novel generation devices (17) (18).

1.1 Research hypothesis

The overall hypothesis of the current study is that three months post-PCI of dual antiplatelet therapy with aspirin and ticagrelor, continued monotherapy with ticagrelor alone versus ticagrelor plus aspirin for an additional year will be superior with respect to bleeding and non-inferior with respect to ischemic events in high-risk patients undergoing elective or urgent PCI.

This hypothesis will be tested in the following two specific aims:

Aim 1: To determine the efficacy of ticagrelor alone versus ticagrelor plus aspirin in reducing clinically relevant bleeding among high-risk patients who had PCI.	**Hypothesis 1:** A DAPT strategy of ticagrelor + ASA for 3 months followed by ticagrelor alone for an additional 12 months will be superior to ticagrelor plus aspirin with respect to clinically relevant bleeding (BARC ≥ 2) in high-risk patients undergoing PCI.
Aim 2: To determine the safety of ticagrelor versus ticagrelor plus aspirin in reducing ischemic adverse events at one year among high-risk patients undergoing PCI	**Hypothesis 2:** A DAPT strategy of ticagrelor + ASA for 3 months followed by ticagrelor alone for an additional 12 months will be will be non-inferior to ticagrelor plus aspirin for with respect to ischemic adverse events at 1 year in high-risk patients undergoing PCI.

1.2 Rationale for conducting this study

Despite the trend and rationale for shorter DAPT durations following PCI, certain high-risk patients may derive additional benefit from potent and sustained platelet inhibition extending beyond 3 months after PCI. Defined by clinical and/or anatomic criteria, a short course of DAPT in such patients may provide sufficient protection against early stent-related thrombotic events while ongoing platelet inhibition may yield further reductions in systemic atherothrombosis. Among diabetics undergoing PCI, for example, Brar et al. previously demonstrated that the benefits of DAPT compared to antiplatelet monotherapy persisted irrespective of BMS or DES use, suggesting a systemic rather than stent-related effect (19). Analogously, results from the EXCELLENT trial suggested diabetics may derive additional benefit from prolonged DAPT (ASA + clopidogrel) compared to ASA alone (20). Findings from Dangas et al., which demonstrate a link between atherosclerosis and increased platelet reactivity, provide a biological basis for potent platelet inhibition in high-risk patients characterized by diffuse vascular disease (21) These observations are clinically relevant as

many patients undergoing elective or urgent PCI exhibit high-risk features, such as renal dysfunction, diabetes, peripheral arterial disease, that are associated with systemic atherosclerosis. Given the clear benefits of ticagrelor in the setting of high-risk ACS, it is plausible that ticagrelor alone will provide sufficient platelet inhibition to reduce thrombotic events compared to ticagrelor plus ASA among high-risk patients who have completed a requisite short course of DAPT.

Reduction in bleeding with ticagrelor alone while preserving of the anti-ischemic benefit associated with DAPT use would favor such a strategy in high-risk patients undergoing PCI.

Accordingly, the proposed study will examine the comparative safety and efficacy of a strategy of 3 month DAPT with ASA and ticagrelor followed by monotherapy using a potent agent (ticagrelor) compared to continued ASA and ticagrelor among high-risk patients undergoing PCI. Our primary hypothesis is that among such patients, use of ticagrelor alone will yield a significant reduction in clinically relevant bleeding while preserving anti-ischemic protection compared to the combination of ticagrelor and ASA.

1.3 Benefit/risk and ethical assessment

The potential benefits that subjects might realize by participating in this randomized trial is a reduction in clinically relevant bleeding for those who are randomly allocated to the placebo arm. Other benefits applicable to all subjects include close monitoring and surveillance for clinical events that will be performed by study personnel during the course of the trial.

The potential risks for subjects include an increased rate of thrombotic events for those who are randomized to the placebo arm and increased risk for bleeding in subjects randomized to the active treatment arm (low-dose ASA [81 mg]).

From an ethical standpoint, an independent data safety monitoring board will provide external oversight to ensure safety of all trial participants. In addition, subjects will be followed closely with either phone call or in-person visit every 3 months. Also, clinical equipoise exists for conducting a trial with this type of randomized comparison.

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objective of this study is to determine the impact of antiplatelet monotherapy with ticagrelor alone versus DAPT with ticagrelor plus aspirin for 12 months in reducing clinically relevant bleeding (efficacy) among high-risk patients undergoing PCI who have completed a 3-month course of aspirin plus ticagrelor.

2.2 Secondary (safety) objective

The secondary objective of this study is to determine the impact of antiplatelet monotherapy with ticagrelor alone versus DAPT with ticagrelor plus aspirin for 12 months in reducing major ischemic adverse events (safety) among high-risk patients undergoing PCI who have completed a 3-month course of aspirin plus ticagrelor.

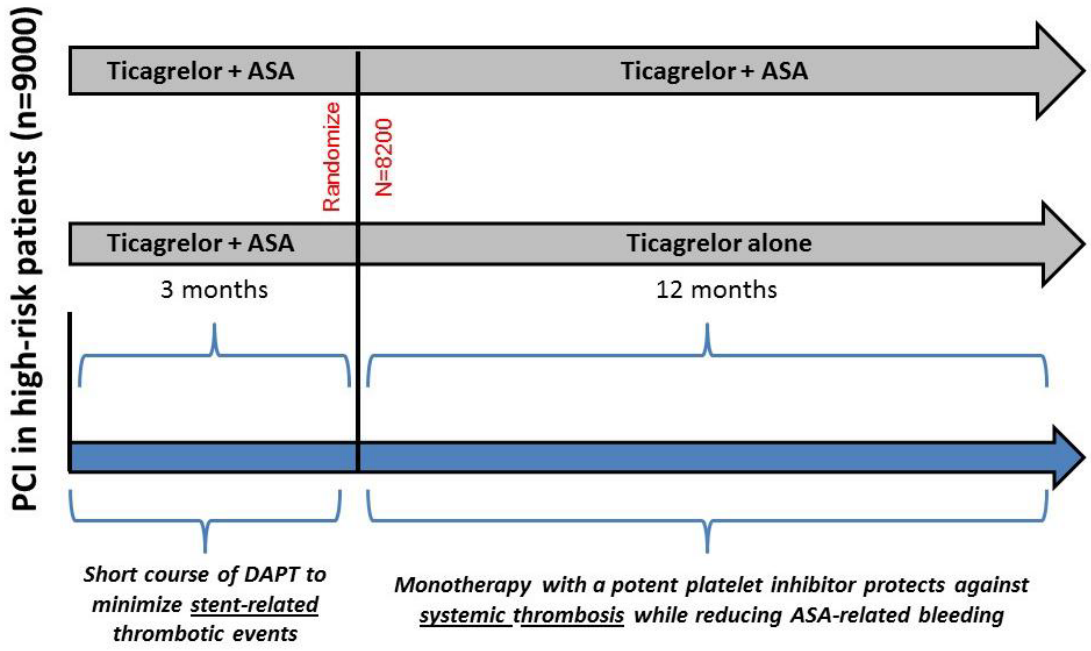
2.3 Exploratory objectives

Exploratory objectives include assessing the comparative safety and efficacy of the different DAPT regimens for individual components of the primary efficacy and secondary safety objectives.

3. STUDY PLAN AND PROCEDURES

3.1 Overall study design and flow chart

Figure 1 TWILIGHT Trial Design



3.2 Rationale for study design, doses and control groups

A randomized, double-blind study design was chosen as the most rigorous experimental approach to formally test the study hypotheses for the efficacy and safety of different DAPT regimens in high-risk patients undergoing PCI. Open label aspirin and ticagrelor per physician discretion will be given for the first 3 months after PCI. A low dose of aspirin (81 mg – 100 mg daily) is recommended during this open-label phase. After 3 months event-free subjects will be randomized to placebo versus non-enteric coated ASA for an additional 12 months.

Open-label ticagrelor at a dose of 90 mg twice daily will be continued in all randomized subjects.

4. SUBJECT SELECTION CRITERIA

4.1 Inclusion criteria

High-risk patients who have undergone successful elective or urgent PCI with at least one locally approved drug eluting stent discharged on DAPT with aspirin and ticagrelor of at least 3 months intended duration will be eligible for the TWILIGHT study. Elective or urgent are defined according to the National Cardiovascular Data Registry (Section 16).

A subject is considered enrolled if all requisite inclusion and none of the exclusion criteria are met and upon provision of informed consent. Enrollment into the study will require meeting at least one clinical inclusion, one angiographic inclusion and none of the exclusion criteria.

Must meet at least ONE clinical inclusion criterion	**Must meet at least ONE angiographic inclusion criterion**
Adult patients ≥ 65 years of age Recent (> 3 days) presentation with acute coronary syndrome with clinical stabilization and decreasing cardiac enzymes Established vascular disease defined as previous MI, documented PAD or CAD/PAD revascularization Diabetes mellitus treated with medications or insulin Chronic kidney disease defined as an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m^2 or creatinine clearance (CrCl) <60 ml/min	Multivessel coronary artery disease (CAD) (see Section 16) Target lesion requiring total stent length >30 mm SYNTAX score ≥23 Bifurcation lesions with Medina X,X,1 classification requiring at least 2 stents (see Section 16) Left main (≥50%) or proximal LAD (≥70%) lesion Calcified target lesion requiring atherectomy

4.2 Exclusion criteria

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

- Under 18 years of age
- Contraindication to aspirin
- Contraindication to ticagrelor

- Planned surgery within 90 days
- Planned coronary revascularization (surgical or percutaneous) within 90 days
- Need for chronic oral anticoagulation
- Prior stroke
- Dialysis-dependent renal failure
- Active bleeding or extreme-risk for major bleeding (eg active peptic ulcer disease, gastrointestinal pathology with a raised risk for bleeding, malignancies with a raised risk for bleeding)
- Emergent or salvage PCI or STEMI presentation. Emergent and salvage are defined as per the National Cardiovascular Data Registry criteria (Section 16)
- Liver cirrhosis
- Life expectancy < 1 year
- Unable or unwilling to provide informed consent
- Women of child bearing potential (as determined by hospital standard of care)
- Fibrinolytic therapy within 24 hours of index PCI
- Concomitant therapy with a strong cytochrome P-450 3A inhibitor or inducer
- Platelet count < 100,000 mm^3
- Requiring ongoing treatment with aspirin > 325 mg daily

5. STUDY CONDUCT

5.1 Restrictions during the study

Enrolled subjects should remain on ticagrelor plus ASA for the first three months after index PCI and ticagrelor plus blinded study drug for 12 months after randomization.

Unless clinically indicated, open label aspirin, non-steroidal anti-inflammatory drugs (NSAIDs) and additional $P2Y_{12}$ inhibitors (ticlopidine, prasugrel, clopidogrel) should not be taken by study participants during the course of the trial.

5.2 Subject randomization and initiation of investigational product

5.2.1 Procedures for randomization

The eligibility for randomization for all enrolled subjects will be evaluated at the in-person 3-month study visit. Subjects with any of the following will not be randomized:

- Refusal of randomization by subject or treating physician
- Withdrawal of consent
- Lost to follow-up
- Death
- Major bleeding (BARC Types 3b or 5)
- Occurrence of an ischemic event after PCI such as myocardial infarction, definite or probable stent thrombosis, ischemic stroke, coronary revascularization with drug-eluting stent
- No longer taking DAPT with aspirin and ticagrelor
- Non physician-guided cessation of aspirin or ticagrelor of 5 days or greater.
- Women of child bearing potential (as determined by hospital standard of care)
- Renal failure requiring dialysis
- Current indication for oral anticoagulation or high dose aspirin

An independent biostatistician, not otherwise part of the study team, will generate the randomization schedule. For this study, the randomization schedule refers to a list that includes the randomization number, randomization block number, treatment code and treatment.

Randomization will be performed by the interactive voice/web response system (IXRS) within the EDC system among subjects eligible for randomization. The IXRS will assign the unique subject identification number, allocate the treatment group assignment for the subject and provide the appropriate drug supply kit number(s). The IXRS will provide study site research personnel with the appropriate drug supply kit number(s).

Upon randomization at the conclusion of the in-person 3 month visit, the study site research personnel will provide a 6 month supply of investigational product (aspirin or matching placebo) and ticagrelor.

Enrolled subjects who do not meet eligibility for randomization will remain in the study. They will not receive study drug and medication will continue as determined by their treating physician.

5.3 Procedures for handling subjects incorrectly enrolled or randomized on investigational product

Subjects who are incorrectly enrolled will be immediately withdrawn from the study. The subject and the treating physician will be notified. If the subject has already been randomized, the investigational drug (aspirin or matching placebo) will be discontinued and further treatment will be per standard of care. Subjects will be advised to continue therapy with ticagrelor until seen by their treating physician.

Subjects who are provided the incorrect investigational drug (drug supply kit was not provided according to IXRS randomization instructions) may be identified during monitoring procedure and/or drug reconciliation. In this case, the subject will be informed immediately and requested to return with all dispensed investigational drugs. The subject will then be provided with the correct investigational drug according to the IXRS randomization instructions. In addition, a protocol deviation form will be completed.

5.4 Blinding and procedures for unblinding the study

5.4.1 Methods for ensuring blinding

This study has a double-blind design with placebo aspirin. Neither the subjects, study site research personnel, academic research organization staff, or treating physicians involved in the treatment or clinical evaluation of the subjects will be aware of treatments received. There will be an independent data safety monitoring board (DSMB) to monitor the data on a periodic basis. An independent statistician, not otherwise involved in the study, will prepare and provide the required reports to the DSMB as per the DSMB charter.

5.4.2 Methods for unblinding the study

In the event of a medical emergency, in which knowledge of the investigational drug is critical to the subject's medical management, the blind for that subject may be broken by the treating physician. The investigator should follow the instructions provided in the IXRS manual to obtain the necessary treatment information from the randomization system. As the active study drug in this trial is low-dose aspirin, in most instances the subject may be properly managed without the need for unblinding.

5.5 Treatments

5.5.1 Identity of investigational product

In this protocol, the investigational product is non-enteric coated aspirin 81 mg tablets and matching aspirin-placebo tablets.

Table 1 Identity of Investigational Product

Investigational product	Dosage form and strength
Aspirin, non-EC	81 mg tablet daily
Placebo for aspirin	N/A

5.5.2 Doses and treatment regimens

Non-enteric coated aspirin at a dose of 81 mg daily and matching placebo will be administered daily. Subjects will receive 2 bottles of study drug at randomization (3-month study visit) and at the 9-month study visit.

5.5.3 Additional study drug

Ticagrelor will be administered to all subjects regardless of randomization assignment.

5.5.4 Labeling

Each aspirin/placebo bottle will be labeled in black ink. On this label the protocol number, blinded batch number, container number, blinded drug name, tablet quantity, storage conditions, directions for use and route of administration will be indicated. Storage

At the study site, the investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that the investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

The storage conditions for the subjects to follow will be included in the labeling on the bottles.

5.6 Concomitant and post-study treatment

There are no protocol specific concomitant treatments. After study completion, the physician will determine the ongoing medical treatment for each subject.

5.7 Treatment compliance

Study drug compliance will be assessed using manual pill count at the 9-month and 15-month in-person follow-up visits.

5.7.1 Accountability

Reconciliation between the quantity of shipped study drugs versus the allocation of study drugs via IXRS and versus distribution of study drug to subject will be monitored and reconciled.

5.8 Discontinuation of investigational product

5.8.1 Procedures for discontinuation of a subject from investigational product

At the conclusion of the study, subjects will be instructed to discontinue investigational product. Antiplatelet therapy will be prescribed as per individual physician discretion.

In the event that a subject is discontinued from ASA and/or placebo due to repeat coronary intervention, subjects should be considered, where possible, for eligibility to resume study drug. Open-label DAPT (ASA + ticagrelor) is recommended for a minimum period of 2 weeks following POBA, 1 month following PCI with BMS, or 3 months following PCI with DES.

5.9 Withdrawal from study

Each enrolled subject shall remain in the trial until completion of the required follow-up period. However, a subject's participation in any clinical trial is voluntary and the subject has the right to withdraw at any time without penalty or loss of benefit. Conceivable reasons for discontinuation may include, but not be limited to, the following:

- Subject voluntary withdrawal
- Subject withdrawal by physician as clinically indicated
- Subject lost-to follow-up

The reason for subject discontinuation must be documented on the CRF and source documents. The Primary Investigators must also report all subject discontinuations to their IRB/EC as defined by their institution's procedure.

All data from evaluations and treatments performed prior to the withdrawal should be documented on the CRFs. Source documents that pre-date the withdrawal should be submitted as required by the protocol. No data that post-dates the withdrawal will be collected.

Once a subject has withdrawn from the trial, no further follow-up contact will be performed. However, vital status may be obtained from public records. Medical therapy after stopping the study will be as prescribed by the subject's physician.

6. COLLECTION OF STUDY VARIABLES

6.1 Recording of data

The Investigator is responsible for maintaining complete and accurate documentation of the trial including but not limited to medical records, trial progress records, laboratory results, case report forms, signed informed consent forms, investigational product accountability records, correspondence with the IRB or EC as well as trial monitors and sponsor, adverse event reports, and information regarding subject discontinuations.

The Investigator is required to maintain information in the subject's medical records which documents and corroborates data entered in the case report forms. As a minimum the subject record should contain:

- Medical history/physical exam documenting that subject meets inclusion/exclusion criteria
- Documentation of subject's consent and subject ID number in the trial
- Dated and signed notes from each subject visit
- Adverse events reported and their resolution or lack thereof including supporting documents such as hospital records, discharge summaries, catheterization reports, ECGs, etc.
- Record of protocol required medications during the trial
- Record of the subject's condition upon completion of or withdrawal from the trial

6.2 Data collection at enrollment and follow-up

Data collection commences after the subject has provided informed consent. Data collection including subject demographic information, laboratory tests, and procedural data as well as follow-up visits or telephone contacts will be conducted by an Investigator or site coordinator who has been trained on the protocol and Case Report Forms (CRF).

Data required for analysis will be obtained as outlined in Table 2. After discharge from the hospital, each enrolled subject will be followed with an in-clinic visit at 3months. Subjects who are randomized at 3 months will return for additional in-clinic visits at 9 and 15 months. Subjects who did not meet eligibility for randomization at the 3 month visit will be followed by telephone contact only at 9 and 15 months to ascertain occurrence of adverse events and compliance with their standard of care DAPT regimen.

Table 2 Schedule of Data Collection

Type of Data to be Collected	Stenting Procedure	Enrollment Procedure	Post-Procedure or Discharge	3 Month (90d) (±30 days) Office Visit	9 Month (270d) (± 30 days) Phone Contact non-randomized	9 Month (270d) (± 30 days) Office Visit randomized	15 Month (450d) (± 30 days) Phone Contact non-randomized	15 Month (450d) (± 30 days) Office Visit randomized
Stent Implantation	X							
Eligibility Criteria		X		X				
Patient Informed Consent		X						
Physical Assessment		X						
Medical/Clinical History		X						

Type of Data to be Collected	Stenting Procedure	Enrollment Procedure	Post-Procedure or Discharge	3 Month (90d) (±30 days) Office Visit	9 Month (270d) (± 30 days) Phone Contact non-randomized	9 Month (270d) (± 30 days) Office Visit randomized	15 Month (450d) (± 30 days) Phone Contact non-randomized	15 Month (450d) (± 30 days) Office Visit randomized
Concomitant Medications		X						
Cardiac Status		X						
Clinical Tests* Lab tests, ECG		X						
Angina Status				X	X	X	X	X
DAPT Medication Prescribed			X					
Randomization (IXRS) – if applicable				X				
Randomized Medications – provide medication according to IXRS				X		X		
Randomized Medications – reconciliation of provided medication						X		X
Randomized Medications – subject self-reporting of compliance to medications				X		X		X
Non-randomized – subject self-reporting of compliance to medications					X		X	
Adverse Events / Serious Adverse Events		X	X	X	X	X	X	X

*If performed, as per standard of care

6.2.1 Enrollment procedures

After successful elective or urgent PCI with implantation of at least one locally approved drug eluting stent and physician decision to treat subject with low-dose aspirin (81 mg – 100 mg) daily and ticagrelor 90 mg twice daily for 3 months, the investigator or designee will:

- Obtain written informed consent
- Confirm inclusion/exclusion criteria

- Obtain a complete medical history including lab values for hemoglobin and creatinine as well as an ECG, if performed per standard of care
- Review concomitant medications taken within the last 30 days
- Prescribe 3 month duration of low-dose aspirin daily and ticagrelor 90 mg twice daily
- Instruct the subject to notify the investigator of any occurrence of death, myocardial infarction, stroke, hospitalization for ischemia and bleeding
- Schedule next clinic visit at 3 months

6.2.2 In-person follow-up procedure at 3 months

-
- Assess for adverse events including MI, unstable angina, stroke, and bleeding.
- Review concomitant medications with subject
- Counsel subject about importance of study drug compliance
- Assess for randomization eligibility – If applicable:
    - Register visit with IXRS and obtain container/kit number
    - Dispense study medication for next 6 months
    - Schedule next clinic visit at 9 months (for randomized subjects)
- Instruct the subject and/or caregiver to notify the investigator of any occurrence of death, myocardial infarction, stroke, hospitalization for ischemia and bleeding

6.2.3 In-person follow-up procedure at 9 and 15 months (for randomized subjects)

- Assess for adverse events including MI, unstable angina, stroke, and bleeding.
- Review concomitant medications with subject
- Collect pill bottles, perform study medication accountability, and remind subject about importance of study drug compliance.
- Dispense study medication for next 6 months (9 month visit only)
- Instruct the subject to notify the investigator of any occurrence of death, myocardial infarction, stroke, hospitalization for ischemia and bleeding
- Schedule next clinic visit at 15 months

6.2.4 Phone follow-up contact at 9 and 15 months (for non-randomized subjects)

- Assess for adverse events including MI, unstable angina, stroke, and bleeding.
- Review concomitant medications with subject
- Instruct the subject to notify the investigator of any occurrence of death, myocardial infarction, stroke, hospitalization for ischemia and bleeding

6.3 Efficacy and safety variables

The study site research personnel will collect data from the subjects during the follow-up contact for identification of the efficacy and safety variables, defined as the first occurrence of bleeding (efficacy variable) and death, myocardial infarction, stent thrombosis, ischemic stroke, or ischemia-driven revascularization (safety variables).

7. SAFETY

The Principal Investigator at each participating study site is responsible for ensuring that all staff involved in the study is familiar with the content of this section.

7.1 Definition of adverse events

An adverse event 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 (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

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

7.2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (i.e., run-in, treatment, wash-out, follow-up), that fulfills one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions

- Results in a congenital abnormality or 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.

The severity and causality of SAEs (their relationship to all study treatments and/or procedures) will be assessed by the investigator(s) and communicated to the ARO.

7.3 Recording of adverse events or serious adverse events

7.3.1 Time period for collection of adverse events

All AEs related to bleeding and SAEs related to bleeding, death or cardiac events should be collected from the time the subject signs the informed consent through study exit.

Each complication meeting the definition for SAE will be reported upon discovery to the ARO and within 72 hours of the study site research personnel's knowledge of the event. The Investigator will further report the event to the IRB/EC according to the institution's IRB/EC reporting requirements. The subject's course must be monitored until the event has subsided or, in a case of permanent impairment, until the event stabilizes and the overall clinical outcome has been ascertained.

7.3.2 Follow-up of unresolved adverse events

The subject's course must be monitored until the event has subsided or, in a case of permanent impairment, until the event stabilizes and the overall clinical outcome has been ascertained.

7.3.3 Information to be collected for each AE/SAE

- Description of AE/SAE
- The dates when the AE/SAE started and stopped
- Whether the AE/SAE is serious or not
- Investigator causality rating against the investigational product
- Action taken with regard to investigational product
- Whether the AE/SAE caused subject's withdrawal from study
- Outcome

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

- Date the study site research personnel became aware of SAE
- Date when decision was made for meeting SAE criteria

- Criteria met leading to classification as SAE
- Date of hospitalization (if applicable)
- Date of discharge (if applicable)
- Date of death (if applicable)
- Probable cause of death (if applicable)
- Autopsy performed (if applicable)

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 7.2. 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 an 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 an SAE.

7.3.4 Adverse Events based on signs and symptoms

When collecting AEs, the recording of diagnoses (when possible) is preferred 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.

7.3.5 Adverse Events based on examinations and tests

Deterioration as compared to baseline in laboratory values or vital signs should therefore only be reported as AEs if they fulfill 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 (e.g., anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

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.

7.3.6 Disease progression or pre-existing conditions

Disease progression can be considered as a worsening of a subject's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. For example, continued angina should be considered as disease progression and not an AE.

Planned hospitalization for a pre-existing condition without serious deterioration in health, is not considered a serious adverse event.

7.3.7 Reporting of serious adverse events

Investigators and other site personnel must inform the FDA, via a MedWatch/AdEERs form, of any serious or unexpected adverse events that occur in accordance with the reporting obligations of 21 CFR 312.32, and will concurrently forward all such reports to the ARO. A copy of the MedWatch/AdEERs report must be faxed or scanned and sent to the ARO at the time the event is reported to the FDA. It is the responsibility of the investigator to compile all necessary information and ensure that the FDA receives a report according to the FDA reporting requirement timelines and to ensure that these reports are also submitted to the ARO at the same time.

When reporting to the ARO, a cover page should accompany the MedWatch/AdEERs form indicating the following:

- Investigator Sponsored Study (ISS) number
- The Research IND number assigned by the FDA
- The investigator's name and address
- The trial name/title and the ARO reference number

Investigative site must also indicate, either in the SAE report or the cover page, the causality of events in relation to all study medications and if the SAE is related to disease progression, as determined by the principal investigator.

Serious adverse events that do not require expedited reporting to the FDA need to be reported to the ARO preferably using the MedDRA coding language for serious adverse events.

In the case of blinded trials, the ARO will request that the ARO either provide a copy of the randomization code/ code break information or unblind those SAEs which require expedited reporting.

All SAEs have to be reported to the ARO, whether or not considered causally related to the investigational product. All SAEs will be documented. The investigator is responsible for informing the IRB and/or the Regulatory Authority of the SAE as per local requirements.

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 Ethical conduct of the study

The trial will be conducted in compliance with the protocol, ISO 14155:2011 (Clinical investigation of medical devices for human subjects - good clinical practice), and the ethical

principles of the Declaration of Helsinki as well as local regulations, and applicable regional regulatory requirements.

The clinical investigation shall not begin until the required approvals/favorable opinions from the respective regulatory authority and ethics committee have been obtained. Any additional requirements imposed by the respective regulatory authority and/or ethics committee will also be followed, where specified.

8.2 Ethics and regulatory review

Institutional Review Board (IRB) or Ethics Committee (EC) approval for the protocol, informed consent form and other trial related documents will be obtained by the Primary Investigator at each investigational site prior to participation in this trial. The approval letter must be signed by the IRB/EC chairperson or authorized representative prior to the start of this trial and a copy must be provided to the ARO. In addition, the Investigator or designee will provide the ARO with all required documentation necessary for initial and ongoing trial approval at their site.

In accordance with the investigational site IRB/EC requirements, the Investigator will
(a) advise the IRB/EC of the progress of this trial on a regular basis until trial completion;
(b) obtain written IRB/EC approval at predetermined time points to continue the trial; and
(c) submit any amendments to the protocol as well as associated informed consent form changes and obtain written IRB/EC approval obtained prior to implementation.

8.3 Informed consent

All subjects must provide written informed consent in accordance with the site's IRB/EC, using an IRB/EC-approved informed consent form. All subjects are to be fully informed and trial conduct must be in accordance to the World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects.

Protocol-specific procedures or alterations of patient care must not be performed until the prospective subject has provided a signed informed consent. The informed consent will be in the prospective subject's native language and will contain non-technical language to describe the investigational procedures. The informed consent should also include a clause that ensures important new information will be provided to the subject throughout the clinical investigation.

After a review of the prospective subject's medical records to determine general eligibility, the investigator or authorized designee who has been trained on the protocol, will approach the prospective subject to explain the purpose and scope of the clinical trial, prospective risks, and benefits of participation. The prospective subject must be given the opportunity to ask questions about the trial and must be given sufficient time to decide to participate in the trial or not. Additional information requested by the prospective subject should be provided. Any coercion or undue improper influence on the prospective subject is to be avoided.

If the prospective subject agrees to participate, the informed consent form must be signed and personally dated by the prospective subject. The investigator or an authorized member of the research team who has witnessed the prospective subject's signature must also sign and date the informed consent, prior to enrollment of the prospective subject. A copy of the completed informed consent form must be provided to the subject. Local IRB/EC regulations regarding obtaining informed consent must be followed. The subject's medical record should have a notation regarding the signing of the informed consent.

The subject is to be made aware that their participation in the trial is voluntary, their legal rights will not be waived, and that they may withdraw from the trial at any time, without giving specific reason for doing so. The subject must also be informed that withdrawal from the trial will not affect their future treatment.

The investigator is responsible for the achievement of written consent from the prospective subject before they are included in the trial. All subjects must provide informed consent in accordance with the local IRB/EC requirements, using an IRB/EC-approved informed consent form.

8.4 Changes to the protocol and informed consent form

If the protocol or informed consent form (ICF) needs an amendment, the ARO is required to submit such amendment to the Regulatory Agencies and/or other regulating body in each participating country for approval. Approved protocol or ICF amendments will be provided to the Investigators by the ARO prior to implementing the amendment.

For administrative changes, the Primary Investigator is responsible for notifying the IRB/EC of the protocol or ICF amendment. For changes involving subject care or safety, the Primary Investigator is responsible for obtaining IRB/EC approval of the protocol or ICF amendment according to the instructions provided by the ARO with the protocol or ICF amendment.

Acknowledgement/approval by the IRB/EC of the protocol or ICF amendment must be documented in writing prior to implementation of the protocol or ICF amendment. Copies of this documentation must also be provided to the ARO.

8.5 Deviations from protocol

8.5.1 Compliance to protocol

No investigative procedures other than those defined in this clinical investigational plan will be undertaken on the enrolled subjects without the written agreement of the IRB/EC and ARO.
It is the Investigator's responsibility to ensure that there are no deviations from the clinical investigational plan and full compliance with all established procedures of the IRB/EC is maintained. The Investigator will not deviate from the clinical investigational plan for any reason except in cases of medical emergencies, when the deviation is necessary to protect the life or physical well-being of the subject.

8.5.2 Procedures for recording, reporting, and analyzing protocol deviations

A deviation is an instance(s) of failure to follow, intentionally or unintentionally, the requirements of the protocol. All deviations must be reported to the ARO. The occurrence of clinical investigational plan deviations will be monitored by the ARO or designee. It is the Investigator's responsibility to inform their IRB/EC of clinical investigational plan deviations in accordance with their specific IRB/EC reporting policies and procedures.

In the event that an investigative site does not comply with the Investigator Agreement or clinical investigational plan, the ARO will notify the Investigator of the site's non-compliance. Continued non-compliance may result in further escalation in accordance with the ARO's standard procedures.

8.5.3 Corrective and preventative actions and principal investigator disqualification criteria

Protocol deviations and site/PI non-compliance will be closely monitored by the ARO and appointed study personnel. Identifying deviations and taking corrective actions at the earliest possible stage increases the potential for clinical trial success and reduces patient risk. The initiation of a corrective and preventative action (CAPA) to investigate and establish corrective actions may be required in some cases. The ARO reserves the right to close a clinical study site or replace a PI if non-compliance is observed.

8.6 Audits and inspections

In the event that an Investigator is contacted by a Regulatory Agency in relation to this trial, the Investigator will notify the ARO immediately. The Investigator and study site research personnel must be available to respond to reasonable requests and inspection queries made during the inspection process. The Investigator must provide the ARO with copies of all correspondence that may affect the review of this trial. The ARO will provide any needed assistance in response to regulatory inspections.

9. STUDY MANAGEMENT

9.1 Training

9.1.1 Training of Monitors

The ARO's monitors or designee will be trained to the protocol, randomization instructions, electronic case report forms, and study drug usage. The ARO or designee is responsible for the training. Training will be conducted in accordance with the ARO's and/or designee's standard procedures.

9.1.2 Training of study site research personnel

Participating investigators and study site research personnel will be trained during site initiation visits conducted by the Mount Sinai Clinical Coordinating Center or designee.

All training must be documented and must include or reference the revision of materials used for training, who was trained, the trainer and date of training. Original training records should be maintained at the site in the Regulatory Binder and copies should be dispensed to Mount Sinai Clinical Coordinating Center.

Site initiation/training involves a didactic session whereby the protocol, including screening procedures, clinical follow-up procedures, and study drug procedures are reviewed in detail along with investigator responsibilities.

In addition, the Mount Sinai Clinical Coordinating Center will assure that all participating investigators and study personnel are trained in the following:

- Protocol requirements, including patient screening requirements, inclusion/exclusion criteria, procedural requirements and subject follow-up requirements
- Study and personnel requirements
- Informed consent requirements
- Adverse event reporting
- Drug accountability procedures
- Electronic CRF completion
- Regulatory binder maintenance.

9.2 Monitoring of the study

The ARO and/or designee will monitor the trial over its duration according to the pre-specified monitoring plan. The trial monitor will contact each site at appropriate intervals to review investigational data for accuracy and completeness and ensure compliance with the clinical investigation plan. The trial monitor may request all documents and required records that are maintained by the Investigator/Site, including medical records (office, clinic, or hospital) for the subjects in this trial. Source documentation must be available to substantiate proper informed consent procedures, adherence to protocol procedures, adequate reporting and follow-up of adverse events, accuracy of data collected on case report forms, and study drug information. The Investigator and/or study site research personnel will be available for monitoring contact. If a site visit is required, it is expected that the Investigator/Site will provide the trial monitor with a suitable working environment for review of study-related documents.

9.2.1 Source data

The Investigator is responsible for maintaining complete and accurate documentation of the trial including but not limited to medical records, trial progress records, laboratory results, case report forms, signed informed consent forms, study drug accountability records,

correspondence with the IRB/EC, the trial monitors, and the ARO, as well as adverse event reports and information regarding subject discontinuations.

The Investigator is required to maintain information in the subject's medical records which documents and corroborates data entered in the case report forms. As a minimum the subject record should contain:

- Medical history/physical exam documenting that subject meets inclusion/exclusion criteria
- Documentation of subject's consent and subject ID number in the trial
- Dated and signed notes from each subject visit
- Adverse events reported and their resolution or lack thereof including supporting documents such as hospital records, discharge summaries, catheterization reports, and ECGs.
- Record of protocol required medications during the trial
- Record of the subject's condition upon completion of or withdrawal from the trial

The Investigator and the associated institution will permit direct access to source data/documents for study-related monitoring, audits, IRB/EC review, and regulatory inspections.

Subjects providing informed consent agree to allow the ARO or designee access and copying rights to pertinent information in their medical records concerning their participation in this trial. The Investigator will obtain, as part of the informed consent, permission for trial monitors or regulatory authorities to review, in confidence, any records identifying the subjects in this trial. This information may be shared with regulatory agencies; however, the ARO undertakes not to otherwise release the patient's personal and private information.

9.3 Study timetable and end of study

The clinical investigation is estimated to commence [start date]. Evaluation of primary end point is estimated by [date]. The last subject follow-up at 15 months post-procedure (12 months post-randomization) is expected to occur in [month/year]. Total expected duration of the clinical investigation is [time frame]. The subjects will not be provided any follow-up contact or medical care related to the trial after the clinical investigation has been completed. Final subject visit will take place at 15 months and this will end their participation in the study. Medical therapy after stopping the study will be as prescribed by the subject's physician.

10. DATA MANAGEMENT

A computerized data entry and management system will be developed during the initial project months by an independent academic research organization. A closed and password protected data entry system has been designed to ensure that only the responsible data entry person and the Data Management site supervisor can enter and/or edit data and this can be done only by using the programs and/or utilities available on the menu system. An audit trail will be created by date/time and user stamping. Range checks, review screens, and various error trapping routines are built into the system as quality control procedures. All possible relevant information on the forms is pre-coded. Specific instructions and explanation of choices will be provided for all data forms.

The statistical programmer will perform additional data checks, data cleaning, and variable coding to create analysis datasets using SAS. The programmer will also create a reporting system that generates study specific tables, listings, and figures, which will be run periodically to monitor study and data entry. As a final check on data integrity, the Director of Clinical Biometrics and study biostatistician will check these outputs against the raw data in order to resolve any discrepancies. The Biometrics lead, statistician, and statistical programmer will be responsible for working with the project staff to ensure the integrity of the data entry process.

11. EVALUATION AND CALCULATION OF VARIABLES

11.1 Calculation or derivation of efficacy variable(s)

11.1.1 Primary Efficacy Outcome

The primary efficacy outcome of the present study is the time to first occurrence of clinically relevant bleeding, defined as Bleeding Academic Research Consortium (BARC) Types 2, 3 or 5 bleeding.

11.1.2 Secondary Efficacy Outcomes

Time to first occurrence of:

- Types 3 or 5 bleeding according to definitions from BARC
- Minor or major bleeding according to definitions from Thrombolysis in Myocardial Infarction (TIMI)
- Moderate or severe or life-threatening bleeding according to definitions from GUSTO
- Major bleeding according to definitions from International Society of Thrombosis or Haemostasis (ISTH)

11.2 Calculation or derivation of safety variable(s)

11.2.1 Primary Safety Outcome

The primary safety outcome of the present study is the time to first occurrence of confirmed cardiovascular death, non-fatal myocardial infarction, ischemic stroke or ischemia-driven revascularization

11.2.2 Secondary Safety Outcomes

Time to first occurrence of:

- cardiovascular death, non-fatal myocardial infarction, ischemic stroke or ischemia-driven revascularization
- cardiovascular death, non-fatal myocardial infarction or ischemic stroke
- definite or probable stent thrombosis
- cardiovascular death
- non-fatal myocardial infarction
- cardiovascular death, non-fatal myocardial infarction or definite or probable stent thrombosis
- ischemic stroke
- all-cause mortality

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

The statistical analyses will be performed using SAS version 9.0 or greater and Stata versions 12.0 or greater.

12.1 Description of analysis sets

The Enrolled Population consists of all subjects who signed informed consent.

The intention-to-treat (ITT) population will consist of all subjects who have been randomized (i.e. when the subject number and allocated treatment are recorded in the IXRS database). Subjects will be analyzed in the treatment group assigned by the IXRS.

The per-protocol population (PP) will consist of all randomized subjects without any major deviations from the protocol. The following deviations will lead to exclusion from the PP population

- Subjects not receiving the assigned treatment as allocated by the IXRS or no treatment at all
- Non-compliance to study drug (aspirin or placebo) or ticagrelor. Non-compliance is defined as taking less than 80% of dispensed tablets based on manual pill bottle count at each study visit.

12.1.1 Efficacy analysis set

All efficacy analyses will be performed on the ITT and PP population. The primary efficacy analysis will be performed on the ITT population. This analysis will be repeated in the PP population to support the primary results.

The primary efficacy endpoint is the composite of BARC Types 2, 3 or 5 bleeding.

12.1.2 Safety analysis set

Safety analyses will be performed on the PP cohort.

12.2 Methods of statistical analyses

Unless otherwise stated, all hypothesis tests will be performed using two-sided tests at the 5% significance level. Continuous variables will be summarized using descriptive statistics including means and standard deviations if normally distributed or median with interquartile ranges for skewed distributions. Discrete variables will be summarized using absolute and relative frequencies.

Demographic and baseline characteristics will be summarized by randomized treatment group and for all randomized subjects combined. Baseline characteristics that will define subgroups of interest for the efficacy and safety analyses are:

- Age group (< 65, >= 65 years)
- Race (Caucasian, non-Caucasian)
- Gender (Male, Female)
- Geographic Region (US, non-US)
- Diabetes Mellitus (yes, no)
- Chronic Kidney Disease (yes, no)
- CAD Presentation (Stable, Unstable)
- PCI Status (Elective, Urgent)
- Stent length implanted (< 30 mm, >=30 mm)

- BMI (above median, below median)
- History of Prior MI (yes, no)
- Multivessel disease (yes, no)

Censoring Subjects not experiencing any endpoint will be censored at time of death, last contact date (for subjects who withdraw consent or are lost to follow-up) or 365 days after randomization, whichever comes first.

Primary Efficacy Analysis This analysis will be performed on the ITT population. The primary objective is to determine if ticagrelor monotherapy is superior to ticagrelor plus aspirin for the primary efficacy endpoint (BARC Types 2, 3 or 5 bleeding). The null hypothesis for this analysis is that the HR for the experimental group (H_0) = 1. The alternative hypothesis is that the HR for the experimental group (H_A) ≠ 1. A test of superiority at the two-sided 0.05 level will be performed using a Cox proportional hazard model that includes treatment group as a covariate. A point estimate and two-sided 95% CI for the relative risk as measured by the hazard ratio will be calculated based on the Cox proportional hazards model. Event rates will be estimated at one year and Kaplan-Meier curves will be plotted for the time from randomization to the first occurrence of confirmed BARC Type 2, 3 or 5 bleeding by treatment group. This analysis will be repeated in the PP cohort to support the primary results.

Primary Safety Analysis This analysis will be performed on the PP cohort. The primary objective is to determine if ticagrelor monotherapy is non-inferior to ticagrelor plus aspirin for the primary safety endpoint (cardiovascular death, non-fatal myocardial infarction, ischemic stroke or ischemia-driven revascularization). The null hypothesis for this analysis is that the HR for the experimental group (H_0) > 1.22. The alternative hypothesis is that the HR for the experimental group (H_A) ≤ 1.22. A test of non-inferiority at the two-sided 0.05 level will be performed using a Cox proportional hazard model that includes treatment group as a covariate. A point estimate and two-sided 95% CI for the relative risk as measured by the hazard ratio will be calculated based on the Cox proportional hazards model. Event rates will be estimated at one year and Kaplan-Meier curves will be plotted for the time from randomization to the first occurrence of confirmed cardiovascular death, non-fatal myocardial infarction, ischemic stroke or ischemia-driven revascularization by treatment group. If the upper limit of the 95% CI for the point estimate is less than or equal to 1.22 then the criteria for non-inferiority will be met.

Subgroup Analysis One year event rates for the primary efficacy and safety endpoints will be calculated in all subgroups described in section 12.2. Stratum-specific HRs and corresponding 95% CI will be calculated for each subgroup using a Cox proportional hazards model. Formal interaction testing will be performed using the subgroup X treatment allocation as an additional term in the Cox model.

12.3 Determination of sample size

Power calculations are based on a superiority comparison for the primary efficacy endpoint of clinically relevant bleeding (BARC Types 2, 3 or 5) at 1 year from randomization (15 months after enrollment). Based on bleeding rates as shown in Table 2, a cumulative bleeding rate of 4.5% is anticipated between time of randomization and 1 year. This estimate is more conservative than rates shown in Table 2 as subjects sustaining a major hemorrhagic event in the first 3 months after PCI will not be randomized. Assuming a 2% loss to follow-up and non-compliance / cross-over rate of 4%, the current trial will require 8200 subjects to detect a relative reduction in bleeding of 28% with ticagrelor monotherapy with 80% power with a Type I error of 0.05. It is anticipated that approximately 8% - 10% of enrolled subjects will not be eligible for randomization and therefore 9000 subjects will be enrolled. Additional sample size estimates are provided in Table 4 assuming different control bleeding rates and risk reductions. References for the sample size estimates include Lakatos 1988, Biometrics volume 44 pages 229-241; and Lakatos 2002, Statistics in Medicine, Volume 21 pages 1969-1989.

Sample size estimates for the non-inferiority comparison of ischemic events are provided in Table 5. Assuming a 1 year ischemic adverse event rate of 8% the current study will have 81% power to exclude a non-inferiority margin of 1.22 (upper limit of 95% CI for risk ratio).

Table 3 Bleeding Rates/Effect Sizes for Primary Endpoint Power Calculations

Basis for Proposed Bleeding Event Rates in TWILIGHT Power Calculations			
Study	**Study Type**	**Time Point**	**BARC ≥ 2 Rate**
PARIS (unpublished data)	Registry		
Age > 65	Registry	1 year	8.6%
Diabetes Mellitus (on insulin) Diabetes Mellitus (orals)	Registry	1 year	8.3% 6.3%
Renal disease	Registry	1 year	13.2%
Vranckx et al., EHJ 2013	Post-hoc (TRACER)	500 days	14%
ADAPT-DES			
CrCl < 60 (Baber et al, TCT 2013)	Registry	1 year	10.0%
Rao et al., JACC Int 2013	NCDR CathPCI	In-hospital (women)	8.5%

Basis for Proposed Effect Size in TWILIGHT Power Calculations			
Study	**Study Type**	**Comparators**	**Relative Bleeding Increase**
Baigent et al., Lancet 2009	Pooled Data from Randomized trials	ASA vs. placebo/control	50% (1° prevention) 170% (2° prevention)
WOEST, Lancet 2013	RCT	ASA vs. placebo	~ 60%
CAPRIE, Lancet 1996	RCT	ASA vs. clopidogrel	~35% (GI hemorrhage)
Physician Health Study, NEJM 1989	RCT	ASA vs. Placebo	~35%
De Berardis et al., JAMA 2012	Cohort study	ASA vs. No ASA	55%
Seshasai et al., Archives Int Med 2012	Meta-analysis of 9 RCTs	ASA vs. Placebo	~31%
HOT Trial, Lancet 1998	RCT	ASA vs. Placebo	~ 80%

Table 4 Power and Sample Size Scenarios for Primary Superiority Endpoint of BARC ≥ 2 Bleeding

Control Bleeding Rate	Relative Risk Reduction	Total Randomized Sample Size	Total Sample Size (Enrolled + Randomized) with 8% loss after enrollment*	Total Sample Size (Enrolled + Randomized) with 10% loss after enrollment*
5%	30%	6400	7000	7111
5%	28%	7400	8040	8222
5%	26%	8030	9800	10000
4.5%	30%	7090	7706	7900
4.5%	28%	8200	8913	9111
4.5%	26%	9700	10500	10800
4.0%	30%	8000	8700	8888
4.0%	28%	9300	10100	10333
4.0%	26%	10900	11800	12111

We anticipate that ~10% of enrolled subjects will not be eligible or lost for randomization. Power calculations assume 2% loss to follow-up and 4% cross-over/non-compliance.

Table 5 Sample Size/Poser Calculations for Non-inferiority MACE Comparison between Groups at 1 Year

Power	MACE rate	Randomized Sample Size	Non-inferiority Margin
0.75	8%	8200	1.20
0.81	8%	8200	1.22
0.84	8%	8200	1.23
0.80	9%	8200	1.20
0.85	9%	8200	1.22
0.88	9%	8200	1.23

12.4 Data and safety monitoring board

The TWILIGHT study will be conducted under the auspices of an independent Data and Safety Monitoring Board (DSMB), whose activities will be described in a DSMB charter. DSMB members will not have primary affiliation with the study sponsor, the EDC supplier or the principal investigator of the trial. Members of the Board will be determined prior to study enrollment.

The DSMB will review data and determine reporting and stopping rules as specified in the DSMB charter. The DSMB members will review safety data while maintaining the scientific integrity of the trial. The data to be reviewed will consist of adjudicated and non-adjudicated MACE, Bleeding, and other Serious Adverse Events and their incidence, in order to identify potential safety issues. Based on the safety data, the DSMB may recommend modifications to the protocol, suspension or termination of the trial, and advise the Executive Committee.

Members of the DSMB will meet or conference with steering group members before the trial starts to review the protocol, to determine the meeting schedule, the logistics of reporting the safety data and the stopping rules. Frequency of meetings can change during the study and will be determined by the DSMB and its charter.

All adverse events will be reported to the DSMB and reviewed on an on-going basis throughout the subject enrollment and follow-up period as specified in the DSMB charter to ensure the safety of subjects enrolled in this trial. The DSMB may request additional information as needed. Based on safety data, the DSMB may recommend that the Executive Committee modify or discontinue the trial. All final decisions, regarding trial modifications, however, rest with the Executive Committee.

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Overdose

If an overdose on the study drug occurs in the course of the study, then investigators or other site personnel inform appropriate the ARO **within one day**, i.e., immediately but no later than **the end of the next business day** of when he or she becomes aware of it.

The ARO will work with the investigator to ensure that all relevant information is provided to the ARO.

13.2 Pregnancy

Due to the study enrollment criteria and proposed population, women of child bearing potential (as determined by hospital standard of care) are excluded from participation in this study. In the unlikely event that pregnancy should occur during the course of the study, all outcomes of pregnancy should be reported to the ARO.

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15. APPENDIX A – DEFINITIONS FOR STUDY ENDPOINTS

15.1 Bleeding events

15.1.1 Bleeding Academic Research Consortium definition of bleeding

Clinically relevant bleeding is defined as any bleeding event that meets the BARC criteria types 2, 3 or 5.

Table 6 BARC Bleeding Definition, modified from Mehran et al (22)

Type	Definition
0	No evidence of bleeding.
1	Bleeding that is not actionable and patient does not have unscheduled studies, hospitalization or treatment by a health care professional
2	Any clinically overt sign of hemorrhage that is actionable but does not meet criteria for type 3, 4 or 5 bleeding. It must meet at least one of the following criteria: • requiring medical or percutaneous intervention guided by a health care profession, includes (but are not limited to) temporary/permanent cessation of a medication, coiling, compression, local injection • leading to hospitalization or an increased level of care • prompting evaluation defined as an unscheduled visit to a healthcare professional resulting in diagnostic testing (laboratory or imaging)
3	Clinical, laboratory and/or imaging evidence of bleeding with specific healthcare provider responses, as listed below:
3a	• Any transfusion with overt bleeding • Overt bleeding plus hemoglobin (Hb) drop ≥3 to <5g/dL* (provided Hb drop is related to bleeding)
3b	• Overt bleeding plus Hb drop ≥5g/dL* (Hb drop is related to bleed) • Cardiac tamponade • Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid) • Bleeding requiring intravenous vasoactive drugs
3c	• Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation; does include intraspinal). Subcategories: confirmed by autopsy, imaging or lumbar puncture

* Hemoglobin drop should be corrected for for intracurrent transfusion in which 1 unit of packed red blood cells or whole blood should be expected to increase hemoglobin by 1g/dL.

Type	Definition
	• Intraocular bleed compromising vision
4	CABG – Related Bleeding • Perioperative intracranial bleeding within 48 hours • Reoperation following closure of sternotomy for the purpose of controlling bleeding • Transfusion of ≥5 units of whole blood or packed red blood cells within a 48 hour period • Chest tube output ≥2L within a 24 hour period
5	Fatal Bleeding. Bleeding directly causes death with no other explainable cause. Categorized further as either definite or probable.
5a	Probable fatal bleeding is bleeding that is clinically suspicious as the cause of death, but the bleeding is not directly observed and there is no autopsy or confirmatory imaging.
5b	Definite fatal bleeding is bleeding that is directly observed (either by clinical specimen – blood, emesis, stool, etc. – or by imaging) or confirmed on autopsy.

15.1.2 Thrombolysis in Myocardial Infarction definition of bleeding

Table 7 TIMI Bleeding Definition(23)

Type	Definition
Non-CABG related bleeding	
Major	• Any intracranial bleeding (excluding microhemorrhages <10 mm evident only on gradient-echo MRI) • Clinically overt signs of hemorrhage associated with a drop in hemoglobin of ≥5 g/dL or a ≥15% absolute decrease in haematocrit • Fatal bleeding (bleeding that directly results in death within 7 days) **Life threatening** bleeding is a TIMI major bleeding event that meets any of the following criteria: • Symptomatic intracranial hemorrhage • Fatal bleeding • Leads to hypotension requiring inotropic agents • Requires surgical intervention for ongoing bleeding • Necessitates transfusion of 4 or more units of whole blood or packed red blood cells over a 48-hour period

Type	Definition

Minor	• Clinically overt (including imaging), resulting in hemoglobin drop of 3 to <5 g/dL or ≥10% decrease in haematocrit
	• No observed blood loss: ≥4 g/dL decrease in the haemoglobin concentration or ≥12% decrease in haematocrit
	• Any overt sign of hemorrhage that meets one of the following criteria and does not meet criteria for a major bleeding event:
	  o Requiring intervention (medical practitioner-guided medical or surgical treatment to stop or treat bleeding, including temporarily or permanently discontinuing or changing the dose of a medication or study drug)
	  o Leading to or prolonging hospitalization
	  o Prompting evaluation (leading to an unscheduled visit to a healthcare professional and diagnostic testing, either laboratory or imaging)

Minimal	• Any overt bleeding event that does not meet the criteria above • Any clinically overt sign of haemorrhage (including imaging) associated with a <3 g/dL decrease in haemoglobin concentration or <9% decrease in haematocrit
Bleeding in the setting of CABG	
	• Fatal bleeding (bleeding that directly results in death) • Perioperative intracranial bleeding • Reoperation after closure of the sternotomy incision for the purpose of controlling bleeding • Transfusion of ≥5 U PRBCs or whole blood within a 48-h period; cell saver transfusion will not be counted in calculations of blood products. • Chest tube output >2 L within a 24-h period

15.1.3 Global Utilization of Streptokinase and TPA for Occluded Arteries (GUSTO) definition of bleeding

Table 8 GUSTO Bleeding Definition (24)

Type	Definition
Severe or life-threatening	Intracerebral bleeding or bleeding resulting in substantial hemodynamic compromise requiring treatment
Moderate	Any bleeding not meeting the requirements for severe / life-threatening bleeding that requires transfusion
Minor	Other bleeding not requiring transfusion or causing hemodynamic compromise

15.1.4 International Society on Thrombosis and Haemostasis definition of bleeding

The ISTH classification of major bleeding in non-surgical patients includes any one of the following:

- Fatal bleeding,
- Symptomatic bleeding in a critical area or organ such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome,
- Bleeding causing a fall in haemoglobin level of 2 g/dL (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells.(25)

15.2 Major Adverse Cardiovascular Events

Major adverse cardiovascular events (MACE) is the composite of cardiovascular death, non-fatal myocardial infarction, ischemic stroke, or clinically-driven revascularization. The definitions of the individual components of MACE are given below.

15.2.1 Death

All-cause death comprises several subclassifications (Table 9). In general, all deaths are considered cardiac unless an alternate cause is unequivocally established, even among subjects with serious noncardiac comorbidities.

Table 9 Classification of Death(25)

Cardiac death	Any death due to proximate cardiac cause (eg, MI, low-output failure, fatal arrhythmia), unwitnessed death and death of unknown cause, all procedure-related deaths including those related to concomitant treatment, will be classified as cardiac death.
Vascular death	Death caused by noncoronary vascular causes, such as cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm or other causes.
Noncardiovascular death	Any death not covered by the above definitions, such as death caused by infection, malignancy, sepsis, pulmonary causes, accident, suicide or trauma.

15.2.2 Myocardial Infarction

Myocardial infarction is defined according to the third universal definition(26) and includes:

- Type 1: spontaneous MI
- Type 2: MI secondary to an ischemic imbalance
- Type 3: MI resulting in death when biomarker values are unavailable
- Type 4a. MI related to PCI
- Type 4b: MI related to stent thrombosis

- Type 5: MI related to CABG

Any one of the following criteria meets the diagnosis of MI:

- Detection of a rise and/or fall of cardiac biomarker values (preferably cardiac troponin) with at least one value above the 99th percentile URL and with at least one of the following:
    - Symptoms of ischemia
    - (Presumed) new significant ST-T wave changes or new LBBB
    - Development of pathological Q waves
    - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
    - Identification of an intracoronary thrombus by angiography or autopsy
- Cardiac death with symptoms suggestive of MI and presumed new ischemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased
- PCI related MI is arbitrarily defined by elevation of cardiac biomarkers
    - (>5 x 99th percentile URL) in patients with normal baseline values or
    - > 20% if the baseline values are elevated and are stable or falling

In addition, one of the following is required

- symptoms suggestive of ischemia
- new ischemic ECG changes
- angiographic findings consistent with a procedural complication OR
- imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality

- Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL
- CABG related MI is arbitrarily defined by elevation of cardiac biomarkers >10 x 99th percentile URL in patients with normal baseline values, AND one of the following:

- New pathological Q waves or new LBBB
- Angiographic documented new graft or new native coronary artery occlusion, or
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

15.2.3 Stroke

Stroke is defined as an acute symptomatic episode of neurological dysfunction, more than 24 hours in duration in the absence of therapeutic intervention or death, due to cerebral, spinal or retinal tissue injury as evidenced by neuroimaging or lumbar puncture. It includes the following subclassifications:

- Ischemic stroke: infarction due to prolonged ischemia. Causes include (but are not limited to) arterial and venous thrombosis, embolism, and systemic hypoperfusion.
- Hemorrhagic stroke: caused by a non-traumatic intraperenchymal, intraventricular or subarachnoid hemorrhage
- Undetermined: stroke with insufficient information to determine ischemic or hemorrhagic cause

Transient ischemic attack (TIA) is a transient episode of neurological dysfunction (< 24 hours) caused by temporary cerebral, spinal or retinal ischemia with no evidence of acute infarction on neuroimaging.

15.2.4 Stent thrombosis

Stent thrombosis is classified according to the level of certainty and timing following PCI(25) (Table 10).

- Definite stent thrombosis: is highly specific and requires angiographic or pathological confirmation of stent thrombosis in or within 5 mm of the stent in the setting of at least one of the following criteria with a 48-hour time window
    - Acute ischemic symptoms at rest
    - New ischemic ECG changes
    - Typical rise and fall in cardiac biomarkers
- Probable stent thrombosis includes
    - Any unexplained death within the first 30 days following PCI

- Any MI at any time following PCI that is related to documented acute ischemia in the territory of the implanted stent, in the absence of angiographic/pathological confirmation of stent thrombosis and no other obvious cause

- Possible stent thrombosis
  - Any unexplained death after the first 30 days following PCI until the end of trial follow-up

Table 10 Timing of Stent Thrombosis

Acute	0-24 hours following PCI
Subacute	>24 hours to 30 days following PCI
Late	>30 days to 1 year following PCI
Very late	>1 year following PCI

15.2.5 Clinically driven revascularization

Clinically driven revascularization includes repeat PCI or CABG for recurrent or persistent symptomatic ischemia and can be defined according to the relationship to the index PCI (target lesion)(25):

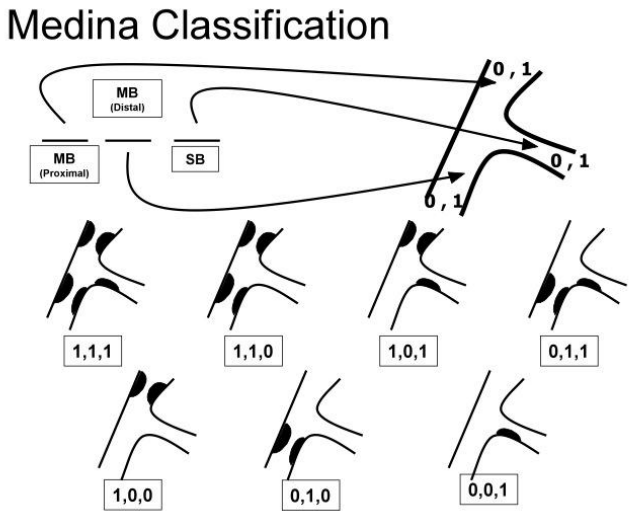
- Target lesion revascularization, at the previously stented segment
- Non-target lesion, target vessel revascularization, of the previously treated vessel or its side branches AND
- Non-target vessel lesion revascularization, of a vessel other than the previously treated vessel

16. APPENDIX B - OTHER DEFINITIONS

Coronary Artery Disease (CAD)

Multivessel (CAD), defined as significant disease in at least 2 major epicardial vessels or significant left main disease plus one major epicardial vessel. Significant coronary artery disease is defined as angiographic stenosis of at least 70% in a major epicardial vessel or at least 50% in the left main trunk. For intermediate stenosis in major epicardial vessels (50%-70%), an invasive hemodynamic assessment using fractional flow reserve (FFR) with values less than or equal to 0.8 will be considered significant. For intermediate left main lesions, a minimal lumen area by intravascular ultrasound (IVUS) less than 6.0 mm^2 will be considered significant.

Medina Classification of Bifurcations



Indication for PCI according to National Cardiovascular Data Registry

PCI indication consisted of

(1) elective;

(2) urgent (required during same hospitalization to minimize further clinical deterioration, worsening or sudden chest pain, congestive heart failure, acute MI, anatomy, intra-aortic balloon pump, unstable angina with intravenous nitroglycerin, or angina at rest);

(3) emergency (to procedure or in transit to the catheterization laboratory, ongoing ischemia despite maximal medical therapy, acute MI ≤24 hours before procedure, pulmonary edema requiring intubation, or shock with or without circulatory support); or

(4) salvage (undergoing CPR en route to PCI).

Drug Substance	Ticagrelor and Aspirin
Study Number	ISSBRIL0345
EudraCT No.	2014-005498-35
ClinicalTrials.gov ID	NCT02270242
Version Number	4.0
Date	28-Mar-2016

TWILIGHT Study

Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention

Funding Agency: **AstraZeneca**

Sponsor-Investigator/Academic Research Center (ARC): **The Office of Interventional Cardiovascular Research and Clinical Trials at Icahn School of Medicine at Mount Sinai**

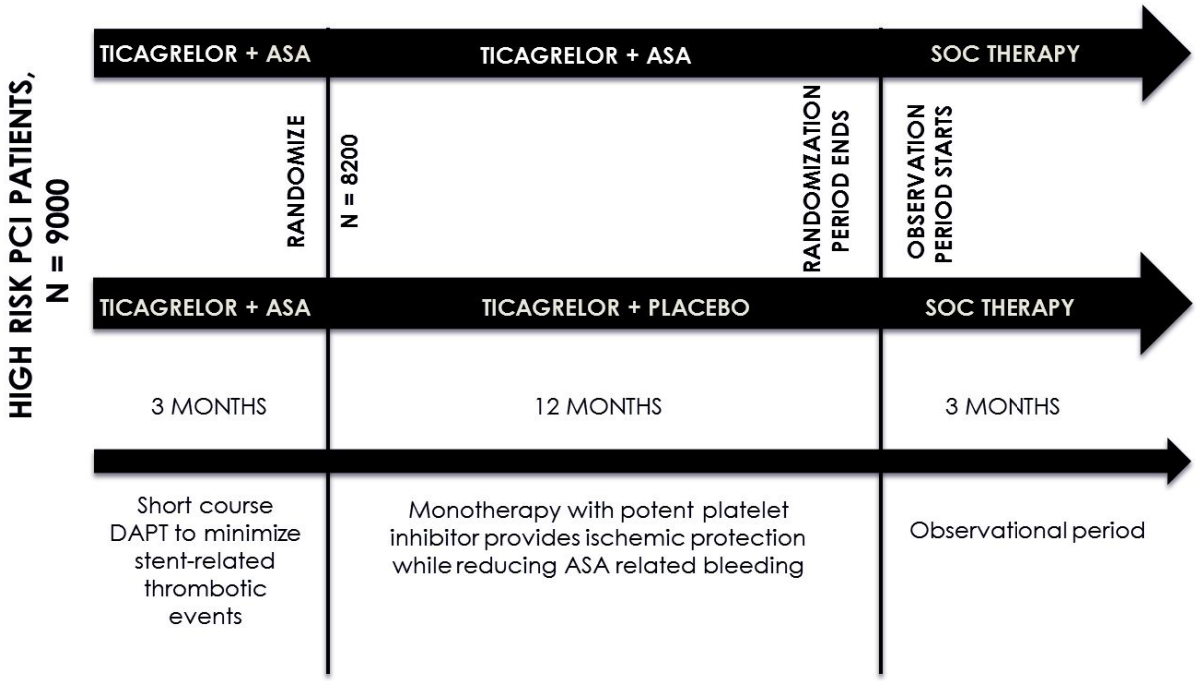
PROTOCOL SYNOPSIS

Title of Study	TWLIGHT Study - Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention
Primary Investigator:	Roxana Mehran, MD, FACC, FACP, FCCP, FESC, FAHA, FSCAI Professor of Medicine and Director of Interventional Cardiovascular Research and Clinical Trials Icahn School of Medicine at Mount Sinai
Study Centers:	Approximately 100 sites in U.S., Canada, South America, Europe, and China
Study Design	Multicenter, prospective, blinded dual-arm study
Purposes	**Aim 1:** To determine the impact of ticagrelor alone versus ticagrelor plus aspirin in reducing clinically relevant bleeding among high-risk patients who had PCI with at least one drug-eluting stent. **Aim 2:** To determine the impact of ticagrelor alone versus ticagrelor plus aspirin in reducing ischemic adverse events at one year among high-risk patients undergoing PCI with at least one drug-eluting stent.
Enrollment and Patient Population	Up to 9000 high-risk patients who have undergone successful PCI with at least one locally approved drug eluting stent discharged on DAPT with aspirin and ticagrelor of at least 3 months intended duration.
Primary Objective	The primary objective of this study is to determine the impact of antiplatelet monotherapy with ticagrelor alone versus DAPT with ticagrelor plus aspirin for 12 months in reducing clinically relevant bleeding among high-risk patients undergoing PCI who have completed a 3-month course of aspirin plus ticagrelor.
Secondary Objectives	The secondary objective of this study is to determine the impact of antiplatelet monotherapy with ticagrelor alone versus DAPT with ticagrelor plus aspirin for 12 months in reducing major ischemic adverse events among high-risk patients undergoing PCI who have completed a 3-month course of aspirin plus ticagrelor.
Eligibility Criteria	High-risk patients who have undergone successful PCI with at least one locally approved drug eluting stent AND discharged on DAPT with aspirin and ticagrelor of at least 3 months intended duration will be eligible for the TWILIGHT study.

	Enrollment into the study will require meeting at least one clinical inclusion AND at least one angiographic inclusion AND none of the exclusion criteria. <u>Clinical Inclusion Criteria (MUST MEET AT LEAST ONE):</u> • Adult patients ≥ 65 years of age • Female gender • Troponin positive acute coronary syndrome • Established vascular disease defined as previous MI, documented PAD or CAD/PAD revascularization • Diabetes mellitus treated with medications (oral hypoglycemic, subcutaneous injection of insulin) • Chronic kidney disease defined as an estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73m^2 or creatinine clearance (CrCl) < 60 ml/min <u>Angiographic Inclusion Criteria (MUST MEET AT LEAST ONE):</u> • Multivessel coronary artery disease • Target lesion requiring total stent length >30 mm • Thrombotic target lesion(s) • Bifurcation lesions with Medina X,1,1 classification requiring at least 2 stents • Left main (≥50%) or proximal LAD (≥70%) lesion • Calcified target lesion(s) requiring atherectomy <u>Exclusion Criteria:</u> • Under 18 years of age • Contraindication to aspirin (listed in appendix D) • Contraindication to ticagrelor (listed in appendix E) • Planned surgery within 90 days • Planned coronary revascularization (surgical or percutaneous) within 90 days • Need for chronic oral anticoagulation • Prior stroke • Dialysis-dependent renal failure • Active bleeding or extreme-risk for major bleeding (e.g. acute gastrointestinal ulcer or history of chronic gastrointestinal ulceration, gastrointestinal pathology with a raised risk for bleeding, malignancies with a raised risk for bleeding) • Salvage PCI or STEMI presentation. • Liver cirrhosis • Life expectancy < 1 year • Unable or unwilling to provide informed consent • Women of child bearing potential (as defined in Section 4.2)

	• Fibrinolytic therapy within 24 hours of index PCI • Concomitant therapy with a strong cytochrome P-450 3A inhibitor or inducer • Platelet count < 100,000 mm^3 • Requiring ongoing treatment with aspirin ≥ 325 mg daily
Randomization	The eligibility for randomization for all enrolled subjects will be evaluated at the in-person 3-month study visit. Subjects with any of the following will not be randomized: • Refusal of randomization by subject or treating physician • Withdrawal of consent • Lost to follow-up • Death • Major bleeding (BARC Types 3b or greater) • Occurrence of an ischemic event after PCI such as myocardial infarction, definite or probable stent thrombosis, ischemic stroke, coronary revascularization with drug-eluting stent • No longer taking DAPT with aspirin and ticagrelor • Non physician-guided cessation of aspirin or ticagrelor of 5 consecutive days or greater. • Women of child bearing potential (as defined in Section 4.2) • Renal failure requiring dialysis • Current indication for oral anticoagulation or high dose aspirin
Statistical Methods	
Analysis for Primary Bleeding Endpoint	The analysis for the primary bleeding endpoint will be performed on the ITT population. The primary objective is to determine if ticagrelor monotherapy is superior to ticagrelor plus aspirin for the primary bleeding endpoint (BARC Types 2, 3 or 5 bleeding). The null hypothesis for this analysis is that the HR for the experimental group (H_0) = 1. The alternative hypothesis is that the HR for the experimental group (H_A) ≠ 1. A test of superiority at the two-sided 0.05 level will be performed using a Cox proportional hazard model that includes treatment group as a covariate. A point estimate and two-sided 95% CI for the relative risk as measured by the hazard ratio will be calculated based on the Cox proportional hazards model. Event rates will be estimated at one year and Kaplan-Meier curves will be plotted for the time from randomization to the first occurrence of confirmed BARC Type 2, 3 or 5 bleeding by treatment group. This analysis will be repeated in the per protocol (PP) cohort to support the primary results.

Analysis for Primary Ischemic Endpoint	The analysis for the primary ischemic endpoint will be performed on the PP cohort. The primary objective is to determine if ticagrelor monotherapy is non-inferior to ticagrelor plus aspirin for the primary ischemic endpoint (all-cause death, non-fatal myocardial infarction, or stroke). Event rates will be estimated at one year and Kaplan-Meier curves will be plotted for the time from randomization to the first occurrence of confirmed all-cause death, non-fatal myocardial infarction, or stroke or by treatment group. A test of non-inferiority at the one-sided 0.025 level will be performed. . . . Assuming an event rate of 8.0% in the control group, a sample size of 8200 will yield 80% power to exclude an absolute non-inferiority margin of 1.6%. If the upper limit of the 95% CI for the point estimate of the absolute risk difference between groups is less than or equal to 1.6% then the criteria for non-inferiority will be met. This non-inferiority margin translates to a relative risk of 20% assuming the observed event rate equals 8.0% in the control arm.
Statistical Methods	Unless otherwise stated, all hypothesis tests will be performed using two-sided tests at the 5% significance level. Continuous variables will be summarized using descriptive statistics including means and standard deviations if normally distributed or median with interquartile ranges for skewed distributions. Discrete variables will be summarized using absolute and relative frequencies.
Sample Size Parameters	A cumulative bleeding rate of 4.5% is anticipated between time of randomization and 1 year. Assuming a 2% loss to follow-up and non-compliance / cross-over rate of 4%, the current trial will require 8200 subjects to detect a relative reduction in bleeding of 28% with ticagrelor monotherapy with 80% power and a Type I error of 0.05. It is anticipated that approximately 8% - 10% of enrolled subjects will not be eligible for randomization and therefore 9000 subjects will be enrolled at the time of PCI.


HIGH RISK PCI PATIENTS, N = 9000
TICAGRELOR + ASA
TICAGRELOR + ASA
SOC THERAPY
RANDOMIZE
N = 8200
RANDOMIZATION PERIOD ENDS
OBSERVATION PERIOD STARTS
TICAGRELOR + ASA
TICAGRELOR + PLACEBO
SOC THERAPY
3 MONTHS
12 MONTHS
3 MONTHS
Short course DAPT to minimize stent-related thrombotic events
Monotherapy with potent platelet inhibitor provides ischemic protection while reducing ASA related bleeding
Observational period

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PROTOCOL SIGNATURE PAGE

I have read this clinical investigation plan and appendices and agree to adhere to the requirements. I will provide copies of this clinical investigation plan and all pertinent information to the trial personnel under my supervision. I will discuss this material with them and ensure they are fully informed regarding the study drugs and the conduct of the trial.

I will conduct the trial in accordance with the clinical investigation plan, Good Clinical Practice guidelines, World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects, as well as local regulations. I also accept respective revisions to the clinical investigation plan approved by authorized personnel of the ARCC and by regulatory authorities.

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ROXANA MEHRAN
Investigator Name (print)

Roxana Mehran
Investigator Name (signature)

4/15/2016
Date

ICAHN SCHOOL OF MEDICINE AT MOUNT SINAI
Institution Name (print)

LIST OF ABBREVIATIONS

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

Abbreviation or special term	Explanation
AE	Adverse Event
ARC	Academic Research Center
ASA	Acetylsalicylic Acid (Aspirin)
BMI	Body Mass Index
BMS	Bare Metal Stent
CAD	Coronary Artery Disease
CEC	Clinical Events Committee
CRF	Case Report Form
DAPT	Dual Antiplatelet Therapy
DES	Drug Eluting Stent
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
FDA	Food and Drug Administration (U.S.)
FFR	Fractional Flow Reserve
ICF	Informed Consent Form
IND	Investigational New Drug Application (FDA)
IRB	Institutional Review Board
ISS	Investigator Sponsored Study
ITT	Intention-to-Treat (analysis dataset)
IVUS	Intravascular Ultrasound
IXRS	Interactive Voice/Web Response System
LAD	Left Anterior Descending (Coronary Artery)
MI	Myocardial Infarction
NSAID	Non-Steroidal Anti-Inflammatory Drug
NSTEMI	Non ST Elevation Myocardial Infarction
$P2Y_{12}$	The $P2Y_{12}$ protein is found mainly but not exclusively on the surface of blood platelets, and is an important regulator in blood clotting.
PAD	Peripheral Artery Disease
PCI	Percutaneous Coronary Intervention
PP	Per Protocol (analysis dataset)
SAE	Serious Adverse Event
STEMI	ST Elevation Myocardial Infarction

The following abbreviations and special terms describe other clinical protocols or academic bodies.

Abbreviation or special term	**Explanation**
BARC	Bleeding Academic Research Consortium
EXCELLENT	*Trial Name:* Efficacy of Xience/Promus versus Cypher in Reducing Late Loss after Stenting
GUSTO	Trial Name: Global Utilization of Streptokinase and TPA for Occluded Arteries
OPTIMIZE	*Trial Name:* Optimized Duration of Clopidogrel Therapy following Treatment with the Endeavor Zotarolimus-Eluting Stent in the Real World Clinical Practice
PLATO	*Trial Name:* Platelet Inhibition and Patient Outcomes Trial
PRODIGY	*Trial Name:* Synergy between Stent and Drugs to Avoid Ischemic Recurrences after Percutaneous Coronary Intervention
SYNTAX	*Trial Name:* TAXUS Drug-Eluting Stent versus Coronary Artery Bypass Surgery for the Treatment of Narrowed Arteries
TIMI	*Trial Name:* Thrombolysis in Myocardial Infarction

1. INTRODUCTION

Pharmacologic platelet inhibition with aspirin and a $P2Y_{12}$ inhibitor is a requirement in all patients undergoing percutaneous coronary intervention (PCI) with stenting. Such dual antiplatelet therapy (DAPT) is recommended by international guidelines, with duration varying according to clinical presentation (i.e. acute coronary syndrome) or type of stent implanted during PCI (bare metal vs. drug eluting)(1-3). The paradigm for DAPT is shifting to shorter durations, as evidenced by most recent ESC /EACTS Guidelines on myocardial revascularization giving a class Ib recommendation for 6 months of DAPT after DES (4).While clopidogrel is the most widely used $P2Y_{12}$ inhibitor, its efficacy is hampered by substantial variability in platelet inhibition that may be attributable to clinical, genetic and procedural parameters (5-8). Moreover, although the novel thienopyridine prasugrel has a more potent and consistent effect on platelet inhibition (9, 10), bleeding risk is significantly higher compared to clopidogrel in acute coronary syndrome (ACS) patients following PCI (11). In contrast, ticagrelor, an oral, reversible, direct-acting inhibitor of the adenosine diphosphate $P2Y_{12}$ receptor (12) has proven faster, greater and more consistent $P2Y_{12}$ inhibition than either clopidogrel or prasugrel (13-15). In the landmark Study of Platelet Inhibition and Patient Outcomes (PLATO) trial, ticagrelor significantly reduced death from vascular causes, myocardial infarction, or stroke, without significantly increasing overall major bleeding in patients presenting with acute coronary syndromes (16).

Along with the advent of more potent antiplatelet pharmacotherapy, stent technology has also advanced in a concordant fashion with the introduction of safer and less thrombogenic

platforms. These devices, compared to their older-generation counterparts, yield significant reductions in thrombotic events that are durable over the long term (17). As a consequence, classical paradigms favoring a minimum of DAPT duration of 1 year, particularly in elective patients, are being challenged as PCI safety continues to evolve and improve. Randomized comparisons of different DAPT durations such as the OPTIMIZE and the PRODIGY trials suggest no increased risk for thrombotic events after only 3-6 months of DAPT in PCI patients treated primarily with novel generation devices (18-22).

1.1 Research hypothesis

The overall hypothesis of the current study is that three months post-PCI of dual antiplatelet therapy with aspirin and ticagrelor, continued monotherapy with ticagrelor alone versus ticagrelor plus aspirin for an additional year will be superior with respect to bleeding and non-inferior with respect to ischemic events in high-risk patients undergoing elective or urgent PCI.

This hypothesis will be tested in the following two specific aims:

Aim 1: To determine the impact of ticagrelor alone versus ticagrelor plus aspirin in reducing clinically relevant bleeding among high-risk patients who had PCI.	**Hypothesis 1:** A DAPT strategy of ticagrelor + ASA for 3 months followed by ticagrelor alone for an additional 12 months will be superior to ticagrelor plus aspirin with respect to clinically relevant bleeding (BARC ≥ 2) in high-risk patients undergoing PCI.
Aim 2: To determine the impact of ticagrelor alone versus ticagrelor plus aspirin in reducing ischemic adverse events at one year among high-risk patients undergoing PCI	**Hypothesis 2:** A DAPT strategy of ticagrelor + ASA for 3 months followed by ticagrelor alone for an additional 12 months will be will be non-inferior to ticagrelor plus aspirin for with respect to ischemic adverse events at 1 year in high-risk patients undergoing PCI.

1.2 Rationale for conducting this study

Despite the trend and rationale for shorter DAPT durations following PCI, certain high-risk patients may derive additional benefit from potent and sustained platelet inhibition extending beyond 3 months after PCI. Defined by clinical and/or anatomic criteria, a short course of DAPT in such patients may provide sufficient protection against early stent-related thrombotic events while ongoing platelet inhibition may yield further reductions in systemic atherothrombosis. Among diabetics undergoing PCI, for example, Brar et al. previously demonstrated that the benefits of DAPT compared to antiplatelet monotherapy persisted irrespective of BMS or DES use, suggesting a systemic rather than stent-related effect (23). Analogously, results from the EXCELLENT trial suggested diabetics may derive additional benefit from prolonged DAPT (ASA + clopidogrel) compared to ASA alone (24). Findings from Dangas et al., which demonstrate a link between atherosclerosis and increased platelet

reactivity, provide a biological basis for potent platelet inhibition in high-risk patients characterized by diffuse vascular disease (25). These observations are clinically relevant as many patients undergoing elective or urgent PCI exhibit high-risk features, such as renal dysfunction, diabetes, peripheral arterial disease, that are associated with systemic atherosclerosis. Given the clear benefits of ticagrelor in the setting of high-risk ACS, it is plausible that ticagrelor alone will provide sufficient platelet inhibition to reduce thrombotic events compared to ticagrelor plus ASA among high-risk patients who have completed a requisite short course of DAPT.

Reduction in bleeding with ticagrelor alone while preserving of the anti-ischemic benefit associated with DAPT use would favor such a strategy in high-risk patients undergoing PCI.

Accordingly, the proposed study will examine the comparative safety and efficacy of a strategy of 3 month DAPT with ASA and ticagrelor followed by monotherapy using a potent agent (ticagrelor) compared to continued ASA and ticagrelor among high-risk patients undergoing PCI with DES. Our primary hypothesis is that, among such patients, use of ticagrelor alone will yield a significant reduction in clinically relevant bleeding while preserving anti-ischemic protection compared to the combination of ticagrelor and ASA.

1.3 Benefit/risk and ethical assessment

The potential benefits that subjects might realize by participating in this randomized trial is a reduction in clinically relevant bleeding for those who are randomly allocated to the placebo arm. Other benefits applicable to all subjects include close monitoring and surveillance for clinical events that will be performed by study personnel during the course of the trial.

The potential risks for subjects include an increased rate of thrombotic events for those who are randomized to the placebo arm and increased risk for bleeding in subjects randomized to the active treatment arm (low-dose ASA [81 mg – 100 mg]).

An independent data safety monitoring board will provide external oversight to ensure safety of all trial participants. In addition, subjects will be followed closely with periodic study contacts. Also, clinical equipoise exists for conducting a trial with this type of randomized comparison.

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objective of this study is to determine the impact of antiplatelet monotherapy with ticagrelor alone versus DAPT with ticagrelor plus aspirin for 12 months in reducing clinically relevant bleeding among high-risk patients undergoing PCI who have completed a 3-month course of aspirin plus ticagrelor.

2.2 Secondary objective

The secondary objective of this study is to determine the impact of antiplatelet monotherapy with ticagrelor alone versus DAPT with ticagrelor plus aspirin for 12 months in reducing major ischemic adverse events among high-risk patients undergoing PCI who have completed a 3-month course of aspirin plus ticagrelor.

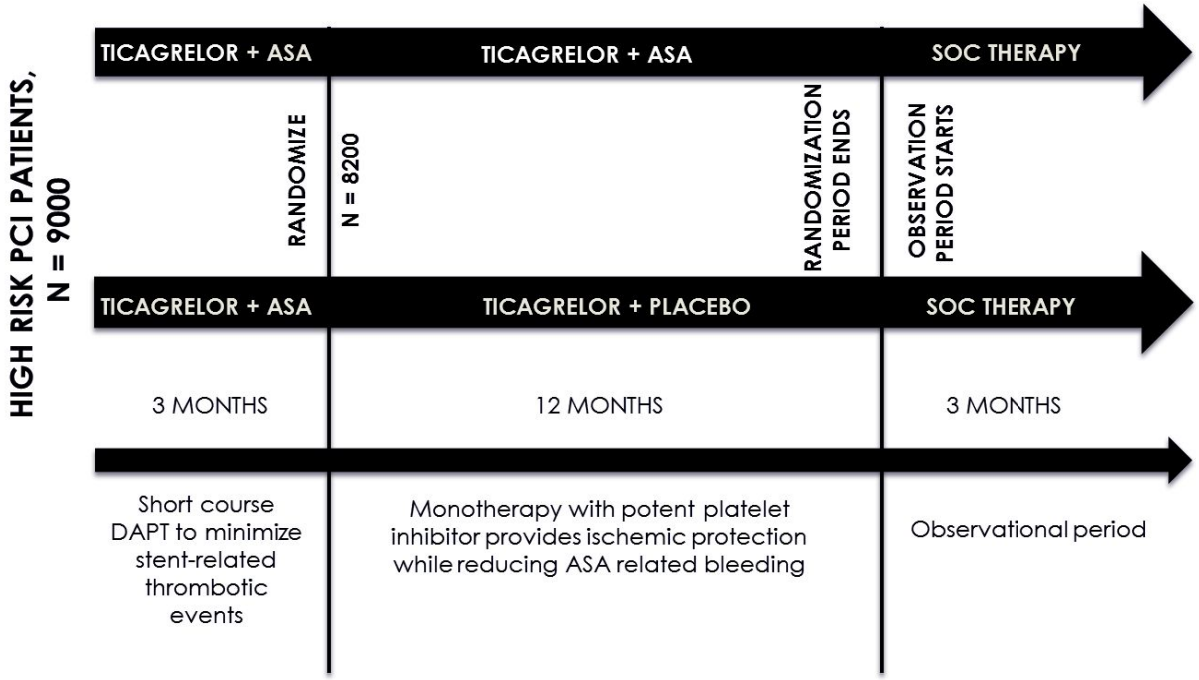
2.3 Exploratory objectives

Exploratory objectives include assessing the comparative safety and efficacy of the different DAPT regimens for individual components of the primary efficacy and secondary safety objectives.

3. STUDY PLAN AND PROCEDURES

3.1 Overall study design and flow chart

Figure 1 TWILIGHT Trial Design



3.2 Rationale for study design, doses and control groups

A randomized, double-blind study design was chosen as the most rigorous experimental approach to formally test the study hypotheses for the efficacy and safety of different DAPT regimens in high-risk patients undergoing PCI. Open label aspirin and ticagrelor per physician discretion will be given for the first 3 months after PCI. After 3 months, event-free subjects

will be randomized to placebo versus enteric-coated ASA for an additional 12 months. Open-label ticagrelor at a dose of 90 mg twice daily will be continued in all randomized subjects.

4. SUBJECT SELECTION CRITERIA

4.1 Inclusion criteria

High-risk patients who have undergone successful PCI with at least one locally approved drug eluting stent (DES) discharged on DAPT with aspirin and ticagrelor of at least 3 months intended duration will be eligible for the TWILIGHT study.

Enrollment into the study will require meeting at least one clinical inclusion AND at least one angiographic inclusion AND none of the exclusion criteria. A subject is considered enrolled if all these criteria are met and upon provision of informed consent.

Must meet AT LEAST ONE clinical inclusion criterion	**Must meet AT LEAST ONE angiographic inclusion criterion**
Adult patients ≥ 65 years of age Female gender Troponin positive acute coronary syndrome Established vascular disease defined as previous MI, documented PAD or CAD/PAD revascularization Diabetes mellitus treated with medications or insulin Chronic kidney disease defined as an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m^2 or creatinine clearance (CrCl) <60 ml/min	Multivessel coronary artery disease (CAD)* (see Section 16) Target lesion requiring total stent length >30 mm Thrombotic target lesion(s) Bifurcation lesion(s) with Medina X,1,1 classification requiring at least 2 stents (see Section 16) Left main (≥50%) or proximal LAD (≥70%) lesion Calcified target lesion(s) requiring atherectomy
*The diagnosis of multivessel CAD may be established with the angiogram performed at enrollment or an earlier angiogram. A vessel previously treated with either a stent or bypass graft may also be considered diseased for purposes of meeting the multivessel CAD angiographic inclusion criterion.	

4.2 Exclusion criteria

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

- Under 18 years of age
- Contraindication to aspirin, as listed in Appendix D
- Contraindication to ticagrelor, as listed in Appendix E
- Planned surgery within 90 days
- Planned coronary revascularization (surgical or percutaneous) within 90 days
- Need for chronic oral anticoagulation
- Prior stroke
- Dialysis-dependent renal failure
- Active bleeding or extreme-risk for major bleeding (e.g. acute gastrointestinal ulcer or history of chronic gastrointestinal ulceration, gastrointestinal pathology with a raised risk for bleeding, malignancies with a raised risk for bleeding)
- Salvage PCI or STEMI presentation.
- Liver cirrhosis
- Life expectancy < 1 year
- Unable or unwilling to provide informed consent
- Women of child bearing potential as defined below:
  A woman is considered of childbearing potential (WOBCP) following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
- Fibrinolytic therapy within 24 hours of index PCI
- Concomitant therapy with a strong cytochrome P-450 3A inhibitor or inducer
- Platelet count < 100,000 mm^3
- Requiring ongoing treatment with aspirin ≥325 mg daily

5. STUDY CONDUCT

5.1 Restrictions during the study

Enrolled subjects should remain on study-provided open-label ticagrelor plus open-label aspirin for the first three months after index PCI followed by study-provided open-label ticagrelor plus blinded study drug for 12 months after randomization.

Unless clinically indicated, non-steroidal anti-inflammatory drugs (NSAIDs) and additional $P2Y_{12}$ inhibitors (ticlopidine, prasugrel, clopidogrel) should not be taken by study participants during the course of the trial. In addition, ticagrelor should be administered with caution in patients with history of hyperuricemia or gouty arthritis.

5.2 Subject randomization and initiation of investigational product

5.2.1 Procedures for randomization

The eligibility for randomization for all enrolled subjects will be evaluated at the in-person 3-month study visit. Subjects with any of the following will not be randomized:

- Refusal of randomization by subject or treating physician
- Withdrawal of consent
- Lost to follow-up
- Death
- Major bleeding (BARC Types 3b or greater)
- Occurrence of an ischemic event after PCI such as myocardial infarction, definite or probable stent thrombosis, ischemic stroke, coronary revascularization with drug-eluting stent
- No longer taking DAPT with aspirin and ticagrelor
- Non physician-guided cessation of aspirin or ticagrelor of 5 consecutive days or greater.
- Women of child bearing potential (as defined in Section 4.2)
- Renal failure requiring dialysis
- Current indication for oral anticoagulation or high dose aspirin

Randomization will be performed within the EDC system among subjects eligible for randomization. The EDC will allocate the treatment group assignment for the subject and provide study site research personnel the appropriate bottle ID number(s).

Upon randomization at the conclusion of the in-person 3-month visit, the study site research personnel will provide a 6-month supply of blinded investigational product (aspirin or matching placebo) and open-label ticagrelor.

Enrolled subjects who do not meet eligibility for randomization will have completed their protocol required activities and therefore will not receive any further study-provided medications. Their treating physician will also be notified that the patient's protocol-mandated study activities have concluded. Further antiplatelet therapy will be at the discretion of the subject's treating physician in accordance with local standard of care. Vital status of these subjects will be determined at the 18-month time point.

Enrolled subjects who do not meet eligibility for randomization *prior to* the in-person 3-month visit will not be required to complete the 3-month in-person visit.

5.3 Procedures for handling subjects incorrectly enrolled or randomized on investigational product

Subjects who are incorrectly enrolled will be immediately withdrawn from the study. The subject and the treating physician will be notified. If the subject has already been randomized, the investigational drug (aspirin or matching placebo) will be discontinued and further treatment will be as per standard of care. Subjects will be advised to continue therapy with ticagrelor until seen by their treating physician.

Subjects who are provided the incorrect investigational drug (study drug bottle(s) were not provided according to EDC randomization instructions) may be identified during monitoring procedure and/or drug reconciliation. In this case, the subject will be informed immediately and requested to return with all dispensed investigational drugs. The subject will then be provided with the correct investigational drug according to the randomization instructions. In addition, a protocol deviation form will be completed.

5.4 Blinding and procedures for unblinding the study

5.4.1 Methods for ensuring blinding

This study has a double-blind design with aspirin and matching placebo. The subjects, study site research personnel, academic research center staff, and treating physicians involved in the treatment and/or clinical evaluation of the subjects will not be aware of treatments received. There will be an independent data safety monitoring board (DSMB) to monitor the data on a periodic basis. An independent statistician, not otherwise involved in the study, will prepare and provide the required reports to the DSMB as per the DSMB charter.

5.4.2 Methods for unblinding the study

In the event of a medical emergency, in which knowledge of the investigational drug is critical to the subject's medical management, the blind for that subject may be broken by the treating physician. The investigator should follow the instructions provided in the EDC to obtain the necessary treatment information or call the 24/7 TWILIGHT Medical Monitoring Hotline at 347-541-1376. As the active study drug in this trial is low-dose aspirin, in most instances the subject may be properly managed without the need for unblinding.

5.5 Treatments

5.5.1 Identity of investigational product

In this protocol, the investigational product is enteric coated aspirin (81 mg – 100 mg) tablets and matching aspirin-placebo tablets.

Table 1 Identity of Investigational Product

Investigational product	Dosage form and strength
Aspirin, EC	81 mg – 100 mg tablet, daily
Placebo for aspirin	tablet daily

5.5.2 Doses and treatment regimens

Study-provided medications including open-label ticagrelor at a dose of 90 mg twice daily plus open-label EC aspirin at a dose of 81mg – 100 mg daily will be dispensed to enrolled participants at the time of discharge and should be taken daily until the in-person 3-month study visit. Study-provided medications including open-label ticagrelor at a dose of 90 mg twice daily plus blinded study drug will be dispensed to randomized participants at the 3-month in-person visit and should be taken daily until end of study.

5.5.3 Additional study drug

Open-label ticagrelor will be administered to all subjects regardless of randomization assignment.

5.5.4 Labeling

Each aspirin/placebo bottle will be labeled in black ink. This label will indicate the protocol number, blinded batch number, container number, blinded drug name, tablet quantity, storage conditions, directions for use and route of administration.

At the study site, the investigational product should be stored in a secure area according to local regulations. It is the responsibility of each site investigator to ensure that the investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

The storage conditions for the subjects to follow will be included in the labeling on the bottles.

5.6 Concomitant and post-study treatment

There are no protocol specific concomitant treatments.

At the End of Study visit physicians caring for the patient will decide which antiplatelet medication the patient should receive as part of his/her ongoing clinical care. This medication(s) will be open label and obtained locally.

5.7 Treatment compliance

Study drug compliance will be assessed using manual pill count at the 9-month and 15-month in-person follow-up visits.

5.7.1 Accountability

Reconciliation between the quantity of shipped study drugs versus the allocation of study drugs via the EDC and versus distribution of study drug to subject will be monitored and reconciled.

5.8 Discontinuation of investigational product or study drug

Study-provided medications (open-label ticagrelor or blinded study drug) may require *temporary interruption* for the following reasons:

1. **Surgery or invasive procedure**: Study-provided medications should be resumed after surgery once the risk of bleeding is no longer considered prohibitive in the judgment of the treating physician. Minor surgeries and procedures, including but not limited to tooth extraction, colonoscopy and endoscopy, may be safely performed on low-dose aspirin and therefore do not require temporary interruption of blinded study drug. However, if deemed necessary and at the discretion of the treating physician, open-label ASA may be substituted for blinded study drug in the peri-operative period. Blinded study drug may then be restarted at the discretion of the treating physician after completing the mandatory course of open-label ASA.

2. **Balloon angioplasty or PCI with bare-metal stent**: In the event of coronary revascularization with balloon angioplasty alone or PCI with bare metal stent, blinded study drug may be temporarily interrupted for 2-4 weeks while patients receive open-label ASA at the discretion of the treating physician in accordance with local practice and standard of care. Blinded study drug may then be restarted at the discretion of the treating physician after completing the mandatory course of open-label ASA.

3. **Clinically Significant Bleeding**: Study-provided medications should be temporarily interrupted pending resolution of the acute bleeding episode and

may be restarted at the discretion of the treating physician if deemed clinically safe and in accordance with local practice and standard of care.

4. Details surrounding the date, duration and reason for each episode of temporary interruption should be entered in the appropriate section of the EDC.

Study-provided medications (open-label ticagrelor or blinded study drug) may require *permanent discontinuation* for the following reasons:

1. Patient decision: The patient is at any time free to discontinue treatment, without prejudice to further treatment.
2. Investigator's decision:
    a. Incorrectly enrolled patient in whom the inclusion/exclusion criteria violation would put the patient at undue risk
    b. Adverse Events felt to be related to either study medication for which Investigator feels continued treatment would put the patient at undue risk, such as severe or life-threatening bleeding, myocardial infarction, stent thrombosis, ischemic stroke or coronary revascularization with a DES.
3. Renal failure requiring dialysis
4. Chronic oral anticoagulation
5. Details surrounding the date, duration and reason for permanent discontinuation of study medication should be entered in the appropriate section of the EDC.
6. In the event of permanent discontinuation of either study medication, further antiplatelet therapy is at the discretion of and is to be provided by the patient's treating physician. Any remaining study-provided medication should be returned to the local site at the next scheduled follow-up visit. Although these patients will no longer receive study-related medication, follow-up will continue in all randomized patients until end of study

5.9 Withdrawal from study

Each enrolled subject shall remain in the trial until completion of the required follow-up period. However, a subject's participation in any clinical trial is voluntary and the subject has the right to withdraw at any time without penalty or loss of benefit. Conceivable reasons for discontinuation may include, but not be limited to, the following:

- Subject voluntary withdrawal
- Subject withdrawal by physician as clinically indicated
- Subject lost-to follow-up

The reason for subject discontinuation must be documented in the eCRF and source documents. The individual site Principal Investigators must also report all subject discontinuations to their IRB/EC as defined by their institution's procedure.

All data from evaluations and treatments performed prior to the withdrawal should be documented in the eCRFs. Source documents that pre-date the withdrawal should be submitted as required by the protocol. No data that post-dates the withdrawal will be collected.

Once a subject has withdrawn from the trial, no further follow-up contact will be performed. However, vital status may be obtained from public records. Medical therapy after stopping the study will be as prescribed by the subject's physician.

6. COLLECTION OF STUDY VARIABLES

6.1 Recording of data

The Investigator is responsible for maintaining complete and accurate documentation of the trial including but not limited to medical records, trial progress records, laboratory results, electronic case report forms, signed informed consent forms, investigational product accountability records, correspondence with the IRB or EC as well as trial monitors and sponsor, adverse event reports, and information regarding subject discontinuations.

The Investigator is required to maintain information in the subject's medical records which documents and corroborates data entered in the case report forms. As a minimum the subject record should contain:

- Medical history/physical exam documenting that subject meets inclusion/exclusion criteria
- Documentation of subject's consent and subject ID number in the trial
- Dated and signed notes from each subject visit
- Adverse events reported and their resolution or lack thereof including supporting documents such as hospital records, discharge summaries, catheterization reports, ECGs, etc.
- Record of protocol required medications during the trial
- Record of the subject's condition upon completion of or withdrawal from the trial

6.2 Data collection at enrollment and follow-up

Data collection commences after the subject has provided informed consent and has been enrolled in the study. Data collection, including subject demographic information, laboratory tests, and procedural data as well as follow-up visits or telephone contacts will be conducted

by an Investigator or site coordinator who has been trained on the protocol and electronic Case Report Forms (eCRFs).

Data required for analysis will be obtained as outlined in Table 1. After discharge from the hospital, each enrolled subject will be followed with a phone call at 1 month post enrollment and an in-clinic visit at 3 months post enrollment. Enrolled subjects who do not meet eligibility for randomization *prior to* the in-person 3-month visit will not be required to complete the 3-month in-person visit. Subjects who are randomized at 3 months post enrollment will be followed with a phone call at 4 months post enrollment and will return for additional in-clinic visits at 9 and 15 months post enrollment. A final follow-up phone call will be performed at 18 months post enrollment for randomized subjects. No further follow-up contact will be performed for subjects who did not meet eligibility for randomization at the 3 month visit; however, vital status may be obtained from medical or public records at 18 months post enrollment. A flow chart listing the planned visits and their timing can be found in appendix C).

Table 1 Schedule of Data Collection

Type of Data to be Collected	Enrollment	Post-Procedure or Discharge	1 Month (30d) (±7 days) Phone Call	3 Month (90d) (±14 days) Office Visit	4 Month (120d) (±7 days) Phone Call randomized	9 Month (270d) (± 30 days) Office Visit randomized	15 Month (450d) (± 30 days) Office Visit randomized	18 Month (540d) (± 14 days) Phone Call randomized
Eligibility Criteria	X			X				
Patient Informed Consent	X							
Physical Assessment	X							
Medical History/Risk Factors	X							
Cardiac Status	X							
Medications/Antiplatelets	X							
Clinical Tests* Lab tests, ECG	X			X		X	X	
Procedure Information	X							
DAPT Medication Status		X	X		X			X
Angina Status				X	X	X	X	X
Randomization– if eligible				X				
Dispense medication according to EDC		X		X		X		
Randomized Medications – reconciliation of provided medication						X	X	
Randomized Medications – subject self-reporting of compliance to medications				X	X	X	X	X
Adverse Events / Serious Adverse Events	X	X	X	X	X	X	X	X

*If performed, as per standard of care. Subject may be asked to provide an additional blood sample (10cc) for lipid profile testing if not already performed per standard of care.

6.2.1 Enrollment procedures

After successful PCI with implantation of at least one locally approved drug eluting stent and physician decision to treat subject with low–dose aspirin (81 mg – 100 mg) daily and ticagrelor 90 mg twice daily for 3 months, the investigator or designee will:

- Confirm inclusion/exclusion criteria
- Obtain written informed consent
- Obtain a complete medical history, including lab values for hemoglobin and creatinine as well as an ECG, if performed per standard of care. Subject may be asked to provide an additional blood sample (10cc) for lipid profile testing if not already performed per standard of care.
- Review concomitant medications taken within the last 30 days
- Instruct the subject to notify the investigator of any occurrence of adverse events
- Schedule next clinic visit at 3 months
- Dispense 3- month supply of study medications (open-label ticagrelor and EC aspirin)
- Instruct patients to return all study-provided medication at next in-person clinic visit

6.2.2 In-person follow-up procedure at 3 months

- Assess for adverse events including MI, unstable angina, stroke, and bleeding.
- Review concomitant medications with subject
- Counsel subject about importance of study drug compliance
- Assess for randomization eligibility , if applicable:
    - Randomize subject within EDC and obtain bottle numbers
    - Dispense study medication for next 6 months
    - Schedule next clinic visit at 9 months
- Instruct the subject and/or caregiver to notify the investigator of any occurrence of adverse events
- Instruct patients to return all study-provided medication at next in-person clinic visit

6.2.3 In-person follow-up procedure at 9 and 15 months (for randomized subjects)

- Assess for adverse events including MI, unstable angina, stroke, and bleeding.
- Review concomitant medications with subject
- Collect pill bottles, perform study medication accountability, and remind subject about importance of study drug compliance.
- Dispense study medication for next 6 months for those patients still taking study provided medications at the 9-month in-person visit. Patients who have permanently stopped study-provided medications prior to the 9-month in-person visit will continue to be followed but will not be provided additional study medication.
- Instruct the subject to notify the investigator of any occurrence of any adverse events.
- Schedule next clinic visit at 15 months
- Instruct patients to return all study-provided medication at next in-person clinic visit (only pertains to 9-month in-person clinic visit)

6.2.4 Phone-call follow-up contact at 1, 4 and 18 months post enrollment

- Assess for adverse events including MI, unstable angina, stroke, and bleeding.
- Review all medications and compliance with subject
- Instruct the subject to notify the investigator of any occurrence of adverse events

6.3 Efficacy and safety variables

The study site research personnel will collect data from the subjects during the follow-up contact for identification of the efficacy and safety variables, defined as the first occurrence of bleeding (efficacy variable) and all-cause death, myocardial infarction, stent thrombosis, or stroke (safety variables).

7. SAFETY

The Principal Investigator at each participating study site is responsible for ensuring that all staff involved in the study is familiar with the content of this section.

7.1 Definition of adverse events

An adverse event 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 (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the

abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

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

7.2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (i.e., run-in, treatment, wash-out, follow-up), that fulfills one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Results in a congenital abnormality or 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.

The severity and causality of SAEs (their relationship to all study treatments and/or procedures) will be assessed by the investigator(s) and communicated to the ARC.

7.2.1 Definition of suspected unexpected serious adverse reactions (SUSARs)

A SUSAR is a Suspected Unexpected Serious Adverse Reaction. To qualify as a SUSAR, the event must be:

- Serious
- Undesirable reaction to medicinal product
- Unexpected - NOT listed as a potential risk or reaction to the product as outlined in the protocol, informed consent document or literature.

7.3 Recording of adverse events or serious adverse events

7.3.1 Time period for collection of adverse events

All AEs related to bleeding and SAEs should be collected from the time the subject signs the informed consent through study exit.

7.3.2 Follow-up of unresolved adverse events

For ALL SAEs the subject's course must be monitored until the event has subsided or, in a case of permanent impairment, until the event stabilizes and the overall clinical outcome has been ascertained.

7.3.3 Information to be collected for each AE/SAE

- Description of AE/SAE
- The dates when the AE/SAE started and stopped
- Whether the AE/SAE is serious or not
- Investigator causality rating against the investigational product
- Action taken with regard to investigational product
- Whether the AE/SAE caused subject's withdrawal from study
- Outcome

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

- Date the study site research personnel became aware of SAE
- Date when decision was made for meeting SAE criteria
- Criteria met leading to classification as SAE
- Date of hospitalization (if applicable)
- Date of discharge (if applicable)
- Date of death (if applicable)
- Probable cause of death (if applicable)
- Autopsy performed (if applicable)

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 7.2. 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 an 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 an SAE.

7.3.4 Adverse Events based on signs and symptoms

When collecting AEs, the recording of diagnoses (when possible) is preferred 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.

7.3.5 Adverse Events based on examinations and tests

Deterioration as compared to baseline in laboratory values or vital signs should therefore only be reported as AEs if they fulfill 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 (e.g., anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

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.

7.3.6 Disease progression or pre-existing conditions

Disease progression can be considered as a worsening of a subject's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. For example, continued angina should be considered as disease progression and not an AE. Planned hospitalization for a pre-existing condition without serious deterioration in health, is not considered a serious adverse event.

7.3.7 Reporting of adverse events

AEs must be reported to the sponsor within 7 business days of the study site research personnel's knowledge of the event via the EDC.

SAEs must be reported to the sponsor immediately, but no later than 24 hours, of the study site research personnel's knowledge of the event via the EDC.

The ARC Safety Monitor will review all submitted SAEs for qualification as a Suspected Unexpected Serious Adverse Reactions (SUSARs). The ARC will further report SAEs determined to qualify as SUSARs to the local regulatory body (IRB/EC).

The ARC Safety Monitor will voluntarily inform the FDA, via a MedWatch/AdEERs form, and EudraVigilance, of any serious adverse events which qualify as SUSARs in accordance with reporting requirements.

A copy of the MedWatch/AdEERs report will be faxed or scanned and sent to the Principal Investigator of the applicable site for reporting according to the site's local regulatory body's reporting requirements.

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 Ethical conduct of the study

The trial will be conducted in compliance with the protocol, Good Clinical Practice guidelines, and World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects as well as local regulations, and applicable regional regulatory requirements.

The clinical investigation shall not begin until the required approvals/favorable opinions from the respective regulatory authority and ethics committee have been obtained. Any additional requirements imposed by the respective regulatory authority and/or ethics committee will also be followed, where specified.

8.2 Ethics and regulatory review

Institutional Review Board (IRB) or Ethics Committee (EC) approval for the protocol, informed consent form and other trial related documents will be obtained by the Principal Investigator at each investigational site prior to participation in this trial. The approval letter must be signed by the IRB/EC chairperson or authorized representative prior to the start of this trial and a copy must be provided to the ARC. In addition, the Investigator or designee will provide the ARC with all required documentation necessary for initial and ongoing trial approval at their site.

In accordance with the investigational site IRB/EC requirements, the Investigator will
(a) advise the IRB/EC of the progress of this trial on a regular basis until trial completion;
(b) obtain written IRB/EC approval at predetermined time points to continue the trial; and
(c) submit any amendments to the protocol as well as associated informed consent form changes and obtain written IRB/EC approval obtained prior to implementation.

8.3 Informed consent

All subjects must provide written informed consent in accordance with the site's IRB/EC, using an IRB/EC-approved informed consent form. All subjects are to be fully informed and trial conduct must be in accordance to the World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects.

Protocol-specific procedures or alterations of patient care must not be performed until the prospective subject has provided a signed informed consent. The informed consent will be in the prospective subject's native language and will contain non-technical language to describe the investigational procedures. The informed consent form should also include a clause that

ensures important new information will be provided to the subject throughout the clinical investigation.

After a review of the prospective subject's medical records to determine general eligibility, the investigator or authorized designee who has been trained on the protocol, will approach the prospective subject to explain the purpose and scope of the clinical trial, prospective risks, and benefits of participation. The prospective subject must be given the opportunity to ask questions about the trial and must be given sufficient time to decide to participate in the trial or not. Additional information requested by the prospective subject should be provided. Any coercion or undue improper influence on the prospective subject is to be avoided.

If the prospective subject agrees to participate, the informed consent form must be signed and personally dated by the prospective subject. The investigator or an authorized member of the research team who has witnessed the prospective subject's signature must also sign and date the informed consent, prior to enrollment of the prospective subject. A copy of the completed informed consent form must be provided to the subject. Local IRB/EC regulations regarding obtaining informed consent must be followed. The subject's medical record should have a notation regarding the signing of the informed consent.

The subject is to be made aware that their participation in the trial is voluntary, their legal rights will not be waived, and that they may withdraw from the trial at any time, without giving specific reason for doing so. The subject must also be informed that withdrawal from the trial will not affect their future treatment.

The investigator is responsible for the achievement of written consent from the prospective subject before they are included in the trial. All subjects must provide informed consent in accordance with the local IRB/EC requirements, using an IRB/EC-approved informed consent form.

8.4 Changes to the protocol and informed consent form

If the protocol or informed consent form (ICF) needs an amendment, the ARC is required to submit such amendment to the Regulatory Agencies and/or other regulating body in each participating country for approval. Approved protocol or ICF amendments will be provided to the Investigators by the ARC prior to implementing the amendment.

For administrative changes, the Principal Investigator is responsible for notifying the IRB/EC of the protocol or ICF amendment. For changes involving subject care or safety, the Principal Investigator is responsible for obtaining IRB/EC approval of the protocol or ICF amendment according to the instructions provided by the ARC with the protocol or ICF amendment.

Acknowledgement/approval by the IRB/EC of the protocol or ICF amendment must be documented in writing prior to implementation of the protocol or ICF amendment. Copies of this documentation must also be provided to the ARC.

8.5 Deviations from protocol

8.5.1 Compliance to protocol

No investigative procedures other than those defined in this clinical investigational plan will be undertaken on the enrolled subjects without the written agreement of the IRB/EC and ARC.
It is the Investigator's responsibility to ensure that there are no deviations from the clinical investigational plan and full compliance with all established procedures of the IRB/EC is maintained. The Investigator will not deviate from the clinical investigational plan for any reason except in cases of medical emergencies, when the deviation is necessary to protect the life or physical well-being of the subject.

8.5.2 Procedures for recording, reporting, and analyzing protocol deviations

A deviation is an instance(s) of failure to follow, intentionally or unintentionally, the requirements of the protocol. All deviations must be reported to the ARC. The occurrence of clinical investigational plan deviations will be monitored by the ARC or designee. It is the Investigator's responsibility to inform their IRB/EC of clinical investigational plan deviations in accordance with their specific IRB/EC reporting policies and procedures.

In the event that an investigative site does not comply with the Investigator Agreement or clinical investigational plan, the ARC will notify the Investigator of the site's non-compliance. Continued non-compliance may result in further escalation in accordance with the ARC's standard procedures.

8.5.3 Corrective and preventative actions and principal investigator disqualification criteria

Protocol deviations and site/PI non-compliance will be closely monitored by the ARC and appointed study personnel. Identifying deviations and taking corrective actions at the earliest possible stage increases the potential for clinical trial success and reduces patient risk. The initiation of a corrective and preventative action (CAPA) to investigate and establish corrective actions may be required in some cases. The ARC reserves the right to close a clinical study site or replace a PI if non-compliance is observed.

8.6 Audits and inspections

In the event that an Investigator is contacted by a Regulatory Agency in relation to this trial, the Investigator will notify the ARC immediately. The Investigator and study site research personnel must be available to respond to reasonable requests and inspection queries made during the inspection process. The Investigator must provide the ARC with copies of all correspondence that may affect the review of this trial. The ARC will provide any needed assistance in response to regulatory inspections.

9. STUDY MANAGEMENT

9.1 Training

9.1.1 Training of Monitors

The ARC's monitors or designee will be trained to the protocol, randomization instructions, electronic case report forms, and study drug usage. The ARC or designee is responsible for the training. Training will be conducted in accordance with the ARC's and/or designee's standard procedures.

9.1.2 Training of study site research personnel

Participating investigators and study site research personnel will be trained during site initiation visits conducted by the Mount Sinai Clinical Coordinating Center or designee.

All training must be documented and must include or reference the revision of materials used for training, who was trained, the trainer and date of training. Original training records should be maintained at the site in the Regulatory Binder and copies should be dispensed to Mount Sinai Clinical Coordinating Center.

Site initiation/training involves a didactic session whereby the protocol, including screening procedures, clinical follow-up procedures, and study drug procedures are reviewed in detail along with investigator responsibilities.

In addition, the Mount Sinai Clinical Coordinating Center will assure that all participating investigators and study personnel are trained in the following:

- Protocol requirements, including patient screening requirements, inclusion/exclusion criteria, procedural requirements and subject follow-up requirements
- Study and personnel requirements
- Informed consent requirements
- Adverse event reporting
- Drug accountability procedures
- Electronic CRF completion
- Regulatory binder maintenance.

9.2 Monitoring of the study

The ARC and/or designee will monitor the trial over its duration according to the pre-specified monitoring plan. The trial monitor will contact each site at appropriate intervals to review investigational data for accuracy and completeness and ensure compliance with the

clinical investigation plan. The trial monitor may request all documents and required records that are maintained by the Investigator/Site, including medical records (office, clinic, or hospital) for the subjects in this trial. Source documentation must be available to substantiate proper informed consent procedures, adherence to protocol procedures, adequate reporting and follow-up of adverse events, accuracy of data collected on case report forms, and study drug information. The Investigator and/or study site research personnel will be available for monitoring contact. If a site visit is required, it is expected that the Investigator/Site will provide the trial monitor with a suitable working environment for review of study-related documents.

9.2.1 Source data

The Investigator is responsible for maintaining complete and accurate documentation of the trial including but not limited to medical records, trial progress records, laboratory results, case report forms, signed informed consent forms, study drug accountability records, correspondence with the IRB/EC, the trial monitors, and the ARC, as well as adverse event reports and information regarding subject discontinuations.

The Investigator is required to maintain information in the subject's medical records which documents and corroborates data entered in the case report forms. As a minimum the subject record should contain:

- Medical history/physical exam documenting that subject meets inclusion/exclusion criteria
- Documentation of subject's consent and subject ID number in the trial
- Dated and signed notes from each subject visit
- Adverse events reported and their resolution or lack thereof including supporting documents such as hospital records, discharge summaries, catheterization reports, and ECGs.
- Record of protocol required medications during the trial
- Record of the subject's condition upon completion of or withdrawal from the trial

The Investigator and the associated institution will permit direct access to source data/documents for study-related monitoring, audits, IRB/EC review, and regulatory inspections.

Subjects providing informed consent agree to allow the ARC or designee access and copying rights to pertinent information in their medical records concerning their participation in this trial. The Investigator will obtain, as part of the informed consent, permission for trial monitors or regulatory authorities to review, in confidence, any records identifying the

subjects in this trial. This information may be shared with regulatory agencies; however, the ARC undertakes not to otherwise release the patient's personal and private information.

9.3 Study timetable and end of study

The trial is estimated to commence February 1st, 2015. The last subject follow-up at 18 months post-procedure is expected to occur in February 2018. The total expected duration of the trial is 36 months.

10. DATA MANAGEMENT

A computerized data entry and management system will be developed during the initial project months by an independent academic research center. A closed and password protected data entry system has been designed to ensure that only the responsible data entry person and the Data Management site supervisor can enter and/or edit data and this can be done only by using the programs and/or utilities available on the menu system. An audit trail will be created by date/time and user stamping. Range checks, review screens, and various error trapping routines are built into the system as quality control procedures. All possible relevant information on the forms is pre-coded. Specific instructions and explanation of choices will be provided for all data forms.

The statistical programmer will perform additional data checks, data cleaning, and variable coding to create analysis datasets using SAS. The programmer will also create a reporting system that generates study specific tables, listings, and figures, which will be run periodically to monitor study and data entry. As a final check on data integrity, the Director of Clinical Biometrics and study biostatistician will check these outputs against the raw data in order to resolve any discrepancies. The Biometrics lead, statistician, and statistical programmer will be responsible for working with the project staff to ensure the integrity of the data entry process.

11. EVALUATION AND CALCULATION OF VARIABLES

11.1.1 Primary Bleeding Endpoint

The primary bleeding endpoint of the present study is the time to first occurrence of clinically relevant bleeding, defined as Bleeding Academic Research Consortium (BARC) Types 2, 3 or 5 bleeding.

11.1.2 Secondary Bleeding Endpoints

Time to first occurrence of:

- Types 3 or 5 bleeding according to definitions from BARC
- Minor or major bleeding according to definitions from Thrombolysis in Myocardial Infarction (TIMI)

- Moderate or severe or life-threatening bleeding according to definitions from GUSTO
- Major bleeding according to definitions from International Society of Thrombosis or Hemostasis (ISTH)

11.1.3 Primary Ischemic Endpoint

The primary ischemic endpoint of the present study is the time to first occurrence of confirmed all-cause death, non-fatal myocardial infarction, or stroke.

11.1.4 Secondary Ischemic Endpoints

Time to first occurrence of:

- cardiovascular death, non-fatal myocardial infarction, ischemic stroke or clinically-driven revascularization
- cardiovascular death, non-fatal myocardial infarction or ischemic stroke
- definite or probable stent thrombosis
- cardiovascular death
- non-fatal myocardial infarction
- cardiovascular death, non-fatal myocardial infarction or definite or probable stent thrombosis
- ischemic stroke
- all-cause mortality

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

The statistical analyses will be performed using SAS version 9.0 or greater and Stata versions 12.0 or greater.

12.1 Description of analysis sets

The Enrolled Population consists of all subjects who signed informed consent.

The intention-to-treat (ITT) population will consist of all subjects who have been randomized (i.e. when the subject number and allocated treatment are recorded in the EDC). Subjects will be analyzed in the treatment group assigned by the EDC.

The per-protocol population (PP) will consist of all randomized subjects without any major deviations from the protocol. The following deviations will lead to exclusion from the PP population

- Subjects not receiving the assigned treatment as allocated by the EDC or no treatment at all
- Non-compliance to study drug (aspirin or placebo) or ticagrelor. Non-compliance is defined as taking less than 80% of dispensed tablets based on manual pill bottle count at each study visit.

12.1.1 Efficacy analysis set

All analyses for the primary bleeding endpoint will be performed on the ITT and PP population. The primary analysis will be performed on the ITT population. This analysis will be repeated in the PP population to support the primary results.

The primary bleeding endpoint is the composite of BARC Types 2, 3 or 5 bleeding.

12.1.2 Safety analysis set

Analyses for the primary ischemic endpoint will be performed on the PP cohort. A secondary analysis for the primary ischemic endpoint will be performed in the ITT cohort.

12.2 Methods of statistical analyses

Unless otherwise stated, all hypothesis tests will be performed using two-sided tests at the 5% significance level. Continuous variables will be summarized using descriptive statistics including means and standard deviations if normally distributed or median with interquartile ranges for skewed distributions. Discrete variables will be summarized using absolute and relative frequencies.

Demographic and baseline characteristics will be summarized by randomized treatment group and for all randomized subjects combined. Baseline characteristics that will define subgroups of interest for the efficacy and safety analyses are:

- Age group (< 65, >= 65 years)
- Race (Caucasian, non-Caucasian)
- Gender (Male, Female)
- Geographic Region (US, non-US)
- Diabetes Mellitus (yes, no)
- Chronic Kidney Disease (yes, no)

- CAD Presentation (Stable, Unstable)
- PCI Status (Elective, Urgent)
- Stent length implanted (< 30 mm, >=30 mm)
- BMI (above median, below median)
- History of Prior MI (yes, no)
- Multivessel disease (yes, no)

Censoring: Subjects not experiencing any endpoint will be censored at time of death, last contact date (for subjects who withdraw consent or are lost to follow-up) or 365 days after randomization, whichever comes first.

Analysis for the Primary Bleeding Endpoint: This analysis will be performed on the ITT population. The primary objective is to determine if ticagrelor monotherapy is superior to ticagrelor plus aspirin for the primary efficacy endpoint (BARC Types 2, 3 or 5 bleeding). The null hypothesis for this analysis is that the HR for the experimental group (H_0) = 1. The alternative hypothesis is that the HR for the experimental group (H_A) ≠ 1. A test of superiority at the two-sided 0.05 level will be performed using a Cox proportional hazard model that includes treatment group as a covariate. A point estimate and two-sided 95% CI for the relative risk as measured by the hazard ratio will be calculated based on the Cox proportional hazards model. Event rates will be estimated at one year and Kaplan-Meier curves will be plotted for the time from randomization to the first occurrence of confirmed BARC Type 2, 3 or 5 bleeding by treatment group. This analysis will be repeated in the PP cohort to support the primary results.

Analysis for the Primary Ischemic Endpoint: The analysis for the primary ischemic endpoint will be performed on the PP cohort. The primary objective is to determine if ticagrelor monotherapy is non-inferior to ticagrelor plus aspirin for the primary safety endpoint (all-cause death, non-fatal myocardial infarction, or stroke). . A test of non-inferiority at the one-sided 0.025 level will be performed. Event rates will be estimated at one year and Kaplan-Meier curves will be plotted for the time from randomization to the first occurrence of confirmed all-cause death, non-fatal myocardial infarction, or stroke or by treatment group. Assuming an event rate of 8.0% in the control group, a sample size of 8200 will yield 80% to exclude a non-inferiority margin of 1.6%. If the upper limit of the 95% CI for the point estimate of the absolute risk difference is less than or equal to 1.6% then the criteria for non-inferiority will be met. This non-inferiority margin translates to a relative risk of 20% assuming the observed event rate equals 8.0% in the control arm.

Subgroup Analysis One year event rates for the primary efficacy and safety endpoints will be calculated in all subgroups described in section 12.2. Stratum-specific HRs and corresponding 95% CI will be calculated for each subgroup using a Cox proportional hazards

model. Formal interaction testing will be performed using the subgroup X treatment allocation as an additional term in the Cox model.

12.3 Determination of sample size

Power calculations are based on a superiority comparison for the primary efficacy endpoint of clinically relevant bleeding (BARC Types 2, 3 or 5) at 1 year from randomization (15 months after enrollment). Based on bleeding rates as shown in Table 3, a cumulative bleeding rate of 4.5% is anticipated between time of randomization and 1 year. This estimate is more conservative than rates shown in Table 3 as subjects sustaining a major hemorrhagic event in the first 3 months after PCI will not be randomized. Assuming a 2% loss to follow-up and non-compliance / cross-over rate of 4%, the current trial will require 8200 subjects to detect a relative reduction in bleeding of 28% with ticagrelor monotherapy with 80% power with a Type I error of 0.05. It is anticipated that approximately 8% - 10% of enrolled subjects will not be eligible for randomization and therefore 9000 subjects will be enrolled. Additional sample size estimates are provided in Table 4 assuming different control bleeding rates and risk reductions. References for the sample size estimates include Lakatos 1988, Biometrics volume 44 pages 229-241; and Lakatos 2002, Statistics in Medicine, Volume 21 pages 1969-1989.

Assuming a 1 year ischemic adverse event rate of 8% the current study will have 80% power to exclude a non-inferiority margin of 1.6% (upper limit of 95% CI for absolute risk difference).

Table 2 Bleeding Rates/Effect Sizes for Primary Endpoint Power Calculations

Basis for Proposed Bleeding Event Rates in TWILIGHT Power Calculations			
Study	**Study Type**	**Time Point**	**BARC ≥ 2 Rate**
DAPT	RCT	18 months	**~ 4.2%**
PARIS (unpublished data)	Registry		
Age > 65	Registry	1 year	8.6%
Diabetes Mellitus (on insulin) Diabetes Mellitus (orals)	Registry	1 year	8.3% 6.3%
Renal disease	Registry	1 year	13.2%
Vranckx et al., EHJ 2013	Post-hoc (TRACER)	500 days	14%
ADAPT-DES			
CrCl < 60 (Baber et al, TCT 2013)	Registry	1 year	10.0%
Rao et al., JACC Int 2013	NCDR CathPCI	In-hospital (women)	8.5%
Basis for Proposed Effect Size in TWILIGHT Power Calculations			

Study	Study Type	Comparators	Relative Bleeding Increase
Baigent et al., Lancet 2009	Pooled Data from Randomized trials	ASA vs. placebo/control	50% (1° prevention) 170% (2 ° prevention)
WOEST, Lancet 2013	RCT	ASA vs. placebo	~ 60%
CAPRIE, Lancet 1996	RCT	ASA vs. clopidogrel	~35% (GI hemorrhage)
Physician Health Study, NEJM 1989	RCT	ASA vs. Placebo	~35%
De Berardis et al., JAMA 2012	Cohort study	ASA vs. No ASA	55%
Seshasai et al., Archives Int Med 2012	Meta-analysis of 9 RCTs	ASA vs. Placebo	~31%
HOT Trial, Lancet 1998	RCT	ASA vs. Placebo	~ 80%

Table 3 Power and Sample Size Scenarios for Primary Superiority Endpoint of BARC ≥ 2 Bleeding

Control Bleeding Rate	Relative Risk Reduction	Total Randomized Sample Size	Total Sample Size (Enrolled + Randomized) with 8% loss after enrollment*	Total Sample Size (Enrolled + Randomized) with 10% loss after enrollment*
5%	30%	6400	7000	7111
5%	28%	7400	8040	8222
5%	26%	8030	9800	10000
4.5%	30%	7090	7706	7900
4.5%	28%	8200	8913	9111
4.5%	26%	9700	10500	10800
4.0%	30%	8000	8700	8888
4.0%	28%	9300	10100	10333
4.0%	26%	10900	11800	12111

We anticipate that ~10% of enrolled subjects will not be eligible or lost for randomization. Power calculations assume 2% loss to follow-up and 4% cross-over/non-compliance.

12.4 Data and safety monitoring board

The TWILIGHT study will be conducted under the auspices of an independent Data and Safety Monitoring Board (DSMB), whose activities will be described in a DSMB charter. DSMB members will not have primary affiliation with the study sponsor, the EDC supplier or

the principal investigator of the trial. Members of the Board will be determined prior to study enrollment.

The DSMB will review data and determine reporting and stopping rules as specified in the DSMB charter. The DSMB members will review safety data while maintaining the scientific integrity of the trial. The data to be reviewed will consist of adjudicated and non-adjudicated MACE, Bleeding, and other Serious Adverse Events and their incidence, in order to identify potential safety issues. Based on the safety data, the DSMB may recommend modifications to the protocol, suspension or termination of the trial, and advise the Executive Committee.

Members of the DSMB will meet or conference with steering group members before the trial starts to review the protocol, to determine the meeting schedule, the logistics of reporting the safety data and the stopping rules. Frequency of meetings can change during the study and will be determined by the DSMB and its charter.

All adverse events will be reported to the DSMB and reviewed on an on-going basis throughout the subject enrollment and follow-up period as specified in the DSMB charter to ensure the safety of subjects enrolled in this trial. The DSMB may request additional information as needed. Based on safety data, the DSMB may recommend that the Executive Committee modify or discontinue the trial. All final decisions, regarding trial modifications, however, rest with the Executive Committee.

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Overdose

If an overdose on the study drug occurs in the course of the study, then investigators or other site personnel inform appropriate the ARC **within one day**, i.e., immediately but no later than **the end of the next business day** of when he or she becomes aware of it.

The ARC will work with the investigator to ensure that all relevant information is provided to the ARC.

13.2 Pregnancy

Due to the study enrollment criteria and proposed population, women of child bearing potential (as defined in Section 4.2) are excluded from participation in this study. In the unlikely event that pregnancy should occur during the course of the study, all outcomes of pregnancy should be reported to the ARC.

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15. APPENDIX A – DEFINITIONS FOR STUDY ENDPOINTS

15.1 Bleeding events

15.1.1 Bleeding Academic Research Consortium definition of bleeding

Clinically relevant bleeding is defined as any bleeding event that meets the BARC criteria types 2, 3 or 5.

Table 4 BARC Bleeding Definition, modified from Mehran et al (26)

Type	Definition
0	No evidence of bleeding.
1	Bleeding that is not actionable and patient does not have unscheduled studies, hospitalization or treatment by a health care professional
2	Any clinically overt sign of hemorrhage that is actionable but does not meet criteria for type 3, 4 or 5 bleeding. It must meet at least one of the following criteria: • requiring medical or percutaneous intervention guided by a health care profession, includes (but are not limited to) temporary/permanent cessation of a medication, coiling, compression, local injection • leading to hospitalization or an increased level of care • prompting evaluation defined as an unscheduled visit to a healthcare professional resulting in diagnostic testing (laboratory or imaging)
3	Clinical, laboratory and/or imaging evidence of bleeding with specific healthcare provider responses, as listed below:
3a	• Any transfusion with overt bleeding • Overt bleeding plus hemoglobin (Hb) drop ≥3 to <5g/dL* (provided Hb drop is related to bleeding)
3b	• Overt bleeding plus Hb drop ≥5g/dL* (Hb drop is related to bleed) • Cardiac tamponade • Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid) • Bleeding requiring intravenous vasoactive drugs
3c	• Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation; does include intraspinal). Subcategories: confirmed by autopsy, imaging or lumbar puncture

* Hemoglobin drop should be corrected for for intracurrent transfusion in which 1 unit of packed red blood cells or whole blood should be expected to increase hemoglobin by 1g/dL.

Type	Definition
	• Intraocular bleed compromising vision
4	CABG – Related Bleeding • Perioperative intracranial bleeding within 48 hours • Reoperation following closure of sternotomy for the purpose of controlling bleeding • Transfusion of ≥5 units of whole blood or packed red blood cells within a 48 hour period • Chest tube output ≥2L within a 24 hour period
5	Fatal Bleeding. Bleeding directly causes death with no other explainable cause. Categorized further as either definite or probable.
5a	Probable fatal bleeding is bleeding that is clinically suspicious as the cause of death, but the bleeding is not directly observed and there is no autopsy or confirmatory imaging.
5b	Definite fatal bleeding is bleeding that is directly observed (either by clinical specimen – blood, emesis, stool, etc. – or by imaging) or confirmed on autopsy.

15.1.2 Thrombolysis in Myocardial Infarction definition of bleeding

Table 5 TIMI Bleeding Definition(27)

Type	Definition
Non-CABG related bleeding	
Major	• Any intracranial bleeding (excluding microhemorrhages <10 mm evident only on gradient-echo MRI) • Clinically overt signs of hemorrhage associated with a drop in hemoglobin of ≥5 g/dL or a ≥15% absolute decrease in haematocrit • Fatal bleeding (bleeding that directly results in death within 7 days) **Life threatening** bleeding is a TIMI major bleeding event that meets any of the following criteria: • Symptomatic intracranial hemorrhage • Fatal bleeding • Leads to hypotension requiring inotropic agents • Requires surgical intervention for ongoing bleeding • Necessitates transfusion of 4 or more units of whole blood or packed red blood cells over a 48-hour period

Type	Definition

Minor	• Clinically overt (including imaging), resulting in hemoglobin drop of 3 to <5 g/dL or ≥10% decrease in haematocrit
	• No observed blood loss: ≥4 g/dL decrease in the haemoglobin concentration or ≥12% decrease in haematocrit
	• Any overt sign of hemorrhage that meets one of the following criteria and does not meet criteria for a major bleeding event:
	  o Requiring intervention (medical practitioner-guided medical or surgical treatment to stop or treat bleeding, including temporarily or permanently discontinuing or changing the dose of a medication or study drug)
	  o Leading to or prolonging hospitalization
	  o Prompting evaluation (leading to an unscheduled visit to a healthcare professional and diagnostic testing, either laboratory or imaging)

Minimal	• Any overt bleeding event that does not meet the criteria above • Any clinically overt sign of haemorrhage (including imaging) associated with a <3 g/dL decrease in haemoglobin concentration or <9% decrease in haematocrit
Bleeding in the setting of CABG	
	• Fatal bleeding (bleeding that directly results in death) • Perioperative intracranial bleeding • Reoperation after closure of the sternotomy incision for the purpose of controlling bleeding • Transfusion of ≥5 U PRBCs or whole blood within a 48-h period; cell saver transfusion will not be counted in calculations of blood products. • Chest tube output >2 L within a 24-h period

15.1.3 Global Utilization of Streptokinase and TPA for Occluded Arteries (GUSTO) definition of bleeding

Table 6 GUSTO Bleeding Definition (28)

Type	Definition
Severe or life-threatening	Intracerebral bleeding or bleeding resulting in substantial hemodynamic compromise requiring treatment
Moderate	Any bleeding not meeting the requirements for severe / life-threatening bleeding that requires transfusion
Minor	Other bleeding not requiring transfusion or causing hemodynamic compromise

15.1.4 International Society on Thrombosis and Haemostasis definition of bleeding

The ISTH classification of major bleeding in non-surgical patients includes any one of the following:

- Fatal bleeding,
- Symptomatic bleeding in a critical area or organ such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome,
- Bleeding causing a fall in haemoglobin level of 2 g/dL (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells.(25)

15.2 Major Adverse Cardiovascular Events

Major adverse cardiovascular events (MACE) is the composite of cardiovascular death, non-fatal myocardial infarction, ischemic stroke, or clinically-driven revascularization. The definitions of the individual components of MACE are given below.

15.2.1 Death

All-cause death comprises several subclassifications (Table 7). In general, all deaths are considered cardiac unless an alternate cause is unequivocally established, even among subjects with serious noncardiac comorbidities.

Table 7 Classification of Death(29)

Cardiac death	Any death due to proximate cardiac cause (eg, MI, low-output failure, fatal arrhythmia), unwitnessed death and death of unknown cause, all procedure-related deaths including those related to concomitant treatment, will be classified as cardiac death.
Vascular death	Death caused by noncoronary vascular causes, such as cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm or other causes.
Noncardiovascular death	Any death not covered by the above definitions, such as death caused by infection, malignancy, sepsis, pulmonary causes, accident, suicide or trauma.

15.2.2 Myocardial Infarction

Myocardial infarction is defined according to the third universal definition(30) and includes:

- Type 1: spontaneous MI
- Type 2: MI secondary to an ischemic imbalance
- Type 3: MI resulting in death when biomarker values are unavailable
- Type 4a. MI related to PCI
- Type 4b: MI related to stent thrombosis

- Type 5: MI related to CABG

Any one of the following criteria meets the diagnosis of MI:

- Detection of a rise and/or fall of cardiac biomarker values (preferably cardiac troponin) with at least one value above the 99th percentile URL and with at least one of the following:
    - Symptoms of ischemia
    - (Presumed) new significant ST-T wave changes or new LBBB
    - Development of pathological Q waves
    - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
    - Identification of an intracoronary thrombus by angiography or autopsy
- Cardiac death with symptoms suggestive of MI and presumed new ischemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased
- PCI related MI is arbitrarily defined by elevation of cardiac biomarkers
    - (>5 x 99th percentile URL) in patients with normal baseline values or
    - > 20% if the baseline values are elevated and are stable or falling

In addition, one of the following is required

- symptoms suggestive of ischemia
- new ischemic ECG changes
- angiographic findings consistent with a procedural complication OR
- imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality

- Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL
- CABG related MI is arbitrarily defined by elevation of cardiac biomarkers >10 x 99th percentile URL in patients with normal baseline values, AND one of the following:

- New pathological Q waves or new LBBB
- Angiographic documented new graft or new native coronary artery occlusion, or
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

15.2.3 Stroke

Stroke is defined as an acute symptomatic episode of neurological dysfunction, more than 24 hours in duration in the absence of therapeutic intervention or death, due to cerebral, spinal or retinal tissue injury as evidenced by neuroimaging or lumbar puncture. It includes the following subclassifications:

- Ischemic stroke: infarction due to prolonged ischemia. Causes include (but are not limited to) arterial and venous thrombosis, embolism, and systemic hypoperfusion.
- Hemorrhagic stroke: caused by a non-traumatic intraperenchymal, intraventricular or subarachnoid hemorrhage
- Undetermined: stroke with insufficient information to determine ischemic or hemorrhagic cause

Transient ischemic attack (TIA) is a transient episode of neurological dysfunction (< 24 hours) caused by temporary cerebral, spinal or retinal ischemia with no evidence of acute infarction on neuroimaging.

15.2.4 Stent thrombosis

Stent thrombosis is classified according to the level of certainty and timing following PCI(29) (Table 8).

- Definite stent thrombosis: is highly specific and requires angiographic or pathological confirmation of stent thrombosis in or within 5 mm of the stent in the setting of at least one of the following criteria with a 48-hour time window
    - Acute ischemic symptoms at rest
    - New ischemic ECG changes
    - Typical rise and fall in cardiac biomarkers
- Probable stent thrombosis includes
    - Any unexplained death within the first 30 days following PCI

- Any MI at any time following PCI that is related to documented acute ischemia in the territory of the implanted stent, in the absence of angiographic/pathological confirmation of stent thrombosis and no other obvious cause

- Possible stent thrombosis
  - Any unexplained death after the first 30 days following PCI until the end of trial follow-up

Table 8 Timing of Stent Thrombosis

Acute	0-24 hours following PCI
Subacute	>24 hours to 30 days following PCI
Late	>30 days to 1 year following PCI
Very late	>1 year following PCI

15.2.5 Clinically driven revascularization

Clinically driven revascularization includes repeat PCI or CABG for recurrent or persistent symptomatic ischemia and can be defined according to the relationship to the index PCI (target lesion)(29):

- Target lesion revascularization, at the previously stented segment
- Non-target lesion, target vessel revascularization, of the previously treated vessel or its side branches AND
- Non-target vessel lesion revascularization, of a vessel other than the previously treated vessel

16. APPENDIX B - OTHER DEFINITIONS

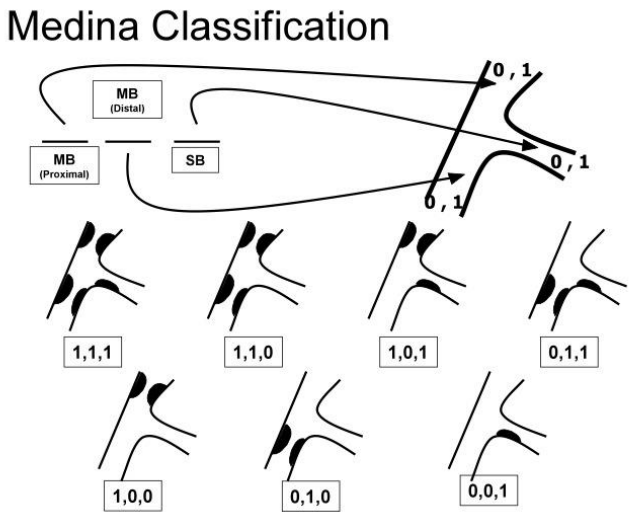
Coronary Artery Disease (CAD)

Multivessel (CAD), defined as significant disease in at least 2 major epicardial vessels or significant left main disease plus one major epicardial vessel. Significant coronary artery disease is defined as angiographic stenosis of at least 70% in a major epicardial vessel or at least 50% in the left main trunk. For intermediate stenosis in major epicardial vessels (50%-70%), an invasive hemodynamic assessment using fractional flow reserve (FFR) with values less than or equal to 0.8 will be considered significant. For intermediate left main lesions, a minimal lumen area by intravascular ultrasound (IVUS) less than 6.0 mm^2 will be considered significant.

Successful PCI

PCI is considered successful for lesions treated with stent implantation if the residual diameter stenosis based on visual estimation is less than or equal to 10% and the final TIMI flow grade is 3. PCI is considered successful for lesions treated without stent implantation if the residual diameter stenosis based on visual estimation is less than or equal to 30% and the final TIMI flow grade is 3.

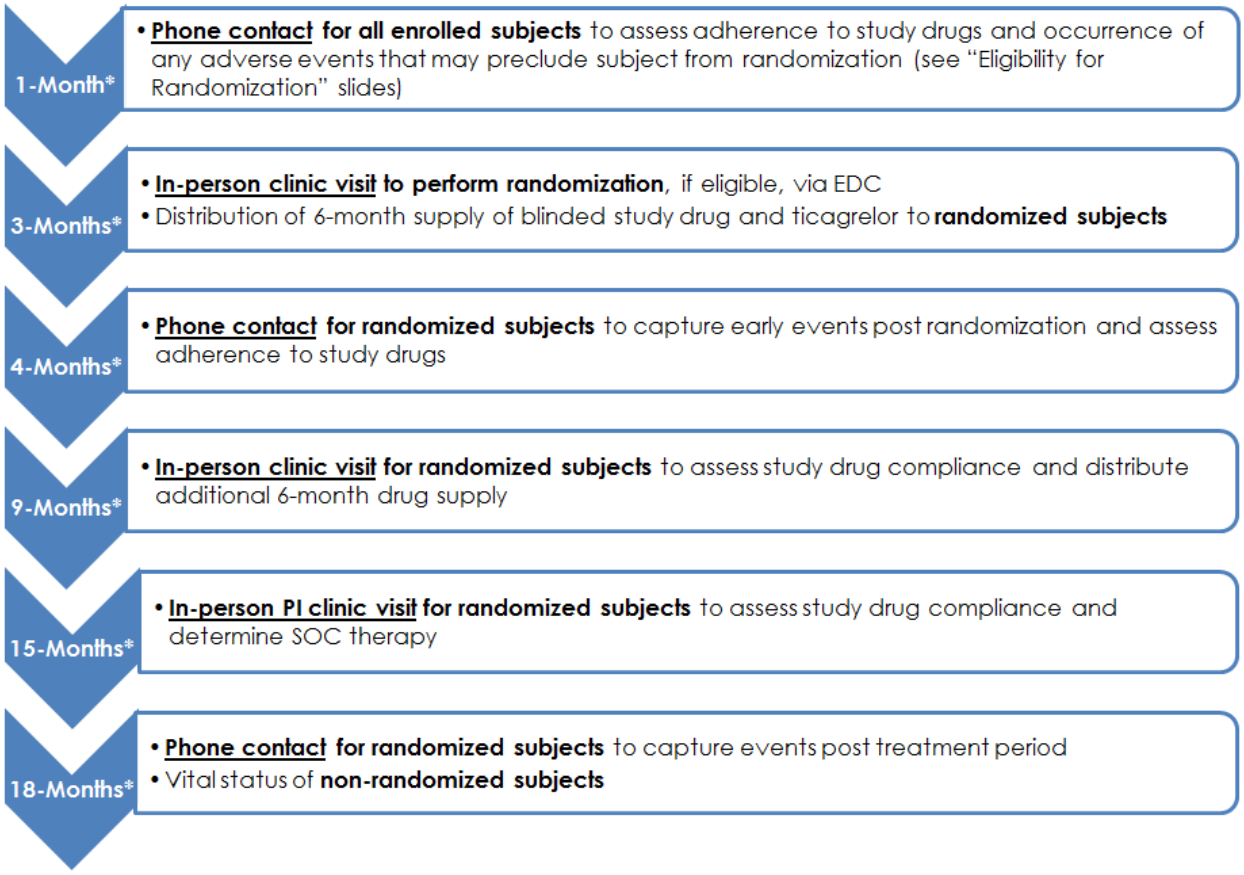
Medina Classification of Bifurcations



Indication for PCI according to National Cardiovascular Data Registry

17. APPENDIX C

Timeline Of In-Person Visits And Phone Calls



18. APPENDIX D

CONTRAINDICATIONS TO ASPIRIN

Hypersensitivity to ASA, salicylates, non-steroidal anti-inflammatory drugs (NSAIDs), analgesics, antipyretics or other ingredients in the product, excipients or component of the container.
Acute gastrointestinal ulcer, history of gastrointestinal ulcers
Hemorrhagic diathesis and severe active bleeding
Active or severe hepatic failure, renal failure requiring dialysis, or acute congestive heart failure
Patients with a history of asthma induced by the administration of salicylates or substances with a similar action, notably NSAIDs
Combination with methotrexate at doses of 15 mg/week or more
Last trimester of pregnancy and nursing women
Glucose-6-phosphate dehydrogenase (G6PD) deficiency

19. APPENDIX E

CONTRAINDICATIONS TO TICAGRELOR:

Hypersensitivity to the active substance or to any of the excipients
Active pathological bleeding
History of intracranial hemorrhage
Moderate to severe hepatic impairment
Co-administration of ticagrelor with strong CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin, nefazodone, ritonavir, and atazanavir) is contraindicated, as co-administration may lead to a substantial increase in exposure to ticagrelor

Section	Original Description (Version 2.2)	Revised to (Version 3.0)	Justification
Title Page	Sponsor: AstraZeneca Academic Research Organization (ARO): The Office of Interventional Cardiovascular Research and Clinical Trials at Icahn School of Medicine at Mount Sinai	Funding Agency: AstraZeneca Sponsor-Investigator/Academic Research Center (ARC): The Office of Interventional Cardiovascular Research and Clinical Trials at Icahn School of Medicine at Mount Sinai	Mount Sinai's Office of Interventional Cardiovascular Research and Clinical Trials will function as the investigator-sponsor for this study. Funds for conducting this study will be provided by AstraZeneca. Role revised to Academic Research Center (ARC) throughout document to accurately reflect office function.
Protocol Synopsis	N/A	Updated	Synopsis sections modified to reflect changes in entirety of protocol.
Protocol Signature Page	'I will discuss this material with them and ensure they are fully informed regarding the ***device*** and the conduct of the trial.'	'I will discuss this material with them and ensure they are fully informed regarding the ***study drugs*** and the conduct of the trial.'	Revised to reflect randomized, double-blinded, placebo controlled drug trial; devices are not being studied in this protocol.
Protocol Signature Page	'I will conduct the trial in accordance with the clinical investigation plan, Good Clinical Practice guidelines, EN ISO 14155:2011 (Clinical Investigation of Medical Devices for Human Subjects – GCP)…'	'I will conduct the trial in accordance with the clinical investigation plan, Good Clinical Practice guidelines, World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects…'	Since this is a drug trial rather than a device trial, references to medical devices regulations (ISO 14155:2011) have been replaced with regulations related to drug evaluation.
Section 1.1 Research Hypothesis	'Aim 1: To determine the efficacy of ticagrelor alone versus ticagrelor plus aspirin… Aim 2: To determine the safety of ticagrelor alone versus ticagrelor plus aspirin…'	'Aim 1: To determine the impact of ticagrelor alone versus ticagrelor plus aspirin… Aim 2: To determine the impact of ticagrelor alone versus ticagrelor plus aspirin…'	Terminology regarding aims of the study have been revised to more accurately reflect what the endpoints represent and to avoid confusion (as the endpoints in this study do not meet conventional definitions of efficacy and safety).

Section 1.2 Rationale for conducting this study	'…compared to continued ASA and ticagrelor among high-risk patients undergoing PCI.'	'…compared to continued ASA and ticagrelor among high-risk patients undergoing PCI ***with DES***.'	Added "with DES" to clarify eligible patients will have had successful PCI with DES.
Section 1.3 Benefit/risk and ethical assessment	'From an ethical standpoint, an independent data safety monitoring board will provide external oversight to ensure safety of all trial participants. In addition, subjects will be followed closely with either phone call or in-person visit every 3 months. Also, clinical equipoise exists for conducting a trial with this type of randomized comparison.'	'An independent data safety monitoring board will provide external oversight to ensure safety of all trial participants. In addition, subjects will be followed closely with periodic study contacts. Also, clinical equipoise exists for conducting a trial with this type of randomized comparison.'	Revised wording to reflect changes in study visits (outlined in section 6).
Section 2 Study Objectives	"efficacy" and "safety"	Removed terminology of "efficacy" and "safety" in this section (and in other sections throughout)	Terminology regarding endpoints has been revised to more accurately reflect what the endpoints represent and to avoid confusion (as the endpoints in this study do not meet conventional definitions of efficacy and safety).
Section 3.1 Overall study design and flow chart	Figure 1 TWILIGHT Trial Design	Figure 1 TWILIGHT Trial Design – UPDATED	Updated to reflect changes in total length of study (added observational period).
Section 3.2 Rationale for study design…	"A low dose of aspirin (81 mg – 100 mg daily) is recommended during this open-label phase." "randomized to placebo versus non-enteric coated ASA"	REMOVED "randomized to placebo versus enteric coated ASA"	Modified throughout to reflect use of enteric coated ASA for this study.
Section 4.1 Inclusion	'High-risk patients who have undergone successful elective or urgent PCI with at	'High-risk patients who have undergone successful PCI with at least one locally	Removed references to "elective" and "urgent" to

criteria	least one locally approved drug eluting stent discharged on DAPT with aspirin and ticagrelor of at least 3 months intended duration will be eligible for the TWILIGHT study. Elective or urgent are defined according to the National Cardiovascular Data Registry (Section 16).'	approved drug eluting stent (DES) discharged on DAPT with aspirin and ticagrelor of at least 3 months intended duration will be eligible for the TWILIGHT study. Successful PCI is defined as a final residual diameter stenosis of < 10% with final TIMI flow grade 3 by visual estimation for any lesions treated with stenting. For lesions treated with balloon angioplasty, successful PCI is defined as a final residual diameter stenosis < 50% with a final TIMI flow grade of 3 by visual estimation (ACC 2011 PCI Guidelines).'	clarify eligibility for study. Only salvage PCI or STEMI presentation will be excluded; all other presentations for PCI are eligible. Definition of successful PCI added for clarification.
Section 4.1 Inclusion criteria	'A subject is considered enrolled if all requisite inclusion and none of the exclusion criteria are met and upon provision of informed consent. Enrollment into the study will require meeting at least one clinical inclusion, one angiographic inclusion and none of the exclusion criteria.'	'Enrollment into the study will require meeting at least one clinical inclusion AND at least one angiographic inclusion AND none of the exclusion criteria. A subject is considered enrolled if all these criteria are met and upon provision of informed consent.'	Simplified wording to clarify inclusion and exclusion criteria.
Section 4.1 Inclusion criteria: Must meet AT LEAST ONE clinical inclusion criterion	'Recent (> 3 days) presentation with acute coronary syndrome with clinical stabilization and decreasing cardiac enzymes.'	Change to: 'Troponin positive acute coronary syndrome.' Add "Female gender" to list.	Modifications to IC as per Executive Committee to encompass additional high risk characteristics.
Section 4.1 Inclusion criteria: Must meet AT LEAST ONE angiographic	'Bifurcation lesions with Medina ***X,X,1*** classification requiring at least 2 stents (see Section 16)'	Change to 'Bifurcation lesion(s) with Medina ***X,1,1*** classification requiring at least 2 stents (see Section 16)' Remove "SYNTAX score ≥23".	Modifications to IC as per Executive Committee to encompass additional high risk characteristics. Bifurcation lesion requirements

inclusion criterion		Add “Thrombotic target lesion(s)”.	were modified to reflect ‘true bifurcations’ as lesions with disease in both the main and side branch vessel (defined as X,1,1). SYNTAX score was removed as this criterion will not be readily available at many sites and is collinear with other inclusion criteria (i.e. multivessel disease). Thrombotic lesion was added as this is a significant risk factor for recurrent thrombotic events.
Section 4.2 Exclusion criteria	‘Emergent or salvage PCI or STEMI presentation. Emergent and salvage are defined as per the National Cardiovascular Data Registry criteria (Section 16).’	‘Salvage PCI or STEMI presentation.’	Modifications to EC as per Executive Committee to include additional high risk subjects (emergent presentation for PCI).
5.1 Restrictions during the study	‘… remain on ticagrelor plus ***ASA*** for the first three months after index PCI ***and*** ticagrelor plus blinded study drug for 12 months after randomization. Unless clinically indicated, ***open label aspirin***, non-steroidal anti-inflammatory drugs (NSAIDs)...’	‘… remain on ***open-label*** ticagrelor plus ***open-label aspirin*** for the first three months after index PCI followed by open-label ticagrelor plus blinded study drug for 12 months after randomization. Unless clinically indicated, non-steroidal anti-inflammatory drugs (NSAIDs)...’	“Open-label” added throughout to clarify. Subject are advised to avoid taking additional OTC open-label ASA in “Risks” sections; subjects requiring treatment with ≥ 325mg of ASA excluded.
5.2.1	‘Non physician-guided cessation of aspirin	‘Non physician-guided cessation of aspirin or	Clarified cessation by defining it

Procedures for randomization	or ticagrelor of 5 days or greater.'	ticagrelor of 5 ***consecutive*** days or greater.'	as 5 consecutive days.
5.2.1 Procedures for randomization	***'An independent biostatistician, not otherwise part of the study team, will generate the randomization schedule. For this study, the randomization schedule refers to a list that includes the randomization number, randomization block number, treatment code and treatment.*** Randomization will be performed ***by the interactive voice/web response system (IXRS)*** within the EDC system among subjects eligible for randomization. The ***IXRS*** will assign the unique subject identification number, allocate the treatment group assignment for the subject and provide the appropriate ***drug supply kit*** number(s). ***The IXRS will provide study site research personnel with the appropriate drug supply kit number(s).***	'Randomization will be performed within the EDC system among subjects eligible for randomization. The ***EDC*** will allocate the treatment group assignment for the subject and provide ***study site research personnel*** the appropriate ***bottle ID*** number(s). Upon randomization at the conclusion of the in-person 3-month visit, the study site research personnel will provide a 6-month supply of **blinded** investigational product (aspirin or matching placebo) and ***open-label*** ticagrelor.	"IXRS" to "EDC" revised throughout protocol to reflect use of built-in randomization generator within EDC system. "drug supply kit" revised to "bottle" throughout to reflect mode of drug supply.
5.2.1 Procedures for randomization	Upon randomization at the conclusion of the in-person 3 month visit, the study site research personnel will provide a 6 month supply of investigational product (aspirin or matching placebo) and ticagrelor. Enrolled subjects who do not meet eligibility for randomization will ***remain in the study***. They will not receive study drug ***and medication will continue as determined by their treating physician.'***	Enrolled subjects who do not meet eligibility for randomization will ***have completed their protocol required activities.*** They will not receive study drug ***but will be distributed an additional 1-week supply of open-label ticagrelor, if clinically appropriate. Vital status of these subjects will be determined at the 18-month time point.*** ***Enrolled subjects who do not meet eligibility for randomization prior to the in-person 3-month visit will not be required to complete the 3-month in-person visit.'***	Procedure modified to include distribution of additional supply of ticagrelor, if clinically appropriate, to those subjects who are not eligible to be randomized - this will serve as interim antiplatelet therapy until those subjects can be seen by their primary cardiologist/PCP. These subjects will have concluded their study related activities and sites will only be required

			to determine vital status at the 18-month time point.
5.5.1 Identity of investigational product	'Table 1:Identity of Investigational Product: Investigation product: Placebo for aspirin Dosage form and strength: ***N/A'***	'Table 1:Identity of Investigational Product: Investigation product: Placebo for aspirin Dosage form and strength: ***tablet daily'***	Dosage form and strength determined and inserted in protocol.
5.5.2 Doses and treatment regimens	'Subjects will receive ***2 bottles of*** study drug at randomization (3-month study visit) and at the 9 month study visit.'	'Subjects will receive a ***3-month supply of open-label ticagrelor and open-label aspirin at the baseline visit and a 6-month supply of blinded*** study drug ***and open-label ticagrelor*** at randomization (3-month study visit) and at the 9 month study visit.'	Study drug supply determined and inserted in protocol as defined at baseline and at randomization.
5.6 Concomitant and post-study treatment and 5.8.1 Procedures for discontinuation of a subject from investigational product	'There are no protocol specific concomitant treatments. ***After study completion, the physician will determine the ongoing medical treatment for each subject***.'	'There are no protocol specific concomitant treatments. ***Subjects who are taking ticagrelor but do not meet eligibility for randomization at the 3-month in-person visit will be provided open-label ticagrelor for an additional 7 days. In addition, these subjects and their treating physicians will be notified that protocol mandated study activities will conclude at this time and that further antiplatelet therapy will not be provided. Further medical therapy will be prescribed by the subject's physician as per local standard of care.*** ***Subjects who remain on ticagrelor at the 15-month in-person visit will be provided open-label ticagrelor for an additional 7 days. In addition, these subjects and their treating physicians will be notified that protocol mandated study activities will conclude at this time and that further antiplatelet therapy will not be provided. Further medical***	Added procedure for subjects who will no longer be receiving study drug. These steps are to ensure that these subjects receive interim antiplatelet therapy until they can be seen by their primary cardiologist/PCP.

		therapy will be prescribed by the subject's physician as per local standard of care.'	
6.2 Data collection at enrollment and follow-up	Data required for analysis will be obtained as outlined in Table 2. After discharge from the hospital, each enrolled subject will be followed with an in-clinic visit at 3 months. Subjects who are randomized at 3 months will return for additional in-clinic visits at 9 and 15 months. Subjects who did not meet eligibility for randomization at the 3 month visit will be followed by telephone contact only at 9 and 15 months to ascertain occurrence of adverse events and compliance with their standard of care DAPT regimen.	Data required for analysis will be obtained as outlined in Table 2. After discharge from the hospital, each enrolled subject will be followed with ***a phone call at 1 month post enrollment and*** an in-clinic visit at 3 months ***post enrollment. Enrolled subjects who do not meet eligibility for randomization prior to the in-person 3-month visit will not be required to complete the 3-month in-person visit.*** Subjects who are randomized at 3 months ***post enrollment*** will ***be followed with a phone call at 4 months post enrollment and will*** return for additional in-clinic visits at 9 and 15 months ***post enrollment. A final follow-up phone call will be performed at 18 months post enrollment for randomized subjects. No further follow-up contact will be performed for s***ubjects who did not meet eligibility for randomization at the 3 month visit***; however, vital status may be obtained from medical or public records at 18 months post enrollment.***	Modified language and table to reflect changes in visit schedule. Phone/mail contact added at 30 days post enrollment to ascertain early events and to remind patient about upcoming 3-month visit (to reduce drop-out). Phone/mail contact added at 4-months post enrollment (30 days after randomization) as the time period after randomization is the highest risk period for those subjects assigned to placebo. Final phone/mail contact added at 18-months post enrollment to ascertain vital status and medication status after all protocol related activities have been completed.
6.2.1 Enrollment procedures	•Obtain a complete medical history including lab values for hemoglobin and creatinine as well as an ECG, if performed per standard of care	•Obtain a complete medical history, including lab values for hemoglobin and creatinine as well as an ECG, if performed per standard of care. ***Subject may be asked to provide an additional blood sample (10cc) for lipid profile testing if not already performed per standard of care.***	Subjects may be asked to provide additional blood samples if lipid profile testing is not routinely performed at an investigational site for the purposes of additional analyses.

6.2.1 and 6.2.2 Enrollment and follow-up procedures	•Instruct the subject to notify the investigator of any occurrence of ***death, myocardial infarction, stroke, hospitalization for ischemia and bleeding***	•Instruct the subject to notify the investigator of any occurrence of ***adverse events***	Broaden question at enrollment and follow-up visits to capture more data on adverse events.
7.2.1 Definition of SUSARs	N/A	Definition of suspected unexpected serious adverse reactions (SUSARs).	Insertion of definition of SUSARs.
7.3.7 Reporting of Adverse Events	Site personnel must inform the FDA, via MedWatch/AdEERs of any serious or unexpected adverse events, and then forward the report to the ARC.	AEs and SAEs are to be reported to the ARC within 7 and 3 business days of the site's knowledge of the event, respectively. The ARC will review all submitted SAEs for qualification as SUSARs and will report qualifying SUSARs to the applicable regulatory bodies as appropriate. ARC will voluntarily inform the FDA or any qualifying SUSARs and will forward copies of the report to the applicable site.	Process of Adverse Event reporting amended to more accurately reflect and clarify roles and responsibilities of site personnel and the ARC. Since this study is not regulated by the FDA, all reports of qualifying SUSARs will be submitted on a voluntary basis by the ARC and the information will be forwarded to the applicable site.
8.1 Ethical Conduct of the Study	The trial will be conducted in compliance with the protocol, **ISO 14155:2011 (Clinical investigation of medical devices for human subjects - good clinical practice), and the ethical principles of the Declaration of Helsinki** as well as local regulations, and applicable regional regulatory requirements.	The trial will be conducted in compliance with the protocol, **Good Clinical Practice guidelines, and World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects** as well as local regulations, and applicable regional regulatory requirements.	Since this is a drug trial rather than a device trial, references to medical devices regulations (ISO 14155:2011) have been replaced with regulations related to drug evaluation.
9.3 Study timetable and end of study	The ***clinical investigation*** is estimated to commence ***[start date]***. Evaluation of primary end point is estimated by [date]. The last subject follow-up at ***15*** months post-procedure ***(12 months post-randomization)*** is expected to occur in ***[month/year]. T***otal expected duration of	The ***trial*** is estimated to commence ***February 1st, 2015.*** The last subject follow-up at ***18*** months post-procedure is expected to occur in ***February 2018***. ***The t***otal expected duration of the ***trial*** is ***36 months***. ***Open-label ticagrelor will be provided for an additional 7 days for participants who***	Inserted dates to reflect updated study timeline.

	the ***clinical investigation*** is ***[time frame]. The subjects will not be provided any follow-up contact or medical care related to the trial after the clinical investigation has been completed.*** Final subject ***visit*** will take place at 1***5*** months and this will end their participation in the study. ***Medical therapy after stopping the study will be as prescribed by the subject's physician.***	***complete the investigational period and who remain on ticagrelor at this time point (15-month in-person visit). Further medical therapy will be as prescribed by the subject's physician as per local standard of care.*** Final subject ***contact (via a phone call)*** will take place at 1***8*** months and this will end their participation in the study.	
11. Evaluation and Calculation of Variables	"Efficacy" vs. "Safety"	"Bleeding Endpoints" vs. "Ischemic Endpoints"	Terminology regarding endpoints has been revised throughout this section to more accurately reflect what the endpoints represent and to avoid confusion (as the endpoints in this study do not meet conventional definitions of efficacy and safety).
11.1.3 Primary Ischemic Endpoint	The primary safety outcome of the present study is the time to first occurrence of confirmed cardiovascular death, non-fatal myocardial infarction, ischemic stroke or ischemia-driven revascularization.	The primary ischemic endpoint of the present study is the time to first occurrence of confirmed all-cause death, non-fatal myocardial infarction, or ischemic stroke.	Modifications to primary ischemic endpoints as per Executive Committee: Modification from cardiovascular death to all-cause death will allow the inclusion of bleeding-related deaths for this outcome, which was felt to be highly relevant given the increased rate of non-cardiac deaths reported in the DAPT trial (recent relevant trial). Revascularization was removed as a primary endpoint as it may be influenced by physician practice and/or

			perception, not necessarily the different medication regimens that are being tested.
11.1.4 Secondary Ischemic Endpoints	"ischemia-driven revascularization"	"clinically-driven revascularization"	This modification was made to conform to the 2007 Academic Research Consortium definitions for revascularization endpoints in clinical trials.
12.1.2	N/A	A secondary analysis for the primary ischemic endpoint will be performed in the ITT cohort.	This was added to assess whether or not findings in the PP cohort are concordant with the ITT cohort.
12.2 Methods of Statistical Analysis and 12.3 Determination of Sample Size	Non-inferiority test at the two-sided 0.05 level; point estimate and two-sided 95% CI for relative risk as measured by the hazard ratio will be calculated based on Cox proportional hazards model. If the upper limit of the 95% CI for the point estimate is less than or equal to 1.22 then the criteria for non-inferiority will be met.	Non-inferiority test at the one-sided 0.025 level; Assuming an event rate of 8.0% in the control group, a sample size of 8200 will yield 80% to exclude a non-inferiority margin of 1.6%. If the upper limit of the 95% CI for the point estimate of the absolute risk difference is less than or equal to 1.6% then the criteria for non-inferiority will be met. This non-inferiority margin translates to a relative risk of 20% assuming the observed event rate equals 8.0% in the control arm.	Modifications to methods of statistical analysis as per Executive Committee: Expression of the NI analysis on an absolute, rather than relative scale, was added in order to provide a more clinically relevant and meaningful margin for this endpoint.
Appendix A – Definitions for Study Endpoints: Section 15.2.3 Stroke	Stroke definition	Stroke definition - UPDATED	Stroke definition and reference updated to 2013 AHA/ASA Expert Consensus Document.

Section	Original Description (Version 3.0)	Revised to (Version 3.1)	Justification
Protocol Synopsis	'Up to 9000 high-risk patients who have undergone successful ***elective or urgent*** PCI with…'	Deleted the words 'elective or urgent'	The words elective or urgent are unnecessary descriptors and are not part of the inclusion/exclusion criteria as indicated in Section 4.1
Section 4.1 Inclusion/Exclusion	Multivessel coronary artery disease	A clarification has been added to the table to indicate that '***the diagnosis of multivessel CAD may be established with the angiogram performed at enrollment or an earlier angiogram***.'	Many patients in this trial will have had prior angiograms that document multivessel disease and therefore this clarification was added.
Section 5.1 Study Conduct	'Enrolled subjects should remain on open-label ticagrelor plus open-label aspirin for the first three months after index PCI followed by open-label ticagrelor plus blinded study drug for 12 months after randomization.'	'Enrolled subjects should remain on ***study-provided*** open-label ticagrelor plus open-label aspirin for the first three months after index PCI followed by ***study-provided*** open-label ticagrelor plus blinded study drug for 12 months after randomization.'	Added explicit clarification that the study is providing enrolled participants their medications from time of enrollment until study end.
Section 5.2 Subject randomization and initiation of investigational product	'Enrolled subjects who do not meet eligibility for randomization will have completed their protocol required activities. ***They will not receive study drug but will be distributed an additional 1-week supply of open-label ticagrelor, if clinically appropriate***.'	'Enrolled subjects who do not meet eligibility for randomization will have completed their protocol required activities ***and therefore will not receive any further study-provided medications. Their treating physician will also be notified that the patient's protocol-mandated study activities have concluded. Further antiplatelet therapy will be at the discretion of the subject's treating physician in accordance with local standard of care***.'	Once a patient is no longer receiving antiplatelet therapy by the study, further medication decisions must be at the discretion of the patient's treating physician. As a result, we have removed references to providing a one-week supply of open-label ticagrelor to study participants who are either ineligible for randomization at the 3-month visit or at end of study.
Section 5.4.2 Methods for	'The investigator should follow the instructions provided in the EDC	'The investigator should follow the instructions provided in the EDC to obtain	Added contact phone number in the rare instance a patient's

unblinding the study	instructions from the randomization system.'	the necessary treatment information ***or call the 24/7 TWILIGHT Medical Monitoring Hotline at 347-541-1376.'***	treatment blind must be broken.
Section 5.5.2 Doses and treatment regimens	'Enteric coated aspirin at a dose of 81 mg daily and matching placebo will be administered daily. Subjects will receive a 3-month supply of open-label ticagrelor and open-label aspirin at the baseline visit and a 6-month supply of blinded study drug and open-label ticagrelor at time of randomization (3-month study visit) and at the 9-month study visit.'	'***Study-provided medications including open-label ticagrelor at a dose of 90 mg twice daily plus open-label EC aspirin at a dose of 81 mg daily will be dispensed to enrolled participants at the time of discharge and should be taken daily until the in-person 3-month study visit. Study-provided medications including open-label ticagrelor at a dose of 90 mg twice daily plus blinded study drug will be dispensed to randomized participants at the 3-month in-person visit and should be taken daily until end of study***. '	We have reworded this section to explicitly clarify which medications and doses study participants will be taking from time of enrollment until randomization and then from randomization until end of study.
Section 5.6 Concomitant and post-study treatments	'Subjects who are taking ticagrelor but do not meet eligibility for randomization at the 3-month in-person visit will be provided open-label ticagrelor for an additional 7 days. In addition, these subjects and their treating physicians will be notified that protocol mandated study activities will conclude at this time and that further antiplatelet therapy will not be provided. Further medical therapy will be prescribed by the subject's physician as per local standard of care.'	REMOVED	Details surrounding treatment of enrolled participants who are not randomized has already been explained in Section 5.2 and is therefore redundant here.
	'Subjects who remain on ticagrelor at the 15-month in-person visit will be provided open-label ticagrelor for an additional 7 days. In addition, these subjects and their treating physicians will be notified that	***'At the End of Study visit physicians caring for the patient will decide which antiplatelet medication the patient should receive as part of his/her ongoing clinical care. This medication(s) will be open label***	Once a study participant reaches end of study, his/her treating physician must dictate ongoing clinical care. As a result, we have removed

	protocol mandated study activities will conclude at this time and that further antiplatelet therapy will not be provided. Further medical therapy will be prescribed by the subject's physician as per local standard of care.'	***and obtained locally.'***	references to providing additional open-label ticagrelor once a patient has reached end of study.
Section 5.8 Discontinuation of investigational product	Discontinuation of investigational product	Discontinuation of investigational product ***or study drug. Section has been updated.***	This section has been expanded to provide guidance on discontinuation of either study medication (blinded study drug or open-label ticagrelor) in instances of temporary interruption or permanent discontinuation.
Section 5.8 Discontinuation of investigational product	'Subjects who remain on ticagrelor at the 15-month in-person visit will be provided open-label ticagrelor for an additional 7 days. In addition, these subjects and their treating physicians will be notified that protocol mandated study activities will conclude at this time and that further antiplatelet therapy will not be provided. Further medical therapy will be prescribed by the subject's physician as per local standard of care. ' In the event that a subject is discontinued from ASA and/or placebo due to repeat coronary intervention, subjects should be considered, where possible, for eligibility to resume study drug. Open-label DAPT	***REMOVED*** ***'Balloon angioplasty or PCI with bare-metal stent: In the event of coronary revascularization with balloon angioplasty alone or PCI with bare metal stent, blinded study drug may be temporarily interrupted***	Details surrounding post-study treatment are included in Section 5.6 and are therefore redundant here. We have modified this section to be clearer with respect to brief interruption of blinded study drug in the event of balloon angioplasty or PCI with

	(ASA + ticagrelor) is recommended for a minimum period of 2 weeks following POBA, 1 month following PCI with BMS, or 3 months following PCI with DES.'	***for 2-4 weeks while patients receive open-label ASA at the discretion of the treating physician in accordance with local practice and standard of care. Blinded study drug may then be restarted at the discretion of the treating physician after completing the mandatory course of open-label ASA.'***	a bare metal stent.
Section 6.2	Table 2 ***Randomized Medications – provide*** medication according to EDC	Table 2 ***Dispense*** medication according to EDC. (An additional 'X' has been added to indicate that medication must be dispensed at discharge)	Medications must be dispensed at time of discharge for enrolled participants and at 3 and 9 months for randomized participants
Section 6.2.1 Enrollment Procedures	N/A	***'Dispense 3- month supply of study medications (open-label ticagrelor and EC aspirin)'*** ***'Instruct patients to return all study-provided medication at next in-person clinic visit'***	These bullet points have been added to be consistent with Table 2 – schedule of data collection.
Section 6.2.2 In-person follow-up at 3 months	N/A	***'Instruct patients to return all study-provided medication at next in-person clinic visit'***	In order to reconcile and assess compliance, patients must return study-provided medication at next visit.
Section 6.2.3 In-person follow-up procedure at 9 and 15 months	N/A	***'Instruct patients to return all study-provided medication at next in-person clinic visit (only pertains to 9-month in-person clinic visit)'***	In order to reconcile and assess compliance, patients must return study-provided medication at next visit.

Section 7.2.1 Definition of suspected unexpected serious adverse reactions (SUSARs)	N/A	***'A SUSAR is a Suspected Unexpected Serious Adverse Reaction. To qualify as a SUSAR, the event must be: Serious; Undesirable reaction to medicinal product; Unexpected - NOT listed as a potential risk or reaction to the product as outlined in the protocol, informed consent document or literature..'***	The prior protocol version did not include a definition or procedure for reporting SUSARs.
Section 7.3.7 Reporting of adverse events	'The ARC Safety Monitor will voluntarily inform the FDA, via a MedWatch/AdEERs form, of any serious adverse events which qualify as SUSARs.'	'The ARC Safety Monitor will voluntarily inform the FDA, via a MedWatch/AdEERs form, ***and EudraVigilance***, of any serious adverse events which qualify as SUSARs.'	As we will include sites in the EU, electronic reporting of SUSARs to EudraVigilance is required according to Directive 2001/20/EC of the European Commission.
Section 9.2 Study timetable and end of study	'Open-label ticagrelor will be provided for an additional 7 days for participants who complete the investigational period and who remain on ticagrelor at this time point (15-month in-person visit). Further medical therapy will be as prescribed by the subject's physician as per local standard of care. Final subject contact (via a phone call) will take place at 18 months and this will end their participation in the study.'	**REMOVED**	Details surrounding handling of study medication at end of study are included in Section 5.6 and are therefore redundant here.
Appendix B Other Definitions	N/A	***'Successful PCI: PCI is considered successful for lesions treated with stent implantation if the residual diameter stenosis based on visual estimation is less than or equal to 10% and the final TIMI flow grade is 3. PCI is considered successful for lesions treated without stent implantation if the residual***	We have added a definition for successful PCI.

		diameter stenosis based on visual estimation is less than or equal to 30% and the final TIMI flow grade is 3.'	

Section	Original Description (Version 3.1)	Revised to (Version 3.1.1)	Justification
Title Page	Version Number 3.1	Version Number 3.1.1	Version number has been updated in order to distinguish between the existing TWILIGHT Study Protocol used for the U.S., Canada, South America, and Europe (v3.1) and the TWILIGHT Study Protocol that will be distributed only to sites in China (v3.1.1).
Title Page	Date 7-AUG-2015	Date 6-JAN-2016	Updated to reflect the date of the TWILIGHT China Protocol changes.
Protocol Synopsis	Study Centers: 'Approximately 100 sites in U.S., Canada, South America, and Europe'	Study Centers: 'Approximately 100 sites in U.S., Canada, South America, Europe, **and China**'	Added China to the list of study center countries.
Section 1.3 Benefit/risk and ethical assessment	'(low-dose ASA [81 mg])'	'(low-dose ASA [81mg **- 100 mg**])'	Changed low-dosage from 81mg to 81mg-100mg, in order to accommodate China, which only uses 100mg ASA tablets (81mg tabs not manufactured in China).
Section 5.5.1 Identity of investigational product	'the investigational product is enteric coated aspirin 81 mg tablets and matching aspirin-placebo tablets.'	'the investigational product is enteric coated aspirin **(81mg- 100mg)** tablets and matching aspirin-placebo tablets.'	Changed low-dosage from 81 to 81mg-100mg, in order to accommodate China, which only uses 100mg ASA tablets (81mg tabs not manufactured in China).
Section 5.5.1	Table 1. Identity of Investigational Product **Dosage form and strength –** Aspirin, EC 81 mg tablet, daily	Table 1. Identity of Investigational Product **Dosage form and strength –** Aspirin, EC **81mg- 100mg** tablet, daily	Changed ASA, EC 'Dosage form and strength' to 81mg-100 mg, in order to accommodate China, which only uses 100mg

			ASA tablets (81mg tabs not manufactured in China).
Section 5.5.2 Doses and treatment regimens	'Study-provided medications including open-label ticagrelor at a dose of 90 mg twice daily plus open-label EC aspirin at a dose of 81 mg daily will be dispensed to enrolled participants at the time of discharge and should be taken daily until the in-person 3-month study visit.'	'Study-provided medications including open-label ticagrelor at a dose of 90 mg twice daily plus open-label EC aspirin at a dose of **81mg-100mg** daily will be dispensed to enrolled participants at the time of discharge and should be taken daily until the in-person 3-month study visit."	Changed open-label EC aspirin dose from 81mg to 81mg-100mg, in order to accommodate China, which only uses 100mg ASA tablets (81mg tabs not manufactured in China).
Section 6.2.1 Enrollment procedures	'After successful PCI with implantation of at least one locally approved drug eluting stent and physician decision to treat subject with low-dose aspirin (81 mg) daily and ticagrelor 90 mg twice daily for 3 months, the investigator or designee will:'	'After successful PCI with implantation of at least one locally approved drug eluting stent and physician decision to treat subject with low-dose aspirin (**81mg-100mg**) daily and ticagrelor 90 mg twice daily for 3 months, the investigator or designee will:'	Changed low-dosage aspirin from 81mg to 81mg-100 mg, in order to accommodate China, which only uses 100mg ASA tablets (81mg tabs not manufactured in China).

Section	Original Description (Version 3.1.1)	Revised to (Version 4.0)	Justification
Title Page	Inserted ClinicalTrials.gov and European regulatory (EudraCT) identifiers	**EudraCT No. 2014-005498-35** **ClinicalTrials.gov ID NCT02270242**	Regulatory trial identifiers required by international competent authorities
Title Page	Version Number 3.1.1	Version Number 4.0	Version number has been updated to reflect necessary protocol changes to meet international regulatory requirements and additional clarifications
Title Page	Date 6-JAN-2016	Date 28-Mar-2016	Updated to reflect the date of the TWILIGHT Protocol changes.
Protocol Synopsis (Randomization)	Major bleeding (BARC Types 3b or 5)	Major bleeding (BARC Types 3b or **greater**)	Substitute the word "greater" for 5 as this is clearer
Protocol Synopsis	Exclusion Criteria: • Contraindication to aspirin • Contraindication to ticagrelor	Exclusion Criteria: • Contraindication to aspirin (**listed in appendix D**) • Contraindication to ticagrelor (**listed in appendix E**)	In response to multiple queries asking for a listing of aspirin and ticagrelor contraindications, we have added Appendices D and E to show these
Protocol Synopsis	Exclusion Criteria: • Active bleeding or extreme-risk for major bleeding (e.g. active peptic ulcer disease, gastrointestinal pathology with a raised risk for bleeding, malignancies with a raised risk for bleeding)	Exclusion Criteria: • Active bleeding or extreme-risk for major bleeding (e.g. **acute gastrointestinal ulcer or history of chronic gastrointestinal ulceration**, gastrointestinal pathology with a raised risk for bleeding, malignancies with a raised risk for bleeding)	Removed the term "active peptic ulcer disease" and replaced with more comprehensive terms acute gastrointestinal ulcer or history of chronic gastrointestinal ulceration as examples of conditions that constitute extreme-risk for major bleeding
Protocol Synopsis	Exclusion Criteria: • Woman of child bearing bearing potential (as determined by hospital standard of care)	Exclusion Criteria: • Woman of child bearing bearing potential (as defined in Section 4.2)	In response to regulatory queries from the UK, Germany and Italy, we have explicitly defined child bearing potential in Section 4.2 using criteria that is aligned across international regulatory

			bodies
Protocol Synopsis	Study Schema Figure	Amended study schema figure to explicitly show that the comparator arms are ticagrelor + ASA vs. ticagrelor + placebo	Figure was amended in order to clarify that the active comparator in this trial is aspirin versus placebo with ticagrelor as background therapy in all participants
Section 1 Introduction	Additional text added	The paradigm for DAPT is shifting to shorter durations, as evidenced by most recent ESC /EACTS Guidelines on myocardial revascularization giving a class Ib recommendation for 6 months of DAPT after DES (4)	Additional text was added to the Introduction in response to German authorities requesting further expansion of the rational of the study and references.
Section 3.1 Overall study design and flow chart	Study Schema Figure	Amended study schema figure to explicitly show that the comparator arms are ticagrelor + ASA vs. ticagrelor + placebo	Figure was amended in order to clarify that the active comparator in this trial is aspirin versus placebo with ticagrelor as background therapy in all participants
Section 4.1 Inclusion Criteria Table	Table footnote: *The diagnosis of multivessel CAD may be established with the angiogram performed at enrollment or an earlier angiogram.	Additional text was added to the Table footnote: **A vessel previously treated with either a stent or bypass graft may also be considered diseased for purposes of meeting the multivessel CAD angiographic inclusion criterion.**	Clarification added as many patients meet the multivessel CAD criterion due to prior treatment with a stent or bypass graft
Section 4.2 Exclusion Criteria	Woman of child bearing potential (as determined by hospital standard of care)	Women of child bearing potential, as defined below: **A woman is considered of childbearing potential (WOBCP) following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.**	Clarification of the definition of woman of child bearing potential was required by multiple international regulatory authorities. This definition is aligned with the FDA and European criteria for child-bearing potential.
Section 5.1 Restrictions during the study	Additional text added	**In addition, ticagrelor should be administered with caution in patients with history of hyperuricemia or gouty arthritis.**	While hyperuricemic conditions are not a contraindication to ticagrelor, the Italian

			authorities requested this statement to be added.
Section 5.8 Discontinuation of investigational product or study drug	Clarifying text added	**However, if deemed necessary and at the discretion of the treating physician, open-label ASA may be substituted for blinded study drug in the peri-operative period. Blinded study drug may then be restarted at the discretion of the treating physician after completing the mandatory course of open-label ASA.**	Conditions may arise when a patient needs a surgical procedure and the physician wants to ensure that antiplatelet therapy is being taken. Since the study drug is blinded, we have added this text to clarify that open-label ASA may be substituted for the blinded drug in the perioperative phase and then blinded study drug should be restarted.
Section 6.2 Data Collection at enrollment and follow-up	Clarifying text added	**A flow chart listing the planned visits and their timing can be found in appendix C).**	We have provided a flow-chart in Appendix C illustrating the different time points for patient visits
Section 6.2.3 In-person follow-up procedure at 9 and 15 months (for randomized subjects)	Dispense study medication for next 6 months	Dispense study medication for next 6 months **for those patients still taking study provided medications at the 9-month in-person visit. Patients who have permanently stopped study-provided medications prior to the 9-month in-person visit will continue to be followed but will not be provided additional study medication.**	Patients who are no longer taking study-provided medications (due to patient/physician discretion, adverse event, other reason) should not receive additional medications from the study. However, all patients will continue to be followed until study termination.
Section 7.3.1 Time period for collection of adverse events	All AEs related to bleeding and SAEs related to bleeding, death or cardiac events should be collected from the time the subject signs the informed consent through study exit.	All AEs related to bleeding and SAEs should be collected from the time the subject signs the informed consent through study exit.	We removed the qualifiers for SAE collection (bleeding, death, cardiac events) as this contradicts Section 7.3.7 and is not in line with international regulatory requirements.

Section 7.3.7 Reporting of adverse events	SAEs must be reported to the sponsor within 3 business days of the study site research personnel's knowledge of the event via the EDC.	SAEs must be reported to the sponsor **immediately, but no later than 24 hours**, of the study site research personnel's knowledge of the event via the EDC.	SAE reporting by investigators within 24 hours is mandatory for international regulatory requirements.
Section 7.3.7 Reporting of adverse events	The ARC Safety Monitor will review all submitted SAEs for qualification as a Suspected Unexpected Serious Adverse Reactions (SUSARs). The ARC will further report SAEs determined to qualify as SUSARs to the local regulatory body (IRB/EC). <u>The ARC will report SUSARs that are classified as fatal or life threatening to the regulatory authorities as soon as possible but no later than 7 calendar days after first knowledge that a case qualifies. All other SUSARs will be reported as soon as possible but no later than 15 calendar days after first knowledge by the sponsor that a case qualifies</u>	The ARC Safety Monitor will review all submitted SAEs for qualification as a Suspected Unexpected Serious Adverse Reactions (SUSARs). The ARC will further report SAEs determined to qualify as SUSARs to the local regulatory body (IRB/EC).	The underlined text in the original version was removed as this is redundant with the next paragraph in this section.

Section 7.3.7 Reporting of adverse events	The ARC Safety Monitor will voluntarily inform the FDA, via a MedWatch/AdEERs form, and EudraVigilance, of any serious adverse events which qualify as SUSARs.	The ARC Safety Monitor will voluntarily inform the FDA, via a MedWatch/AdEERs form, and EudraVigilance, of any serious adverse events which qualify as SUSARs **in accordance with reporting requirements.**	We will notify the relevant regulatory bodies of SUSARs in accordance with reporting requirements, which might vary by country, region and event type.
Appendix C	Inserted new Appendix for Timeline of in-person Visits and phone calls	Flow-chart added	Figure added to illustrate the timing of visits and relevant procedures at each visit.
Appendix D Contraindication to Aspirin	Appendix D added	CONTRAINDICATIONS TO ASPIRIN Hypersensitivity to ASA, salicylates, non-steroidal anti-inflammatory drugs (NSAIDs), analgesics, antipyretics or other ingredients in the product, excipients or component of the container. Acute gastrointestinal ulcer, history of gastrointestinal ulcers Hemorrhagic diathesis and severe active bleeding Active or severe hepatic failure, renal failure requiring dialysis, or acute congestiv heart failure Patients with a history of asthma induced b a similar action, notably NSAIDs Combination with methotrexate at doses of 15 mg/week or more Last trimester of pregnancy and nursing women Glucose-6-phosphate dehydrogenase (G6PD deficiency	Appendix D added to provide a list of aspirin contraindications
Appendix E Contraindications to Ticagrelor	Appendix E added	CONTRAINDICATIONS TO TICAGRELOR: Hypersensitivity to the active substance or to any of the excipients Active pathological bleeding History of intracranial hemorrhage Moderate to severe hepatic impairment Co-administration of ticagrelor with strong CYP3A4 inhibitors (e.g., ketoconazole,	Appendix E added to provide a list of ticagrelor contraindications.

		clarithromycin, nefazodone, ritonavir, and atazanavir) is contraindicated, as co-administration may lead to a substantial increase in exposure to ticagrelor		

Statistical Analysis Plan

TRIAL FULL TITLE	Ticagrelor With Aspirin or Alone In High-Risk Patients After Coronary Intervention
CLINICAL TRIALS.GOV	NCT02270242
EUDRACT NUMBER	ISSBRIL0345
SAP VERSION	1.0
SAP VERSION DATE	4/11/2019
TRIAL STATISTICIAN*	Timothy Collier
TRIAL Principal Investigator	Roxana Mehran
SAP AUTHOR	Usman Baber
Analytic details documented herein supersede those in the TWILIGHT protocol, version 4.1 *All statistical analyses are performed independently by the London School of Hygiene and Tropical Medicine	

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1 Abbreviations and Definitions

AE	Adverse Event
BARC	Bleeding Academic Research Consortium
CRF	Case Report Form
DAPT	Dual Antiplatelet Therapy
ITT	Intent To Treat
PCI	Percutaneous Coronary Intervention
PP	Per Protocol
SAP	Statistical Analysis Plan

2 Introduction

2.1 Preface

Pharmacologic platelet inhibition with aspirin and a $P2Y_{12}$ inhibitor is a requirement in all patients undergoing percutaneous coronary intervention (PCI) with stenting. Such dual antiplatelet therapy (DAPT) is recommended by international guidelines, with duration varying according to clinical presentation (i.e. acute coronary syndrome) or type of stent implanted during PCI (bare metal vs. drug eluting) (1-3).

While clopidogrel is the most widely used $P2Y_{12}$ inhibitor, its efficacy is hampered by substantial variability in platelet inhibition that may be attributable to clinical, genetic and procedural parameters (4-7). Moreover, although the novel thienopyridine prasugrel has a more potent and consistent effect on platelet inhibition (8,9), bleeding risk is significantly higher compared to clopidogrel in acute coronary syndrome (ACS) patients following PCI (10). In contrast, ticagrelor, an oral, reversible, direct-acting inhibitor of the adenosine diphosphate P2Y12 receptor (11) has proven faster, greater and more consistent P2Y12 inhibition than either clopidogrel or prasugrel (12-14). In the landmark Study of Platelet Inhibition and Patient Outcomes (PLATO) trial, ticagrelor significantly reduced death from vascular causes, myocardial infarction, or stroke, without significantly increasing overall major bleeding in patients presenting with acute coronary syndromes(15).

Along with the advent of more potent antiplatelet pharmacotherapy, stent technology has also advanced in a concordant fashion with the introduction of safer and less thrombogenic platforms. These devices, compared to their older-generation counterparts, yield significant reductions in thrombotic events that are durable over the long term (16). As a consequence, classical paradigms favoring a minimum of DAPT duration of 1 year, particularly in elective patients, are being challenged as PCI safety continues to evolve and improve. Randomized comparisons of different DAPT durations such as the OPTIMIZE and the PRODIGY trials suggest no increased risk for thrombotic events after only 3-6 months of DAPT in PCI patients treated primarily with novel generation devices (17,18).

2.2 Research hypothesis

The overall hypothesis of the current study is that three months post-PCI of dual antiplatelet therapy with aspirin and ticagrelor, continued monotherapy with ticagrelor alone versus ticagrelor plus aspirin for an additional year will be superior with respect to bleeding and non-inferior with respect to ischemic events in high-risk patients undergoing PCI.

This hypothesis will be tested in the following two specific aims:

Aim 1: To determine the impact of ticagrelor alone versus ticagrelor plus aspirin in reducing clinically relevant bleeding among high-risk patients who had PCI.	**Hypothesis 1:** A DAPT strategy of ticagrelor + ASA for 3 months followed by ticagrelor alone for an additional 12 months will be superior to ticagrelor plus aspirin with respect to clinically relevant bleeding (BARC 2, 3 or 5) in high-risk patients undergoing PCI.
Aim 2: To determine the impact of ticagrelor alone versus ticagrelor plus aspirin in reducing ischemic adverse events at one year among high-risk patients undergoing PCI	**Hypothesis 2:** A DAPT strategy of ticagrelor + ASA for 3 months followed by ticagrelor alone for an additional 12 months will be non-inferior to ticagrelor plus aspirin with respect to ischemic adverse events (all-cause death, non-fatal MI or stroke) at 1 year in high-risk patients undergoing PCI.

2.3 Rationale for conducting this study

Despite the trend and rationale for shorter DAPT durations following PCI, certain high-risk patients may derive additional benefit from potent and sustained platelet inhibition extending beyond 3 months after PCI. Defined by clinical and/or anatomic criteria, a short course of DAPT in such patients may provide sufficient protection against early stent-related thrombotic events while ongoing platelet inhibition may yield further reductions in systemic atherothrombosis. Among patients with diabetes mellitus (DM) undergoing PCI, for example, Brar et al. previously demonstrated that the benefits of DAPT compared to antiplatelet monotherapy persisted irrespective of BMS or DES use, suggesting a systemic rather than stent-related effect (19). Analogously, among patients with DM enrolled in the EXCELLENT trial a prolonged DAPT strategy was associated with a reduction in adverse events compared with ASA alone (20). Findings from Dangas et al., which demonstrate a link between atherosclerosis and increased platelet reactivity, provide a biological basis for potent platelet inhibition in high-risk patients characterized by diffuse vascular disease (21). These observations are clinically relevant as many patients undergoing elective or urgent PCI exhibit high-risk features, such as renal dysfunction, DM, peripheral arterial disease, that are associated with systemic atherosclerosis. Given the clear benefits of ticagrelor in the setting of high-risk ACS, it is plausible that ticagrelor alone will provide sufficient platelet inhibition to reduce thrombotic events compared to ticagrelor plus ASA among high-risk patients who have completed a requisite short course of DAPT.

Reduction in bleeding with ticagrelor alone while preserving the anti-ischemic benefit associated with DAPT use would favor such a strategy in high-risk patients undergoing PCI.

Accordingly, the proposed study will examine the comparative safety and efficacy of a strategy of 3 months DAPT with ASA and ticagrelor followed by monotherapy using a potent agent (ticagrelor) compared with continued ASA and ticagrelor among high-risk patients undergoing PCI with DES. Our primary hypothesis is that, among such patients, use of ticagrelor alone will yield a significant reduction in clinically relevant bleeding while preserving anti-ischemic benefit compared with ticagrelor and ASA.

2.4 Benefit/risk and ethical assessment

The potential benefits that subjects might realize by participating in this randomized trial is a reduction in clinically relevant bleeding for those who are randomly allocated to the placebo arm. Other benefits applicable to all subjects include close monitoring and surveillance for clinical events that will be performed by study personnel during the course of the trial.

The potential risks for subjects include an increased rate of thrombotic events for those who are randomized to the placebo arm and increased risk for bleeding in subjects randomized to the active treatment arm (low-dose ASA [81 – 100 mg]).

An independent data safety monitoring board will provide external oversight to ensure safety of all trial participants. In addition, subjects will be followed closely with periodic study contacts. Also, clinical equipoise exists for conducting a trial with this type of randomized comparison.

3 Study Objectives and Endpoints

3.1 Primary Objective

The primary objective of this study is to determine the impact of antiplatelet monotherapy with ticagrelor alone versus DAPT with ticagrelor plus aspirin for 12 months in reducing clinically relevant bleeding (BARC 2, 3 or 5) among high-risk patients who have undergone successful PCI and who have completed a 3-month course of DAPT with aspirin plus ticagrelor.

3.2 Secondary Objective

The secondary objective of this study is to determine the impact of antiplatelet monotherapy with ticagrelor alone versus DAPT with ticagrelor plus aspirin for 12 months on major ischemic adverse events (all-cause death, non-fatal MI or stroke) among high-risk patients who have undergone successful PCI and who have completed a 3-month course of DAPT with aspirin plus ticagrelor.

3.3 Exploratory Objectives

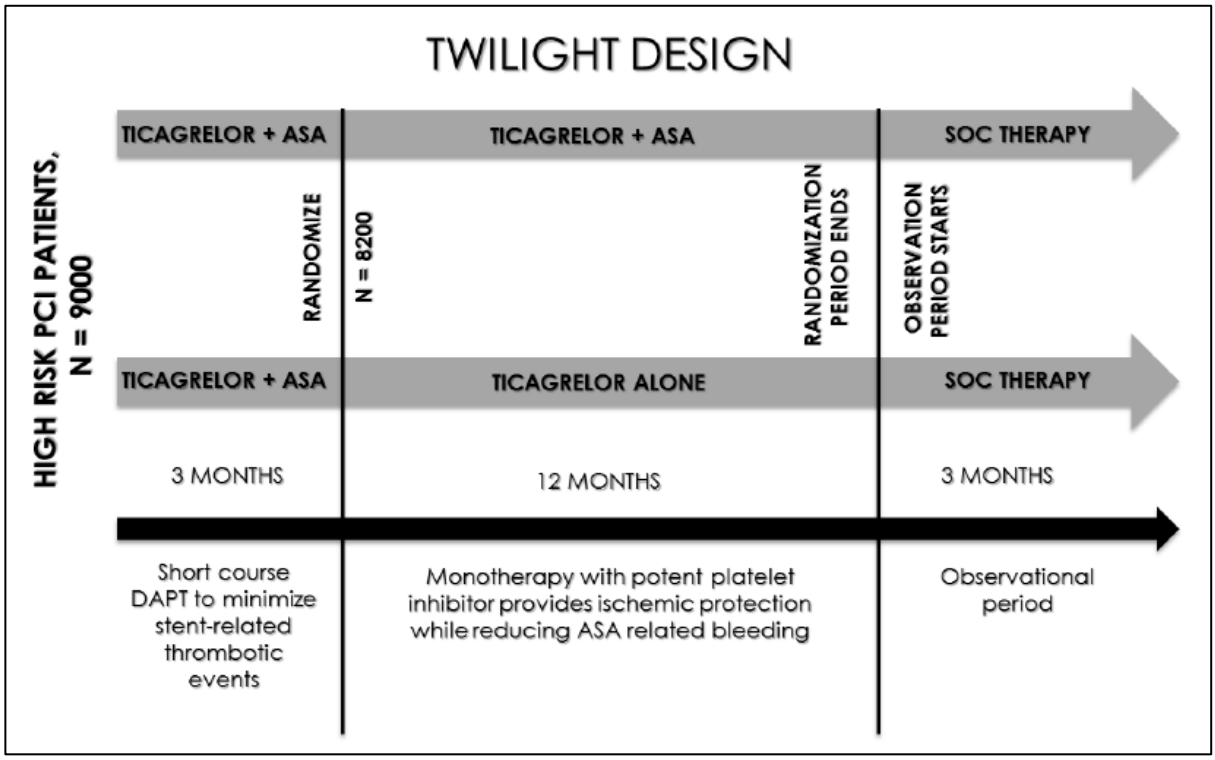
Exploratory objectives include assessing the comparative safety and efficacy of the different DAPT regimens for individual components of the primary and secondary objectives.

4 Study Methods

4.1 Overall study design and flow chart

A randomized, double-blind study design was chosen as the most rigorous experimental approach to formally test the study hypotheses for the efficacy and safety of different DAPT regimens in high-risk patients undergoing PCI. Open label aspirin and ticagrelor per physician discretion will be given for the first 3 months after PCI. After 3 months, event-free subjects will be randomized to placebo versus enteric coated ASA for an additional 12 months. Open-label ticagrelor at a dose of 90 mg twice daily will be continued in all randomized subjects.

Figure 1 TWILIGHT Trial Design



4.2 Inclusion/Exclusion criteria

High-risk patients who have undergone successful PCI with at least one locally approved drug eluting stent AND discharged on DAPT with aspirin and ticagrelor of at least 3 months intended duration will be eligible for the TWILIGHT study.

Enrollment into the study will require meeting at least one clinical inclusion AND at least one angiographic inclusion AND none of the exclusion criteria. A subject is considered enrolled if all these criteria are met and upon provision of informed consent.

Must meet AT LEAST ONE clinical inclusion criterion	**Must meet AT LEAST ONE angiographic inclusion criterion**
Adult patients ≥ 65 years of age Female gender Troponin positive acute coronary syndrome Established vascular disease defined as previous MI, documented PAD or CAD/PAD revascularization Diabetes mellitus treated with medications or insulin Chronic kidney disease defined as an estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73m^2 or creatinine clearance (CrCl) < 60 ml/min	Multivessel coronary artery disease (CAD) (see Section 16) Target lesion requiring total stent length >30 mm Thrombotic target lesion(s) Bifurcation lesion(s) with Medina X,1,1 classification requiring at least 2 stents (see Section 16) Left main (≥50%) or proximal LAD (≥70%) lesion Calcified target lesion(s) requiring atherectomy

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

- Under 18 years of age
- Contraindication to aspirin
- Contraindication to Ticagrelor
- Planned surgery within 90 days
- Planned coronary revascularization (surgical or percutaneous) within 90 days
- Need for chronic oral anticoagulation
- Prior stroke
- Dialysis-dependent renal failure
- Active bleeding or extreme-risk for major bleeding (e.g. active peptic ulcer disease, gastrointestinal pathology with a raised risk for bleeding, malignancies with a raised risk for bleeding)
- Salvage PCI or STEMI presentation.
- Liver cirrhosis
- Life expectancy < 1 year
- Unable or unwilling to provide informed consent
- Women of child bearing potential (as determined by hospital standard of care)
- Fibrinolytic therapy within 24 hours of index PCI
- Concomitant therapy with a strong cytochrome P-450 3A inhibitor or inducer
- Platelet count < 100,000 mm^3
- Requiring ongoing treatment with aspirin ≥ 325 mg daily

4.3 Subject randomization and initiation of investigational product

The eligibility for randomization for all enrolled subjects will be evaluated at the in-person 3-month study visit. Subjects with any of the following will not be randomized:

- Refusal of randomization by subject or treating physician
- Withdrawal of consent
- Lost to follow-up
- Death
- Major bleeding (BARC Types 3b or 5)
- Occurrence of an ischemic event after PCI such as myocardial infarction, definite or probable stent thrombosis, ischemic stroke, coronary revascularization with drug-eluting stent
- No longer taking DAPT with aspirin and ticagrelor
- Non physician-guided cessation of aspirin or ticagrelor of 5 days or greater.
- Women of child bearing potential (as determined by hospital standard of care)
- Renal failure requiring dialysis
- Current indication for oral anticoagulation or high dose aspirin

Randomization will be performed within the EDC system among subjects eligible for randomization. The EDC will allocate the treatment group assignment for the subject and provide study site research personnel the appropriate bottle ID number(s).

Upon randomization at the conclusion of the in-person 3-month visit, the study site research personnel will provide a 6-month supply of blinded investigational product (aspirin or matching placebo) and open-label ticagrelor.

Enrolled subjects who do not meet eligibility for randomization will have completed their protocol required activities. They will not receive study drug but will be distributed an

additional 1-week supply of open-label ticagrelor, if clinically appropriate. Vital status of these subjects will be determined at the 18-month time point.

Enrolled subjects who do not meet eligibility for randomization prior to the in-person 3-month visit will not be required to complete the 3-month in-person visit.

4.4 Blinding and procedures for unblinding the study

4.4.1 Methods for ensuring blinding

This study has a double-blind design with aspirin and matching placebo. The subjects, study site research personnel, academic research center staff, and treating physicians involved in the treatment and/or clinical evaluation of the subjects will not be aware of treatments received. There will be an independent data safety monitoring board (DSMB) to monitor the data on a periodic basis. An independent statistician, not otherwise involved in the study, will prepare and provide the required reports to the DSMB as per the DSMB charter.

4.4.2 Methods for unblinding the study

In the event of a medical emergency, in which knowledge of the investigational drug is critical to the subject's medical management, the blind for that subject may be broken by the treating physician. The investigator should follow the instructions provided in the EDC instructions to obtain the necessary treatment information from the randomization system. As the active study drug in this trial is low-dose aspirin, in most instances the subject may be properly managed without the need for unblinding.

4.5 Treatments

4.5.1 Identity of Investigational Product

The investigational product is enteric coated aspirin 81 - 100 mg tablets and matching aspirin-placebo tablets.

Table 1 Identify of Investigation Product

Investigational product	Dosage form and strength
Aspirin, EC	81-100 mg tablet, daily
Placebo for aspirin	tablet daily

4.5.2 Doses and treatment regimens

Enteric coated aspirin at a dose of 81-100 mg daily and matching placebo will be administered daily. Subjects will receive a 3-month supply of open-label ticagrelor and open-label aspirin at the baseline visit and a 6-month supply of blinded study drug and open-label ticagrelor at randomization (3-month study visit) and at the 9-month study visit.

4.5.3 Additional study drug

Open-label ticagrelor will be administered to all subjects regardless of randomization assignment.

4.6 Study Variables

Data collection commences after the subject has provided informed consent and has been enrolled in the study. Data collection, including subject demographic information, laboratory tests, and procedural data as well as follow-up visits or telephone contacts will be conducted

by an Investigator or site coordinator who has been trained on the protocol and electronic Case Report Forms (eCRFs).

Data required for analysis will be obtained as outlined in Table 2. After discharge from the hospital, each enrolled subject will be followed with a phone call at 1 month post enrollment and an in-clinic visit at 3 months post enrollment. Enrolled subjects who do not meet eligibility for randomization prior to the in-person 3-month visit will not be required to complete the 3-month in-person visit. Subjects who are randomized at 3 months post enrollment will be followed with a phone call at 4 months post enrollment and will return for additional in-clinic visits at 9 and 15 months post enrollment. A final follow-up phone call will be performed at 18 months post enrollment for randomized subjects. No further follow-up contact will be performed for subjects who did not meet eligibility for randomization at the 3 month visit; however, vital status may be obtained from medical or public records at 18 months post enrollment.

Table 2 Schedule of Data Collection

Type of Data to be Collected	Enrollment	Post-Procedure or Discharge	1 Month (30d) (±7 days) Phone Call	3 Month (90d) (±14 days) Office Visit	4 Month (120d) (±7 days) Phone Call randomized	9 Month (270d) (± 30 days) Office Visit randomized	15 Month (450d) (± 30 days) Office Visit randomized	18 Month (540d) (± 14 days) Phone Call randomized
Eligibility Criteria	X			X				
Patient Informed Consent	X							
Physical Assessment	X							
Medical History/Risk Factors	X							
Cardiac Status	X							
Medications/ Antiplatelets	X							
Clinical Tests* Lab tests, ECG	X			X		X	X	
Procedure Information	X							
DAPT Medication Status		X	X		X			X
Angina Status				X	X	X	X	X
Randomization– if eligible				X				

Type of Data to be Collected	Enrollment	Post-Procedure or Discharge	1 Month (30d) (±7 days) Phone Call	3 Month (90d) (±14 days) Office Visit	4 Month (120d) (±7 days) Phone Call randomized	9 Month (270d) (± 30 days) Office Visit randomized	15 Month (450d) (± 30 days) Office Visit randomized	18 Month (540d) (± 14 days) Phone Call randomized
Randomized Medications –provide medication according to EDC				X		X		
Randomized Medications – reconciliation of provided medication						X	X	
Randomized Medications – subject self-reporting of compliance to medications				X	X	X	X	X
Adverse Events / Serious Adverse Events	X	X	X	X	X	X	X	X

*If performed, as per standard of care. Subject may be asked to provide an additional blood sample (10cc) for lipid profile testing if not already performed per standard of care.

4.6.1 Study timetable and end of study

Trial enrolment in TWILIGHT began in July 2015 with the last patient enrolled on December 31, 2017. The last patient follow-up visit will occur in June 2019.

5 Endpoints

5.1 Primary Endpoint (Bleeding)

The primary endpoint of TWILIGHT is the time to first occurrence of BARC 2, 3 or 5 bleeding. All events occurring between the time of randomization and one year thereafter (365 days after randomization) will be included in the analysis for the primary endpoint.

5.2 Key Secondary Endpoint (Ischemic)

The key secondary endpoint is the time to first occurrence of all-cause death, non-fatal MI or stroke. All events occurring between the time of randomization and one year thereafter (365 days after randomization) will be included in the analysis for the key secondary endpoint.

5.3 Other Secondary Endpoints

- *Bleeding*

  - BARC Types 3 or 5
  - Thrombolysis in Myocardial Infarction (TIMI) minor or major bleeding
  - GUSTO moderate or severe or life-threatening bleeding
  - International Society of Thrombosis or Haemostasis (ISTH) major bleeding
- *Ischemic*
  - Cardiovascular death, non-fatal MI, ischemic stroke or clinically-driven revascularization
  - Cardiovascular death, non-fatal MI or ischemic stroke
  - Definite or probable stent thrombosis
  - Cardiovascular death
  - Non-fatal MI
  - Cardiovascular death, non-fatal MI or def/prob stent thrombosis
  - Ischemic stroke
  - All-cause death

6 Sample Size

Power calculations are based on a superiority comparison for the primary endpoint of BARC types 2, 3 or 5 bleeding at 1 year from randomization. We assume a cumulative bleeding rate of 4.5% between time of randomization and 1 year. As shown in **Table 3**, this is a somewhat conservative estimate as subjects sustaining a major hemorrhagic event in the first 3 months after PCI will not be randomized. Assuming a 2% loss to follow-up and non-compliance / cross-over rate of 4%, the current trial will require 8200 subjects to detect a relative reduction in bleeding of 28% with ticagrelor monotherapy with 80% power and a Type I error of 0.05. It is anticipated that approximately 8% - 10% of enrolled subjects will not be eligible for randomization and therefore 9000 subjects will be enrolled. Additional sample size estimates are provided in **Table 4** assuming different control bleeding rates and risk reductions (22,23).

References for the sample size estimates include Lakatos 1988, Biometrics volume 44 pages 229-241; and Lakatos 2002, Statistics in Medicine, Volume 21 pages 1969-1989.

Assuming a one-year rate for the key secondary endpoint of all-cause death, non-fatal MI or ischemic stroke of 8%, the current study will have 80% power to exclude a non-inferiority margin of 1.6% (upper limit of 95% CI for absolute risk difference in the one year event rate).

Table 3 Event rate and Effect Size Assumptions for Primary Endpoint Sample Size Calculations

Basis for Proposed Bleeding Event Rates in TWILIGHT Power Calculations			
Study	**Study Type**	**Time Point**	**BARC ≥ 2 Rate**
DAPT	RCT	18 months	**~ 4.2%**
PARIS (unpublished data)			
Age > 65	Registry	1 year	8.6%
Diabetes Mellitus (on insulin) Diabetes Mellitus (orals)	Registry	1 year	8.3% 6.3%
Renal disease	Registry	1 year	13.2%

Vranckx et al., EHJ 2013 (24)	Post-hoc (TRACER)	500 days	14%
ADAPT-DES			
CrCl < 60 cc/min (Baber et al, TCT 2013)	Registry	1 year	10.0%
Rao et al., JACC Int 2013 (25)	NCDR CathPCI	In-hospital (women)	8.5%
Basis for Proposed Effect Size in TWILIGHT Power Calculations			
Study	**Study Type**	**Comparators**	**Relative Bleeding Increase**
Baigent et al., Lancet 2009 (26)	Pooled Data from Randomized trials	ASA vs. placebo/control	50% (1° prevention) 170% (2° prevention)
WOEST, Lancet 2013 (27)	RCT	ASA vs. placebo	~ 60%
CAPRIE, Lancet 1996 (28)	RCT	ASA vs. clopidogrel	~35% (GI hemorrhage)
Physician Health Study, NEJM 1989 (29)	RCT	ASA vs. Placebo	~35%
De Berardis et al., JAMA 2012 (30)	Cohort study	ASA vs. No ASA	55%
Seshasai et al., Archives Int Med 2012 (31)	Meta-analysis of 9 RCTs	ASA vs. Placebo	~31%
HOT Trial, Lancet 1998 (32)	RCT	ASA vs. Placebo	~ 80%

Table 4 Alternative Sample Size Estimates for Primary Endpoint

Control Bleeding Rate	Relative Risk Reduction	Total Randomized Sample Size	Total Sample Size (Enrolled + Randomized) with 8% loss after enrollment*	Total Sample Size (Enrolled + Randomized) with 10% loss after enrollment*
5%	30%	6400	7000	7111
5%	28%	7400	8040	8222
5%	26%	8030	9800	10000
4.5%	30%	7090	7706	7900
4.5%	28%	8200	8913	9111
4.5%	26%	9700	10500	10800
4.0%	30%	8000	8700	8888
4.0%	28%	9300	10100	10333
4.0%	26%	10900	11800	12111

7 Study Cohorts

Enrolled: The enrolled cohort consists of all subjects who signed informed consent.

Randomized intention to treat (ITT): The randomized ITT cohort will consist of all subjects who have been randomized (i.e. when the subject number and allocated treatment are recorded in the EDC). Subjects will be analyzed in the treatment group assigned by the EDC, irrespective of subsequent follow-up or medication adherence.

Randomized per protocol (PP): The randomized PP cohort consists of all randomized subjects without any major deviations from the protocol. The following deviations in randomized subjects will lead to exclusion from the PP population

- Not fulfilling inclusion or meeting exclusion criteria at the time of enrollment

- Not fulfilling randomization eligibility criteria at the time of randomization
- Not receiving the assigned treatment at the time of randomization

All analyses for the primary and key secondary endpoints will be performed in the ITT and PP cohorts. The primary analyses will be performed in the ITT population and then repeated in the PP population to support the primary results.

8 Subgroups

Baseline clinical and demographic characteristics that will define subgroups of interest for the primary and key secondary endpoints are listed below:

- Age (< 65, >= 65 years)
- Race/Ethnicity (non-Hispanic White; non-Hispanic Black; Asian; Other)
- Sex (Male, Female)
- Geographic Region (North America; Europe/Israel; Asia)
    - North America includes Canada and the United States
    - Europe/Israel includes UK, Italy, Spain, Austria, Germany, Poland and Israel
    - Asia includes India and China
- Diabetes Mellitus (yes, no)
- Chronic Kidney Disease (yes, no)
    - Chronic kidney disease is defined as an estimated glomerular filtration rate < 60 ml/1.73m^2 per the CKD-EPI formula
- PCI indication (ACS [Unstable angina or NSTEMI] vs. stable)
- Total stent length implanted (< 30 mm, >=30 mm)
- BMI (above or equal to median, below median)
- History of Prior MI (yes, no)
- High Bleeding Risk (Presence or absence)
    - High bleeding risk is defined as the presence of at least one of the following parameters: age >= 75 years; CKD; anemia (haemoglobin < 10 in women or haemoglobin < 11 in men); prior history of bleeding
- High lesion/procedural risk (Presence or absence)
    - High risk lesion or procedure is defined as the presence of at least one of the following parameters: total stent length >= 60 mm; at least 3 lesions treated; vein graft PCI; complex bifurcation (Medina X, 1, 1) requiring 2 stents; severe calcification requiring atherectomy or chronic total occlusion
- Stent type (durable-polymer everolimus-eluting stent; durable-polymer zotarolimus-eluting stent; biodegradable-polymer DES; other)

9 Lost to Follow-up and Missing Data

In keeping with an intent-to-treat philosophy, the primary analyses are performed on all randomized subjects. Those subjects who withdraw, are lost to follow-up or have missing data will be included in the primary ITT analysis.

We anticipate that the amount of missing data will be minimal in the present study as we are specifically asking sites to ensure that the data elements are complete. Missing outcome data will not be imputed.

10 Statistical Methods

Statistical analyses will be performed using SAS version 9.0 or greater and Stata versions 12.0 or greater. Unless otherwise stated, all hypothesis tests will be performed using two-sided tests at the 5% significance level. Continuous variables will be summarized using descriptive statistics including means and standard deviations if normally distributed or median with interquartile ranges for skewed distributions. Discrete variables will be summarized using absolute and relative frequencies.

Baseline clinical, demographic, laboratory and procedural characteristics will be summarized by randomized treatment group and for all randomized subjects combined. Continuous variables will be compared between randomized groups using the Student's t-test or non-parametric Mann-Whitney test for normally and skewed distributions, respectively. Categorical variables will be compared using the chi-square or Fisher's exact test, as appropriate.

10.1 Analysis for the Primary Endpoint (BARC 2, 3 or 5 Bleeding)

The primary objective of TWILIGHT is to determine the impact of ticagrelor monotherapy versus ticagrelor plus aspirin on the endpoint of BARC Types 2, 3 or 5 bleeding that occurs between the time of randomization and one year thereafter. Event rates will be estimated at one year (12 months after randomization) and Kaplan-Meier curves will be plotted from the time of randomization to the first occurrence of confirmed BARC Type 2, 3 or 5 bleeding by treatment group. Patients not experiencing a primary endpoint event during this time interval will be censored at the time of death, last contact date (for subjects withdrawing consent of lost to follow-up) or 365 days after randomization, whichever comes first.

A hazard ratio (HR) and two-sided 95% CI for the primary endpoint will be generated using the Cox proportional hazards model that includes treatment group (ticagrelor monotherapy versus ticagrelor plus ASA) as a covariate. The null hypothesis for this analysis is that the HR for the treatment group (H_0) = 1. The alternative hypothesis is that the HR for the treatment group (H_A) ≠ 1. A test of superiority at the two-sided 0.05 level will be performed and the null hypothesis will be rejected if the HR and 95% CI excludes one. This analysis will be performed in the ITT cohort and repeated in the PP cohort to support the primary results.

10.2 Analysis for the Key Secondary Endpoint (All-Cause Death, Non-fatal MI or Stroke)

The secondary objective of TWILIGHT is to determine the impact of ticagrelor monotherapy versus ticagrelor plus aspirin on the endpoint of all-cause death, non-fatal myocardial infarction, or stroke that occurs between the time of randomization and one year thereafter. Event rates will be estimated at one year (12 months after randomization) and Kaplan-Meier curves will be plotted from the time of randomization to the first occurrence of confirmed all-cause death, non-fatal myocardial infarction or stroke by treatment group. Patients not experiencing a key secondary endpoint event during this time interval will be censored at the time of last contact (for subjects withdrawing consent or lost to follow-up) or 365 days after randomization, whichever comes first.

The point estimate and two-sided 95% CI for the absolute risk difference in the one-year rate of the key secondary endpoint between randomized groups will be calculated. The null hypothesis for this analysis is that the one-year rate of all-cause death, non-fatal MI or stroke

is at least 1.6% higher in the experimental (ticagrelor monotherapy) versus control (ticagrelor plus ASA) group. The alternative hypothesis for this analysis is that absolute risk difference at one year is less than 1.6%. These are expressed below:

$$H_o\text{: (One-year ischemic event rate)}_{exp} - \text{(One-year ischemic event rate)}_{control} \geq 1.6\%$$

$$H_a\text{: (One-year ischemic event rate)}_{exp} - \text{(One-year ischemic event rate)}_{control} < 1.6\%$$

A one-sided non-inferiority test with a type I error of 0.025 will be performed as described by Com Nougue et al. (Statistics in Medicine, 1993) (33). The test is performed at a point in time T, using the Kaplan-Meier estimates for freedom from the endpoint being evaluated, and the Greenwood standard errors for these estimates. The null hypothesis will be rejected if the upper limit of the 95% CI for the absolute risk difference in 12-month event rates is less than 1.6%. This analysis will be performed in the ITT cohort and repeated in the PP cohort to support the primary results.

10.3 Subgroup Analyses

One-year (12 months after randomization) event rates for the primary and key secondary endpoints will be calculated in all subgroups described in section 8.0. Event-free patients will be censored for each outcome as described in sections **10.1** and **10.2**, respectively. Stratum-specific HRs and corresponding two-sided 95% CI will be calculated within each subgroup using a Cox proportional hazards model with treatment group as a covariate. Formal interaction testing will be performed using the subgroup X treatment allocation as an additional term in the Cox model.

10.4 Additional Analyses

10.4.1 18-Month Analyses

The TWILIGHT study design includes a 3-month observational period between 15 and 18 months after enrollment. At the 15-month study visit (one-year after randomization) protocol-guided medications (ticagrelor and blinded study drug) are discontinued and the study subject is switched to standard of care therapy. In order to examine the impact of therapy discontinuation on both primary and key secondary endpoints, additional analyses will be performed that include all events cumulatively up to 15 months after randomization and only those occurring between 12 and 15 months post-randomization using a landmark approach.

For the primary endpoint 15-month event rates will be estimated using the Kaplan-Meier method with event-free patients censored at the time of death, last contact date (for subjects withdrawing consent of lost to follow-up) or 455 days after randomization, whichever comes first. For the key secondary endpoint 15-month event rates will be estimated using the Kaplan-Meier method and event-free patients will be censored at the time of last contact (for subjects withdrawing consent or lost to follow-up) or 455 days after randomization, whichever comes first. HR and 95% CI will be generated for each endpoint to estimate the cumulative treatment effect using the Cox proportional hazards model. Analogous analyses will be performed in the landmark interval defined by 12 to 15 months after randomization. Event-free patients surviving to 12 months after randomization will be considered at risk and included in the landmark analysis. These analyses will be performed in the randomized ITT and PP cohorts.

10.4.2 Mortality Assessment

In randomized subjects lost to follow-up or withdrawing consent, vital status assessments are performed using publicly available registries, medical records or other resources. Site personnel will record the subject's vital status (alive or dead) and the date of vital status search in the EDC. Hence, vital status will be available in a portion of randomized subjects declared lost or following consent withdrawal. Accordingly, for the analysis of all-cause death alone these participants will be censored at the time of vital status search, rather than at last known contact, assuming the subject is alive at the time of vital status assessment. In contrast, for analyses involving non-fatal outcomes or composite events that include all-cause death as a component, event-free subjects will still be censored as described in sections **10.1** and **10.2**, irrespective of final vital status.

10.4.3 Enrolled Cohort

Upon enrollment, all TWILIGHT participants are followed for at least 90 days, at which time point each subject is either randomized or deemed ineligible for randomization. While enrolled and non-randomized patients are no longer followed during the study period a vital status assessment is performed in these subjects at the 18-month time point.

Baseline characteristics will be summarized for the overall enrolled cohort and in relation to 90 day status (randomized versus non-randomized). Analogously, the 90-day frequency of medication cessation and adverse events will be tabulated for the overall enrolled population and compared between those ultimately randomized versus ineligible. Mortality at 18-months will also be calculated and compared between enrolled/non-randomized versus enrolled/randomized groups. The cumulative 18-month mortality rate will be estimated in each respective group using the Kaplan-Meier estimator and compared with the log-rank test.

10.5 DAPT Adherence

Details surrounding medication adherence are collected using site reported cessation forms and the manual pill count at the 9 and 15 month in-person visits. For each medication taken by a study participant, the following details are collected in the EDC for each cessation occurrence: date of cessation and restart; new medication in the event the patient permanently discontinued; reason for cessation.

Using these data elements the frequency of cessation (temporary and permanent) for each agent (blinded drug and ticagrelor) will be calculated at the 4, 9 and 15 months study visits and compared between randomized groups using the chi-square test. In addition, the rate of cessation (temporary and permanent) for each agent will also be estimated using the Kaplan-Meier method at each time point and compared between groups using the log-rank test. As cessation may occur more than once in an individual patient, these analyses will consider the time to first cessation.

Adherence data is also available based upon manual pill count from returned bottles at the 9 and 15-month study visits. Subject compliance will be calculated for each medication using the following formula:

$$\text{Compliance} = \frac{\text{(number of supplied doses of medication taken by subject)}}{\text{(number of doses of medication required for continuous treatment during period)}}$$

The numerator of the above formula will be obtained from counting the returned pills and subtracting this value from the total number of pills provided. The acceptable percentage of compliance will be at least 80%. Any subject found to be taking less than 80% of the prescribed study medications will be considered non-compliant. Once randomized, subjects should not be discontinued from study drug for noncompliance; however, the investigator or designee will determine factors that result in poor compliance with the study drug and will take steps to improve compliance. Compliance based upon manual pill count will be summarized for ticagrelor and blinded study drug at the 9 and 15 month study visits and compared between randomized groups using the chi-square test. Compliance will also be assessed using an alternative definition of 80% to 120% wherein values less than 80% or above 120% are deemed non-compliant.

Cessations will also be adjudicated for each occurrence of open-label aspirin; blinded study drug; ticagrelor; other $P2Y_{12}$ inhibitor that is recorded in the EDC over the course of the study. The original PARIS framework will be used for these assessments, with slight modification as outlined below. Each cessation will be adjudicated according to duration (brief; temporary; permanent); mode (discontinuation; interruption; disruption) and guidance (recommended versus non-recommended).

Interruption

Interruptions are defined as temporary (<=14) day cessation of any antiplatelet therapy for surgical or other invasive procedure. By definition all interruptions are recommended.

Disruption

Disruptions are defined as cessations due to antecedent non-compliance or bleeding. In general disruption due to non-compliance is not recommended and disruption due to bleeding should be recommended. Protocol non-compliance (either by patient or physician) will also be considered a disruption. Examples include switching to clopidogrel for no apparent reason; stopping blinded drug for open-label ASA due to patient or physician preference.

Discontinuation

Discontinuations will be defined as protocol-guided cessations rather than physician-guided as in the original PARIS criteria. Hence patients who discontinue because of side effects that render a medication intolerable or because of a safety concern (thrombotic event; development of AF etc.) would be considered protocol-guided discontinuers as this is permissible in the TWILIGHT protocol. By definition, all discontinuations are recommended.

10.6 Sensitivity Analyses

In order to evaluate the consistency and robustness of the treatment effect on both primary and key secondary endpoints, the following sensitivity analyses will be performed:

10.6.1 As-treated

As-treated analyses for the primary and key secondary endpoints will be performed in the randomized PP cohort. All events occurring between the time of randomization and one year thereafter will be included in these analyses. Event rates will be estimated at one year (12 months after randomization) using the Kaplan-Meier method for each treatment group. In addition to the censoring criteria listed in sections **10.1** and **10.2**, in these analyses event-free patients will also be censored at the time of permanent cessation of either ticagrelor or

blinded study drug + 5 days. Cessation of either agent without restarting or lasting at least 30 days is considered permanent. Hence, for the as-treated analyses of the primary endpoint event-free patients will be censored at the time of death, last known contact, permanent cessation + 5 days or 365 days, whichever comes first. HR and 2-sided 95% CI will be generated for each endpoint using the Cox proportional hazards model with treatment group (ticagrelor monotherapy versus ticagrelor plus ASA) as a covariate.

10.6.2 Baseline imbalance adjustment

Randomization lowers, but does not eliminate, the probability of baseline imbalance in parameters with prognostic relevance. Accordingly, differences in all baseline data elements will be formally compared between randomized groups. Variables displaying significant differences with prognostic impact on either the primary or key secondary endpoints will be included as additional covariates in Cox models estimating treatment effects.

10.6.3 Site-specific Effects

Regional and site-level differences in study performance and patient case-mix may influence study endpoints in large clinical trials (34). In TWILIGHT randomization is stratified by site and a pre-specified subgroup analysis by enrolled region will examine for heterogeneity in treatment effect at a country level. To further explore the influence of site enrolment on the primary and secondary endpoints and corresponding treatment effects the following will be performed:

The number of patients enrolled at each site will be tabulated and sites will be categorized by total number of patients enrolled as follows: <=20; 21-50; > 50. These values approximate the tertiles for site enrolment. Within each site enrolment stratum, the pooled one-year (12 months after randomization) event rate for the primary and key secondary endpoints will be calculated using the Kaplan-Meier estimator. A trend test will be performed to test for differences across strata. The treatment effect for ticagrelor monotherapy versus ticagrelor and ASA will be examined within each stratum using the Cox proportional hazards model. Heterogeneity across strata will be examined with a stratum X treatment interaction term. These analyses will be performed in the randomized ITT cohort and will consider all events occurring between randomization and one year thereafter.

10.7 Pre-defined Sub-studies

The following sub-studies are either embedded within the ongoing framework of TWILIGHT or will be performed after completion of the primary trial and database lock. Full protocols with statistical plans will be developed for each respective study. A general description of each planned sub-study is provided below.

10.7.1 Blood thrombogenicity

The impact of aspirin withdrawal on whole blood thrombogenicity will be examined in a physiologic sub-study using the validated ex-vivo Badimon perfusion chamber. Blood thrombogenicity will be assessed at the time of randomization when patients are on maintenance DAPT with ASA and ticagrelor and then at 4 weeks after randomization. The expected results are that ticagrelor monotherapy will show similar antithrombotic effects to that of ASA + ticagrelor. Whole blood thrombus area will be quantified as previously described and compared between groups at 8 weeks post randomization.

10.7.2 Biodegradable-Polymer Everolimus-Eluting Stent (SYNERGY, Boston Scientific)

The SYNERGY stent platform is an FDA-approved DES and therefore permissible in TWILIGHT study participants. The unique features of this stent include a biodegradable polymer that may result in an enhanced safety and/or efficacy profile compared with conventional durable-polymer DES. However, approval trials for the SYNERGY stent included relatively low-risk subjects with respect to lesion or procedural parameters. In a separate study that included elderly patients treated with a short duration of DAPT (35), use of the SYNERGY stent was superior to BMS in reducing major ischemic adverse events. Accordingly, it is plausible that clinicians may preferentially use the SYNERGY platform in patients perceived to be at high bleeding risk. This sub-study will include all enrolled participants receiving either durable-polymer DES or SYNERGY stent and will examine the following aims:

To profile the clinical and angiographic characteristics of TWILIGHT patients treated with SYNERGY versus DP-DES and to compare the effectiveness of SYNERGY absorbable polymer stent versus DP-DES on the outcome of target lesion failure in the high risk TWILIGHT study population.

10.7.3 Chinese Participants

The pharmacodynamic properties of antiplatelet agents vary substantially by race and ethnicity. With respect to ticagrelor, mean exposure in healthy Chinese volunteers is approximately 40% higher than in Caucasians (36). In a separate report ticagrelor at a 45 mg dose displayed a rapid and large platelet inhibitory effect with modest differences with dose increase to 60 mg (37). The TWILIGHT study has enrolled a large number of Chinese participants, providing a unique opportunity to examine the effect of ticagrelor monotherapy versus DAPT with ticagrelor plus ASA on both bleeding and ischemic endpoint among this population. Accordingly, the Chinese TWILIGHT sub-study will include all Chinese participants enrolled in the trial and will examine the impact of ticagrelor monotherapy on both primary and key secondary endpoints.

10.7.4 Acute Coronary Syndrome

Patients presenting with acute coronary syndrome (ACS) display elevated risks for both ischemic and hemorrhagic complications after PCI. At present, current guidelines stipulate a minimum of 12-month duration of DAPT in such patients, although a recently reported study suggested that ticagrelor monotherapy may yield comparable efficacy and safety to conventional DAPT over a 2-year treatment. In TWILIGHT PCI indication is captured on the baseline case report form as unstable angina or NSTEMI. For purposes of this sub-study these clinical designations will be supplemented by baseline serum cardiac biomarkers to categorize all ACS patients as either Troponin negative or positive, respectively. The ACS sub-study will include all enrolled TWILIGHT participants and will examine the following primary aims:

The impact of clinical presentation (stable vs. Tn (-) ACS vs. Tn (+) ACS) on bleeding and ischemic events occurring between time of enrolment and 15-months thereafter.

The impact of ticagrelor monotherapy versus DAPT with ticagrelor plus ASA on the primary bleeding and key secondary endpoints among randomized participants in relation to ACS presence or absence.

10.8 Multiplicity

The primary endpoint of interest in the present study is BARC 2, 3 or 5 bleeding, for which a Type I error rate of 0.05 will be used. All other endpoints are secondary and therefore no multiplicity adjustments will be performed.

10.9 Robustness

The primary analysis will involve Cox proportional hazards regression as described above with treatment (ticagrelor monotherapy versus ticagrelor plus ASA) as a covariate. Multiple secondary analyses (per protocol, as-treated) will be performed as described above to examine the overall consistency of our primary findings. These additional analyses are meant to be confirmatory (that is, yield approximately the same answer) to the primary analysis.

11 Table Listings

1. Enrolled Cohort

1.1 Registration (Clinical Inclusion, Angiographic Inclusion, Exclusion)

1.1.1 Baseline demographics (age, sex, race, country)

1.1.2 Baseline clinical and medical history (risk factors)

1.1.3 Baseline medications (taken chronically as recorded in EDC)

1.1.4 Baseline Laboratory assessment

1.1.5 Baseline Angiographic details

1.1.6 Baseline Intervention details

1.1.7 Discharge Medications

1.2.1 Site-Reported Cessation

1.2.1.1 30-day binary frequency and KM estimates

1.2.1.2 90-day binary frequency and KM estimates

1.2.2 Adjudicated Cessation

1.2.2.1 30-day binary frequency and KM estimates

1.2.2.2 90-day binary frequency and KM estimates

1.2.3 Site reported Bleeding Events

1.2.3.1 30-day binary frequency and KM estimates

1.2.3.2 90-day binary frequency and KM estimates

1.2.4 Adjudicated Bleeding Events

1.2.4.1 30-day binary frequency and KM estimates

1.2.4.2 90-day binary frequency and KM estimates

1.2.5 Site reported ischemic events

1.2.5.1 30-day binary frequency and KM estimates

1.2.5.2 90-day binary frequency and KM estimates

1.2.6 Adjudicated ischemic events

1.2.6.1 30-day binary frequency and KM estimates

1.2.6.2 90-day binary frequency and KM estimates

1.2.7 Mortality assessment

1.2.7.1 30-day, 90-day, 18-month binary frequency and KM estimates

1.2.8 Subject disposition

1.2.8.1 Lost/Consent withdrawn at 30 and 90 days

1.2.9 Randomization disposition

1.2.9.1 Reasons for randomization ineligibility

2 Randomized ITT Cohort (37 tables)

2.2 Registration (Clinical Inclusion, Angiographic Inclusion, Exclusion)

2.2.1 Baseline demographics (age, sex, race, country)
2.2.2 Baseline clinical and medical history (risk factors)
2.2.3 Baseline medications (taken chronically as recorded in EDC)
2.2.4 Baseline Laboratory assessment
2.2.5 Baseline Angiographic details
2.2.6 Baseline Intervention details
2.2.7 Discharge Medications
2.2.8 Site-Reported Cessation
2.2.8.1 4-month binary frequency, KM estimates, pill count (30 day post randomization)
2.2.8.2 9-month binary frequency, KM estimates, pill count (180 days post randomization)
2.2.8.3 15-month binary frequency, KM estimates, pill count (365 days post randomization)
2.2.9 Adjudicated Cessation
2.2.9.1 4-month binary frequency, KM estimates (30 day post randomization)
2.2.9.2 9-month binary frequency, KM estimates (180 days post randomization)
2.2.9.3 15-month binary frequency, KM estimates (365 days post randomization)
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12 Reporting Conventions

P-values ≥0.001 will be reported to 3 decimal places; p-values less than 0.001 will be reported as "<0.001". The mean, standard deviation, and any other statistics other than quantiles will be reported to one decimal place greater than the original data. Quantiles, such as median, or minimum and maximum will use the same number of decimal places as the original data. Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) will be reported to 3 significant figures.

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Statistical Analysis Plan

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Analytic details documented herein supersede those in the TWILIGHT protocol, version 4.0 *All statistical analyses are performed independently by the London School of Hygiene and Tropical Medicine	

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1.0 Abbreviations and Definitions

AE	Adverse Event
BARC	Bleeding Academic Research Consortium
CRF	Case Report Form
DAPT	Dual Antiplatelet Therapy
ITT	Intent To Treat
PCI	Percutaneous Coronary Intervention
PP	Per Protocol
SAP	Statistical Analysis Plan

2.0 Introduction

2.1 Preface

Pharmacologic platelet inhibition with aspirin and a $P2Y_{12}$ inhibitor is a requirement in all patients undergoing percutaneous coronary intervention (PCI) with stenting. Such dual antiplatelet therapy (DAPT) is recommended by international guidelines, with duration varying according to clinical presentation (i.e. acute coronary syndrome) or type of stent implanted during PCI (bare metal vs. drug eluting) (1-3).

While clopidogrel is the most widely used $P2Y_{12}$ inhibitor, its efficacy is hampered by substantial variability in platelet inhibition that may be attributable to clinical, genetic and procedural parameters (4-7). Moreover, although the novel thienopyridine, prasugrel has a more potent and consistent effect on platelet inhibition (8,9), bleeding risk is significantly higher compared to clopidogrel in acute coronary syndrome (ACS) patients following PCI (10). In contrast, ticagrelor, an oral, reversible, direct-acting inhibitor of the adenosine diphosphate $P2Y_{12}$ receptor (11) has proven faster, greater and more consistent P2Y12 inhibition than either clopidogrel or prasugrel (12-14). In the landmark Study of Platelet Inhibition and Patient Outcomes (PLATO) trial, ticagrelor significantly reduced death from vascular causes, myocardial infarction, or stroke, without significantly increasing overall major bleeding in patients presenting with acute coronary syndromes(15).

Along with the advent of more potent antiplatelet pharmacotherapy, stent technology has also advanced in a concordant fashion with the introduction of safer and less thrombogenic platforms. These devices, compared to their older-generation counterparts, yield significant reductions in thrombotic events that are durable over the long term (16). As a consequence, classical paradigms favoring a minimum of DAPT duration of 1 year, particularly in elective patients, are being challenged as PCI safety continues to evolve and improve. Randomized comparisons of different DAPT durations such as the OPTIMIZE and the PRODIGY trials suggest no increased risk for thrombotic events after only 3-6 months of DAPT in PCI patients treated primarily with novel generation devices (17,18).

2.2 Research hypothesis

The overall hypothesis of the current study is that three months post-PCI of dual antiplatelet therapy with aspirin and ticagrelor, continued monotherapy with ticagrelor alone versus ticagrelor plus aspirin for an additional year will be superior with respect to bleeding and non-inferior with respect to ischemic events in high-risk patients undergoing PCI.

This hypothesis will be tested in the following two specific aims:

Aim 1: To determine the impact of ticagrelor alone versus ticagrelor plus aspirin in reducing clinically relevant bleeding among high-risk patients who had PCI.	**Hypothesis 1:** A DAPT strategy of ticagrelor + ASA for 3 months followed by ticagrelor alone for an additional 12 months will be superior to ticagrelor plus aspirin with respect to clinically relevant bleeding (BARC 2, 3 or 5) in high-risk patients undergoing PCI.
Aim 2: To determine the impact of ticagrelor alone versus ticagrelor plus aspirin in reducing ischemic adverse events at one year among high-risk patients undergoing PCI	**Hypothesis 2:** A DAPT strategy of ticagrelor + ASA for 3 months followed by ticagrelor alone for an additional 12 months will be non-inferior to ticagrelor plus aspirin with respect to ischemic adverse events (all-cause death, non-fatal MI or stroke) at 1 year in high-risk patients undergoing PCI.

2.3 Rationale for conducting this study

Despite the trend and rationale for shorter DAPT durations following PCI, certain high-risk patients may derive additional benefit from potent and sustained platelet inhibition extending beyond 3 months after PCI. Defined by clinical and/or anatomic criteria, a short course of DAPT in such patients may provide sufficient protection against early stent-related thrombotic events while ongoing platelet inhibition may yield further reductions in systemic atherothrombosis. Among patients with diabetes mellitus (DM) undergoing PCI, for example, Brar et al. previously demonstrated that the benefits of DAPT compared to antiplatelet monotherapy persisted irrespective of BMS or DES use, suggesting a systemic rather than stent-related effect (19). Analogously, among patients with DM enrolled in the EXCELLENT trial a prolonged DAPT strategy was associated with a reduction in adverse events compared with ASA alone (20). Findings from Dangas et al., which demonstrate a link between atherosclerosis and increased platelet reactivity, provide a biological basis for potent platelet inhibition in high-risk patients characterized by diffuse vascular disease (21). These observations are clinically relevant as many patients undergoing elective or urgent PCI exhibit high-risk features, such as renal dysfunction, DM, peripheral arterial disease, that are associated with systemic atherosclerosis. Given the clear benefits of ticagrelor in the setting of high-risk ACS, it is plausible that ticagrelor alone will provide sufficient platelet inhibition to reduce thrombotic events compared to ticagrelor plus ASA among high-risk patients who have completed a requisite short course of DAPT.

Reduction in bleeding with ticagrelor alone while preserving the anti-ischemic benefit associated with DAPT use would favor such a strategy in high-risk patients undergoing PCI.

Accordingly, the proposed study will examine the comparative safety and efficacy of a strategy of 3 months DAPT with ASA and ticagrelor followed by monotherapy using a potent agent (ticagrelor) compared with continued ASA and ticagrelor among high-risk patients undergoing PCI with DES. Our primary hypothesis is that, among such patients, use of ticagrelor alone will yield a significant reduction in clinically relevant bleeding while preserving anti-ischemic benefit compared with ticagrelor and ASA.

2.4 Benefit/risk and ethical assessment

The potential benefits that subjects might realize by participating in this randomized trial is a reduction in clinically relevant bleeding for those who are randomly allocated to the placebo arm. Other benefits applicable to all subjects include close monitoring and surveillance for clinical events that will be performed by study personnel during the course of the trial.

The potential risks for subjects include an increased rate of thrombotic events for those who are randomized to the placebo arm and increased risk for bleeding in subjects randomized to the active treatment arm (low-dose ASA [81 – 100 mg]).

An independent data safety monitoring board will provide external oversight to ensure safety of all trial participants. In addition, subjects will be followed closely with periodic study contacts. Also, clinical equipoise exists for conducting a trial with this type of randomized comparison.

3.0 Study Objectives and Endpoints

3.1 Primary Objective

The primary objective of this study is to determine the impact of antiplatelet monotherapy with ticagrelor alone versus DAPT with ticagrelor plus aspirin for 12 months in reducing clinically relevant bleeding (BARC 2, 3 or 5) among high-risk patients who have undergone successful PCI and who have completed a 3-month course of DAPT with aspirin plus ticagrelor.

3.2 Secondary Objective

The secondary objective of this study is to determine the impact of antiplatelet monotherapy with ticagrelor alone versus DAPT with ticagrelor plus aspirin for 12 months on major ischemic adverse events (all-cause death, non-fatal MI or stroke) among high-risk patients who have undergone successful PCI and who have completed a 3-month course of DAPT with aspirin plus ticagrelor.

3.3 Exploratory Objectives

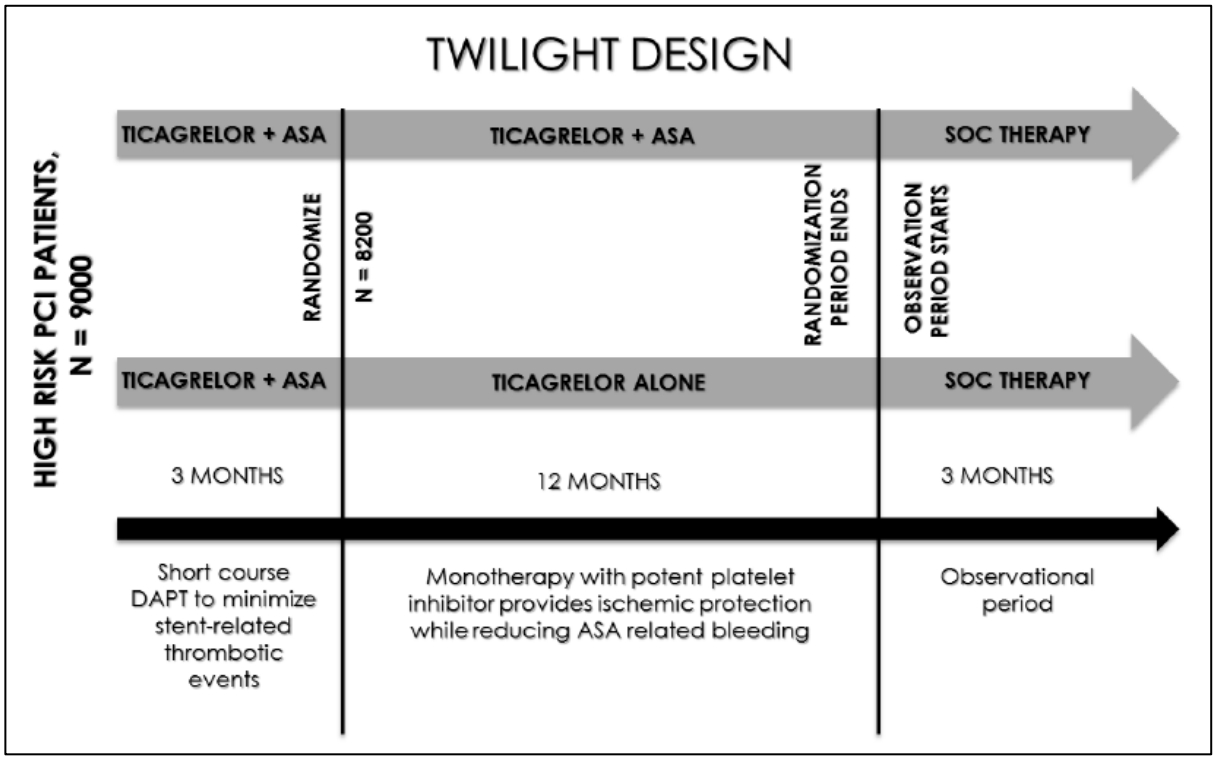
Exploratory objectives include assessing the comparative safety and efficacy of the different DAPT regimens for individual components of the primary and secondary objectives.

4.0 Study Methods

4.1 Overall study design and flow chart

A randomized, double-blind study design was chosen as the most rigorous experimental approach to formally test the study hypotheses for the efficacy and safety of different DAPT regimens in high-risk patients undergoing PCI. Open label aspirin and ticagrelor per physician discretion will be given for the first 3 months after PCI. After 3 months, event-free subjects will be randomized to placebo versus enteric coated ASA for an additional 12 months. Open-label ticagrelor at a dose of 90 mg twice daily will be continued in all randomized subjects.

Figure 1 TWILIGHT Trial Design



4.2 Inclusion/Exclusion criteria

High-risk patients who have undergone successful PCI with at least one locally approved drug eluting stent AND discharged on DAPT with aspirin and ticagrelor of at least 3 months intended duration will be eligible for the TWILIGHT study.

Enrollment into the study will require meeting at least one clinical inclusion AND at least one angiographic inclusion AND none of the exclusion criteria. A subject is considered enrolled if all these criteria are met and upon provision of informed consent.

Must meet AT LEAST ONE clinical inclusion criterion	Must meet AT LEAST ONE angiographic inclusion criterion
Adult patients ≥ 65 years of age Female gender Troponin positive acute coronary syndrome Established vascular disease defined as previous MI, documented PAD or CAD/PAD revascularization Diabetes mellitus treated with medications or insulin Chronic kidney disease defined as an estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73m^2 or creatinine clearance (CrCl) < 60 ml/min	Multivessel coronary artery disease (CAD) (see Section 16) Target lesion requiring total stent length >30 mm Thrombotic target lesion(s) Bifurcation lesion(s) with Medina X,1,1 classification requiring at least 2 stents (see Section 16) Left main (≥50%) or proximal LAD (≥70%) lesion Calcified target lesion(s) requiring atherectomy

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

- Under 18 years of age
- Contraindication to aspirin
- Contraindication to Ticagrelor
- Planned surgery within 90 days
- Planned coronary revascularization (surgical or percutaneous) within 90 days
- Need for chronic oral anticoagulation
- Prior stroke
- Dialysis-dependent renal failure
- Active bleeding or extreme-risk for major bleeding (e.g. active peptic ulcer disease, gastrointestinal pathology with a raised risk for bleeding, malignancies with a raised risk for bleeding)
- Salvage PCI or STEMI presentation.
- Liver cirrhosis
- Life expectancy < 1 year
- Unable or unwilling to provide informed consent
- Women of child bearing potential (as determined by hospital standard of care)
- Fibrinolytic therapy within 24 hours of index PCI
- Concomitant therapy with a strong cytochrome P-450 3A inhibitor or inducer
- Platelet count < 100,000 mm^3
- Requiring ongoing treatment with aspirin ≥ 325 mg daily

4.3 Subject randomization and initiation of investigational product

The eligibility for randomization for all enrolled subjects will be evaluated at the in-person 3-month study visit. Subjects with any of the following will not be randomized:

- Refusal of randomization by subject or treating physician
- Withdrawal of consent
- Lost to follow-up
- Death
- Major bleeding (BARC Types 3b or 5)
- Occurrence of an ischemic event after PCI such as myocardial infarction, definite or probable stent thrombosis, ischemic stroke, coronary revascularization with drug-eluting stent
- No longer taking DAPT with aspirin and ticagrelor
- Non physician-guided cessation of aspirin or ticagrelor of 5 days or greater.
- Women of child bearing potential (as determined by hospital standard of care)
- Renal failure requiring dialysis
- Current indication for oral anticoagulation or high dose aspirin

Randomization will be performed within the EDC system among subjects eligible for randomization. The EDC will allocate the treatment group assignment for the subject and provide study site research personnel the appropriate bottle ID number(s). Randomization is stratified by site and will be performed in permuted blocks of sizes 4, 6 and 8.

Upon randomization at the conclusion of the in-person 3-month visit, the study site research personnel will provide a 6-month supply of blinded investigational product (aspirin or matching placebo) and open-label ticagrelor.

Enrolled subjects who do not meet eligibility for randomization will have completed their protocol required activities. They will not receive study drug but will be distributed an additional 1-week supply of open-label ticagrelor, if clinically appropriate. Vital status of these subjects will be determined at the 18-month time point.

Enrolled subjects who do not meet eligibility for randomization prior to the in-person 3-month visit will not be required to complete the 3-month in-person visit.

4.4 Blinding and procedures for unblinding the study

4.4.1 Methods for ensuring blinding

This study has a double-blind design with aspirin and matching placebo. The subjects, study site research personnel, academic research center staff, and treating physicians involved in the treatment and/or clinical evaluation of the subjects will not be aware of treatments received. There will be an independent data safety monitoring board (DSMB) to monitor the data on a periodic basis. An independent statistician, not otherwise involved in the study, will prepare and provide the required reports to the DSMB as per the DSMB charter.

4.4.2 Methods for unblinding the study

In the event of a medical emergency, in which knowledge of the investigational drug is critical to the subject's medical management, the blind for that subject may be broken by the treating physician. The investigator should follow the instructions provided in the EDC instructions to obtain the necessary treatment information from the randomization system. As the active study drug in this trial is low-dose aspirin, in most instances the subject may be properly managed without the need for unblinding.

4.5 Treatments

4.5.1 Identity of Investigational Product

The investigational product is enteric coated aspirin 81 - 100 mg tablets and matching aspirin-placebo tablets.

Table 1 Identify of Investigation Product

Investigational product	Dosage form and strength
Aspirin, EC	81-100 mg tablet, daily
Placebo for aspirin	tablet daily

4.5.2 Doses and treatment regimens

Enteric coated aspirin at a dose of 81-100 mg daily and matching placebo will be administered daily. Subjects will receive a 3-month supply of open-label ticagrelor and open-label aspirin at the baseline visit and a 6-month supply of blinded study drug and open-label ticagrelor at randomization (3-month study visit) and at the 9-month study visit.

4.5.3 Additional study drug

Open-label ticagrelor will be administered to all subjects regardless of randomization assignment.

4.6 Study Variables

Data collection commences after the subject has provided informed consent and has been enrolled in the study. Data collection, including subject demographic information, laboratory

tests, and procedural data as well as follow-up visits or telephone contacts will be conducted by an Investigator or site coordinator who has been trained on the protocol and electronic Case Report Forms (eCRFs).

Data required for analysis will be obtained as outlined in Table 2. After discharge from the hospital, each enrolled subject will be followed with a phone call at 1 month post enrollment and an in-clinic visit at 3 months post enrollment. Enrolled subjects who do not meet eligibility for randomization prior to the in-person 3-month visit will not be required to complete the 3-month in-person visit. Subjects who are randomized at 3 months post enrollment will be followed with a phone call at 4 months post enrollment and will return for additional in-clinic visits at 9 and 15 months post enrollment. A final follow-up phone call will be performed at 18 months post enrollment for randomized subjects. No further follow-up contact will be performed for subjects who did not meet eligibility for randomization at the 3 month visit; however, vital status may be obtained from medical or public records at 18 months post enrollment.

Table 2 Schedule of Data Collection

Type of Data to be Collected	Enrollment	Post-Procedure or Discharge	1 Month (30d) (±7 days) Phone Call	3 Month (90d) (±14 days) Office Visit	4 Month (120d) (±7 days) Phone Call randomized	9 Month (270d) (± 30 days) Office Visit randomized	15 Month (450d) (± 30 days) Office Visit randomized	18 Month (540d) (± 14 days) Phone Call randomized
Eligibility Criteria	X			X				
Patient Informed Consent	X							
Physical Assessment	X							
Medical History/Risk Factors	X							
Cardiac Status	X							
Medications/ Antiplatelets	X							
Clinical Tests* Lab tests, ECG	X			X		X	X	
Procedure Information	X							
DAPT Medication Status		X	X		X			X
Angina Status				X	X	X	X	X
Randomization– if eligible				X				

Type of Data to be Collected	Enrollment	Post-Procedure or Discharge	1 Month (30d) (±7 days) Phone Call	3 Month (90d) (±14 days) Office Visit	4 Month (120d) (±7 days) Phone Call randomized	9 Month (270d) (± 30 days) Office Visit randomized	15 Month (450d) (± 30 days) Office Visit randomized	18 Month (540d) (± 14 days) Phone Call randomized
Randomized Medications –provide medication according to EDC				X		X		
Randomized Medications – reconciliation of provided medication						X	X	
Randomized Medications – subject self-reporting of compliance to medications				X	X	X	X	X
Adverse Events / Serious Adverse Events	X	X	X	X	X	X	X	X

*If performed, as per standard of care. Subject may be asked to provide an additional blood sample (10cc) for lipid profile testing if not already performed per standard of care.

4.6.1 Study timetable and end of study

Trial enrolment in TWILIGHT began in July 2015 with the last patient enrolled on December 31, 2017. The last patient follow-up visit will occur in June 2019.

5.0 Endpoints

5.1 Primary Endpoint (Bleeding)

The primary endpoint of TWILIGHT is the time to first occurrence of BARC 2, 3 or 5 bleeding. All events occurring between the time of randomization and one year thereafter (365 days after randomization) will be included in the analysis for the primary endpoint.

5.2 Key Secondary Endpoint (Ischemic)

The key secondary endpoint is the time to first occurrence of all-cause death, non-fatal MI or stroke. All events occurring between the time of randomization and one year thereafter (365 days after randomization) will be included in the analysis for the key secondary endpoint.

5.3 Other Secondary Endpoints

Secondary endpoints listed below will be evaluated at both 15 month (one year after randomization) and 18 month (15 months after randomization) time points.

- *Bleeding*
  - BARC Types 3 or 5
  - Thrombolysis in Myocardial Infarction (TIMI) minor or major (includes life threatening) bleeding
  - TIMI major (includes life threatening) bleeding
  - GUSTO moderate or severe or life-threatening bleeding
  - GUSTO severe or life-threatening bleeding
  - International Society of Thrombosis or Haemostasis (ISTH) major bleeding
- *Ischemic*
  - All-cause death, MI, stroke
  - All-cause death, MI, ischemic stroke
  - Cardiovascular death, non-fatal MI, ischemic stroke or clinically-driven revascularization
  - Clinically-driven revascularization
  - Cardiovascular death, MI or ischemic stroke
  - Definite or probable stent thrombosis
  - Cardiovascular death
  - MI (fatal or non-fatal)
  - Cardiovascular death, MI or def/prob stent thrombosis
  - Ischemic stroke
  - Any stroke
  - All-cause death
  - All-cause hospitalization (based upon site-reported adverse event listings)

6.0 Sample Size

Power calculations are based on a superiority comparison for the primary endpoint of BARC types 2, 3 or 5 bleeding at 1 year from randomization. We assume a cumulative bleeding rate of 4.5% between time of randomization and 1 year. As shown in **Table 3**, this is a somewhat conservative estimate as subjects sustaining a major hemorrhagic event in the first 3 months after PCI will not be randomized. Assuming a 2% loss to follow-up and non-compliance / cross-over rate of 4%, the current trial will require 8200 subjects to detect a relative reduction in bleeding of 28% with ticagrelor monotherapy with 80% power and a Type I error of 0.05. It is anticipated that approximately 8% - 10% of enrolled subjects will not be eligible for randomization and therefore 9000 subjects will be enrolled. Additional sample size estimates are provided in **Table 4** assuming different control bleeding rates and risk reductions (22,23).

References for the sample size estimates include Lakatos 1988, Biometrics volume 44 pages 229-241; and Lakatos 2002, Statistics in Medicine, Volume 21 pages 1969-1989.

Assuming a one-year rate for the key secondary endpoint of all-cause death, non-fatal MI or stroke of 8%, the current study will have 80% power to exclude a non-inferiority margin of 1.6% (upper limit of 95% CI for absolute risk difference in the one year event rate).

Table 3 Event rate and Effect Size Assumptions for Primary Endpoint Sample Size Calculations

Basis for Proposed Bleeding Event Rates in TWILIGHT Power Calculations			
Study	**Study Type**	**Time Point**	**BARC ≥ 2 Rate**
DAPT	RCT	18 months	**~ 4.2%**
PARIS (unpublished data)			
Age > 65	Registry	1 year	8.6%
Diabetes Mellitus (on insulin) Diabetes Mellitus (orals)	Registry	1 year	8.3% 6.3%
Renal disease	Registry	1 year	13.2%
Vranckx et al., EHJ 2013 (24)	Post-hoc (TRACER)	500 days	14%
ADAPT-DES			
CrCl < 60 cc/min (Baber et al, TCT 2013)	Registry	1 year	10.0%
Rao et al., JACC Int 2013 (25)	NCDR CathPCI	In-hospital (women)	8.5%
Basis for Proposed Effect Size in TWILIGHT Power Calculations			
Study	**Study Type**	**Comparators**	**Relative Bleeding Increase**
Baigent et al., Lancet 2009 (26)	Pooled Data from Randomized trials	ASA vs. placebo/control	50% (1° prevention) 170% (2° prevention)
WOEST, Lancet 2013 (27)	RCT	ASA vs. placebo	~ 60%
CAPRIE, Lancet 1996 (28)	RCT	ASA vs. clopidogrel	~35% (GI hemorrhage)
Physician Health Study, NEJM 1989 (29)	RCT	ASA vs. Placebo	~35%
De Berardis et al., JAMA 2012 (30)	Cohort study	ASA vs. No ASA	55%
Seshasai et al., Archives Int Med 2012 (31)	Meta-analysis of 9 RCTs	ASA vs. Placebo	~31%
HOT Trial, Lancet 1998 (32)	RCT	ASA vs. Placebo	~ 80%

Table 4 Alternative Sample Size Estimates for Primary Endpoint

Control Bleeding Rate	Relative Risk Reduction	Total Randomized Sample Size	Total Sample Size (Enrolled + Randomized) with 8% loss after enrollment*	Total Sample Size (Enrolled + Randomized) with 10% loss after enrollment*
5%	30%	6400	7000	7111
5%	28%	7400	8040	8222
5%	26%	8030	9800	10000
4.5%	30%	7090	7706	7900
4.5%	28%	8200	8913	9111
4.5%	26%	9700	10500	10800
4.0%	30%	8000	8700	8888
4.0%	28%	9300	10100	10333
4.0%	26%	10900	11800	12111

7.0 Study Cohorts

Enrolled: The enrolled cohort consists of all subjects who signed informed consent.

Randomized intention to treat (ITT): The randomized ITT cohort will consist of all subjects who have been randomized (i.e. when the subject number and allocated treatment are recorded in the EDC). Subjects will be analyzed in the treatment group assigned by the EDC, irrespective of subsequent follow-up or medication adherence.

Randomized per protocol (PP): The randomized PP cohort consists of all randomized subjects without any major deviations from the protocol. The following deviations in randomized subjects will lead to exclusion from the PP population

- Not fulfilling inclusion or meeting exclusion criteria at the time of enrollment
- Not fulfilling randomization eligibility criteria at the time of randomization
- Not receiving the assigned treatment at the time of randomization

All analyses for the primary and key secondary endpoints will be performed in the ITT and PP cohorts. The primary analyses will be performed in the ITT population and then repeated in the PP population to support the primary results.

8.0 Subgroups

Baseline clinical and demographic characteristics that will define subgroups of interest for the primary and key secondary endpoints are listed below:

- Age (< 65, >= 65 years)
- Race/Ethnicity (non-Hispanic White; non-Hispanic Black; Asian; Other)
- Sex (Male, Female)
- Geographic Region (North America; Europe/Israel; Asia)
    - North America includes Canada and the United States
    - Europe/Israel includes UK, Italy, Spain, Austria, Germany, Poland and Israel
    - Asia includes India and China
- Diabetes Mellitus (yes, no)
- Chronic Kidney Disease (yes, no)
    - Chronic kidney disease is defined as an estimated glomerular filtration rate < 60 ml/1.73m^2 per the CKD-EPI formula
- PCI indication (ACS [Unstable angina or NSTEMI] vs. stable)
- Total stent length implanted (< 30 mm, >=30 mm)
- BMI (above or equal to median, below median)
- History of Prior MI (yes, no)
- High Bleeding Risk (Presence or absence)
    - High bleeding risk (HBR) will be defined according to the Academic Research Consortium criteria. *Alternative definitions of HBR using the PARIS, PRECISE-DAPT and DAPT scores will also be evaluated.*
- High lesion/procedural risk (Presence or absence)
    - High risk lesion or procedure is defined as the presence of at least one of the following parameters: total stent length >= 60 mm; at least 3 lesions treated; vein

graft PCI; complex bifurcation (Medina X, 1, 1) requiring 2 stents; moderate or severe calcification; chronic total occlusion; use of atherectomy.

- Stent type (durable-polymer everolimus-eluting stent; durable-polymer zotarolimus-eluting stent; biodegradable-polymer DES; other)

9.0 Lost to Follow-up and Missing Data

In keeping with an intent-to-treat philosophy, the primary analyses are performed on all randomized subjects. Those subjects who withdraw, are lost to follow-up or have missing data will be included in the primary ITT analysis.

We anticipate that the amount of missing data will be minimal in the present study as we are specifically asking sites to ensure that the data elements are complete. Missing outcome data will not be imputed.

10.0 Statistical Methods

Statistical analyses will be performed using SAS version 9.0 or greater and Stata version 15.0. Unless otherwise stated, all hypothesis tests will be performed using two-sided tests at the 5% significance level. Continuous variables will be summarized using descriptive statistics including means and standard deviations if normally distributed or median with interquartile ranges for skewed distributions. Discrete variables will be summarized using absolute and relative frequencies. Baseline clinical, demographic, laboratory and procedural characteristics will be summarized by randomized treatment group.

10.1 Analysis for the Primary Endpoint (BARC 2, 3 or 5 Bleeding)

The primary objective of TWILIGHT is to determine the impact of ticagrelor monotherapy versus ticagrelor plus aspirin on the composite endpoint of BARC Types 2, 3 or 5 bleeding that occurs between the time of randomization and one year thereafter. Event rates will be estimated at one year (12 months after randomization) and Kaplan-Meier curves will be plotted from the time of randomization to the first occurrence of confirmed BARC Type 2, 3 or 5 bleeding by treatment group. Patients not experiencing a primary endpoint event during this time interval will be censored at the time of death, last contact date (for subjects withdrawing consent or lost to follow-up) or 365 days after randomization, whichever comes first.

A hazard ratio (HR) and two-sided 95% CI for the primary endpoint will be generated using the Cox proportional hazards model that includes treatment group (ticagrelor monotherapy versus ticagrelor plus ASA) as a covariate. This analysis will be carried out in the ITT cohort. The null hypothesis (H_0) for this analysis is that the HR = 1. The two-sided alternative hypothesis (H_A) is that the HR ≠ 1. A test of superiority at the two-sided 0.05 level will be performed using a p-value from a log-rank test and **serves as the main hypothesis test for the primary endpoint**. The treatment effect for the primary endpoint will also be expressed as an absolute risk difference with a two-sided 95% CI, calculating using the Kaplan-Meier estimates at the 15 month (12 months after randomization) time point. The analysis will be repeated in the PP cohort as a sensitivity analysis.

10.2 Analysis for the Key Secondary Endpoint (All-Cause Death, Non-fatal MI or Stroke)

The secondary objective of TWILIGHT is to determine the impact of ticagrelor monotherapy versus ticagrelor plus aspirin on the composite endpoint of all-cause death, non-fatal myocardial infarction, or stroke that occurs between the time of randomization and one year thereafter. Event rates will be estimated at one year (12 months after randomization) and Kaplan-Meier curves will be plotted from the time of randomization to the first occurrence of confirmed all-cause death, non-fatal myocardial infarction or stroke by treatment group. Patients not experiencing a key secondary endpoint event during this time interval will be censored at the time of last contact (for subjects withdrawing consent or lost to follow-up) or 365 days after randomization, whichever comes first.

The point estimate and two-sided 95% CI for the absolute risk difference in the one-year rate of the key secondary endpoint between randomized groups will be calculated. The null hypothesis for this analysis is that the one-year rate of all-cause death, non-fatal MI or stroke is at least 1.6% higher in the experimental (ticagrelor monotherapy) versus control (ticagrelor plus ASA) group. The alternative hypothesis for this analysis is that absolute risk difference at one year is less than 1.6%. These are expressed below:

$$H_o\text{: (One-year ischemic event rate)}_{exp} - \text{(One-year ischemic event rate)}_{control} \geq 1.6\%$$

$$H_a\text{: (One-year ischemic event rate)}_{exp} - \text{(One-year ischemic event rate)}_{control} < 1.6\%$$

A one-sided non-inferiority test with a type I error of 0.025 will be performed as described by Com Nougue et al. (Statistics in Medicine, 1993) and **serves as the main hypothesis test for the key secondary endpoint** (33). The test is performed at a point in time T, using the Kaplan-Meier estimates for freedom from the endpoint being evaluated, and the Greenwood standard errors for these estimates. The null hypothesis will be rejected if the upper limit of the 95% CI for the absolute risk difference in 12-month event rates is less than 1.6%. The treatment effect for the key secondary endpoint will also be expressed as a HR and two-sided 95% CI generated from a Cox proportional hazards model that includes treatment group (ticagrelor monotherapy versus ticagrelor plus ASA) as a covariate. This analysis will be performed in the ITT cohort and repeated in the PP cohort to support the primary results.

10.3 Subgroup Analyses

HRs and two-sided 95% CI for the primary and key secondary endpoints will be calculated within each subgroup using a Cox proportional hazards model with treatment group as a covariate. Formal interaction testing on the ratio scale will be performed using the subgroup X treatment group as an additional term in the Cox model.

10.4 Additional Analyses

10.4.1 18-Month Analyses

The TWILIGHT study design includes a 3-month observational period between 15 and 18 months after enrollment. At the 15-month study visit (one-year after randomization) protocol-guided medications (ticagrelor and blinded study drug) are discontinued and the study subject is switched to standard of care therapy. In order to examine the impact of therapy discontinuation on both primary and key secondary endpoints, additional analyses will be

performed that (i) include all events cumulatively up to 15 months after randomization and (ii) only those occurring between 12 and 15 months post-randomization using a landmark approach.

For each respective endpoint the 15-month event rates will be estimated using the Kaplan-Meier method with event-free patients censored at the time of death, last contact date (for subjects withdrawing consent or lost to follow-up) or 456 days after randomization, whichever comes first. HRs and 95% CIs will be generated using the Cox proportional hazards model that includes treatment group (ticagrelor monotherapy versus ticagrelor plus ASA) as a covariate. Two-sided superiority tests at the 0.05 level will be performed using a p-value from a log-rank test. The cumulative treatment effect for both primary and key secondary endpoints will also be expressed as absolute risk differences with 95% CI using the Kaplan-Meier estimates at the 18-month time point (15 months after randomization). Analogous analyses will be performed in the landmark interval defined by 12 to 15 months after randomization. Event-free patients surviving to 12 months after randomization will be considered at risk and included in the landmark analysis. These analyses will be performed in the randomized ITT and PP cohorts.

10.4.2 Mortality Assessment

In randomized subjects lost to follow-up or withdrawing consent, vital status assessments are performed using publicly available registries, medical records or other resources. Site personnel will record the subject's vital status (alive or dead) and the date of vital status search in the EDC. Hence, vital status will be available in a portion of randomized subjects declared lost or following consent withdrawal. Accordingly, for the analysis of all-cause death alone these participants will be censored at the time of vital status search, rather than at last known contact, assuming the subject is alive at the time of vital status assessment. In contrast, for analyses involving non-fatal outcomes or composite events that include all-cause death as a component, event-free subjects will still be censored as described in sections **10.1** and **10.2**, irrespective of final vital status.

10.4.3 Enrolled Cohort

Upon enrollment, all TWILIGHT participants are followed for at least 90 days, at which time point each subject is either randomized or deemed ineligible for randomization. While enrolled and non-randomized patients are no longer followed during the study period a vital status assessment is performed in these subjects at the 18-month time point.

Baseline characteristics will be summarized for the overall enrolled cohort and in relation to 90 day status (randomized versus non-randomized). Analogously, the 90-day frequency of medication cessation and adverse events will be tabulated for the overall enrolled population and compared between those ultimately randomized versus ineligible. Mortality at 18-months will also be calculated and compared between enrolled/non-randomized versus enrolled/randomized groups. The cumulative 18-month mortality rate will be estimated in each respective group using the Kaplan-Meier estimator and compared with the log-rank test.

10.5 DAPT Adherence

Details surrounding medication adherence are collected using site reported cessation forms and the manual pill count at the 9 and 15 month in-person visits. For each medication taken by a study participant, the following details are collected in the EDC for each cessation occurrence: date of cessation and restart; new medication in the event the patient permanently discontinued; reason for cessation.

Using these data elements the frequency of cessation (temporary and permanent) for each agent (blinded drug and ticagrelor) will be calculated at the 4, 9 and 15 months study visits and compared between randomized groups using the chi-square test. In addition, the rate of cessation (temporary and permanent) for each agent will also be estimated using the Kaplan-Meier method at each time point and compared between groups using the log-rank test. As cessation may occur more than once in an individual patient, these analyses will consider the time to first cessation.

Adherence data is also available based upon manual pill count from returned bottles at the 9 and 15-month study visits. Subject compliance will be calculated for each medication using the following formula:

$$\text{Compliance} = \frac{\text{(number of supplied doses of medication taken by subject)}}{\text{(number of doses of medication required for continuous treatment during period)}}$$

The numerator of the above formula will be obtained from counting the returned pills and subtracting this value from the total number of pills provided. The acceptable percentage of compliance will be at least 80%. Any subject found to be taking less than 80% of the prescribed study medications will be considered non-compliant. Once randomized, subjects should not be discontinued from study drug for noncompliance; however, the investigator or designee will determine factors that result in poor compliance with the study drug and will take steps to improve compliance. Compliance based upon manual pill count will be summarized for ticagrelor and blinded study drug at the 9 and 15 month study visits and compared between randomized groups using the chi-square test. Compliance will also be assessed using an alternative definition of 80% to 120% wherein values less than 80% or above 120% are deemed non-compliant.

Cessations will also be adjudicated for each occurrence of open-label aspirin; blinded study drug; ticagrelor; other $P2Y_{12}$ inhibitor that is recorded in the EDC over the course of the study. The original PARIS framework will be used for these assessments, with slight modification as outlined below. Each cessation will be adjudicated according to duration (brief; temporary; permanent); mode (discontinuation; interruption; disruption) and guidance (recommended versus non-recommended).

Interruption

Interruptions are defined as temporary (<=14) day cessation of any antiplatelet therapy for surgical or other invasive procedure. By definition all interruptions are recommended.

Disruption

Disruptions are defined as cessations due to antecedent non-compliance or bleeding. In general disruption due to non-compliance is not recommended and disruption due to bleeding should be recommended. Protocol non-compliance (either by patient or physician)

will also be considered a disruption. Examples include switching to clopidogrel for no apparent reason; stopping blinded drug for open-label ASA due to patient or physician preference.

Discontinuation

Discontinuations will be defined as protocol-guided cessations rather than physician-guided as in the original PARIS criteria. Hence patients who discontinue because of side effects that render a medication intolerable or because of a safety concern (thrombotic event; development of AF etc.) would be considered protocol-guided discontinuers as this is permissible in the TWILIGHT protocol. By definition, all discontinuations are recommended.

10.6 Sensitivity Analyses

In order to evaluate the consistency and robustness of the treatment effect on both primary and key secondary endpoints, the following sensitivity analyses will be performed:

10.6.1 As-treated

As-treated analyses for the primary and key secondary endpoints will be performed in the randomized PP cohort. All events occurring between the time of randomization and one year thereafter will be included in these analyses. Event rates will be estimated at one year (12 months after randomization) using the Kaplan-Meier method for each treatment group. In addition to the censoring criteria listed in sections **10.1** and **10.2**, in these analyses event-free patients will also be censored at the time of permanent cessation of either ticagrelor or blinded study drug + 5 days. Cessation of either agent without restarting or lasting at least 30 days is considered permanent. Hence, for the as-treated analyses of the primary endpoint event-free patients will be censored at the time of death, last known contact, permanent cessation + 5 days or 365 days, whichever comes first. HRs and 2-sided 95% CIs will be generated for each endpoint using the Cox proportional hazards model with treatment group (ticagrelor monotherapy versus ticagrelor plus ASA) as a covariate.

10.6.2 Covariate adjustment

Randomization lowers, but does not eliminate, the probability of baseline imbalance in parameters with prognostic relevance. Accordingly, the treatment effects for both primary and key secondary endpoints will be adjusted for covariates that are plausibly related to each respective outcome and included in the Cox models as described in Sections **10.1** and **10.2**:

Primary endpoint: age (continuous); sex; body mass index (weight [kg]/height [m]^2); NSAID use; haemoglobin (continuous); estimated glomerular filtration rate (eGFR, continuous); prior bleeding.

Key secondary endpoint: age (continuous); sex; PCI indication (NSTEMI/Unstable angina/stable or asymptomatic); diabetes mellitus (insulin requiring/non-insulin requiring/none); current cigarette smoking; prior MI; prior coronary revascularization (prior PCI or prior CABG); stent length (continuous); minimum stent diameter (continuous); stent type (durable-polymer everolimus-eluting stent/durable-polymer zotarolimus-eluting stent/biodegradable-polymer DES/other)

10.6.3 Site-specific Effects

Regional and site-level differences in study performance and patient case-mix may influence study endpoints in large clinical trials (34). In TWILIGHT randomization is stratified by site and a pre-specified subgroup analysis by enrolled region will examine for heterogeneity in treatment effect at a country level. To further explore the influence of site enrolment on the primary and secondary endpoints and corresponding treatment effects the following will be performed:

The number of patients enrolled at each site will be tabulated and sites will be categorized by total number of patients enrolled as follows: <=20; 21-50; > 50. These values approximate the tertiles for site enrolment. Within each site enrolment stratum, the pooled one-year (12 months after randomization) event rate for the primary and key secondary endpoints will be calculated using the Kaplan-Meier estimator. A trend test will be performed to test for differences across strata. The treatment effect for ticagrelor monotherapy versus ticagrelor and ASA will be examined within each stratum using the Cox proportional hazards model. Heterogeneity across strata will be examined with a stratum X treatment interaction term. These analyses will be performed in the randomized ITT cohort and will consider all events occurring between randomization and one year thereafter.

10.7 Pre-defined Sub-studies

The following sub-studies are either embedded within the ongoing framework of TWILIGHT or will be performed after completion of the primary trial and database lock. Full protocols with statistical plans will be developed for each respective study. A general description of each planned sub-study is provided below.

10.7.1 Blood thrombogenicity

The impact of aspirin withdrawal on whole blood thrombogenicity will be examined in a physiologic sub-study using the validated *ex-vivo* Badimon perfusion chamber. Blood thrombogenicity will be assessed at the time of randomization when patients are on maintenance DAPT with ASA and ticagrelor and then at least 4 weeks after randomization. The expected results are that ticagrelor monotherapy will show similar antithrombotic effects to that of ASA + ticagrelor. Whole blood thrombus area will be quantified as previously described and compared between groups at 8 weeks post randomization.

10.7.2 Biodegradable-Polymer Everolimus-Eluting Stent (SYNERGY, Boston Scientific)

The SYNERGY stent platform is an FDA-approved DES and therefore permissible in TWILIGHT study participants. The unique features of this stent include a biodegradable polymer that may result in an enhanced safety and/or efficacy profile compared with conventional durable-polymer DES. However, approval trials for the SYNERGY stent included relatively low-risk subjects with respect to lesion or procedural parameters. In a separate study that included elderly patients treated with a short duration of DAPT (35), use of the SYNERGY stent was superior to BMS in reducing major ischemic adverse events. Accordingly, it is plausible that clinicians may preferentially use the SYNERGY platform in patients perceived to be at high bleeding risk. This sub-study will include all enrolled participants receiving either durable-polymer DES or SYNERGY stent and will examine the following aims:

To profile the clinical and angiographic characteristics of TWILIGHT patients treated with SYNERGY versus DP-DES and to compare the effectiveness of SYNERGY absorbable

polymer stent versus DP-DES on the outcome of target lesion failure in the high risk TWILIGHT study population.

10.7.3 Chinese Participants- TWILIGHT -CHINA

The pharmacodynamic properties of antiplatelet agents vary substantially by race and ethnicity. With respect to ticagrelor, mean exposure in healthy Chinese volunteers is approximately 40% higher than in Caucasians (36). In a separate report ticagrelor at a 45 mg dose displayed a rapid and large platelet inhibitory effect with modest differences with dose increase to 60 mg (37). The TWILIGHT study has enrolled a large number of Chinese participants, providing a unique opportunity to examine the effect of ticagrelor monotherapy versus DAPT with ticagrelor plus ASA on both bleeding and ischemic endpoint among this population. Accordingly, the Chinese TWILIGHT sub-study will include all Chinese participants enrolled in the trial and will examine the impact of ticagrelor monotherapy on both primary and key secondary endpoints.

10.7.4 Acute Coronary Syndrome

Patients presenting with acute coronary syndrome (ACS) display elevated risks for both ischemic and hemorrhagic complications after PCI. At present, current guidelines stipulate a minimum of 12-month duration of DAPT in such patients, although a recently reported study suggested that ticagrelor monotherapy may yield comparable efficacy and safety to conventional DAPT over a 2-year treatment. In TWILIGHT PCI indication is captured on the baseline case report form as unstable angina or NSTEMI. For purposes of this sub-study these clinical designations will be supplemented by baseline serum cardiac biomarkers to categorize all ACS patients as either Troponin negative or positive, respectively. The ACS sub-study will include all enrolled TWILIGHT participants and will examine the following primary aims:

The impact of clinical presentation (stable vs. Tn (-) ACS vs. Tn (+) ACS) on bleeding and ischemic events occurring between time of enrolment and 15-months thereafter.

The impact of ticagrelor monotherapy versus DAPT with ticagrelor plus ASA on the primary bleeding and key secondary endpoints among randomized participants in relation to ACS presence or absence.

10.7.5 Stable ischemic heart disease

Residual thrombotic risk remains substantial in select patients with SIHD undergoing PCI, particularly among those with renal impairment, DM or presenting with complex lesion phenotypes. In usual care settings, potent $P2Y_{12}$ inhibitors are administered even in the setting of PCI for SIHD in order to mitigate excess thrombotic risk. The TWILIGHT trial provides a unique opportunity to better examine determinants of thrombotic risk and impact of ticagrelor monotherapy in such patients. Accordingly, the SIHD substudy will include all enrolled TWILIGHT participants with stable (i.e. non-ACS) clinical presentation. The following analyses will be pursued in this cohort: identifying clinical, anatomic and procedural determinants of coronary thrombosis and evaluate the impact of ticagrelor monotherapy versus ticagrelor plus ASA on the primary and key secondary endpoints of the trial.

10.8 Multiplicity

The primary endpoint of interest in the present study is BARC 2, 3 or 5 bleeding, for which a Type I error rate of 0.05 will be used. For the pre-specified key secondary endpoint a Type I

error rate of 0.025 will be used in the context of a one-sided non-inferiority hypothesis test. All other endpoints are secondary and therefore no multiplicity adjustments will be performed.

10.9 Robustness

The primary analysis will involve Cox proportional hazards regression as described above with treatment (ticagrelor monotherapy versus ticagrelor plus ASA) as a covariate. Multiple secondary analyses (per protocol, as-treated) will be performed as described above to examine the overall consistency of our primary findings. These additional analyses are meant to be confirmatory (that is, yield approximately the same answer) to the primary analysis.

11.0 Randomization Ineligibility Assumption

The TWILIGHT study was designed as a randomized, superiority trial comparing the occurrence of BARC type 2, 3 or 5 bleeding events over one year between patients undergoing PCI treated with ticagrelor plus ASA versus ticagrelor plus placebo. Assuming a one-year event rate of 4.5%, the trial would require a total randomized cohort of 8200 patients to detect a hazard ratio of 0.72 with 80% power. As randomization occurs 3 months after PCI, a total enrolled sample of 9,000 participants was estimated to achieve the required sample size.

During the course of the trial the rate of randomization ineligibility was higher than originally anticipated (~ 20% vs. expected 10%), implying a final randomized sample smaller than 8200. To inform whether or not this might influence study power the TWILIGHT Executive Committee requested that the DSMB statistician perform an independent evaluation of the overall pooled primary EP event rate and estimate sample size using original trial assumptions.

This analysis took place in 10/2017, at which point 5074 patients had been randomized. The estimated one-year event rate for BARC 2, 3 or 5 bleeding was higher than originally projected, thus yielding adequate power to detect an effect size of 0.72 under original sample size assumptions. Accordingly, the TWILIGHT EC elected to not modify the sample size or other statistical assumptions.

12.0 Table Listings

1. Enrolled Cohort

1.1 Registration (Clinical Inclusion, Angiographic Inclusion, Exclusion)

1.1.1 Baseline demographics (age, sex, race, country)
1.1.2 Baseline clinical and medical history (risk factors)
1.1.3 Baseline medications (taken chronically as recorded in EDC)
1.1.4 Baseline Laboratory assessment
1.1.5 Baseline Angiographic details
1.1.6 Baseline Intervention details
1.1.7 Discharge Medications
1.2.1 Site-Reported Cessation
1.2.1.1 30-day binary frequency and KM estimates
1.2.1.2 90-day binary frequency and KM estimates
1.2.2 Adjudicated Cessation
1.2.2.1 30-day binary frequency and KM estimates
1.2.2.2 90-day binary frequency and KM estimates
1.2.3 Site reported Bleeding Events
1.2.3.1 30-day binary frequency and KM estimates
1.2.3.2 90-day binary frequency and KM estimates
1.2.4 Adjudicated Bleeding Events
1.2.4.1 30-day binary frequency and KM estimates
1.2.4.2 90-day binary frequency and KM estimates
1.2.5 Site reported ischemic events
1.2.5.1 30-day binary frequency and KM estimates
1.2.5.2 90-day binary frequency and KM estimates
1.2.6 Adjudicated ischemic events
1.2.6.1 30-day binary frequency and KM estimates
1.2.6.2 90-day binary frequency and KM estimates
1.2.7 Mortality assessment
1.2.7.1 30-day, 90-day, 18-month binary frequency and KM estimates
1.2.8 Subject disposition
1.2.8.1 Lost/Consent withdrawn at 30 and 90 days
1.2.9 Randomization disposition
1.2.9.1 Reasons for randomization ineligibility

2 Randomized ITT Cohort (37 tables)

2.2 Registration (Clinical Inclusion, Angiographic Inclusion, Exclusion)

2.2.1 Baseline demographics (age, sex, race, country)
2.2.2 Baseline clinical and medical history (risk factors)
2.2.3 Baseline medications (taken chronically as recorded in EDC)
2.2.4 Baseline Laboratory assessment
2.2.5 Baseline Angiographic details
2.2.6 Baseline Intervention details
2.2.7 Discharge Medications
2.2.8 Site-Reported Cessation
2.2.8.1 4-month binary frequency, KM estimates, pill count (30 day post randomization)
2.2.8.2 9-month binary frequency, KM estimates, pill count (180 days post randomization)
2.2.8.3 15-month binary frequency, KM estimates, pill count (365 days post randomization)
2.2.9 Adjudicated Cessation
2.2.9.1 4-month binary frequency, KM estimates (30 day post randomization)

2.2.9.2 9-month binary frequency, KM estimates (180 days post randomization)
2.2.9.3 15-month binary frequency, KM estimates (365 days post randomization)
2.2.10 Site reported Bleeding Events
2.2.10.1 4-month binary frequency and KM estimates
2.2.10.2 9-month binary frequency and KM estimates
2.2.10.3 15-month binary frequency and KM estimates
2.2.10.4 18-month binary frequency and KM estimates
2.2.11 Adjudicated Bleeding Events
2.2.11.1 4-month binary frequency and KM estimates
2.2.11.2 9-month binary frequency and KM estimates
2.2.11.3 15-month binary frequency and KM estimates
2.2.11.4 18-month binary frequency and KM estimates
2.2.12 Site reported ischemic events
2.2.12.1 4-month binary frequency and KM estimates
2.2.12.2 9-month binary frequency and KM estimates
2.2.12.3 15-month binary frequency and KM estimates
2.2.12.4 18-month binary frequency and KM estimates
2.2.13 Adjudicated ischemic events
2.2.13.1 4-month binary frequency and KM estimates
2.2.13.2 9-month binary frequency and KM estimates
2.2.13.3 15-month binary frequency and KM estimates
2.2.13.4 18-month binary frequency and KM estimates
2.2.14 15 Month Study Visit
2.2.14.1 Standard of care therapy
2.2.15 Landmark Events (Between 15 and 18 months)
2.2.15.1 Site-reported Bleeding (binary frequency/KM estimates)
2.2.15.2 Site-reported Ischemic (binary frequency/KM estimates)
2.2.15.3 Adjudicated Bleeding (binary frequency/KM estimates)
2.2.15.4 Adjudicated Ischemic (binary frequency/KM estimates)
2.2.16 Subject disposition
2.2.16.1 Lost/Consent withdrawn at 4, 9, 15 and 18 months
2.2.16.2 Vital status obtained at 4, 9, 15 and 18 months

13.0 Reporting Conventions

P-values ≥0.001 will be reported to 3 decimal places; p-values less than 0.001 will be reported as “<0.001”. The mean, standard deviation, and any other statistics other than quantiles will be reported to one decimal place greater than the original data. Quantiles, such as median, or minimum and maximum will use the same number of decimal places as the original data. Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) will be reported to 3 significant figures.

14.0 List of References

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Statistical Analysis Plan – Summary of Changes for TWILIGHT trial (NCT02270242)

Section	Version 1.0	Version 1.4	Summary
5.3 Other Secondary Endpoints	• BARC types 3 or 5 • TIMI minor or major • GUSTO mod/severe/life-threatening • ISTH major	• BARC types 3 or 5 • TIMI minor or major • GUSTO mod/severe/life-threatening • ISTH major TIMI major • GUSTO severe/life threatening	Inclusion of TIMI major and GUSTO severe/life-threatening
5.3 Other Secondary Endpoints	• Cardiovascular death, non-fatal MI, ischemic stroke or clinically-driven revascularization • Cardiovascular death, non-fatal MI or ischemic stroke • Definite or probable stent thrombosis • Cardiovascular death • Non-fatal MI • Cardiovascular death, non-fatal MI or def/prob stent thrombosis • Ischemic stroke • All-cause death	• All-cause death, MI, ischemic stroke • Cardiovascular death, non-fatal MI, ischemic stroke or clinically-driven revascularization • Clinically-driven revascularization • Cardiovascular death, MI or ischemic stroke • Definite or probable stent thrombosis • Cardiovascular death • MI (fatal or non-fatal) • Cardiovascular death, MI or def/prob stent thrombosis • Ischemic stroke • Any stroke • All-cause death • All-cause hospitalization (based upon site-reported adverse event listings)	Inclusion of additional EP: • hospitalization, • any stroke, • all-cause death, MI, ischemic stroke • clinically driven revasc
8.0 Subgroups	High bleeding Risk criteria	Modified to conform to HBR ARC definition	Updated criteria to reflect consensus definition of HBR
8.0 Subgroups	High Lesion Procedural risk criteria (severe calcification requiring atherectomy)	Changed to: moderate or severe calcification or atherectomy use	Modified to be more inclusive of high risk lesion features
10.1 Analysis for Primary Endpoints	The null hypothesis for this analysis is that the HR for the treatment group (H0) = 1. The alternative hypothesis is that the HR for the treatment group (HA) ≠ 1. A test of superiority at the two-sided 0.05 level will be performed and the null hypothesis will be rejected if the HR and 95% CI excludes one	The null hypothesis (H0) for this analysis is that the HR = 1. The two-sided alternative hypothesis (HA) is that the HR ≠ 1. A test of superiority at the two-sided 0.05 level will be performed using a p-value from a log-rank test and serves as the main hypothesis test for the primary endpoint. The treatment effect for the primary endpoint will also be expressed as an absolute risk difference with a two-sided 95% CI, calculating using the Kaplan-Meier estimates at the 15 month (12 months after randomization) time point.	Modified language to be more clear and explicit. Also added that treatment effect will be expressed as absolute risk difference to be consistent with key secondary endpoint.
10.2 Analysis for the Key Secondary EP	(New Text)	The treatment effect for the key secondary endpoint will also be expressed as a HR and two-sided 95% CI generated from a Cox proportional hazards model that includes treatment group (ticagrelor monotherapy versus ticagrelor plus ASA) as a covariate.	New language to indicate that the key secondary EP will also be expressed as HR (95% CI) to maintain consistency with the primary EP.
10.4.1 18-Month Analyses	"… with event-free patients censored at the time of death, last contact date (for subjects withdrawing consent of lost to follow-up) or 455 days after randomization"	"… with event-free patients censored at the time of death, last contact date (for subjects withdrawing consent of lost to follow-up) or 456 days after randomization"	Modified censoring rule as 15 months after randomization (30.4 * 15) = 456
10.6.2 Baseline imbalance adjustment	Accordingly, differences in all baseline data elements will be formally compared between randomized groups. Variables displaying significant differences with prognostic impact on either the primary or key secondary endpoints will be included as additional covariates in Cox models estimating treatment effects.	Covariate Adjustment: Accordingly, the treatment effects for both primary and key secondary endpoints will be adjusted for covariates that are plausibly related to each respective outcome and included in the Cox models as described in Sections 10.1 and 10.2: Primary endpoint: age (continuous); sex; body mass index (weight [kg]/height [m]2); NSAID use; haemoglobin (continuous); estimated glomerular filtration rate (eGFR, continuous); prior bleeding.	Modified section from baseline imbalance to covariate adjustment and pre-specified criteria that will be used to adjust treatment effect in sensitivity analyses

		Key secondary endpoint: age (continuous); sex; PCI indication (NSTEMI/Unstable angina/stable or asymptomatic); diabetes mellitus (insulin requiring/non-insulin requiring/none); current cigarette smoking; prior MI; prior coronary revascularization (prior PCI or prior CABG); stent length (continuous); minimum stent diameter (continuous); stent type (durable-polymer everolimus-eluting stent/durable-polymer zotarolimus-eluting stent/biodegradable-polymer DES/other)	
10.7.5 Subgroups (Stable ischemic heart disease)	(New text)	Included new language for analyses relating to stable presentations	Added additional subgroup for SIHD
11.0 Randomization Ineligibility	(New text)	Added new paragraph to summarize actions taken by the Executive committee in response to higher than anticipated rate of randomization ineligibility at 90 days. As pooled event rate for the primary EP (as assessed by the DSMB) was higher than anticipate, trial power was thought to be preserved. Therefore no changes to sample size, power, analytic approach were made	New language to document rationale for EC to not alter sample size or study assumptions although randomization rate was lower than projected

Statistical Analysis Plan Signature Page

Ticagrelor With Aspirin or Alone In High-Risk Patients After Coronary Intervention

Sponsor: Icahn School of Medicine at Mount Sinai

Date: April 11, 2019

Version: 1.4

We, the undersigned, have read and approve this Statistical Analysis Plan and agree to its content.

Trial Statistician, Timothy Collier

06/18/2019

Date

Trial Principal Investigator, Roxana Mehran MD

June 18, 2019

Date

Statistical Analysis Plan Author, Usman Baber, MD MS

6/18/2019

Date