CLINICAL STUDY PROTOCOL

Protocol title:	A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety, Tolerability, and Effect on Microvascular Obstruction of Temanogrel in Subjects Undergoing Percutaneous Coronary Intervention
Protocol number:	APD791-202
Version:	Amendment 3.0, dated 17 May 2022
Compound name or number:	Temanogrel (APD791)
Study phase:	Phase 2
Indication:	Prevention and treatment of microvascular obstruction
EudraCT:	2020-000238-16
Sponsor name:	Arena Pharmaceuticals, Inc.
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Sponsor approval:	This protocol was approved by the Sponsor's Responsible Medical Officer, or delegate. The electronic signature manifest is appended.

Confidentiality Statement

PROTOCOL HISTORY

Document	Amendment Type	Date
Amendment 3.0	Global	17 May 2022
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PROTOCOL SYNOPSIS

Sponsor: Arena Pharmaceuticals, Inc.

Name of investigational study drug: Temanogrel (APD791)

Protocol title: A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety, Tolerability, and Effect on Microvascular Obstruction of Temanogrel in Subjects Undergoing Percutaneous Coronary Intervention

Protocol number: APD791-202

Phase: 2

Country(ies)/region(s) (planned): United States, Europe, and Australia

Objectives:

Primary:

- To assess the effect of temanogrel on MVO following PCI

Secondary:

- To assess the effect of temanogrel on selected coronary physiology indices and angiographic measures following PCI
- To assess the effect of temanogrel on myocardial injury following PCI
- To assess the pharmacokinetics (PK) of temanogrel and its active metabolites AR295980 (M1) and AR295981 (M2) in subjects undergoing PCI
- To assess the safety and tolerability of temanogrel in subjects undergoing PCI

Study Design:

This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled study to be conducted in 2 stages (Stage A and Stage B). Each stage includes a Screening Period of up to 14 days, a single dose of randomized study treatment (temanogrel or placebo) on Day 1 (day of PCI procedure), and a Follow-Up phone call 7 days (± 2 days) after administration of study treatment for a total study duration of 6 to 24 days.

Upon confirmation of all inclusion/exclusion criteria, eligible subjects will be randomized on Day 1. Study treatment will be administered following assessment of Baseline angiographic measures, index of microcirculatory resistance (IMR) and additional coronary physiology indices, and blood sample collection (for assessment of peripheral serotonin concentration and additional laboratory assessments). Each subject will receive an intravenous (IV) single dose of study treatment. Assessment of IMR and additional coronary physiology indices will be repeated after administration of study treatment and before the start of the PCI procedure to obtain Pre-PCI values. Immediately after completion of PCI, the following assessments will be performed to obtain Post-PCI values: Assessment of IMR and additional coronary physiology indices, angiographic measures, and collection of blood samples (obtained from the coronary ostium and coronary artery distal to the lesion for assessment of coronary artery serotonin

concentration, as well as venous blood samples for peripheral serotonin concentration and additional laboratory assessments).

Stage A is an ascending single-dose study planned to consist of 2 cohorts. After treatment of each cohort in Stage A, a safety/tolerability assessment will be conducted by the Data and Safety Monitoring Board (DSMB). Following the safety review of the first cohort in Stage A, the DSMB will recommend whether dose escalation to the next planned dose level in Stage A should occur; the DSMB may also recommend evaluation of an alternative dose in the second cohort in Stage A. Following the safety review of the second cohort in Stage A, the DSMB will recommend whether progression to Stage B should occur; the DSMB may also recommend evaluation of an alternative dose in an additional third dose cohort in Stage A prior to progression to Stage B. After conduct of the final cohort and safety review of Stage A, Stage B may begin. Stage B is a parallel-treatment group study planned to consist of a placebo group and 2 active treatment groups (temanogrel doses selected based on safety and tolerability data in Stage A). In Stage B, enrollment will consist of no more than 25% elective PCI subjects and randomization will be stratified subject type (elective PCI or PCI for non-ST-elevation myocardial infarction [NSTEMI]/unstable angina [UA]).

Subjects should be treated with aspirin and an oral $P2Y_{12}$ inhibitor (ie, dual antiplatelet therapy [DAPT]) per site standard of care; however, subjects in Stage A may only be treated with clopidogrel as the $P2Y_{12}$ inhibitor DAPT component and may not be treated with prasugrel or ticagrelor until after the subject has completed study participation.

Number of subjects (planned):

Approximately 99 subjects are planned to be enrolled in this study. In Stage A, 2 cohorts are planned and approximately 6 subjects will be enrolled in each cohort (4 temanogrel:2 placebo per cohort). One additional cohort (4 temanogrel:2 placebo per cohort) may be enrolled to explore an additional dose if deemed appropriate based upon data reviews of prior cohorts. In Stage B, approximately 87 subjects are planned to be enrolled (29 subjects in each of the 2 temanogrel treatment groups and the placebo group).

Eligibility criteria:

Inclusion criteria:

Subjects must meet ALL of the following inclusion criteria to be eligible for enrollment into the study:

1. Stable angina patients suitable for elective PCI or patients suitable for PCI for diagnosis of NSTEMI/UA. NSTEMI/UA patients are to be consistently hemodynamically stable until the time of PCI and have a thrombolysis in myocardial infarction (TIMI) Flow Grade () 2 or 3 on the diagnostic angiography.
2. Target lesions for PCI must appear suitable for stenting as confirmed on the diagnostic angiography. Acceptable lesions cannot be in the left main artery or in a vein or arterial graft, or be a chronic total occlusion or in-stent restenosis. Two or more sequential lesions may be treated in the same artery, as long as they are treated in the same session and at least one of the lesions meets inclusion criteria.

- For elective PCI patients and non-urgent NSTEMI/UA patients (PCI >12 hours after diagnosis), the lesion must be located in a ≥ 2.75 mm diameter coronary artery; the lesion must also be ≥ 18 mm long and require the use of one or more stents that in total must be ≥ 20 mm long.
- For NSTEMI patients treated with PCI urgently (within 12 hours after diagnosis), the coronary artery diameter of the culprit lesion must be ≥ 2.75 mm.

3. 30 to 80 years of age, inclusive
4. Female subjects must not be lactating at the time of Screening
5. Females must meet criterion a and males must meet criterion b to qualify for the study:
   a. Females must not be of childbearing potential by one of the following:
      - Postmenopausal, defined as no menses for 12 months without an alternative medical cause
      - Permanent sterilization procedure, such as hysterectomy, bilateral salpingectomy, or bilateral oophorectomy
   b. Males with pregnant or non-pregnant female partners of childbearing potential must agree to using a condom during treatment and for 90 days following treatment
6. Body mass index 18.0 to 40.0 kg/m^2, inclusive
7. Willing to participate in the study and provide written informed consent

Exclusion criteria:

Subjects will be excluded from the study if they meet ANY of the following key exclusion criteria:

1. Planned or anticipated use of rotational atherectomy/ablation or shockwave therapies during the PCI procedure
2. Any history of stroke, seizure, intracranial bleeding, or intracranial aneurysm
3. Transient ischemic attack within the 6 months prior to Screening
4. History of major trauma, major surgery, and/or clinically significant head injury or hemorrhage within the last 6 months of Screening
5. Any ST-elevation myocardial infarction (STEMI) within 10 days of Screening or STEMI within the target vessel territory within the last 4 months of Screening (eg, a patient with a NSTEMI because of a lesion in a diagonal may not be included if there is a history of anterior STEMI due to left anterior descending artery [LAD] lesion that occurred within the last 4 months)
6. Known history of heart failure with reduced ejection fraction (HFrEF) defined as left ventricular ejection fraction ≤ 40% prior to current hospital admission
7. Vasculitis within the last 6 months of Screening
8. Known contraindication or allergy to heparin (eg, history of heparin-induced thrombocytopenia [HIT]), any antiplatelet agents (ie, aspirin, $P2Y_{12}$ inhibitors), or adenosine

9. Use of any strong inhibitors or inducers of cytochrome P450 (CYP)3A4 or P-glycoprotein (examples include, but are not limited to, St. John's wort, ketoconazole, itraconazole, clarithromycin, erythromycin, rifampicin, and verapamil) within 14 days or 5 half-lives (whichever is longer), relative to Check-in. Intra-arterial use of verapamil for subjects undergoing radial artery PCI is permitted
10. Consumption of grapefruit within 3 days of Check-in
11. Use of medications affecting the serotonin system (eg, selective serotonin reuptake inhibitors [SSRIs], serotonin-norepinephrine reuptake inhibitors [SNRIs], atypical [second generation] antipsychotics possessing 5-HT_{2A} pharmacology, or any other serotonergic agents possessing 5-HT_{2A} pharmacology [eg, the triazolopyridine antidepressant, trazodone]) within 14 days of Check-in
12. Treatment with cangrelor or glycoprotein IIb/IIIa inhibitors within 24 hours of Check-in
13. Need for chronic oral anticoagulant (eg, warfarin or direct oral anticoagulants [DOACs], including direct oral thrombin inhibitors) for any condition (eg, treatment of atrial fibrillation, deep vein thrombosis, or prosthetic cardiac valve) within 1 week of Check-in
14. For subjects in Stage A ONLY: Use of prasugrel or ticagrelor within 14 days of Check-in

Additional exclusion criteria are listed in Section 4.2.

Test product, dose, and mode of administration:

Temanogrel is an IV formulation containing active pharmaceutical ingredient provided as 25 mg/mL strength. Temanogrel IV solution will be prepared by blinded study staff. Subjects assigned to active treatment will receive 1 single dose in total as a 5 mL IV bolus administered in the forearm over duration of at least 5 minutes.

The temanogrel dose to be administered to Cohort 1 of Stage A will be 20 mg. The dose administered in Cohort 2 is planned to be 40 mg. One additional dose cohort may be explored in Stage A if deemed appropriate based upon data reviews of prior cohorts. Selected doses from Stage A are planned to be investigated in Stage B of the study. Planned doses in Stage A and Stage B may be adjusted depending on the safety and tolerability results of previous cohort(s). Doses in this study will not exceed 40 mg.

Duration of treatment:

Subjects will receive a single IV dose of study treatment on Day 1 of the study.

Reference therapy, dose, and mode of administration:

Placebo will be packaged to match temanogrel. Volume and mode of administration of placebo will match that of temanogrel to maintain the blind.

Endpoints:

Primary endpoint:

- Change in IMR from Baseline to Post-PCI

Secondary endpoints:

- Change from Baseline to Post-PCI for the following assessments:
  - Coronary physiology indices (coronary flow reserve [CFR], fractional flow reserve [FFR])
  - Angiographic measures (corrected thrombolysis in myocardial infarction frame count [cTFC], TFG, thrombolysis in myocardial infarction myocardial perfusion grade [TMPG])
  - Myocardial injury markers (creatine kinase [CK], creatine kinase-myocardial band [CK-MB], cTn)

  Note: Post-PCI measure for CK, CK-MB, and cTn, is collected 4 to 6 hours after completion of the PCI procedure and not immediately after completion of the procedure.
- The incidence of procedural myocardial injury defined as elevation of cTn values > 99th percentile upper reference limit (URL) in subjects with normal Baseline values (≤ 99th percentile URL) or elevation of cTn by > 20% of the Baseline value in subjects with elevated cTn levels (> 99th percentile URL)
- Concentration of temanogrel and active metabolites AR295980 and AR295981 prior to PCI and at selected post-PCI timepoints until discharge
- Safety and tolerability of temanogrel

Pharmacokinetic assessments:

Plasma concentrations of temanogrel (and its metabolites, AR295980 and AR295981) will be measured for each PK collection timepoint. Collected plasma PK samples may also be used for profiling of drug binding proteins, bioanalytical method validation purposes, stability assessments or to assess other actions of temanogrel (and/or its metabolites) with plasma constituents.

Relationships between plasma concentration of selected analytes (temanogrel, its active metabolites, and/or all analytes combined) and selected PD measures (eg, change from Baseline to Post-PCI in IMR and other cardiac physiology indices, angiographic measures, markers of myocardial injury/infarction, or markers of inflammation) may be explored.

Pharmacodynamic assessments

Assessments of PD will include coronary physiology indices (IMR, coronary flow reserve [CFR], FFR), angiographic measures (cTFC, TFG, TMPG, QCA, assessment of lesion and vessel characteristics), markers of myocardial injury (CK, CK-MB, cTn), and markers of inflammation.

Safety assessments:

Safety assessments will include assessment of adverse events, vital signs, clinical laboratory tests, ECGs, and physical examinations.

Statistical methods:

Sample size:

Approximately 99 subjects are planned to be enrolled in this study (12 in Stage A, 87 in Stage B).

It is assumed that the primary endpoint, which is the change from Baseline in IMR measured immediately after PCI, is normally distributed with a mean of 6 and standard deviation (SD) of 3.5. Assuming a 1:1:1 randomization, 90 evaluable subjects (30 subjects in each of the two temanogrel treatment groups and placebo) is sufficient to achieve at least 90% power to detect a treatment effect of 3 (a clinically significant reduction of 50% from placebo) between each of the temanogrel treatment groups and placebo by a 2-sample t-test using a 2-sided significance level of 0.05.

The primary endpoint analysis will be based on pooled data from subjects in Stage A and Stage B.

Stratification:

Randomization in Part B will be stratified by subject type (elective PCI or PCI for NSTEMI/UA).

Testing strategy:

No formal testing strategy or adjustments of the Type I error will be employed for the evaluation of secondary or exploratory endpoints. Estimates and confidence intervals (CI) for treatment groups and from pairwise comparisons will be reported in an exploratory manner.

Statistical analysis:

The primary and secondary endpoints will be analyzed using the Full Analysis Set (FAS) and safety endpoints will be performed using the Safety Set. Other important statistical considerations, such as sensitivity analyses, and subgroup analyses will be described in the Statistical Analysis Plan (SAP).

The primary endpoint of the study is the change from Baseline in IMR measured immediately after PCI. The primary PD analysis will be analyzed using analysis of covariance (ANCOVA) with a model that includes treatment group and randomization stratification factor as factors and Baseline IMR as a covariate. Least square means, standard errors (SEs), and 95% CIs for the treatments and their difference will be presented together with their p-values.

Unless otherwise specified, secondary continuous endpoints will be analyzed using ANCOVA with a model that includes treatment group and randomization stratification factor as factors and Baseline IMR value and Baseline values as covariates. Least square means, SEs, and 95% CIs for the treatments and their difference will be presented together with their p-values. Proportion-based secondary endpoints will be analyzed in the FAS using the Cochran-Mantel-Haenszel method adjusted for randomization stratification factor. The number and percentage of subjects achieving the goal and the difference in proportion between treatment groups achieving the goal, along with p-value and the 95% CIs will be

reported. The odds ratio relative to placebo and percentage of difference from placebo will be presented together with corresponding 95% CIs and the p-values.

Pairwise comparisons of each temanogrel treatment group compared to placebo will be conducted. In addition, analyses of the pooled temanogrel treatment groups compared to placebo will be conducted.

Where statistical assumptions (eg, normality, proportional odds) are not met, alternative approaches will be evaluated (eg, non-parametric analysis, log transformation).

Details regarding the statistical analyses will be provided in the SAP.

Pharmacokinetic analysis:

The PK analysis will be conducted using model independent methods and based on plasma concentrations of temanogrel and its metabolites from subjects who have received temanogrel and have evaluable plasma concentration versus time profiles. The Pharmacokinetic Set will be used to analyze plasma concentrations. Detailed PK analysis procedures will be provided in the SAP.

Safety analysis:

Adverse Event will be listed and summarized by system organ class and preferred term, as well as according to severity and causality/relationship to temanogrel. Treatment-emergent adverse events (TEAEs) will be summarized by stage, cohort, and treatment group. In addition, TEAEs will be pooled across treatment groups (ie, placebo, temanogrel). Similarly, bleeding events will be summarized by Bleeding Academic Research Consortium (BARC) classification by stage, cohort, and treatment group and pooled across treatment groups. Observed values for clinical laboratory tests, vital signs, and safety 12-lead ECGs, will be summarized by stage, cohort, treatment group, and timepoint. Individual data listings of clinical laboratory tests results will be presented for each subject. Observed values and changes from Baseline will be summarized descriptively. Safety 12-lead ECG data (observed values and change from Baseline) will be listed for each subject and timepoint. Observed values will be classified for normal, abnormality that is not clinically significant, and clinically significant abnormality by stage, cohort, treatment, and timepoint of collection. Results of other safety assessments will be listed and summarized as appropriate.

Interim analysis:

No formal interim analysis of efficacy is planned.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Explanation
5-HT	serotonin
ACC	American College of Cardiology
ACS	acute coronary syndrome
ADP	adenosine diphosphate
ADR	adverse drug reaction
AHA	American Heart Association
ALP	alkaline phosphate
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
APD791	temanogrel
aPTT	activated partial thromboplastin time
Arena	Arena Pharmaceuticals, Inc.
AST	aspartate aminotransferase
$AUC_{0-\infty}$	area under the single-dose plasma or serum concentration-time curve extrapolated to infinity
AUC_{0-t}	area under the plasma concentration vs. time curve from time zero to the time of the last quantifiable plasma sample
BARC	Bleeding Academic Research Consortium
BUN	blood urea nitrogen
CABG	coronary artery bypass graft
CAD	coronary artery disease
CFR	coronary flow reserve
CI	confidence interval
CK	creatine kinase
CKD-Epi	Chronic Kidney Disease Epidemiology Collaboration
CK-MB	creatine kinase-myocardial band
C_{max}	observed maximum plasma concentration
CMP	Clinical Monitoring Plan
CMR	cardiac magnetic resonance
CRO	Contract Research Organization
cTFC	corrected thrombolysis in myocardial infarction frame count
cTn	cardiac troponin
cTnI	cardiac troponin I
CVD	cardiovascular disease

Abbreviation	Explanation
CYP	cytochrome P450
DAPT	dual antiplatelet therapy
DNA	deoxyribonucleic acid
DOAC	direct oral anticoagulants
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
ESC	European Society of Cardiology
FAS	Full Analysis Set
FDA	Food and Drug Administration
FFR	fractional flow reserve
GCP	Good Clinical Practice
HIT	heparin-induced thrombocytopenia
HIV	human immunodeficiency virus
HR	heart rate
hs-CRP	highly sensitive C-reactive protein
hs-cTnT	high-sensitive cardiac troponin T
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IL	interleukin
IMR	index of microcirculatory resistance
IMR_{corr}	IMR corrected for the influence from collateral supply
IND	Investigational New Drug
INR	international normalized ratio
IRB	Institutional Review Board
IRT	interactive response technology
IV	intravenous
K_i	inhibition constant
LAD	left anterior descending artery
LDH	lactate dehydrogenase
M1	AR295980

Abbreviation	Explanation
M2	AR295981
MBG	myocardial blush grade
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	modified Full Analysis Set
MI	myocardial infarction
MVO	microvascular obstruction
NSTEMI	non-ST-elevation myocardial infarction
P_a	mean aortic pressure at max hyperemia
PCI	percutaneous coronary intervention
PD	pharmacodynamic
P_d	mean distal coronary pressure at max hyperemia
PK	pharmacokinetic
PRP	platelet-rich plasma
PT	prothrombin time
PTX-3	Pentraxin-3
P_w	coronary wedge pressure
q8h	every 8 hours
QCA	quantitative coronary analysis
QTcB	corrected QT interval using Bazett's formula
QTcF	corrected QT interval using Fridericia's formula
RBC	red blood cell
RNA	ribonucleic acid
RSI	reference safety information
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SE	standard error
SNRI	serotonin-norepinephrine reuptake inhibitor
SOP	standard operating procedure
SSRI	selective serotonin reuptake inhibitor
STEMI	ST-elevation myocardial infarction

Abbreviation	Explanation
$t_{½}$	apparent terminal elimination half-life
TEAE	treatment emergent adverse event
TFG	thrombolysis in myocardial infarction flow grade
TIMI	thrombolysis in myocardial infarction
t_{max}	observed time of C_{max}
TMF	trial master file
T_{mn}	mean transit time at maximal hyperemia
TMPG	TIMI myocardial perfusion grade
TNF-α	tumor necrosis factor alpha
TSH	thyroid-stimulating hormone
UA	unstable angina
ULN	upper limit of normal
URL	upper reference limit
US	United States
V_d	volume of distribution
WBC	white blood cell
WHF	World Heart Federation

1. INTRODUCTION

Cardiovascular disease (CVD), is the leading cause of death globally (WHO 2017). Among CVD, coronary artery disease (CAD) is the single most common cause of death, resulting in 1 in every 4 deaths in the US (CDC 2017). The main cause of CAD is atherosclerosis, an inflammatory disease characterized by focal thickenings of the arterial intima containing lipids, connective tissue, and various cell types. Atherosclerotic plaque build-up progressively narrows the lumen of coronary arteries and leads to clinical symptoms such as angina. Highly inflammatory and unstable plaques (vulnerable plaques) may eventually rupture and lead to potentially fatal events such as myocardial infarction (MI) (Hansson 2011). In both cases, the prevention of oxygen delivery to the myocardium through impaired or blocked coronary blood flow gives rise to clinical events.

Significant advances have been made in medical therapy to prevent or treat CAD; however, since the disease is often detected in a late stage and difficult to reverse, a large percentage of patients remain symptomatic or develop complications and require invasive, mechanical interventions such as percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) (Kolh 2014, Neumann 2019). Despite broad implementation of primary PCI and an improvement in "door-to-balloon" times, corresponding improvement in mortality has plateaued in recent years (Menees 2013). Notably, a significant proportion of patients undergoing PCI, mainly for treatment of acute coronary syndrome (ACS), fail to achieve full myocardial or microcirculatory reperfusion despite resolution of the epicardial coronary occlusion (Bouleti 2015, Rezkalla 2017). This is sometimes expressed angiographically as slow/no-reflow, but even in cases with normal epicardial flow, microvascular obstruction (MVO) can detrimentally affect microcirculatory perfusion and has been reported in approximately 40-60% of patients undergoing PCI for ST-elevation myocardial infarction (STEMI) and in up to 30% of cases in the non-STEMI (NSTEMI) population (higher in severe NSTEMI cases) (Carrick 2016, Cuculi 2014, de Waha 2017, Durante 2017, Guerra 2014, McGeoch 2010, Niccoli 2016, Van Assche 2011, van Kranenburg 2014). Importantly, the presence of MVO post-PCI has been associated with worse clinical outcomes including mortality and hospitalization for heart failure, related to suboptimal cardiac function and recovery in the days and months following the PCI procedure (Carrick 2016, de Waha 2017, Fearon 2013, McGeoch 2010, Niccoli 2016, Nijveldt 2008, Orn 2009). Several treatment options have been explored including the use of vasodilators and antiplatelet agents; however, clinical efficacy data from these interventions is limited and currently no treatment has been demonstrated to be beneficial for prevention or treatment of MVO following PCI (Jaffe 2010, Niccoli 2016, Rezkalla 2017, Salinas 2012). Therefore, there is an unmet need for safe and effective agents to prevent and treat MVO in the PCI setting, resulting in improved cardiac functional recovery and clinical outcomes.

In patients with CAD/ACS, particularly those with complex lesion morphology, levels of serotonin (5-HT) are elevated and associated with cardiac events (Rouzaud Laborde 2013, van den Berg 1989, Vikenes 1999). During angioplasty or PCI, levels of 5-HT may be further increased when platelets become activated following rupture of the atherosclerotic plaque, which can be either procedure-induced or occur spontaneously (Adlbrecht 2007, Golino 1994, Kleinbongard 2013, Kleinbongard 2011, Leosco 1999). Upon activation, platelets release 5-HT in substantial quantities causing amplification of platelet aggregation, vasoconstriction, and cardiac remodeling (Mc Fadden 1993, Rouzaud-Laborde 2015). Specifically, 5-HT acts on

5-HT_{2A} receptors on the surface of platelets to amplify aggregation induced by other factors such as adenosine diphosphate (ADP), collagen, or damaged endothelium (De Clerck 1983, De Clerck 1990) and acts as a potent stimulator of vasoconstriction by activating 5-HT_{2A} receptors on smooth muscle cells (Wright 1992). 5-HT release from activated platelets has been implicated in mediating an exaggerated platelet response in patients with ACS (Shimbo 2002), resulting in platelet aggregation and thrombus formation (Benedict 1986, Li 1997). Additionally, release of 5-HT in the coronary circulation during angioplasty or PCI is associated with vasoconstriction distal to the lesion site, and this effect could be attenuated with 5-HT_{2A} antagonism (Golino 1994, Kleinbongard 2011, Leosco 1999). Thus, 5-HT is elevated in the PCI setting and is implicated in pathological mechanisms associated with development of MVO (eg, vasoconstriction, platelet activation), which may contribute to slow/no reflow and more severe myocardial damage (Carrick 2016, De Maria 2019, Niccoli 2009, Payne 2012). Based on evidence suggesting an important role of 5-HT in amplification of platelet aggregation and vasoconstriction within the microcirculation at the time of PCI, blocking the 5-HT-mediated effects in this setting is anticipated to prevent or minimize the development of MVO.

Study APD791-202 is a multicenter, randomized, blinded, placebo-controlled, Phase 2 study to assess the safety, tolerability, pharmacokinetic (PK), and pharmacodynamic (PD) of intravenous (IV) temanogrel after administration of single doses to subjects undergoing PCI. The study will be conducted in compliance with ICH guidelines for GCP and applicable regulatory requirements, the study protocol, and where applicable, Sponsor and/or Contract Research Organization (CRO) standard operating procedures (SOPs).

1.1. Background

Temanogrel (APD791) is a chemical entity being developed by Arena Pharmaceuticals, Inc. (Arena) for the treatment of MVO. As a potent inverse agonist of the 5-HT_{2A} receptor, temanogrel inhibits 5-HT-mediated amplification of platelet aggregation and blocks 5-HT-mediated vasoconstriction through its action at 5-HT_{2A} receptors on the surface of platelets and smooth muscle cells, respectively. CCI [redacted]

Studies using rabbit aorta showed that temanogrel blocked 5-HT-induced vasoconstriction, and dose dependently inhibited 5-HT-stimulated proliferation of rabbit aortic smooth muscle cells (Adams 2007, Adams 2009). Furthermore, temanogrel inhibited 5-HT-mediated amplification of in vitro ADP-induced platelet aggregation in human, monkey, and canine platelet-rich plasma (PRP) in a dose-dependent manner. Oral administration of temanogrel to canines was highly effective at inhibiting 5-HT-mediated amplification of collagen-induced platelet aggregation ex vivo at 1 hour after study treatment administration. In the canine Folts model of coronary artery occlusion (Przyklenk 2010), IV temanogrel infusion over a 3-hour period was associated with increased flow-time area and reduced duration of zero flow over the same time period compared to placebo. These improvements were not accompanied by any increase in bleeding.

A complete summary of the nonclinical data relevant to the investigational product and its study in human subjects is provided in the current edition of the Investigator's Brochure (IB).

1.1.1. Clinical Experience

The safety, tolerability, pharmacokinetic (PK), and pharmacodynamic (PD) of orally administered temanogrel and its primary metabolites AR295980 and AR295981 have been evaluated in 4 completed Phase 1 studies in healthy adult human subjects, 2 in the US and 2 in South Korea. The US studies evaluated safety, tolerability, PK, and PD effects of single and repeated doses of oral temanogrel. The 2 studies conducted in South Korea evaluated safety, tolerability, PK, and PD effects of single and repeated doses of temanogrel alone and co-administered with aspirin and clopidogrel (dual antiplatelet therapy [DAPT]).

Intravenously administered temanogrel has been evaluated in 1 Phase 1 clinical study in healthy adult human subjects. The study evaluated safety, tolerability, PK, and PD of temanogrel and its primary metabolites AR295980 and AR295981 after administration of single IV doses.

A complete summary of the clinical data relevant to the investigational product and its study in human subjects is provided in the current edition of the IB.

1.2. Benefit-Risk Considerations

As of the date of this protocol, the safety, tolerability, PK, and PD of temanogrel have been assessed in 5 Phase 1 studies in healthy subjects. Single and repeated doses of oral temanogrel were evaluated in 4 studies, and single IV doses of temanogrel were evaluated in a separate study. In completed clinical studies, doses of temanogrel planned to be used in this study were well-tolerated and there were no associated safety concerns. The most common adverse events in subjects treated with single doses of IV temanogrel were mild pain and redness at the treatment administration site. In healthy volunteers who received single oral doses of temanogrel, the most common side effects were dizziness and headache, and less commonly tiredness, back pain, skin rash, and nausea.

Although the incidence and severity of MVO in the PCI setting with the chosen study population (elective PCI or PCI for NSTEMU/UA) is reduced compared to primary PCI for STEMI, MVO remains a problem in the chosen study population as impaired microcirculation is often observed in this setting as well. In all patients undergoing PCI, temanogrel is expected to exert antiplatelet and anti-vasoconstrictive effects and improve microvascular coronary perfusion.

Antiplatelet agents, such as temanogrel, can be associated with increased bleeding risk (Wallentin 2009, Wiviott 2007, Yusuf 2001). Platelet aggregation is primarily triggered by factors such as ADP, thrombin, collagen, or damaged endothelium (Saini 2004, Vikenes 1999), while 5-HT mediates amplification of platelet aggregation induced by these factors via activation the 5-HT_{2A} receptors present on the surface of platelets. Targeting the 5-HT pathway with temanogrel is predicted to exert the greatest antiplatelet effect at sites of vascular injury where 5-HT levels are high. Hence, bleeding risk may be greatest during invasive procedures, injuries, or pathological processes that affect the integrity of vascular endothelium. However, considering that temanogrel does not inhibit primary platelet aggregation pathways but instead attenuates the amplification of platelet aggregation mediated by 5-HT, the associated bleeding risk is expected to be significantly lower compared to standard antiplatelet agents. Completed clinical studies include the assessment of IV temanogrel alone and oral temanogrel administered alone or co-administered with dual antiplatelet therapy (DAPT) consisting of aspirin and clopidogrel. Bleeding-related side effects seen in healthy subjects who received single doses of IV

temanogrel alone up to 40 mg were mild bruising at the site of blood vessel puncture, and 2 of the 47 participants (including a participant treated with placebo) experienced nosebleed. When oral temanogrel was given to healthy subjects as single dose alone (up to 320 mg), there were no observed bleeding events. Two cases of nosebleed occurred with the highest evaluated dose of oral temanogrel alone (total daily dose 240 mg) following multiple days of dosing. In the studies where single doses of oral temanogrel were co-administered with DAPT, there was an increase in mild bleeding-related events (primarily bruising at the site of blood draw and red spots on the skin). Mild bleeding events were also observed with lower multiple doses of oral temanogrel co-administered with DAPT; however, the bleeding risk was generally similar in the placebo and temanogrel treatment groups.

Convulsions were noted in rats following a single IV (bolus) at ≥ 60 mg/kg temanogrel, and generalized seizures in monkeys at oral doses ≥ 100 mg/kg/day temanogrel. The no-observed-adverse-effect levels (NOAELs) in these studies were 20 mg/kg (acute IV rat study) and 35 mg/kg/day (oral 4-week monkey study). Similar nervous system-related findings have not been observed with temanogrel administration to healthy subjects at exposure margins of at least 2.3-fold following a single 320 mg oral dose (based on the lowest C_{max} at the oral 4-week monkey study NOAEL) and 7.3-fold following a single 40 mg IV dose (based on the lowest C_{max} at the acute IV rat study NOAEL).

Additional risks of participation in the study are primarily those associated with adverse reactions to the study treatments, although there may also be some discomfort from collection of blood samples and other study procedures. Further description of identified risks, any potential risks, and the reference safety information for temanogrel are provided in the current edition of the IB.

2. OBJECTIVES

Primary Objective

- To assess the effect of temanogrel on MVO following PCI

Secondary Objectives

- To assess the effect of temanogrel on selected coronary physiology indices and angiographic measures following PCI
- To assess the effect of temanogrel on myocardial injury following PCI
- To assess the PK of temanogrel and its active metabolites AR295980 (M1) and AR295981 (M2) in subjects undergoing PCI
- To assess the safety and tolerability of temanogrel in subjects undergoing PCI

Exploratory Objectives

- To assess selected exposure-response (PK/PD) relationships
- To assess the relationship between selected coronary physiology indices/angiographic measures and serotonin concentrations
- To assess the relationship between the level of $P2Y_{12}$ platelet inhibition and serotonin concentrations
- To assess the effect of temanogrel on:
  - Selected coronary physiology indices prior to PCI
  - Selected angiographic measures following PCI
  - Post-procedural markers of inflammation

3. STUDY DESIGN

3.1. Overall Design

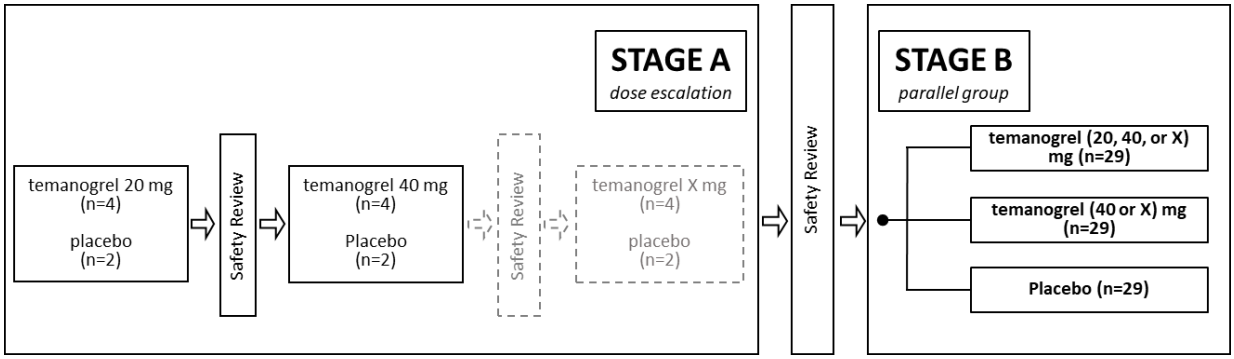
This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled study to be conducted in 2 stages (Stage A and Stage B) (Figure 1). Each stage includes a Screening Period of up to 14 days, a single dose of randomized study treatment (temanogrel or placebo) on Day 1 (day of PCI procedure), and a Follow-Up phone call 7 days (± 2 days) after administration of study treatment for a total study duration of 6 to 24 days.

Upon confirmation of all inclusion/exclusion criteria, eligible subjects will be randomized on Day 1. Study treatment will be administered following assessment of Baseline angiographic measures, index of microcirculatory resistance (IMR) and additional coronary physiology indices, and blood sample collection (for assessment of peripheral serotonin concentration and additional laboratory assessments). Each subject will receive an intravenous (IV) single dose of study treatment. Assessment of IMR and additional coronary physiology indices will be repeated after administration of study treatment and before the start of the PCI procedure to obtain Pre-PCI values. Immediately after completion of PCI, the following assessments will be performed to obtain Post-PCI values: Assessment of IMR and additional coronary physiology indices, angiographic measures, and collection of blood samples (obtained from the coronary ostium and coronary artery distal to the lesion for assessment of coronary artery serotonin concentration, as well as venous blood samples for peripheral serotonin concentration and additional laboratory assessments) (Figure 2).

Stage A is an ascending single dose study planned to consist of 2 cohorts. After treatment of each cohort in Stage A, a safety/tolerability assessment will be conducted by the Data and Safety Monitoring Board (DSMB). Following the safety review of the first cohort in Stage A, the DSMB will recommend whether dose escalation to the next planned dose level in Stage A should occur; the DSMB may also recommend evaluation of an alternative dose in the second cohort in Stage A. Following the safety review of the second cohort in Stage A, the DSMB will recommend whether progression to Stage B should occur; the DSMB may also recommend evaluation of an alternative dose in an additional third dose cohort in Stage A prior to progression to Stage B. After conduct of the final cohort and safety review of Stage A, Stage B may begin. Stage B is a parallel treatment group study planned to consist of a placebo group and 2 active treatment groups (temanogrel doses selected based on safety and tolerability data in Stage A). In Stage B, enrollment will consist of no more than 25% elective PCI subjects and randomization will be stratified by subject type (elective PCI or PCI for non-ST-elevation myocardial infarction [NSTEMI]/unstable angina [UA]).

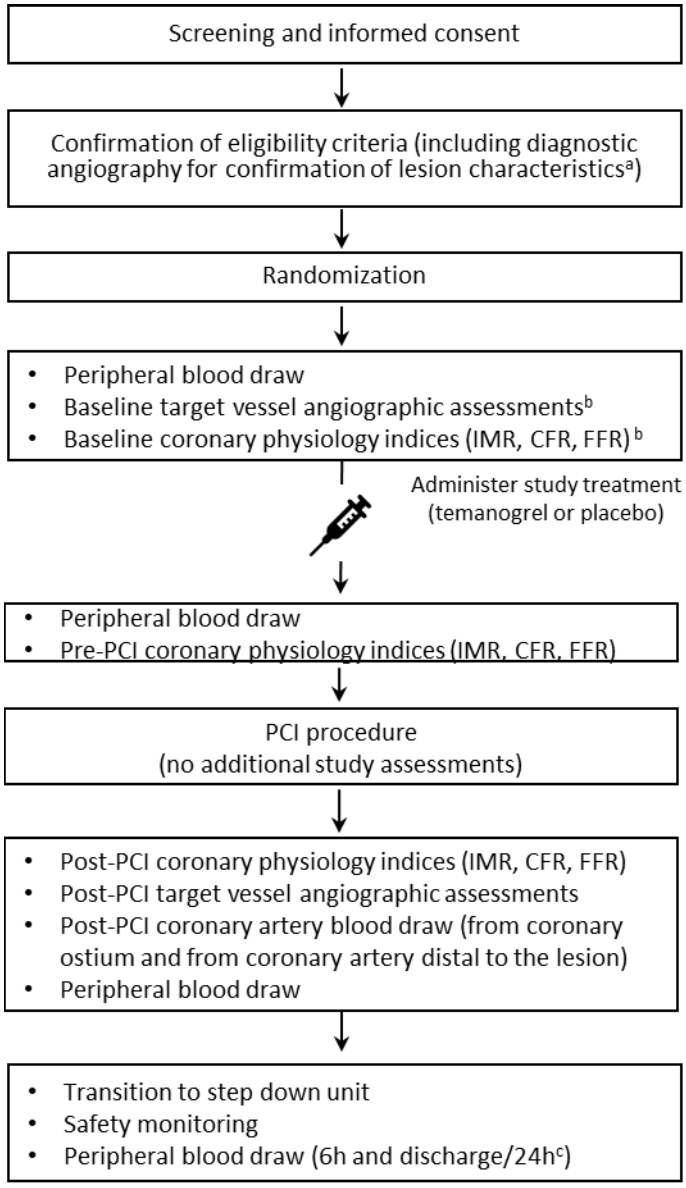
Subjects should be treated with aspirin and an oral $P2Y_{12}$ inhibitor (ie, DAPT) per site standard of care; however, subjects in Stage A may only be treated with clopidogrel as the $P2Y_{12}$ inhibitor DAPT component and may not be treated with prasugrel or ticagrelor until after the subject has completed study participation.

Figure 1: Schematic Diagram of Study Design



Note: Stage A is an ascending single dose study including 2 planned cohorts with an optional third cohort. After completion of Stage A, 2 temanogrel doses will be selected for evaluation in Stage B which will consist of 3 parallel treatment groups (2 temanogrel doses and placebo). Dose escalation procedures in Stage A are described in Section 10.11 and procedures for transitioning from Stage A to Stage B are described in Section 11.11.

Figure 2: Subject Flow of Events



[a] Diagnostic angiography including confirmation of lesion-related eligibility can be performed prior to randomization at Check-in or within 60 days prior to Day 1.
[b] Can be performed as part of eligibility confirmation/confirmation of suitability for PCI per institutional standards prior to randomization at Check-in.
[c] The final peripheral blood draw is to occur at 24 hours after PCI or at the time of discharge, whichever occurs first. Refer to the Schedule of Assessments (Appendix 1) for additional details regarding specific timing and allowable windows for all assessments.
CFR, coronary flow reserve; FFR, fractional flow reserve; h, hour; IMR, index of microcirculatory resistance; PCI, percutaneous coronary intervention

3.2. Scientific Rationale for Study Design

The purpose of this Phase 2 study is to assess the safety, tolerability, PK, and PD of IV temanogrel in adult subjects undergoing PCI for NSTEMI, UA, or elective PCI. Temanogrel is an inverse agonist of the 5-HT_{2A} receptor that inhibits 5-HT-mediated amplification of platelet aggregation and vasoconstriction; therefore, it is expected to improve microvascular blood flow and provide benefit to patients at risk of MVO, such as those undergoing PCI.

Temanogrel is being developed to treat and prevent MVO mainly in ACS (STEMI and high-risk NSTEMI patients); however, for this first-in-patient and proof-of-mechanism assessment of temanogrel in the setting of PCI, only less severe populations undergoing PCI, including NSTEMI, UA, and stable angina patients, will be evaluated. In the setting of NSTEMI/UA and elective PCI, the effects on the microcirculation are commonly transient and of smaller magnitude than in primary PCI for STEMI. IMR is an invasive assessment of the coronary microvascular physiology that can provide quantitative and highly sensitive evaluation of coronary microcirculation, and increased IMR values Post-PCI have been demonstrated to be a strong predictor of MVO-associated myocardial damage, impaired cardiac functional recovery, and adverse clinical outcomes in STEMI patients (Fearon 2008, Fearon 2013). Therefore, IMR is uniquely suited to detect the beneficial effect of temanogrel in this setting, and in the context of the other planned assessments of MVO (including other coronary physiology indices and angiographic measures) and myocardial injury, will inform the design and dose selection of future clinical studies with temanogrel.

For the purpose of assessing MVO in this study, IMR will be measured at Baseline (prior to administration of study treatment), Pre-PCI (after administration of study treatment and before start of PCI procedure), and Post-PCI (upon completion of the PCI procedure). The primary PD endpoint is the change from Baseline to Post-PCI measurement of IMR, with increased IMR values (resistance in the microcirculation) indicative of MVO. The change in IMR from Baseline to Pre-PCI will inform of a potential effect of temanogrel on microcirculation independent from the PCI procedure. Additional coronary physiology and angiographic assessments will be performed to provide additional information on the vascular effects of temanogrel.

Serotonin plasma concentrations will be measured in peripheral blood (from blood samples drawn by venipuncture or indwelling catheter) and coronary artery (from blood samples drawn from the coronary ostium and from coronary artery distal to the lesion) to assess the relationship between serotonin release and change in IMR (and potentially other coronary physiology and/or angiographic measures), and the effect of temanogrel in this setting. Considering that serotonin release requires activation of platelets, the extent of platelet inhibition due to DAPT background therapy (including $P2Y_{12}$ inhibitors) will also be assessed. The aim of these assessments is to evaluate the relevance of the serotonin pathway in this setting and to establish the proof-of-mechanism for temanogrel.

Bleeding complications have been associated with an increased risk of subsequent adverse outcomes in patients undergoing PCI. Therefore, an important safety measure throughout this study is the monitoring of all adverse events including bleeding events which will be classified using the Bleeding Academic Research Consortium (BARC) bleeding criteria (Mehran 2011), a universal standardized criteria of bleeding severity.

This study has been designed as a randomized, double-blind, placebo-controlled study to reduce bias and account for placebo effect in the evaluation of the safety and PD of IV temanogrel.

3.3. Rationale for Dose Selection

Preliminary safety, tolerability, PK, and PD data from APD791-106 Phase 1 clinical study suggests that IV temanogrel administered at single doses up to 40 mg demonstrated an acceptable safety and tolerability profile in healthy adult humans. When administered over a period of 5 minutes, the 40 mg IV temanogrel dose exhibited a similar maximal exposure (mean C_{max} 1840 ± 349 ng/mL) and lower overall exposure (mean area under the plasma concentration vs. time curve from time zero to the time of the last quantifiable plasma sample [AUC_{0-t}] 732 ± 163 ng/mL/h) compared with the highest single oral dose (320 mg) of temanogrel studied in the absence of DAPT (mean C_{max} 1610 ± 473 ng/mL, AUC_{0-t} 2831 ± 1146 ng/mL/h).

A dose-dependent inhibition of 5-HT-mediated platelet aggregation was observed with near maximal inhibition at doses of 20 mg and greater over 4 hours after dosing. Previously, a near-complete attenuation of 5-HT-mediated vasoconstriction in the presence of ketanserin (a $5\text{-}HT_{2A}$ receptor antagonist with receptor binding affinity and functional activity similar to temanogrel) was observed at a concentration of 200 nM. In the Phase 1 study of single doses of IV temanogrel, all subjects who received the 40 mg IV temanogrel maintained exposure above this concentration during the 1 hour following dosing, which should ensure an appropriate coverage over the duration of a PCI procedure.

Thus, in the current study single 20 and 40 mg doses of IV temanogrel will be administered to evaluate a range of doses across concentrations expected to elicit meaningful PD effects in the setting of PCI. In the IV and oral Phase 1 clinical studies, adverse events, cardiovascular parameters, and laboratory tests were closely monitored across the exposures associated with these doses, and no notable adverse effects occurred.

4. STUDY POPULATION

4.1. Inclusion Criteria

Subjects must meet ALL of the following inclusion criteria to be eligible for enrollment into the study:

1. Stable angina patients suitable for elective PCI or patients suitable for PCI for diagnosis of NSTEMI/UA. NSTEMI/UA patients are to be consistently hemodynamically stable until the time of PCI and have a thrombolysis in myocardial infarction (TIMI) flow Grade (TFG) 2 or 3 on the diagnostic angiography
2. Target lesions for PCI must appear suitable for stenting as confirmed on the diagnostic angiography. Acceptable lesions cannot be in the left main artery or in a vein or arterial graft, or be a chronic total occlusion or in-stent restenosis. Two or more sequential lesions may be treated in the same artery, as long as they are treated in the same session and at least one of the lesions meets inclusion criteria
    - For elective PCI patients and non-urgent NSTEMI/UA patients (PCI > 12 hours after diagnosis), the lesion must be located in a ≥ 2.75 mm diameter coronary artery; the lesion must also be ≥ 18 mm long and require the use of one or more stents that in total must be ≥ 20 mm long.
    - For NSTEMI patients treated with PCI urgently (within 12 hours after diagnosis), the coronary artery diameter of the culprit lesion must be ≥ 2.75 mm.
3. 30 to 80 years of age, inclusive
4. Female subjects must not be lactating at the time of Screening
5. Females must meet criterion a and males must meet criterion b to qualify for the study:
    a. Females must not be of childbearing potential by one of the following:
        - Postmenopausal, defined as no menses for 12 months without an alternative medical cause
        - Permanent sterilization procedure, such as hysterectomy, bilateral salpingectomy, or bilateral oophorectomy
    b. Males with pregnant or non-pregnant female partners of childbearing potential must agree to using a condom during treatment and for 90 days following treatment
6. Body mass index 18.0 to 40.0 kg/m^2, inclusive
7. Willing to participate in the study and provide written informed consent

4.2. Exclusion Criteria

Subjects who meet ANY of the following exclusion criteria will not be eligible for enrollment into the study:

1. Planned or anticipated use of rotational atherectomy/ablation or shockwave therapies during the PCI procedure

2. Any history of stroke, seizure, intracranial bleeding, or intracranial aneurysm
3. Transient ischemic attack within the 6 months prior to Screening
4. History of major trauma, major surgery, and/or clinically significant head injury or hemorrhage within the last 6 months of Screening
5. Any STEMI within 10 days of Screening or STEMI within the target vessel territory within the last 4 months of Screening (eg, a patient with a NSTEMI because of a lesion in a diagonal may not be included if there is a history of anterior STEMI due to left anterior descending artery [LAD] lesion that occurred within the last 4 months)
6. Known history of heart failure with reduced ejection fraction (HFrEF) defined as left ventricular ejection fraction ≤ 40% prior to current hospital admission
7. Vasculitis within the last 6 months of Screening
8. Known contraindication or allergy to heparin (eg, history of heparin-induced thrombocytopenia [HIT]), any antiplatelet agents (ie, aspirin, $P2Y_{12}$ inhibitors), or adenosine
9. Use of any strong inhibitors or inducers of cytochrome P450 (CYP)3A4 or P-glycoprotein (examples include, but are not limited to, St. John's wort, ketoconazole, itraconazole, clarithromycin, erythromycin, rifampicin, and verapamil) within 14 days or 5 half-lives (whichever is longer), relative to Check-in. Intra-arterial use of verapamil for subjects undergoing radial artery PCI is permitted.
10. Consumption of grapefruit within 3 days of Check-in
11. Use of medications affecting the serotonin system (eg, selective serotonin reuptake inhibitors [SSRIs], serotonin-norepinephrine reuptake inhibitors [SNRI], atypical [second generation] antipsychotics possessing $5\text{-}HT_{2A}$ pharmacology, or any other serotonergic agents possessing $5\text{-}HT_{2A}$ pharmacology [eg, the triazolopyridine antidepressant, trazodone]) within 14 days of Check-in
12. Treatment with cangrelor or glycoprotein IIb/IIIa inhibitors within 24 hours of Check-in
13. Need for chronic oral anticoagulant (eg, warfarin or direct oral anticoagulants [DOACs], including direct oral thrombin inhibitors) for any condition (eg, treatment of atrial fibrillation, deep vein thrombosis, or prosthetic cardiac valve) within 1 week of Check-in
14. For subjects in Stage A ONLY: Use of prasugrel or ticagrelor within 14 days of Check-in
15. Any other surgeries or interventional procedures planned or anticipated throughout the duration of the study
16. Any history or clinical manifestation of endocrine, allergic, dermatological, hepatic, renal, hematological, pulmonary, gastrointestinal, neurological or psychiatric disorder, or malignancy within 1 year of study participation (with the exception of treated basal cell carcinomas), that in the opinion of the Investigator would prevent the individual from participating in the study due to risk to the scientific validity of study assessments or to the patient's personal well-being

17. Abnormal clinical chemistry, hematology, or physical finding at Screening or electrocardiogram (ECG) at Check-in that in the opinion of the Investigator are clinically significant and that would prevent the individual from participating in the study due to risk to the scientific validity of study assessments or to the patient's personal well-being
18. Clinically significant renal insufficiency (ie, serum creatinine > 2.5 mg/dL or estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m^2; calculated using the Chronic Kidney Disease Epidemiology Collaboration [CKD-Epi] equation) at Check-in or within 6 months of Check-in
19. Impaired hemostasis (eg, thrombocytopenia [platelet count < 100,000/µL] at Check-in; past or present bleeding disorder, sickle cell or other platelet disorders, or carcinoid disorder)
20. Abnormal sodium, potassium, or hemoglobin values at Check-in that in the opinion of the Investigator are clinically significant and that would prevent the individual from participating in the study due to risk to the scientific validity of study assessments or to the patient's personal well-being
21. Known human immunodeficiency virus (HIV) or hepatitis infection, or known history of cirrhosis
22. Known history of alcohol or substance use disorder that is considered clinically significant per the judgement of the Investigator and that would represent risk to the scientific validity of study assessments or the patient's personal well-being
23. Previous participation in a study with temanogrel
24. Subjects who have received any investigational device or investigational drug within 30 days, or 5 half-lives of the investigational drug (whichever is greater) prior to Screening
25. Hypersensitivity to temanogrel or any of the excipients or placebo compounds

5. SUBJECT RESTRICTIONS

5.1. Restricted Medications

Subjects are to follow the medication restrictions outlined in the Inclusion (Section 4.1) and Exclusion (Section 4.2) criteria throughout study participation (until the Follow-Up phone call), unless otherwise specified. The following concomitant medications are restricted from the time of consent as specified below:

- Strong inhibitors or inducers of CYP3A4 or P-glycoprotein for at least 6 hours after administration of study treatment. Intra-arterial use of verapamil for subjects undergoing radial artery PCI is permitted. Additional information about CYP3A4 inhibitors and inducers can be found at the following FDA website: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table3-1
- Cangrelor or glycoprotein IIb/IIIa inhibitors are restricted until after completion of study participation, unless needed as a bail out therapy in the clinical judgement of the investigator (or designee) for treatment of no reflow or acute stent thrombosis.
- Oral anticoagulants (eg, warfarin or DOACs including oral direct thrombin inhibitors) for at least 6 hours after administration of study treatment.
- Use of medications affecting the serotonin system (eg, SSRIs, SNRIs, atypical [second generation] antipsychotics possessing 5-HT_{2A} pharmacology, or any other serotonergic agents possessing 5-HT_{2A} pharmacology [eg, triazolopyridine antidepressant, trazodone]) for at least 24 hours after administration of study treatment.
- For subjects in Stage A: Prasugrel or ticagrelor until after completion of the study participation.

5.2. Dietary Restrictions

Subjects must avoid grapefruit prior to Check-in as described in Section 4.2 and continue to avoid grapefruit through the completion of scheduled blood draws.

Subjects for whom Screening is not on the same day as Check-in should be advised to avoid food high in indoles (eg, avocado, banana, tomato, plum, walnut, pineapple, and eggplant) as well as alcohol, tobacco, tea, and coffee for a minimum of 24 hours, and ideally 3 days, prior to the PCI procedure to increase the accuracy of serotonin concentration assessments. On Day 1 at Check-in, all subjects should be asked if they consumed foods high in indoles in the preceding 24 hours and/or 3 days and their response should be documented in the source and electronic case report form (eCRF). Blood samples for serotonin concentration assessment will be taken for all subjects, even if dietary restrictions are not adhered to. Subjects should be advised to follow the above restrictions through the completion of scheduled blood draws.

6. STUDY TREATMENT

6.1. Study Treatment(s) Administered

Study treatments include a pharmaceutical form of the active substance being tested (temanogrel) and the placebo being used as a reference (reference therapy). Placebo and temanogrel treatments will be diluted to the same volume within each cohort or group to blind study staff to treatment assignment. Study treatments are listed in Table 1.

Table 1: Study Treatments

Study Treatment	Dose(s)	Mode of Administration	Frequency	Formulation
Temanogrel (Stage A: Dose Cohort 1)	20 mg	IV	Single dose	IV injectable solution
Temanogrel (Stage A: Dose Cohort 2)	40 mg	IV	Single dose	IV injectable solution
Temanogrel (Stage A: Dose Cohort 3 [optional])	X mg	IV	Single dose	IV injectable solution
Temanogrel (Stage B: Dose Group 1)	(20, 40, or X) mg	IV	Single dose	IV injectable solution
Temanogrel (Stage B: Dose Group 2)	(40 or X) mg	IV	Single dose	IV injectable solution
Placebo (Stage A and B)[a]	NA	IV	Single dose	IV injectable solution

[a] Placebo will follow the same dilution instructions as temanogrel.
IV, intravenous; NA, not applicable; X mg, dose to be determined based on the results of prior dose cohorts if an optional cohort is warranted

6.2. Identity of Study Treatments

6.2.1. Temanogrel

Temanogrel will be provided as a 25 mg/mL strength, 8 mL fill of a clear solution (colorless to tinted solution, essentially free from visible particles) in a single-use 10 mL clear glass vial with a grey rubber stopper and flip-off aluminum seal. Each 10 mL vial will be labelled and placed into an individual vial carton. Each vial carton will be labelled and secured via tamper evident seals.

6.2.2. Placebo

Arena will supply placebo for temanogrel injectable solution. Placebo will be provided as an 8 mL fill of a clear solution (colorless to tinted solution, essentially free from visible particles) in a single-use 10 mL clear glass vial with a grey rubber stopper and flip-off aluminum seal. Each 10 mL vial will be labelled and placed into an individual vial carton. Each vial carton will be labelled and secured via tamper evident seals. The placebo drug product has the same pH (3.5 ± 0.3) and contains the same excipients as the temanogrel injectable solution (active) with additional dextrose, to adjust for the tonicity loss associated with absence of active.

6.3. Dosage and Administration

The study treatment will arrive at the site blinded and will be administered in a blinded fashion to the subjects. A delegated study staff will be responsible for providing temanogrel or placebo to study personnel for administration as per the randomization scheme. For each subject, study treatment preparation will occur after the subject has been randomized. All doses will be diluted to a final volume of 25 mL. Each subject will be dosed intravenously with 5 mL of this prepared volume. Dilution instructions will be provided in a separate pharmacy manual.

An aliquot of the prepared dilution (3 mL) will be collected and appropriately stored as described in the Pharmacy Manual. Aliquots may be analyzed to confirm dose concentration.

Study treatment will be administered intravenously. All enrolled subjects will receive a single IV dose of study treatment. Temanogrel dose to be administered to Cohort 1 of Stage A will be a 20 mg IV bolus (to be administered in the forearm over a period of not less than 5 minutes). Planned doses administered to subsequent cohort(s) in Stage A and selected doses for Stage B may be adjusted depending on the safety and tolerability data of previously treated subjects. Doses in this study will not exceed 40 mg. Placebo administration duration, administration location, and volume will match that of temanogrel. Hour 0 will correspond to the start of the IV bolus administration.

6.3.1. Instructions for Missed Dose(s)

Subjects will be administered a single dose of study treatment. No missed doses are expected.

6.3.2. Dose Interruptions

Subjects will be administered a single dose of study treatment. Therefore, there will not be any dose interruptions.

6.4. Method of Assigning Subjects to Treatment

Each subject will be assigned a unique identification number upon Screening. Eligible subjects will be centrally randomized into the study using an interactive response technology (IRT) system. Subjects who complete the study Screening assessments and meet all the eligibility criteria will be assigned a unique randomization identification number at the time of study treatment administration, different from the screening number, and will receive the corresponding product according to a randomization scheme.

Subject identification numbers will be 12 characters in length, including dashes, 202-CCSS-XXX. The first 3 digits represent the study number, the 4 digits following the first dash represent the combination of country code (CC) and the site number (SS), and the last 3 digits represent the subject number. Subject numbers will be assigned strictly sequentially at every site as subjects become eligible for enrollment, starting from 001.

In Stage A, eligible subjects will be randomly assigned to study treatment in a 2:1 ratio (temanogrel:placebo). In Stage B, eligible subjects will be randomly assigned to study treatment in a 1:1:1 ratio (20 mg:40 mg:placebo), stratified by subject type (elective PCI or PCI for NSTEMI/UA).

6.5. Blinding

The study treatment will arrive at the site blinded and will be administered in a blinded fashion to the subjects. The Investigator and other clinical staff will be blinded and will not be unblinded unless needed for safety reasons.

Individuals who are part of the Sponsor's safety team (who are not otherwise involved with study conduct) may be unblinded to the treatment (eg, for the purpose of regulatory reporting).

Representatives from the bioanalytical lab responsible for analyzing PK samples during the study will be unblinded to treatment assignments. These individuals will not be involved in the management of the study and will not have access to other subject data.

Treatment assignments should remain blinded unless that knowledge is necessary to determine subject emergency medical care. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a subject's treatment assignment is warranted to provide appropriate medical care. Subject safety must always be the first consideration in making such a determination. The IRT is programmed with blind-breaking instructions to guide the Investigator on how to obtain treatment assignment in the event of an emergency unblinding. If a subject's treatment assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind. The date and reason the blind was broken must be recorded in the source documentation and eCRF, as applicable.

Procedures for breaking of the blind as part of a DSMB review are described in the DSMB Charter.

6.6. Treatment Compliance

This is a single dose study. Study treatment administration will be performed in a controlled environment by trained, qualified personnel designated by the Investigator. The date and start/end time of study treatment administration will be documented. Any changes in study treatment procedures will be documented as a protocol deviation.

6.7. Concomitant Therapy

Any medication (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) or vaccine that a subject receives from 30 days prior to Screening through Follow-up phone call must be recorded along with:

- Reason for use
- Start and end dates of administration
- Dosage information including dose and frequency

Investigators should carefully evaluate local prescribing information of concomitant therapy for interactions described in Section 5.1. The Medical Monitor should be contacted if there are any questions regarding concomitant therapy.

6.7.1. Required Concomitant Therapy

Subjects should be treated with aspirin and an oral $P2Y_{12}$ inhibitor (ie, DAPT) per standard institutional practices. Subjects may enter the study while on background therapy of DAPT; if subjects are not on background DAPT therapy on the day of their procedure, DAPT treatment should be started prior to the start or during the PCI procedure, per standard institutional practices and according to the American College of Cardiology clinical practice guidelines (Levine 2016) or the European Society of Cardiology (ESC) guidelines (Neumann 2019). Subjects in Stage A may only be treated with clopidogrel as the $P2Y_{12}$ inhibitor DAPT component and may not be treated with prasugrel or ticagrelor until after the subject has completed the study participation. Subjects in Stage B can be treated with any $P2Y_{12}$ inhibitor as part of DAPT. Details of DAPT treatment including the time of administration and exact dose of aspirin and $P2Y_{12}$ inhibitors will be captured in the eCRF.

As part of the IMR assessment, 140 µg/kg/min of adenosine will be infused intravenously for each IMR assessment.

6.7.2. Allowed Concomitant Therapy

Medications deemed by the Investigator to be appropriate and unlikely to interfere with the scientific validity of the study or personal wellbeing of the subject and which are not prohibited as indicated in inclusion and exclusion criteria and/or in Section 5.1 are permitted.

Concomitant medications, including prescription or over-the-counter therapeutics, natural products, and vitamins, should not be changed during Screening or at any time during the study, unless medically necessary; such changes will be captured in the eCRF.

7. STUDY TREATMENT AND MATERIALS MANAGEMENT

7.1. Packaging and Labeling

Temanogrel and placebo will be provided as approximately 8 mL of a clear solution in a single-use 10 mL clear glass vial with a grey rubber stopper and flip-off aluminum seal. Each 10 mL vial will be labelled and placed into an individual vial carton. Each vial carton will be labelled and secured via tamper evident seal.

7.2. Storage and Handling

Study treatment must be stored in an appropriate, restricted-access, secure location within a temperature range between 15°C to 30°C (59°F to 86°F). The study treatment should be stored protected from light during long-term storage, but no special precautions are required for short-term handling (< 24 hours).

The site must maintain a temperature log to document the temperature of study treatment storage conditions. Sites may use their own temperature log as long as it captures, at a minimum, the following required information: min/max values recorded once daily, protocol ID, site ID, and storage location.

Temperature should be monitored on a daily basis, either by continuous temperature registration, or by using a min-max thermometer. A copy of the temperature log should be filed in the Investigator Site File or Pharmacy Binder.

Vials of study treatment should not be used beyond the expiration or retest date printed on the study drug label.

Used and/or partially used vials should be stored separately from the unused study treatment for study treatment accountability as allowed by the site's standard operating procedures.

Dilutions of temanogrel can be stored refrigerated for up to 24 hours or at room temperature for up to 4 hours. Refrigerated solutions must be brought to room temperature prior to administration of a dose.

7.3. Preparation

A separate pharmacy manual will detail the study treatment preparation procedures to be followed for this study. Following preparation of study treatment, an aliquot (3 mL) will be collected and appropriately stored as described in the Pharmacy Manual. Aliquots may be analyzed to confirm dose concentration.

7.4. Study Drug Accountability

The Investigator or pharmacist (or designee) will keep accurate records of the quantities of the study drug (temanogrel and placebo) dispensed. Reasons for any deviation from the expected dispensing regimen must also be recorded. Study drug will be reconciled by the Sponsor, monitor, or contracted designee before the site is closed. The Investigator agrees to provide sufficient access to study drug as required for the reconciliation process to be completed in a timely fashion.

7.5. Study Treatment Retention and Disposal

All study treatment will be reconciled by the clinical monitor and then returned to the Sponsor or destroyed according to applicable country regulations. On-site destruction is permitted following all local regulations and in accordance with the site's SOPs. Final reconciliation will be performed at study completion.

8. REMOVAL OF SUBJECTS FROM THERAPY OR ASSESSMENT

8.1. Discontinuation of Study Treatment

As this is a single-dose study, subjects are not expected to discontinue from study treatment.

8.2. Discontinuation from the Study

Subjects may discontinue/be discontinued from the study at any time for any of the following reasons:

- Adverse event
- Death
- Pregnancy (Section 10.8.6)
- Protocol deviation
- Investigator decision
- Withdrawal by subject
- Study termination by Sponsor
- Other

A subject may elect to discontinue study participation at any time for any reason without prejudice to their future medical care by the physician or at the institution.

Subjects who are randomized but not subsequently dosed and subjects who discontinue study participation will be considered Early Termination subjects. Should a subject become unwilling or unable to complete the remaining scheduled PK/PD and safety assessments (individual missing data points do not count as early discontinuation), the Follow-Up phone contact should be performed as described in protocol Section 9.4 (Early Termination).

If a subject withdraws consent for any further evaluation, no further evaluation will be performed, no additional data should be collected, and samples must be destroyed. The Sponsor may retain and continue to use any data collected before such withdrawal of consent. The Investigator should make a reasonable attempt to document the specific reason why consent was withdrawn.

8.3. Lost to Follow-Up

Subjects are considered lost to follow-up if all reasonable attempts made by the Investigator and study delegated staff to complete the scheduled Follow-Up phone contact with the subject failure. A minimum of 3 attempts must be made to contact the subject. Each attempt must be documented in the subject's records (ie, method of communication, times, and dates). If all 3 attempts fail, site must have receipt of a registered letter sent to the subject as the last attempt before considering the subject lost-to-follow-up in the eCRF.

8.4. Premature Termination of the Study or Study Site

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to subjects
- Subject enrollment is unsatisfactory
- Upon request of Health Authorities

The Sponsor will notify the Investigator if the study is placed on hold or if the Sponsor decides to discontinue the study. Health authorities and (Independent Ethics Committee[s] [IECs])/ (Institutional Review Board[s] [IRBs]) will be informed about the termination of the study in accordance with applicable regulations.

The Sponsor has the right to terminate or replace a study site at any time. Reasons for terminating or replacing a study site may include, but are not limited to:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the ICH guideline for GCP

9. STUDY PERIODS

9.1. Screening and Enrollment

The Screening period is to occur up to 14 days prior to and/or on the day of the PCI procedure (Day −14 to 1). For details of the study Screening and enrollment see the Schedule of Assessments (Appendix 1). Potential subjects will provide written informed consent before any study-specific procedure is performed. Eligible subjects meeting all inclusion/exclusion criteria requirements may be enrolled.

9.2. Treatment Period

Potential eligible subjects (per initial Screening criteria) will undergo Check-in assessments to confirm eligibility on Day 1 (day of PCI procedure) per the Schedule of Assessments (Appendix 1), including confirmation of lesion-related eligibility by diagnostic angiography (unless performed within 60 days prior to Day 1). These assessments will be performed locally and assessed by the Investigator. Upon confirmation that a subject is eligible for study participation, the subject will be randomized.

Following randomization, in cases when diagnostic angiography is not performed at Check-in, lesion and vessel characteristics should be assessed as part of Baseline target vessel angiographic measures assessment. Similarly, in cases when coronary physiology indices have not been assessed at Check-in for confirmation of suitability for PCI per institutional standards, they should be assessed at Baseline. For all subjects, Baseline peripheral blood samples will be collected. The subject will then be administered study treatment intravenously.

Zero (0) to 2 minutes after the completion of the IV administration of randomized study treatment, a Pre-PCI peripheral blood sample will be drawn followed by measurement of the Pre-PCI coronary physiology indices. Once the Pre-PCI coronary physiology indices have been measured, the PCI procedure will begin. Vital signs and ECG changes will be monitored throughout the procedure per site standard of care and any clinically significant findings will be recorded as adverse events in the eCRF but there are no required study-specific assessments during the conduct of the PCI procedure.

Immediately upon completion of the PCI procedure, the following Post-PCI assessments will be performed: Blood sampling from the coronary ostium and from coronary artery distal to the lesion, coronary physiology indices, target vessel angiographic measures, and peripheral blood sampling. Upon completion of all planned assessments and per the site's standard of care, the subject will be transitioned to the step-down unit at the study center. Additional safety assessments and blood draws prior to discharge will occur per the Schedule of Assessments (Appendix 1). Subjects will be discharged at the Investigator's discretion based upon clinical presentation, but not prior to the collection of all 6-hour Post-PCI assessments.

9.3. Follow-Up Phone Call/End of Study

Subjects will have one Follow-Up phone call 7 (± 2) days postdose to assess for adverse events. For each subject, study participation is completed once the Follow-Up phone call has been conducted. The End of Study Date is the date when the last subject completes his/her final Follow-Up phone call.

9.4. Early Termination

Subjects who are randomized but not subsequently dosed and subjects who discontinue study participation will be considered Early Termination subjects. Should a subject become unwilling or unable to complete the remaining scheduled PK/PD and safety assessments (individual missing data points do not count as early discontinuation), the Follow-Up phone call should be performed for subjects who received a dose of randomized study treatment. Site staff should work with subjects who withdraw early to obtain as much follow-up data as possible.

10. STUDY ASSESSMENTS AND PROCEDURES

10.1. Subject Informed Consent

The Investigator, or a person designated by the Investigator, will obtain written informed consent from each subject before any study-specific activity is performed.

10.2. Screening and Eligibility

Subject eligibility will be assessed based on protocol inclusion and exclusion criteria. Certain Screening and eligibility assessments must be performed and/or reviewed on Day 1 prior to randomization as part of Check-in assessments per Table 2 and the Schedule of Assessments (Appendix 1). All other Screening and eligibility assessments must be completed any time within 14 days prior to randomization on Day 1, unless otherwise specified (Appendix 1).

Individuals may qualify for study enrollment following an abnormal laboratory test, vital signs, or ECG finding by having that test repeated once with acceptable results as judged by the Investigator (or designee). The Investigator may consult with the Medical Monitor as needed. If additional retests are considered, the Clinical Lead should be consulted, and the outcome of the conversation should be documented.

10.2.1. Rescreening

Subjects who have not been randomized and do not meet inclusion and/or exclusion criteria may be re-consented and re-screened with a new screening number if the Investigator assesses that the subject is an appropriate candidate for re-screening. The Investigator may consult with the Medical Monitor if there are any questions related to rescreening a subject. Subjects may not be rescreened more than once.

10.2.2. Demography and Other Subject Characteristics

Subject demographic information (ie, year of birth, age at consent, sex at birth, reproductive status for female subjects, ethnicity, and race as described by the subject) will be collected.

10.2.3. Prior and Ongoing Therapies

All medications and procedures conducted within 30 days prior to dosing will be recorded at Screening. Updates to medications or procedures prior to study treatment administration should be made as needed.

10.2.4. Medical History

A complete medical history of each subject will be collected and documented during Screening to determine subject eligibility. The history should include disease characteristics relevant to the study (including date and details of diagnosis, associated interventional procedures and/or hospitalizations), social history (eg, tobacco use, alcohol use), recent blood donations (within 30 days), illnesses, participation in other investigational drug studies, and participation in any medical device clinical investigations.

10.2.5. Clinical Chemistry and Hematology

Select Check-in clinical chemistry and hematology assessments noted in Appendix 1 and Table 2 are required to be resulted for eligibility purposes prior to randomization. For those select lab assessments, laboratory assessments obtained within 48 hours prior to randomization may be referenced for purposes of assessing eligibility. For all other serum chemistry and hematology assessments, laboratory assessments collected within 60 days prior to Day 1 and with a panel relevantly similar to those listed in Table 2 in the clinical judgement of the Investigator (or qualified designee) may be referenced for purposes of assessing eligibility (Section 4.2).

10.2.6. Diagnostic Angiography

Confirmation of lesion and vessel characteristics is required for eligibility purposes prior to randomization. Lesion length should be measured across a distance where stenosis is at least 20% of the vessel diameter for the entirety of the lesion length. For elective PCI patients and non-urgent NSTEMI/UA patients who are undergoing PCI more than 12 hours after diagnosis, the lesion must be located in a ≥ 2.75 mm diameter coronary artery; the lesion must also be ≥ 18 mm long and require the use of one or more stents that in total must be ≥ 20 mm long; and TFG must be 2 or 3. For NSTEMI patients undergoing PCI urgently within 12 hours after diagnosis, the coronary artery diameter of the culprit lesion must be ≥ 2.75 mm and TFG must be 2 or 3. Diagnostic angiography including confirmation of lesion-related eligibility can be performed prior to randomization at Check-in or within 60 days prior to Day 1, as defined in the Schedule of Assessments (Appendix 1). In cases when diagnostic angiography is not performed at Check-in, lesion and vessel characteristics should be assessed as part of Baseline target vessel angiographic measures assessment prior to administration of study treatment. Diagnostic angiography findings used to determine subject eligibility, whether obtained within 60 days prior to Day 1 or at Check-in, must be entered in the eCRF.

10.3. Percutaneous Coronary Intervention

Cardiac catheterization using either trans-radial or femoral artery approach, coronary angiography, and PCI with predilation (if applicable) and stent deployment, will be performed in line with accepted institutional practice.

Periprocedural anticoagulation should be achieved with heparin or bivalirudin using standard institutional practice for the duration of the procedure only. Prolonging the anticoagulation treatment is permitted as bail out therapy for no reflow or acute stent thrombosis only and if done, it should be reported as a concomitant medication in the eCRF; any associated adverse events should also be reported in the eCRF.

10.4. Pharmacodynamic Assessments

10.4.1. Coronary Physiology Indices

Assessment of coronary physiology indices will be performed on all randomized subjects and will be used to characterize the PD effects of temanogrel. Indices of coronary physiology to be assessed in this study include IMR (Section 10.4.1.1), coronary flow reserve (CFR) (Section 10.4.1.2), and fractional flow reserve (FFR) (Section 10.4.1.3). Coronary physiology indices will be assessed and analyzed as previously described (Fearon 2000) using the

Coroventis CoroFlow™ Cardiovascular System, v3.0 or later, and details on the applicable methods can be found in a separate operation manual. The coronary physiology indices will be assessed at three timepoints: Baseline values will be assessed before study treatment administration (after randomization at Baseline, unless already assessed at Check-in for confirmation of suitability for PCI per institutional standards; in that case these values can be used as Baseline values), Pre-PCI values after completion of study treatment administration, but before the PCI procedure, and Post-PCI values within 15 minutes of completion of the PCI procedure. Planned timepoints for assessment of coronary physiology indices are provided in the Schedule of Assessments (Appendix 1). Additional details regarding the procedures for collection and transfer of coronary physiology indices data will be provided in a separate operation manual.

10.4.1.1. Index of Microcirculatory Resistance

IMR will be used as a primary quantitative assessment of MVO. Briefly, IMR will be obtained using an intracoronary pressure and temperature sensor-tipped guidewire by previously described thermodilution technique (De Bruyne 2001, Pijls 2002). Thermodilution curves will be obtained in triplicate from a hand-held 3 mL rapid injection of room temperature saline at baseline and after maximal hyperemia induced by 140 µg/kg/min of adenosine infused intravenously. IMR will be defined as the mean distal pressure at maximum hyperemia multiplied by the mean hyperemic transit time, as previously described (Fearon 2003, Fearon 2013). IMR_{corr} (IMR corrected for the influence from collateral supply) will be calculated using the following equation, to account for the presence of significant epicardial stenosis without the need for balloon dilation to measure the coronary wedge pressure (P_w), as previously described (Yong 2013):

$$IMR_{corr} = P_a \times T_{mn} \times [1.34 \times P_d/P_a - 0.32]$$

where IMR_{corr} is IMR value corrected for the influence from collateral supply, T_{mn} is mean transit time at maximal hyperemia, P_d is mean distal coronary pressure at maximum hyperemia, P_a is mean aortic pressure at maximum hyperemia.

10.4.1.2. Coronary Flow Reserve

The coronary flow reserve (CFR) will be calculated from the ratio of baseline (resting) to hyperemic mean transit time (CFR = [mean resting transit time/mean hyperemic transit time]).

10.4.1.3. Fractional Flow Reserve

The FFR will be calculated from the ratio of distal to proximal mean pressures at maximal hyperemia (FFR = [distal coronary pressure/aortic pressure at max hyperemia]).

10.4.2. Angiographic Measures

Analysis of the target vessel angiographic measures including lesion and vessel characteristics, TFG, corrected thrombolysis in myocardial infarction frame count (cTFC), thrombolysis in myocardial infarction myocardial perfusion grade (TMPG), and quantitative coronary analysis (QCA) will be performed by a blinded central core lab and details on the applicable methods can be found in a separate operation manual. The target vessel angiographic measures will be assessed at two timepoints: Baseline values will be assessed before study treatment

administration (after randomization at Baseline, unless already assessed at Check-in as part of diagnostic angiography for lesion-related eligibility; in that case these values can be used as Baseline values) and Post-PCI values within 15 minutes of completion of the PCI procedure. Planned timepoints for assessment of angiographic measures are provided in the Schedule of Assessments (Appendix 1). Detailed instructions regarding the collection and transfer of angiographic data will be provided in a separate operation manual.

10.4.2.1. TIMI Flow Grade

The TFG, a measure of epicardial perfusion, will be graded on a standard scale from 0 to 3, with TFG Grade 0 being no perfusion and TFG Grade 3 complete perfusion (TIMIStudyGroup 1985).

10.4.2.2. Corrected TIMI Frame Count

The cTFC, a quantitative index of coronary flow, will be calculated based upon the number of cine-frames that the intracoronary dye requires to reach distal coronary landmarks (Gibson 2000, Kunadian 2009).

10.4.2.3. TIMI Myocardial Perfusion Grade

The TMPG (also known as myocardial blush grade [MBG]), is a measure of myocardial perfusion in the capillary bed at the tissues level following contrast injection into the coronary artery. TMPG will be graded on a scale from 0 to 3, with TMPG Grade 0 being no “blush” and TMPG Grade 3 normal “blush” (Gibson 2000).

10.4.2.4. Quantitative Coronary Analysis

QCA will be used to assess the diameter of the coronary artery distal to the lesion. Images of the artery will be taken 1 to 2 cm distally to the distal end of the stent used for the treatment of the qualifying lesion (images will be taken in the same area at all timepoints, avoiding bifurcations) and quantified by the angiographic core lab.

10.4.3. Markers of Myocardial Injury

CK, creatine kinase-myocardial band (CK-MB), and cTn will be measured as markers of myocardial injury (Table 2). Detailed instructions regarding blood sample collection, processing, shipping, and analysis for markers of myocardial injury will be provided in a separate laboratory manual.

10.4.3.1. Creatine Kinase

Blood samples for CK will be collected as specified in the Schedule of Assessments (Appendix 1).

10.4.3.2. Creatine Kinase-Myocardial Band

Blood samples for CK-MB will be collected as specified in the Schedule of Assessments (Appendix 1).

10.4.3.3. Cardiac Troponin

Blood samples for cTn (high-sensitive cardiac troponin T [hs-cTnT] and cardiac troponin I [cTnI]) will be collected as specified in the Schedule of Assessments (Appendix 1). cTn will serve as a cardiac biomarker for assessment of procedural myocardial injury based on the 4th universal definition of myocardial infarction (Thygesen 2018).

10.4.4. Markers of Inflammation

The following markers of inflammation will be measured: Highly sensitive C-reactive protein (hs-CRP) and pentraxin (PTX-3), and cytokines (interleukin [IL]-1, IL-6, IL-8, IL-10, and tumor necrosis factor alpha [TNF-α]) (Table 2). Blood samples for markers of inflammation will be collected as specified in the Schedule of Assessments (Appendix 1). Detailed instructions regarding blood sample collection, processing, shipping, and analysis will be provided in a separate laboratory manual.

10.5. Pharmacokinetic Assessments

Blood samples for plasma PK analysis of temanogrel, AR295980, and AR295981 will be collected for all subjects at specified timepoints according to the Schedule of Assessments (Appendix 1). Blood samples will be obtained by peripheral venipuncture or, preferably, using an indwelling catheter (central line can be used if available). Clock time will be documented for each PK blood sample. Collected plasma PK samples may also be stored for up to 3 years after the closing of the study and used for profiling of drug binding proteins, bioanalytical method validation purposes, stability assessments, or to assess other actions of temanogrel (and/or its metabolites) with plasma constituents or for context pertaining to safety events arising during or after the study.

Detailed instructions regarding sample collection, processing, and shipping will be provided in a separate laboratory manual.

During conduct of each cohort in Stage A and during all conduct of Stage B, drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel.

10.6. Serotonin

Peripheral blood samples and coronary artery blood samples will be collected as described in Section 10.6.1 and Section 10.6.2.

10.6.1. Peripheral Serotonin

Blood samples for assessment of peripheral serotonin concentration will be collected as specified in the Schedule of Assessments (Appendix 1). Blood samples will be obtained by peripheral venipuncture or preferably using an indwelling catheter (central line can be used if available). Detailed instructions regarding blood sample collection, processing, shipping, and analysis will be provided in a separate laboratory manual.

10.6.2. Coronary Artery Serotonin

Blood samples for assessment of coronary artery serotonin concentration will be collected as specified in the Schedule of Assessments (Appendix 1). Blood samples will be obtained from the coronary ostium and from the coronary artery distal to the lesion using an aspiration catheter (such as Export Advance™ thrombus aspiration catheter). Detailed instructions regarding blood sample collection, processing, shipping, and analysis will be provided in a separate laboratory manual.

10.6.3. Future Biomarker Research

Where allowed by the regulatory authorities and if the subject has granted consent, residual plasma from samples collected to measure serotonin may be stored for up to 10 years after the closing of the study. Samples will be stored according to local regulations for study at a facility selected by the Sponsor to enable potential future analysis of biomarkers with the aim to further understand the efficacy, safety, and/or mechanism of action of temanogrel. Tubes will be identified with a barcode using an appropriate label. No diseases/conditions, DNA, or RNA will be the focus of these analyses. Samples will not be submitted to a public database. The Sponsor and CROs involved in the clinical conduct and analyses of the samples/data will have access to the samples and/or the data that result from the analysis, if performed. At any time, the subjects can contact the clinical staff to request destruction of their residual samples after the required assessments are completed.

10.7. $P2Y_{12}$ VerifyNow Assay

Blood samples for assessment of $P2Y_{12}$ inhibition of platelet activity using the $P2Y_{12}$ VerifyNow assay will be collected as specified in the Schedule of Assessments (Appendix 1). Blood sample collection, processing, and analysis will be conducted per the VerifyNow Reference Guide (ACCRIVA 2020a, ACCRIVA 2020b).

10.8. Safety Assessments

Safety assessments will include adverse events, vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature), clinical laboratory tests, ECGs, and physical examinations. Planned timepoints for all safety assessments are indicated in the Schedule of Assessments (Appendix 1). If Screening and Check-in do not occur on the same day (Day 1), safety assessments will be repeated on Day 1 prior to randomization. Safety assessments will also be repeated prior to discharge. Subjects will be discharged at the discretion of the Investigator based upon the clinical presentation.

10.8.1. Vital Signs

Vital signs measurements will include blood pressure, heart rate, body temperature, respiratory rate, and body temperature. Vital signs will be assessed at the timepoints indicated in the Schedule of Assessments (Appendix 1). If Screening and Check-in do not occur on the same day (Day 1), vital signs will be repeated on Day 1 prior to randomization.

Subjects should be resting in the supine or seated position for at least 5 minutes prior to collection of vital signs. Vital signs will be measured prior to any blood draws that occur at an overlapping timepoint.

Vital signs monitoring during catheterization procedures will be conducted per site standard of care and any clinically significant findings will be recorded as adverse events in the eCRF.

10.8.2. Physical Examinations

A physical examination will be performed by a licensed physician or designee per the site's standard of care at Screening. A symptom-based physical exam will be performed prior to discharge.

10.8.3. Electrocardiography

ECGs extractions will be collected during the study as outlined in the Schedule of Assessments (Appendix 1).

ECGs will be recorded from a 12-lead ECG machine. ECGs will be captured, recorded, and analyzed according to the ECG Procedure Manual. Parameters to be provided on the confirmed read for each safety ECG are heart rate (HR), RR, PR, QRS, QT, corrected QT interval (QTc), corrected QT interval using Bazett's formula (QTcB), and corrected QT interval using Fridericia's formula (QTcF). It is recommended to collect ECGs at least 30 minutes after the end of the subject's most recent meal. All ECGs will be recorded with subjects in supine position. Supine rest time prior to ECGs should be at least 5 minutes.

The Investigator will be responsible for review and interpretation of ECGs on site for eligibility purposes, and for determining if the ECG is normal, abnormal clinically insignificant, or abnormal clinically significant and recording any clinically relevant worsening from Baseline occurring during the study in the adverse event section of the eCRF. ECGs will also be analyzed by the core lab. Both local and central reports must be filed with the source documents.

ECG monitoring during catheterization procedures is to occur per site standard of care and any clinically significant findings will be recorded as adverse events in the eCRF.

10.8.4. Clinical Laboratory Assessments

Refer to Table 2 for the list of clinical laboratory tests to be performed and the Schedule of Assessments (Appendix 1) for timing and frequency for each test. All clinical laboratory tests performed prior to randomization will be analyzed at local laboratories. All laboratory assessments conducted after randomization will be analyzed at the central laboratory, with the exception of VerifyNow testing which will be done locally. Details regarding clinical laboratory sample collection, preparation, and shipment of central lab samples will be provided in the laboratory manual by the central laboratory. Lab results that are invalid, or appear to be invalid, should be repeated when possible. If lab tests used to determine subject eligibility are invalid, the tests may be repeated to determine subject eligibility (ie, it is not required to screen-fail a subject prior to repeating the lab test).

Central laboratory reports and, when applicable, local laboratory reports used for Screening and eligibility purposes must be filed with the source documents. The Investigator must review all the laboratory reports from the local and central laboratory, document this review, and record any clinically relevant worsening from Baseline occurring during the study in the adverse event section of the eCRF. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the Investigator to be more severe than

expected for the subject's condition. All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or Baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.

In cases when laboratory values from non-protocol-specified assessments are performed at the institution's local laboratory and result in a change in subject management or are considered clinically significant by the Investigator (eg, adverse event or dose modification), then the details must be documented in the appropriate eCRF.

Table 2: Clinical Laboratory Tests

Coagulation	
Activated partial thromboplastin time (aPTT) International Normalized Ratio (INR) Prothrombin time (PT)	
Hematology	
Hematocrit Hemoglobin[a] Mean corpuscular hemoglobin (MCH) Mean corpuscular hemoglobin concentration (MCHC) Mean corpuscular volume (MCV) Platelet count[a] Red blood cell (RBC) count White blood cell (WBC) count with differential	
Serum Chemistry	
Alanine aminotransferase (ALT) Albumin Alkaline phosphatase (ALP) Aspartate aminotransferase (AST) Bicarbonate Blood urea nitrogen (BUN) Calcium Chloride Creatinine[a]	Glucose Lactate dehydrogenase (LDH) Phosphorus Potassium[a] Sodium[a] Thyroid-stimulating hormone (TSH) Total bilirubin Direct bilirubin Total cholesterol
Markers of Myocardial Injury	**Markers of Inflammation**
Cardiac troponin I (cTnI) CK-myocardial band (CK-MB) Creatine kinase (CK) High-sensitivity cardiac troponin T (hs-cTnT)	Cytokines (interleukin [IL]-1, IL-6, IL-8, IL-10, tumor necrosis factor alpha [TNF-α]) Highly sensitive C-reactive protein (hs-CRP) Pentraxin-3 (PTX-3)
Additional Assessments	
$P2Y_{12}$ VerifyNow Serotonin	
Drugs of Abuse[b] Amphetamine, barbiturates, benzodiazepines, cocaine, marijuana, methadone, methamphetamine, methylenedioxymethamphetamine, opiate, oxycodone, phencyclidine	

[a] Required to be resulted for eligibility purposes prior to randomization. Labs obtained within 48 hours prior to randomization may be referenced for purposes of assessing eligibility. For all other serum chemistry and hematology assessments, laboratory assessments collected within 60 days prior to Day 1 and with a panel relevantly similar to those listed (per the clinical judgement of the Investigator [or qualified designee]) may be referenced for purposes of assessing eligibility.

[b] It is not required to result the urine drug screen prior to randomization. Urine drug screen must be collected prior to discharge.

10.8.4.1. Clinical Chemistry, Hematology, and Coagulation

Clinical chemistry, hematology, and coagulation parameters that will be assessed during the study are identified in Table 2. Blood samples will be collected as defined in the Schedule of Assessments (Appendix 1).

10.8.4.2. Drugs of Abuse

A standard urine drug screen (Table 2) will be performed. It is not required to result the urine drug screen prior to randomization. If urine samples for urine drug screen cannot be obtained prior to study treatment administration due to the timing of events as required by subject safety considerations, then it can be obtained after study treatment administration and prior to discharge.

10.8.5. Adverse Events

10.8.5.1. Definitions

10.8.5.1.1. Adverse Event

An adverse event is any untoward medical occurrence that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse events can include, but are not limited to, any of the following:

- Unfavorable changes in general condition
- Subjective or objective signs/symptoms
- Concomitant disease or accidents
- Clinically relevant adverse changes in laboratory parameters over the course of the study
- Pre-existing conditions that worsen in severity, increase in frequency, or have new signs/symptoms

10.8.5.1.2. Serious Adverse Event

An adverse event should be classified as a serious adverse event (SAE) if it meets one of the following criteria:

Fatal:	The adverse event resulted in death.
Life-threatening:	The adverse event placed the subject at immediate risk of death. This classification does not apply to an adverse event that hypothetically might cause death if it were more severe.
Hospitalization:	The adverse event required or prolonged an existing inpatient hospitalization. Hospitalizations for elective medical or surgical procedures or treatments planned before the signing of informed

	consent in the study or routine check-ups are not SAEs by this definition.
Disabling/ incapacitating:	The adverse event resulted in a persistent or significant incapacity or substantial disruption of the subject's ability to conduct normal life functions.
Congenital anomaly or birth defect:	An adverse outcome in a child or fetus of a subject exposed to the study treatment before conception or during pregnancy.
Medically significant:	The adverse event did not meet any of the above criteria but could have jeopardized the subject and might have required medical or surgical intervention to prevent one of the outcomes listed above or involves suspected transmission via a medicinal product of an infectious agent.

10.8.5.1.3. Adverse Drug Reaction

An adverse drug reaction (ADR) in the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established, is any noxious and unintended response to a medicinal product related to any dose. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility (ie, the relationship cannot be ruled out).

10.8.5.1.4. Adverse Events of Special Interest

Based on the mechanism of action of temanogrel and prior experience with other agents acting via a similar mechanism, potential adverse events of special interest may be identified. In addition to appropriate reporting of these events as an adverse event or SAE, supplementary detailed information may be collected.

10.8.5.1.5. Severity

The severity of each adverse event will be assessed at the onset by a nurse/or physician. When recording the outcome of the adverse event the maximum severity of the adverse event experienced will also be recorded. The severity of each adverse event will be graded according to the Common Terminology Criteria for Adverse Events [version 5.0]:

Grade 1:	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2:	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
Grade 3:	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self-care activities of daily living (eg, preparing meals, shopping for groceries or clothes, using the phone, managing money).
Grade 4:	Life-threatening consequences, urgent intervention indicated.
Grade 5:	Death related to adverse event.

10.8.5.1.6. Relationship

The Investigator is obligated to assess the relationship (causal relationship) between the study treatment and each occurrence of each adverse event. The adverse event relationship (causal relationship) to study treatment must be characterized as one of the following categories:

Not Related:	The adverse event does not follow a reasonable temporal sequence from administration of the drug, does not abate upon discontinuation of the drug, does not follow a known or hypothesized cause-effect relationship, and (if applicable) does not reappear when the drug is reintroduced, furthermore, there may exist a clear alternative medical explanation (ie, underlying disease state) or association with study procedure or study conduct.
Unlikely Related:	The temporal association between the adverse event and the drug is such that the drug is not likely to have any reasonable association with the adverse event.
Probably Related:	The adverse event follows a reasonable temporal sequence from administration of the drug and cannot be reasonably explained by the known characteristics of the subject's clinical state, environmental, or toxic factors, or other modes of therapy administered to the subject.
Related:	The adverse event follows a reasonable temporal sequence from administration of the drug, abates upon discontinuation of the drug, follows a known or hypothesized cause-effect relationship, and (if appropriate) reappears when the drug is reintroduced.

The Investigator will use clinical judgment to determine the relationship. Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to the study treatment administration should be considered and investigated. The Investigator should consult the current edition of the IB and the Product Information of marketed products within the drug class, when applicable. For each adverse event, the Investigator must document in the medical notes that he/she has reviewed the adverse event and has provided an assessment of causality. There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor; however, the Investigator should always make an initial assessment of causality for every event before the initial transmission of the SAE to the Sponsor. The Investigator may change his/her opinion of causality based on subsequent receipt of information and send an SAE follow-up report with the updated causality assessment. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

10.8.5.2. Eliciting, Recording, and Reporting Adverse Events

10.8.5.2.1. Eliciting Adverse Events

Subjects will be instructed that they may report adverse events at any time. An open-ended or nondirected method of questioning should be used at each study visit to elicit the reporting of adverse events.

10.8.5.2.2. Recording Adverse Events

The adverse event reporting period for safety surveillance begins when the subject is initially included in the study (date of first signature of informed consent) and continues up to 30 days after the last study treatment administration. If an adverse event is not resolved or stabilized by this time, the Sponsor in consultation with the Investigator will decide whether to continue to monitor the adverse event or closeout the event in the database if no further follow-up is necessary.

Any SAE suspected to be related to the study treatment must be reported whenever it occurs, irrespective of the time elapsed since the last administration.

Investigator and study personnel will record all adverse events and SAEs whether received through an unsolicited report by a subject, elicited during subject questioning, discovered during physical examination, laboratory testing, and/or other means by recording them on the eCRF and SAE Report Form, as appropriate. The following information should be recorded on the adverse event eCRF:

- Description including onset and resolution dates
- Whether it met SAE criteria
- Severity
- Relationship to study treatment or other causality
- Outcome

For SAEs, events occurring secondary to the primary event should be described on the SAE Report Form in the narrative description of the case.

The following should be considered when recording SAEs:

- Death is an outcome of an event. The event that resulted in the death should be recorded and reported on both the SAE Report Form and eCRF.
- For hospitalizations, surgical, or diagnostic procedures, the illness leading to the surgical or diagnostic procedure should be recorded as the SAE, not the procedure itself. The procedure should be captured in the narrative as part of the action taken in response to the illness.

10.8.5.2.3. Diagnosis Versus Signs or Symptoms

In general, the use of a unifying diagnosis is preferred to the listing out of individual symptoms. Grouping of symptoms into a diagnosis should only be done if each component sign and/or symptom is a medically confirmed component of a diagnosis as evidenced by standard medical

textbooks. If any aspect of a sign or symptom does not fit into a classic pattern of the diagnosis, report the individual symptom as a separate adverse event.

10.8.5.3. Reporting Serious Adverse Events

All SAEs are subject to reporting requirements.

10.8.5.3.1. Serious Adverse Events

All SAEs, whether or not considered related to study treatment, must be reported to the Sponsor Contact **within 24 hours of becoming aware of the event.** In addition, a completed report using the Sponsor's SAE Report Form must be submitted within 24 hours of notification to the designated Sponsor Contact.

IQVIA Pharmacovigilance

Phone: +1-866-599-1341

Fax: +1-866-599-1342

Email (preferred method): ArenaSafety@iqvia.com

If additional follow-up information is required or becomes available for a previously reported SAE, the new information should be reported to the designated Sponsor Contact within 24 hours of awareness.

Elective hospitalization and/or surgery for clearly preexisting conditions (eg, a surgery that has been scheduled prior to the subject's entry into the study) will not be reported as an SAE. All other hospitalizations, including elective hospitalizations for any condition that was not preexisting, will be reported as an SAE.

Any SAE that is ongoing when the subject completes the study or discontinues the study will be followed by the Investigator until the event resolves, stabilizes or returns to Baseline status.

10.8.5.3.2. Serious, Unexpected Adverse Drug Reactions

All ADRs that are both serious and unexpected are subject to expedited reporting to regulatory agencies and will be reported in accordance with Directive 2001.20/EC or as per national regulatory requirements in participating countries. An unexpected ADR is one for which the nature or severity is not consistent with information in the relevant source documents.

The following documents or circumstances will be used (by the Sponsor) to determine whether an adverse event/ADR is expected:

1. For a medicinal product not yet approved for marketing in a country, the Reference Safety Information (RSI) section of a company's current edition of the IB will serve as the source document in that country.
2. Reports that add significant information on specificity or severity of a known, already documented serious ADR constitute unexpected events. For example, an event more specific or more severe than described in the RSI in the IB would be considered "unexpected".

10.8.5.4. BARC Bleeding Criteria Assessment

Based on mild bleeding observed with escalating doses of oral temanogrel when co-administered with aspirin and clopidogrel in healthy adult subjects during Phase 1 studies, administration of single doses of IV temanogrel with DAPT in this study may potentially increase the tendency of bleeding; therefore, the assessment of bleeding will be categorized by the Investigator (or qualified designee) using the BARC definition for bleeding (Mehran 2011) (Table 3). For any bleeding events that occur after discharge and before the Follow-Up phone contact, applicable corresponding medical records should be requested for review by the Investigator (or qualified designee).

Table 3: BARC Definitions for Bleeding

Type	Definition
Type 0	No bleeding
Type 1	Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional
Type 2	Any overt, actionable sign of hemorrhage (ie, more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for Type 3, 4, or 5 but does meet at least one of the following criteria: 1. Requiring nonsurgical, medical intervention by a healthcare professional. 2. Leading to hospitalization or increased level of care. 3. Prompting evaluation.
Type 3	a. Overt bleeding plus hemoglobin drop of 3 to < 5 g/dL[a] (provided hemoglobin drop is related to bleed) Any transfusion with overt bleeding. b. Overt bleeding plus hemoglobin drop ≥ 5 g/dL[a] (provided hemoglobin drop is related to bleed). Cardiac tamponade bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid). Bleeding requiring intravenous vasoactive agents. c. Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal). Subcategories confirmed by autopsy or imaging or lumbar puncture. Intraocular bleed compromising vision.
Type 4	CABG-related bleeding. Perioperative intracranial bleeding within 48 hours. Reoperation after closure of sternotomy for the purpose of controlling bleeding. Transfusion of ≥ 5 U whole blood or packed red blood cells within a 48-hour period.[b] Chest tube output ≥ 2 L within a 24-hour period.
Type 5	Fatal bleeding a. Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious. b. Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation.

[a] Corrected for transfusion (1 U packed red blood cells or 1 unit whole blood = 1 g/dL hemoglobin).

[b] Cell saver products are not counted.

Note: CABG indicates coronary artery bypass graft. Platelet transfusions should be recorded and reported but are not included in these definitions until further information is obtained about the relationship to outcomes. If a CABG-related bleed is not adjudicated as at least a Type 3 severity event, it will be classified as not a bleeding event. If a bleeding event occurs with a clear temporal relationship to CABG (ie, within a 48-hour time frame) but does not meet Type 4 severity criteria, it will be classified as not a bleeding event.

10.8.6. Pregnancy

Women of childbearing potential may not participate in this study. Details of all pregnancies that occur in female subjects and female partners of male subjects that begin between the study treatment administration and 90 days after treatment administration will be collected.

Pregnancy (during maternal or paternal exposure to study treatment) does not meet the definition of an adverse event; however, to fulfill regulatory requirements, any pregnancy and/or pregnancy outcome should be reported via the Pregnancy Report Form to the designated Sponsor Contact **within 24 hours of awareness.**

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and should be reported as such even if outside the SAE reporting period.

10.9. Order of Events and Priority for Timed Assessments

Every effort should be made to perform procedures as closely as possible to the scheduled times indicated in the Schedule of Assessments (Appendix 1).

On Day 1, the timing of events should first be determined by subject safety requirements and then by the scheduled times and sequential order of events as described in this protocol, giving consideration to appropriate posture conditions, practical restrictions, and the other procedures scheduled to be performed at the same timepoint. The preferred order of events in the Peri-PCI period is as follows:

1. Diagnostic angiography including confirmation of lesion-related eligibility (not required if a diagnostic angiography obtained within 60 days prior to Day 1 confirms lesion characteristics)
2. Randomization
3. Baseline peripheral blood draw
4. Baseline target vessel angiographic measures (not required to be repeated if completed during diagnostic angiography at Check-in; in cases when diagnostic angiography is not performed at Check-in, lesion and vessel characteristics should be assessed as part of Baseline target vessel angiographic measures assessment prior to administration of study treatment)
5. Baseline coronary physiology indices (IMR, CFR, FFR; not required to be repeated if completed at Check-in for confirmation of suitability for PCI per institutional standards)
6. Treatment administration
7. Post-treatment / pre-PCI peripheral blood draw (collected 0-2 minutes after the end of the IV administration of randomized study treatment)
8. Post-treatment / pre-PCI coronary physiology indices (IMR, CFR, FFR)
9. PCI with predilation (if applicable) and stent deployment
10. Post-PCI (within 15 minutes of the completion of the PCI procedure) coronary artery (coronary ostium and coronary artery distal to the lesion) blood sampling

11. Post-PCI (within 15 minutes of the completion of the PCI procedure) coronary physiology indices (IMR, CFR, FFR)
12. Post-PCI (within 15 minutes of the completion of the PCI procedure) target vessel angiographic measures
13. Post-PCI (within 15 minutes of the completion of the PCI procedure) peripheral blood draw

Specific timing of the study activities listed above is not critical (unless specified) as long as activities are completed in the order specified.

10.10. Safety-Related Stopping Criteria

Throughout the study, any bleeding event reported as BARC 3c or greater will pause study enrollment and trigger an ad hoc DSMB meeting. Study enrollment will remain paused until the DSMB has made a recommendation as to whether or not the study can continue.

10.11. DSMB Review: Safety-Related Dose Escalation (Stage A)/Dose Recommendation (Stage B) Criteria

At the completion of each cohort in Stage A the DSMB will use the following safety-related criteria to preclude recommendation of further dose escalation in Stage A and use of an associated dose in Stage B:

- Two or more SAEs or two or more BARC 3b or higher events assessed as related to active study treatment within a cohort.
- Two or more subjects on active treatment within a cohort experience an increase in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $\geq 3 \times$ upper limit of normal (ULN), or alkaline phosphate (ALP) or total bilirubin $\geq 2 \times$ ULN, following study treatment administration. For subjects with values $\geq 2 \times$ ULN prior to dosing, a 100% increase from pre-dosing value meets the criterion.
- Seizure assessed as related to study treatment in a subject who received active study treatment.

In addition to the safety-related criteria listed above, the DSMB will review overall safety data of each cohort (including AEs, clinical laboratory, and vital sign data) when recommending dose escalation within Stage A and doses for Stage B (Section 11.11).

10.12. Approximate Blood Volume

During the study, blood will be drawn for various analytes and panels, including chemistry, hematology, coagulation, PK, PD (cardiac markers, inflammatory markers), and serotonin concentration assessments. The approximate amount of blood to be drawn over the course of the study for each subject is expected to be 175 mL.

10.13. Procedures for Overdose

Overdose is not expected as study treatment will be administered in a highly controlled environment by qualified designees at the study centers. The Sponsor does not recommend

specific treatment for an overdose; there is no known antidote to temanogrel. After an overdose or suspected overdose, subjects should be monitored for adverse events.

If a subject receives a dose in excess of the instructed dose (eg, due to pharmacy error) and if symptoms are present, the Investigator or designee should contact the Medical Monitor immediately. In the absence of associated adverse events as assessed per the clinical judgement of the Investigator, no further action is required.

11. PLANNED STATISTICAL METHODS

11.1. General Considerations

Details regarding the statistical analyses will be provided in a Statistical Analysis Plan (SAP), which will be finalized prior to study database lock (unblinding).

Continuous variables will be summarized using the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages.

Unless otherwise specified, continuous endpoints will be analyzed using analysis of covariance (ANCOVA) with a model that includes treatment group and randomization stratification factor as factors and Baseline IMR value and Baseline value as covariates. Least square means, standard errors (SEs), and 95% confidence intervals (CIs) for the treatments and their difference will be presented together with their p-value.

Proportion-based endpoints will be analyzed by either the Cochran-Mantel-Haenszel method adjusting for randomization stratification factor. The number and percentage of subjects achieving the goal and the difference in proportion between treatment groups achieving the goal, along with p-value and the 95% CIs will be reported. The odds ratio relative to placebo and percentage of difference from placebo will be presented together with corresponding 95% CIs and the p-value.

Pairwise comparisons of each temanogrel treatment group compared to placebo will be conducted. In addition, analyses of the pooled temanogrel treatment groups compared to placebo will be conducted.

Where statistical assumptions (eg, normality, proportional odds) are not met, alternative approaches will be evaluated (eg, non-parametric analysis, log transformation).

Efficacy data will be analyzed by randomized treatment, while safety data will be analyzed by actual treatment received.

All secondary and exploratory analyses will be interpreted in an exploratory manner.

11.2. Determination of Sample Size

This study is planned to randomize, treat, and complete safety, tolerability, PK, and PD assessments in approximately 99 subjects (12 in Stage A, 87 in Stage B).

It is assumed that the primary endpoint, which is the change from Baseline in IMR measured immediately after PCI, is normally distributed with a mean of 6 and SD of 3.5. Assuming a 1:1:1 randomization, 90 evaluable subjects (30 subjects in each of the 2 temanogrel treatment groups and placebo) is sufficient to achieve at least 90% power to detect a treatment effect of 3 (a clinically significant reduction of 50% from placebo) between each of the temanogrel treatment groups and placebo by a 2-sample t-test using a 2-sided significance level of 0.05.

The primary endpoint analysis will be based on pooled data from subjects in Stage A and Stage B.

11.3. Analysis Sets

For purposes of analysis, analysis sets are defined in Table 4.

Table 4: Analysis Sets

Analysis Set	Description
Full Analysis Set (FAS)	The FAS will include all randomized subjects, irrespective of whether they received any study treatment.
Modified Full Analysis Set (mFAS)	The mFAS will include all subjects in the FAS who receive any study treatment and have at least a Baseline and Post-PCI IMR measurement.
Per Protocol Set	The Per Protocol Set will include all subjects in the FAS who receive the full dose of study treatment, have a Baseline and Post-PCI IMR measurement, and are without major protocol violations that might affect the evaluation of the effect of study treatment on the primary endpoint, which will be defined in the SAP.
Pharmacokinetic Set	The Pharmacokinetic Set will include all subjects in the Safety Set with at least 1 postdose PK measurement.
Safety Set	The Safety Set will include all subjects in the FAS who receive any study treatment.

11.4. Missing Data

Due to the trial design and short study duration, minimal missing data is expected. As a result, no algorithm for missing data imputation will be employed.

11.5. Efficacy Analyses

The primary and secondary endpoints will be analyzed using the Full Analysis Set (FAS). Other important statistical considerations such as sensitivity analyses and subgroup analyses will be described in the SAP.

The primary endpoint of the study is the change from Baseline in IMR measured immediately after PCI. The primary PD analysis will be analyzed using ANCOVA with a model that includes treatment group and randomization stratification factor as factors and Baseline IMR as a covariate. Least square means, standard errors (SEs), and 95% CIs for the treatments and their difference will be presented together with their p-values.

11.6. Study Endpoints

The following definitions will be used to assess efficacy outcomes:

11.6.1. Primary Endpoint

- Change in IMR from Baseline to Post-PCI

11.6.2. Secondary Endpoints

- Change from Baseline to Post-PCI for the following assessments:
  - Coronary physiology indices (CFR, FFR)

- Angiographic measures (cTFC, TFG, TMPG)
- Myocardial injury markers (CK, CK-MB, cTn)

Note: Post-PCI measure for CK, CK-MB, and cTn, is collected 4 to 6 hours after completion of the PCI procedure and not immediately after completion of the procedure.

- The incidence of procedural myocardial injury defined as: Elevation of cTn values > 99th percentile upper reference limit (URL) in subjects with normal Baseline values (≤ 99th percentile URL) or elevation of cTn by > 20% of the Baseline value in subjects with elevated cTn levels (> 99th percentile URL)
- Concentration of temanogrel and active metabolites AR295980 and AR295981 prior to PCI and at selected post-PCI timepoints until discharge
- Safety and tolerability of temanogrel

11.6.3. Exploratory Endpoints

- The relationship between temanogrel/active metabolite exposure and change in IMR from Baseline to Post-PCI (and potentially other PD assessments)
- The relationship between coronary physiology indices/angiographic measures and peripheral serotonin concentrations at Baseline and Post-PCI
- The relationship between coronary physiology indices/angiographic measures and coronary artery serotonin concentration (obtained on blood samples drawn from the coronary ostium and from coronary artery distal to the lesion) Post-PCI
- The relationship between the level of $P2Y_{12}$ platelet inhibition and peripheral/ coronary artery (obtained on blood samples drawn from the coronary ostium and from coronary artery distal to the lesion) serotonin concentrations
- Change in IMR (and potentially other coronary physiology indices) from Baseline to Pre-PCI
- Change in QCA from Baseline to Post-PCI
- Change in the following markers of inflammation from Baseline to post-procedure:
  - hs-CRP, PTX-3
  - Cytokines (IL-1, IL-6, IL-8, IL-10, and TNF-α)

11.6.4. Pharmacokinetic Analysis

The PK analysis will be conducted using model independent methods and based on plasma concentrations of temanogrel and its metabolites from subjects who have received temanogrel. C_{max} and potentially additional pharmacokinetic parameters, will be derived from subjects with evaluable plasma concentration versus time profiles.

Individual plasma concentrations of temanogrel and metabolites will be listed for each subject using the actual sampling time and dose level. The Pharmacokinetic Set will be used to analyze plasma concentrations. Mean, SD, CV (%), median, minimum, and maximum values will be

summarized descriptively as appropriate per dose level. Individual subject plasma concentration versus time profiles of temanogrel and its metabolites will be plotted on both a linear and a semilogarithmic scale for each dose level. Mean values, as appropriate, will also be presented graphically for each dose level.

Detailed PK analysis procedures of temanogrel and its metabolites will be provided in the SAP.

11.6.5. Pharmacokinetic/Pharmacodynamic Relationship

Relationships will be explored between selected plasma exposure measures (to be determined) of selected analytes (temanogrel, its active metabolites, and/or all analytes combined) and selected PD measures (eg, change from Baseline to Post-PCI in IMR and/or other cardiac physiology indices, angiographic measures, markers of myocardial injury/infarction, or markers of inflammation).

Detailed description of the exploratory PK/PD analyses will be provided in the SAP.

11.7. Subgroup Analysis

- Sex (male, female)
- Race (white, non-white)
- Age (≤ or > median)
- Baseline IMR (≤ or > median)
- Subject type (elective PCI or PCI for NSTEMI/UA)
- Lesion length (≤ or > median)
- $P2Y_{12}$ inhibitor exposure (ticagrelor, prasugrel, clopidogrel)
- Time of $P2Y_{12}$ administration (long-term or procedure loading dose)

Details of the subgroup analyses will be provided in the SAP.

11.8. Testing Strategy

Since this is an exploratory proof of concept study, no formal testing strategy or adjustments of the Type I error will be employed for the evaluation of secondary or exploratory endpoints. Estimates and CIs for treatment groups and from pairwise comparisons will be reported in an exploratory manner.

11.9. Interim Analysis

No formal interim analysis of efficacy is planned.

11.10. Safety Analyses

Adverse events will be listed and summarized by system organ class and preferred term, as well as according to severity and causality/relationship to temanogrel. Treatment-emergent adverse events (TEAEs) will be summarized by stage, cohort, and treatment group. In addition, TEAEs will be pooled across treatment groups (ie, placebo, temanogrel). Similarly, bleeding events will

be summarized by BARC classification by stage, cohort, and treatment group and pooled across treatment groups. Observed values for clinical laboratory tests, vital signs, and safety 12-lead ECGs, will be summarized by stage, cohort, treatment group, and timepoint. Individual data listings of clinical laboratory tests results will be presented for each subject. Observed values and changes from Baseline will be summarized descriptively. Safety 12-lead ECG data (observed values and change from Baseline) will be listed for each subject and timepoint. Observed values will be classified for normal, abnormality that is not clinically significant, and clinically significant abnormality by stage, cohort, treatment group, and timepoint of collection. Results of other safety assessments will be listed and summarized as appropriate.

A detailed description of all safety analyses will be provided in the SAP.

11.10.1. Safety Endpoints

The safety endpoints will be analyzed using the Safety Set. The primary safety endpoint of the study is the assessment of TEAEs. All bleeding-related adverse events will be classified using the BARC criteria.

- Incidence of all TEAEs
- Incidence of TEAEs by severity
- Incidence treatment-related TEAEs
- Incidence of bleeding-related TEAEs classified using BARC criteria
- Incidence of adverse events leading to discontinuation (if any)
- Incidence of SAEs (if any)
- Incidence and severity of laboratory abnormalities, and change from Baseline in laboratory values (to include hematology, serum chemistry, and coagulation)
- Incidence of clinically significant vital sign abnormalities and changes from Baseline
- Incidence of clinically significant ECG abnormalities and changes from Baseline

11.10.2. Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

For each treatment group, the proportion of subjects with treatment emergent adverse events will be summarized overall, by severity, and by relationship to study treatment. SAEs will also be summarized by treatment group. A treatment emergent adverse event is defined as:

- An adverse event that occurs after initiation of study treatment that was not present at the time of treatment start.
- An adverse event that increases in severity after the initiation of medication, if the event was present at the time of treatment start.

Adverse events occurring before the first dose of study treatment will be summarized separately.

11.10.3. Clinical Laboratory Parameters

Clinical laboratory parameters will be summarized by treatment group at each scheduled assessment timepoint using descriptive statistics.

In the event of abnormal clinical laboratory values, the Investigator will make a judgment whether or not the abnormality is clinically significant. Clinically significant abnormal values should be reported as adverse events as described in Section 10.8.5.2.

11.10.4. Electrocardiograms

The Investigator is responsible for interpretation of ECG data for eligibility purposes and safety monitoring. ECG data will also be read and interpreted by a central ECG lab. Individual ECG values will be listed by timepoint and summarized using descriptive statistics. Parameters to be provided for each ECG are: HR, RR, PR, QRS, QT, QTc, QTcB, and QTcF. Post-Baseline ECGs for each subject will be compared with the Baseline ECG. Any clinically significant change from Baseline may be recorded as an adverse event if deemed appropriate by the Investigator, or Investigator in consultation with the Clinical Lead. Outlier analysis will be performed on all subjects with QTcF values greater than 500 ms or change from Baseline > 60 ms in the absence of Baseline ECG abnormalities that preclude accurate surface ECG assessment of ventricular repolarization (eg, bundle branch block).

ECG monitoring during catheterization procedures will occur per site standard of care and any clinically significant findings will be recorded as adverse events in the eCRF.

11.10.5. Vital Signs

Vital signs measurements will include blood pressure, heart rate, respiratory rate, and temperature. Vital signs values collected at Screening, Check-in, and prior to discharge will be recorded in the eCRF.

Vital signs monitoring during catheterization procedures will be conducted per site standard of care and any clinically significant findings will be recorded as adverse events in the eCRF.

11.10.6. Physical Examination

Clinically significant physical examination abnormalities will be included in the medical history or recorded and summarized as an adverse event.

11.11. Data and Safety Monitoring Board

An independent DSMB will be established for the regular and ad hoc review of safety data. Membership of the DSMB, meeting frequency, and safety review criteria are defined in a separate DSMB charter. The DSMB will review unblinded safety data at each meeting. At the conclusion of each meeting, the DSMB will provide a recommendation to the Sponsor Liaison.

During Stage A, the DSMB will review unblinded safety data at the completion of each cohort. At the conclusion of the first cohort in Stage A, taking into account safety-related dose escalation stopping criteria (Section 10.11), and in consideration of other AEs, laboratory, and vital sign data, the DSMB will provide a recommendation as to whether or not dose escalation to the next planned dose level in Stage A should occur; the DSMB may also recommend evaluation of an

alternative dose in the second cohort in Stage A. At the conclusion of the second dose cohort in Stage A, the same criteria will be used by the DSMB to provide a recommendation as to whether or not the study should proceed with Stage B; the DSMB may recommend evaluation of an alternative dose (not to exceed the maximum planned dose of 40 mg) in an additional third dose cohort in Stage A prior to progression to Stage B. At the conclusion of the final cohort in Stage A, the DSMB will provide recommendation on temanogrel doses to be evaluated in Stage B, based on safety and tolerability data in Stage A.

During Stage B, the DSMB will conduct safety data reviews at specified intervals in accordance with the DSMB Charter.

Throughout the study, any bleeding event reported as BARC 3c or greater will pause study enrollment and trigger an ad hoc DSMB meeting (Section 10.10). Study enrollment will remain paused until the DSMB has made a recommendation as to whether or not the study can continue.

To ensure the scientific integrity of the study, members of the DSMB will not be directly involved in the ongoing management of the study.

In addition to members of the DSMB, an independent statistician responsible for interacting with the DSMB will have access to unblinded study data. This statistician will not be directly involved in the conduct of the study.

12. ETHICAL CONSIDERATIONS

12.1. Ethical Conduct of the Study

This study shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with GCP, ICH guidelines, and other applicable regulatory requirements (eg, local requirements).

12.2. Institutional Review Board or Independent Ethics Committee Approval

Before initiating a study, the Investigator must have written and dated approval from the IRB/IEC for the study protocol, written informed consent form (ICF), subject recruitment materials and procedures (eg, advertisements or websites), and any other written information to be provided to subjects. Approval from the committee must be documented in a letter to the Investigator specifying the protocol number, protocol version, documents reviewed, and the date on which the committee met and granted the approval.

All documents subject to review during the study, including any modifications made to the protocol after receipt of IRB/IEC approval, must also be submitted to the committee for approval prior to implementation. The Investigator must also provide periodic reports as required and promptly report important safety information (ie, SAEs) and protocol violations, as appropriate, to the IRB/IEC.

As part of the Investigator's written application to the IRB/IEC, the Investigator should provide the committee with a current copy of the IB. If the IB is updated during the study, the Investigator should supply an updated copy to the committee.

12.3. Informed Consent

The Investigator will fully inform the subject of all pertinent aspects of the study, including the approval of the study by the IRB/IEC. Before informed consent may be obtained, the Investigator should provide the subject ample time and opportunity to inquire about details of the study and to decide whether to participate.

Prior to a subject's participation in the study, the IRB/IEC-approved ICF must be signed and personally dated by the subject and by the person who conducted the informed consent discussion. If a subject is unable to read, an impartial witness will be present during the entire informed consent discussion and will sign the informed consent form.

The written ICF and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written ICF or study materials to be available and/or supplied to subjects should receive the IRB/IEC's approval in advance of use. Revised ICFs require subjects to reconsent, sign, and date the new ICF. The subject will be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information should be documented.

12.4. Confidentiality

All information generated in this study is considered highly confidential and must not be disclosed to any person or entity not directly involved with the study unless prior written consent is provided from the Sponsor.

Prior to study participation, the Investigator shall inform the subject that the monitor(s), auditor(s), IRB/IEC, and the regulatory authorities will be granted direct access to the subject's original medical records for verification of clinical study procedures and/or data, and that, by signing a written ICF, the subject is authorizing such access.

In addition, prior to study participation, the subject must be informed that the records identifying the subject will not be made publicly available; if the results of the study are published, the subject's identity will remain confidential.

12.5. Protocol Compliance

The Investigator/institution will conduct the study in compliance with the protocol agreed to by the Sponsor and regulatory authorities (if applicable) and that was approved by the IRB/IEC. The Investigator/institution and the Sponsor should sign the protocol, or an alternative contract, to confirm agreement.

The Investigator should not implement any deviation from, or changes to, the protocol without agreement by the Sponsor and prior review and documented approval from the IRB/IEC of an amendment, except where necessary to eliminate immediate hazard(s) to study subjects or when the change involves only logistical or administrative aspects of the study (eg, change in monitor, change of phone number).

When an important deviation from the protocol is deemed necessary for an individual subject, the Investigator must contact the Medical Monitor for the study. Such contact must be made as soon as possible to permit a review by the Sponsor to determine the impact of the deviation on the subject's participation and/or the assessment of safety or other outcomes in the study. Any significant protocol deviations affecting subject eligibility and/or safety must be reported by Investigator or site delegate to the IRB/IEC and regulatory authorities, as applicable, prior to implementation.

The Investigator should document and explain any deviation from the approved protocol.

13. QUALITY CONTROL AND QUALITY ASSURANCE

Quality assurance and quality control systems shall be implemented and maintained with written SOPs to ensure that the study is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s). Quality control shall be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

An agreement must be secured from all involved parties to ensure direct access to all study-related sites, source documents, and reports for the purpose of monitoring and auditing by the Sponsor and inspection by regulatory authorities.

13.1. Training of Study Site Personnel

Prior to study activities being initiated at the study site, the Sponsor or designee will train study site personnel on the protocol and applicable procedures. Training should be documented.

If new study site personnel are assigned to the study after the initial training, study sites should contact the study monitor to coordinate training. Qualified study personnel may conduct training, as appropriate, if deemed acceptable by the monitor and Sponsor. Training of new study personnel should also be documented.

13.2. Monitoring

Study site monitoring is conducted to ensure the study is progressing as expected, the rights and well-being of human subjects are protected, the reported study data are accurate, complete, and verifiable, and the conduct of the study is in compliance with the currently approved protocol, with GCP and with applicable regulatory requirements. Protocol deviations identified will be documented.

Details of study site monitoring are documented in the study Clinical Monitoring Plan (CMP) or similar document. The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed (eg, targeted and/or risk based), and the distribution of monitoring reports. Monitoring may include a study site selection visit, which may be conducted in person or via communication media (eg, teleconference, online meeting) or may be waived in accordance with policy and procedures being followed for the study, if appropriate. Monitoring will include a study site initiation visit, interim monitoring visit(s), and a study site closeout visit. An interim monitoring visit may be combined with a closeout visit, if applicable.

13.3. Audit

An audit of one or more participating study sites may be performed independently of, and separately from, routine monitoring to evaluate clinical study conduct and compliance with the protocol, SOPs, GCP, and the applicable regulatory requirements.

14. DATA HANDLING AND RECORD KEEPING

14.1. Data Management

14.1.1. Case Report Forms

An eCRF must be completed for each subject screened/enrolled in this study. These forms will be used to transmit information collected during the study to the Sponsor and regulatory authorities, as applicable.

The documentation related to the validation of the eCRFs will be maintained in the Trial Master File (TMF). The TMF will be maintained by the clinical research organization and will be archived by the Sponsor.

The Investigator will document subject data in his/her own subject files. These subject files will serve as source data for the study. All eCRF data required by this protocol will be recorded by study site personnel. All data entered into the eCRF will be supported by source documentation.

The Investigator or an authorized member of the Investigator's staff will make any necessary corrections to the eCRF. All changed information, including the date and person performing the corrections, will be available via the audit trail, which will be part of the electronic data capture system. For any correction, a reason for the alteration will be provided. The eCRFs will be reviewed periodically for completeness and acceptability by Sponsor personnel (or their representatives). The Sponsor (or their representatives) will also be allowed access to all source documents pertinent to the study in order to verify eCRF entries. The Investigator will review the eCRFs for completeness and accuracy and provide his or her electronic signature and date to the eCRFs as evidence thereof.

14.1.2. Source Documents

Per regulatory requirements, the Investigator or designee will maintain accurate and up-to-date study documentation, including source documentation for each study subject. Source documents are defined as original documents, data, and records. These may include, but are not limited to, hospital records, clinical and office charts, laboratory data/information, evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, ECGs, X-rays, ultrasounds, right heart catheterization reports, or echocardiograms. Data collected during this study must be recorded on the appropriate source documents.

The Investigator(s)/institution(s) will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspection(s) and will provide direct access to the source data.

14.2. Study Documentation and Records Retention

The Investigator and study staff have the responsibility of maintaining a comprehensive and centralized filing system containing all study-related documentation. These files must be available for inspection by the Sponsor, representatives of the Sponsor, the IRB/IEC, and regulatory authorities (ie, FDA or international regulatory authorities) at any time, and should consist of the following elements:

- Subject files containing the completed eCRFs (if applicable), supporting source documentation including medical records, laboratory data, and signed ICFs.
- Regulatory files containing the protocol with all amendments and Investigator signature pages, copies of all other regulatory documentation, all correspondence between the study site and the IRB/IEC and Sponsor, and drug accountability files, including a complete account of the receipt and disposition of the study treatment.

Records will be available for 2 years after the last marketing application approval, or if the application is not approved or never submitted, 2 years after the appropriate regulatory authorities have been notified of the discontinuation of clinical development of the investigational product. After the 2 years period has elapsed, the site will contact the Sponsor to inquire about the desired sponsor-approved destination for the study documents. Shipment of the appropriate study files will be arranged by the sponsor and site.

During the record retention period, the Investigator or designee must inform the Sponsor or designee (eg, CRO), of the following:

- Location of study documentation
- If the Investigator is unable to retain documentation for the specified period

14.3. Clinical Study Report

Whether the study is completed or prematurely terminated, a clinical study report will be prepared and provided to the regulatory agencies according to applicable regulatory requirement(s).

14.4. Disclosure of Study Results

The Sponsor will post the results of the study in a publicly accessible database in accordance with the applicable laws and regulations.

15. RESPONSIBILITIES

15.1. Investigator Responsibilities

The Investigator must comply with this protocol and the conduct of all study procedures. The Investigator will disclose to the Sponsor sufficient, accurate, financial information to allow the Sponsor to submit accurate disclosure statements to the FDA per 21 Code of Federal Regulations Part 54 (Financial Disclosure by Clinical Investigators) or to other regulatory authorities that have similar requirements. The Investigator is responsible for compliance with applicable sections of ICH GCP requirements. The investigator may also be responsible for compliance with 21 Code of Federal Regulations Part 312, Subpart D (Responsibilities of Investigators) and other, federal, and local laws, applicable to conducting drug studies.

The Investigator is responsible for ensuring an investigation is conducted according to the signed Investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the Investigator's care; and for the control of drugs under investigation. An Investigator shall, in accordance with the provisions of ICH GCP guidelines and/or 21 Code of Federal Regulations Part 50, obtain the informed consent of each human subject to whom the drug is administered.

15.2. Sponsor Responsibilities

The Sponsor is responsible for compliance with applicable sections of ICH E6(R2) and 21 Code of Federal Regulations Part 312, Subpart D (Responsibilities of Sponsors). The Sponsor is responsible for selecting qualified Investigators, providing them with the information they need to conduct an investigation properly, and ensuring proper monitoring of the investigation(s), ensuring the investigation(s). Sponsors are also responsible for ensuring the investigation(s) is conducted in accordance with the general investigational plan and protocols contained in the Investigational New Drug (IND) application (or equivalent), maintaining an effective IND (or equivalent) with respect to the investigations, and ensuring the FDA (and/or other regulatory authorities as applicable), and all participating Investigators are promptly informed of significant new adverse effects or risks with respect to the drug.

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APPENDIX 1: SCHEDULE OF ASSESSMENTS

Timepoint	Screening	Check-in[a]	Peri-PCI: Baseline[b]	Peri-PCI: Dosing	Peri-PCI: Pre-PCI	Peri-PCI: Post-PCI[c]	Post-PCI: 6 h (± 2 h) Post-PCI[d]	Post-PCI: 24 h (± 2 h) Post-Procedure/ Discharge[e]	Post-PCI: Follow-Up Phone Call[f]
Study Day	**–14 to 1**	**1**	**1**					**1 or 2**	**8 (± 2 Days)**
Informed consent	X								
Inclusion/exclusion	X	X							
Demographics	X								
Medical history	X	X							
Physical examination[g]	X							X	
Prior/concomitant medications	→								
Height	X								
Body weight	X	X							
Clinical chemistry and hematology[h]	X		X					X	
Selected clinical chemistry/hematology Check-in assessments[h]		X							
Coagulation panel[h]			X			X	X	X	
Urine drug screen[h]		X							

Timepoint	Screening	Check-in[a]	Peri-PCI				Post-PCI		
			Baseline[b]	Dosing	Pre-PCI	Post-PCI[c]	6 h (± 2 h) Post-PCI[d]	24 h (± 2 h) Post-Procedure/ Discharge[e]	Follow-Up Phone Call[f]
Study Day	**–14 to 1**	**1**	**1**					**1 or 2**	**8 (± 2 Days)**
ECG[i]		X				X[j]		X	
Blood pressure and heart rate[k]	X	X						X	
Respiratory rate and body temperature		X						X	
Adverse event reporting	→								
Randomization		X[l]							
Study treatment administration				X					
$P2Y_{12}$ VerifyNow			X			X			
Peripheral serotonin assessment[m]			X			X			
Coronary artery serotonin assessment[n]						X[o]			
Coronary physiology indices[p]			X		X	X[o]			
Markers of inflammation[h]			X			X	X	X	
Markers of myocardial injury[h]			X			X	X	X	
Diagnostic angiography with confirmation of lesion characteristics[q]		X							

Timepoint	Screening	Check-in[a]	Peri-PCI				Post-PCI		
			Baseline[b]	Dosing	Pre-PCI	Post-PCI[c]	6 h (± 2 h) Post-PCI[d]	24 h (± 2 h) Post-Procedure/ Discharge[e]	Follow-Up Phone Call[f]
Study Day	**–14 to 1**	**1**	**1**					**1 or 2**	**8 (± 2 Days)**
Assessment of target vessel angiographic measures[r]			X			X			
PK blood draw			X		X[s]	X	X	X[t]	

[a] Check-in assessments include pre-randomization confirmation of eligibility on Day 1. Screening assessments are not required to be repeated at Check-in for subjects for whom Screening occurs on the same day as Check-in (Day 1).
[b] Baseline assessments are to occur after confirmation of eligibility/randomization and prior to study treatment administration.
[c] Post-PCI assessments are to occur within 15 minutes of the completion of the PCI procedure. For ECG assessment, follow footnote "j" below.
[d] If subjects are discharged less than 2 hours after the 6-hour Post-PCI assessments have been completed, any assessments scheduled for discharge must be performed, but assessments scheduled at both 6 hours Post-PCI and discharge do not need to be repeated.
[e] Subjects will be discharged at the Investigator's discretion based upon clinical presentation, but not prior to the collection of all 6-hour Post-PCI assessments.
[f] Site staff will work with subjects who withdraw early to obtain as much follow-up data as possible.
[g] A physical examination is performed per the site's standard of care at Screening. A symptom-based physical exam is performed prior to discharge.
[h] Refer to Table 2 for additional information.
[i] ECG monitoring during catheterization procedures is to occur per site standard of care and any clinically significant findings will be recorded as adverse events in the eCRF.
[j] To be collected after the completion of the PCI procedure and at least 1-hour postdose.
[k] Blood pressure and heart rate monitoring during catheterization lab procedures will be conducted per site standard of care and any clinically significant findings will be recorded as adverse events in the eCRF.
[l] Randomization is to occur after confirmation of all inclusion and exclusion criteria on Day 1.
[m] Peripheral serotonin is assessed from a blood sample obtained by peripheral venipuncture or preferably using an indwelling catheter (central line can be used if available).
[n] Coronary artery serotonin is assessed from blood samples obtained from the coronary ostium and from coronary artery distal to the lesion using an aspiration catheter.
[o] To be performed as soon as possible after completion of the PCI procedure.
[p] Coronary physiology indices include IMR, CFR, and FFR. Assessment of Baseline coronary physiology indices can be performed prior to randomization at Check-in for confirmation of suitability for PCI per institutional standards.
[q] Confirmation of lesion and vessel characteristics is required for eligibility purposes prior to randomization. Diagnostic angiography including confirmation of lesion-related eligibility can be performed prior to randomization at Check-in or within 60 days prior to Day 1. In cases when diagnostic angiography is not performed at Check-in, lesion and vessel characteristics should be assessed as part of Baseline target vessel angiographic measures assessment prior to administration of study treatment.
[r] Angiographic measures of target vessel include cTFC, TFG, TMPG, QCA, and assessment of lesion and vessel characteristics. Assessment of Baseline target vessel angiographic measures can be performed during diagnostic angiography at Check-in.
[s] To occur 0-2 minutes after the IV administration of study treatment has been completed and prior to coronary physiology measurements.
[t] The final PK blood draw is to occur at 24 hours post-PCI or at discharge, whichever occurs first.

CFR, coronary flow reserve; eCRF, electronic case report form; cTFC, corrected TIMI frame count; ECG, electrocardiogram; FFR, fractional flow reserve; h, hour; IMR, index of microcirculatory resistance; IV, intravenous; PCI, percutaneous coronary intervention; PK, pharmacokinetic; QCA, quantitative coronary analysis; TFG, TIMI flow grade; TIMI, thrombolysis in myocardial infarction; TMPG, thrombolysis in myocardial infarction myocardial perfusion grade

APPENDIX 2: INVESTIGATOR SIGNATURE

Study title: A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety, Tolerability, and Effect on Microvascular Obstruction of Temanogrel in Subjects Undergoing Percutaneous Coronary Intervention

Study number: APD791-202

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol.

Investigator Signature	**Date**

Investigator Name and Credentials - Printed
Institution Name – Printed

Name: Clinical Study Protocol: APD791-202 Amendment 3.0
Description: A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlle

User Nam PPD Capacity: PPD	Meaning: Approval Task Date: 17-May-2022 05:38:07 GMT+0000

Note to File, Addendum

Date:	09 December 2022
To:	TMF
From:	PPD PPD
Protocol No.:	APD791-202
Subject:	Document the status of documents and outline plans for select post-database lock pharmacokinetic analyses

---

Background: On 25 August 2022, the decision was made to discontinue development of the Arena cardiovascular programs, which includes APD791.

As a result of the immediate termination, the biostatistics aspects related to finalizing documents (e.g., statistical analysis plan [SAP]) and other downstream activities pertaining to pharmacokinetic analyses were either immature and/or had not been established. These tasks would have taken significant time and resources by both the Arena and Medpace team to finalize, which was not feasible given the accelerated study close-out timeline, including the database lock (DBL) which occurred on 10 October 2022. The document here serves as the addendum to APD791-202 NTF (approved on 07 October 2022) to outline the plans for select post-database lock pharmacokinetic analyses.

Final Status:

Pharmacokinetic Analysis

- As per draft statistical analysis plan (SAP) v0.3
- Final pharmacokinetic parameters received from Medpace on December 5, 2022

Pharmacokinetics-Pharmacodynamics Analysis

- Development has not begun.

Serotonin Analysis

- Development has not begun.
- Raw data for plasma serotonin concentrations were received on 19 October 2022

Deliverables & Analyses: Pharmacokinetic(PK) parameters were estimated as per stated in SAP (v0.3) by Medpace Personnel. TFLs containing key pharmacokinetic information were

produced as presented in Appendix A of this Note to File, Addendum. Arena utilized this existing report structure in place of SAP-based TFLs for the final report.

Signatures:

PPD

REASON: I am the author of this document.

09 Dec 2022 11:51:024-0500

38a6da24-b5d4-4829-9686-778a64390ad5

PPD

PPD

REASON: I approve this document.

09 Dec 2022 12:21:001-0500

27617dd7-8cd6-4ce9-8a3a-25966a6aeafd

PPD

Distribution:

☒ TMF or applicable document repository

Appendix A – Table of Contents of APD791-202 PK Analysis

14.2.6.2.2 Individual Values and Summary of Plasma AR295980 (M1) Pharmacokinetic Parameters by Treatment Pharmacokinetic Set

14.2.6.2.3 Individual Values and Summary of Plasma AR295981 (M2) Pharmacokinetic Parameters by Treatment Pharmacokinetic Set

Note to File

Date:	07 October 2022
To:	TMF
From:	PPD
Protocol No.:	APD791-202
Subject:	Document the status of biometrics-related documents/processes and outline plan for select post-database lock safety and efficacy analyses

Background:

On 25 August 2022, the decision was made to discontinue development of the Arena cardiovascular programs, which includes APD791 (temanogrel). Enrollment into the ongoing clinical trial APD791-202 was terminated effective immediately and study team activities were reprioritized to focus and accelerate study close-out activities. For this study, the biostatistics, data management, and statistical programming deliverables and activities are outsourced to the clinical research organization (CRO) Medpace.

As a result of the immediate termination, the biostatistics aspects related to finalizing documents (e.g., statistical analysis plan [SAP]) and other downstream activities are either immature and/or have not been established. These tasks would take significant time and resources by both the Arena and Medpace team to finalize, which is not feasible given the accelerated study close-out timeline, which includes the database lock (DBL) planned for 10 October 2022.

Final Status:

Statistical Analysis Plan

- Draft SAP (v0.3)

Statistical Analysis Plan: Table, Listing, and Figure (TLF) Shells

- Draft TLF specifications (v0.2)

CDISC Specifications and Datasets (aCRF/SDTM/ADaM)

- aCRF (dbCRF; based on protocol amendment v3.0)
- SDTM: Specifications and datasets by 28 October 2022
- ADaM: Draft specifications (Round 1 review by Arena)

Statistical Analysis Plan: Table, Listing, and Figure (TLF) Programming

- Development has not begun for output programming

Define.xml

- Development has not begun for either SDTM or ADaM Defines

Reviewer's Guide (SDTM/ADaM)

- Development has not begun for either SDTM or ADaM Reviewer's Guides

Unblinding Procedure: Following completion of the DBL sign-off form, the Medpace project statistician will circulate the Unblinding form for signature by Arena (Lead Study Statistician, Head of Biostatistics and Data Management) and by appropriate Medpace team members. The Medpace project statistician will then present both the signed DBL and Unblinding forms to the IRT group to document that the unblinded treatment assignments could be shared with the Biostatistics team for incorporation into the final database. The signed DBL and Unblinding forms will be included in TMF.

Deliverables & Analyses: Since the SAP, CDISC ADaM data, and statistical programming (e.g., dataset level, table level) will not be finalized, alternative solutions are being utilized to provide post-DBL safety and efficacy analyses. No substudy data will be analyzed.

As outlined in protocol Section 10.11, Study APD791-202 was under the purview of a Data Safety Monitoring Board (DSMB) and three meetings (Organizational and two data review) have been convened. As part of the DSMB process, Open (blinded) and Closed (unblinded) Reports were developed and produced by Axio (a Cytel company). Arena will be utilizing and augmenting these existing report structures in place of SAP-based TLFs for the final report.

Following DBL, raw datasets, both eCRF (EDC) and external non-CRF, will be made available to Axio for production of the unblinded safety and efficacy outputs. The table of contents of the final report is contained in Appendix A.

Signatures:

DocuSigned by:
PPD
Signing Reason: I approve this document
Signing Time: 07-Oct-2022 | 16:49 PDT
814EA675CEDB4734B8004A0126E54B28

PPD

DocuSigned by:
PPD
Signing Reason: I approve this document
Signing Time: 07-Oct-2022 | 17:15 PDT
B7E1C3B44A974871B89E74FA4C079B70

PPD

Distribution:

☒ TMF or applicable document repository

ARENA PHARMACEUTICALS

Appendix A – Table of Contents of Final Report