CLINICAL STUDY PROTOCOL

Protocol title:	A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Crossover Study to Assess the Effect of Oral Temanogrel on Digital Blood Flow in Subjects with Raynaud's Phenomenon Secondary to Systemic Sclerosis
Protocol number:	APD791-204
Version:	Amendment 3.0, dated 22 February 2022
Compound name:	Temanogrel (APD791)
Study phase:	2
Indication:	Treatment of Raynaud's Phenomenon Secondary to Systemic Sclerosis
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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.

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PROTOCOL HISTORY

Document	Amendment Type	Date
Amendment 3.0	Global	22 February 2022
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Amendment 1.0	Global	12 February 2021
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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, Crossover Study to Assess the Effect of Oral Temanogrel on Digital Blood Flow in Subjects with Raynaud's Phenomenon Secondary to Systemic Sclerosis

Protocol Number: APD791-204

Phase: 2

Country(ies)/Region(s) (planned): United States and United Kingdom

Objectives:

Primary:

- To assess the effect of temanogrel on digital blood flow following a cold challenge in subjects with Raynaud's phenomenon secondary to systemic sclerosis (SSc-RP)

Secondary:

- To assess the effect of temanogrel on additional measures related to digital blood flow at room temperature and following a cold challenge in subjects with SSc-RP
- To assess the safety and tolerability of temanogrel in subjects with SSc-RP

Study Design:

This is a Phase 2, multicenter, randomized, placebo-controlled, crossover study assessing the effect of oral temanogrel on digital blood flow in subjects with SSc-RP. The study will be conducted in 2 stages (Stage A and Stage B). Separate cohorts of subjects will participate in each stage. Subjects who participate in Stage A may not participate in Stage B.

In Stage A, subjects will be equally randomized in a double-blind manner to a 3-period crossover treatment sequence. The Screening Period will last for up to 28 days prior to Day 1 (Treatment Visit 1). Each subject will participate in 3 Treatment Visits, which will each be separated by a Washout Period of at least 72 hours and up to approximately 7 days between study treatment administrations. During each Treatment Visit, subjects will receive a single dose of study treatment (placebo, 60 mg temanogrel, or 120 mg temanogrel) according to their crossover treatment sequence assignment.

On Day 1, subjects will be admitted to the clinic for Treatment Visit 1. After Check-in assessments including blood sampling for clinical laboratory assessments, pharmacokinetics (PK), and biomarkers, subjects will acclimatize for at least 20 minutes in a temperature-controlled room (23 [± 1]°C), followed by Predose digital blood flow assessments for 5 minutes at room temperature based on simultaneous collection of temperature and perfusion data using infrared (IR) thermography and laser speckle contrast imaging (LSCI), respectively. After study treatment administration, subjects will undergo re-acclimatization for at least 20 minutes, followed by Postdose assessments. Postdose assessments will start 45 (± 5) minutes after dosing with digital blood flow assessments performed once again for 5 minutes at room temperature. A cold challenge will then be conducted by immersing the hands in a temperature-controlled water bath (15 [± 1]°C) for 1 minute, followed by post-cold

challenge digital blood flow assessments for 30 minutes. Blood samples for clinical laboratory assessments, PK and biomarkers will be collected again after post-cold challenge digital blood flow assessments are complete. Subjects will be discharged from the study unit once all planned Postdose assessments have been completed. For Treatment Visit 2 and Treatment Visit 3, subjects will return to the clinic at approximately the same time of the day as for Treatment Visit 1 (between 0800 and 1200 hours) and will undergo the same assessments as for Treatment Visit 1. A Follow-Up Visit will occur 4 (± 1) days after administration of final study treatment for a total study duration of 10 to 47 days.

Following the double-blinded conduct of Stage A, the Sponsor will conduct an unblinded evaluation of the efficacy and safety results prior to proceeding to Stage B. In Stage B, 2 single doses of temanogrel (doses to be determined after review of Stage A data, but not exceeding 240 mg) and placebo are planned to be evaluated with a study design identical to Stage A.

Number of Subjects (Planned):

Approximately 48 subjects are planned to be enrolled in the study. Approximately 24 subjects are planned to be enrolled in Stage A. The number of subjects planned to be enrolled in Stage B is approximately 24; however, sample size may be adjusted based on the results of Stage A. Subjects participating in Stage A may not participate in Stage B.

Eligibility Criteria:

Inclusion Criteria:

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

1. Raynaud's phenomenon (defined as a history of digital cold sensitivity associated with color changes of cyanosis and pallor, with on average at least 5 attacks per week during the winter period) secondary to systemic sclerosis (SSc) based on either:
   a. Diagnosis of SSc (using the American College of Rheumatology/European League Against Rheumatism [ACR/EULAR 2013] and/or LeRoy and Medsger classification)
   b. Diagnosis of very early SSc (using the Very Early Diagnosis of Systemic Sclerosis [VEDOSS] criteria)
2. 18 to 75 years of age, inclusive
3. Females must meet a and c or b and males must meet d to qualify for the study:
   a. Female and not pregnant or breastfeeding
   b. Female and not of child-bearing 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

   c. Female of child-bearing potential and using a highly effective contraception method during treatment and for 30 days following treatment that can achieve a

failure rate of less than 1% per year when used consistently and correctly. The following methods are considered highly effective birth control methods:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation, which may be oral, intravaginal, or transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation, which may be oral, injected, or implanted
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence (complete sexual abstinence defined as refraining from heterosexual intercourse for the entire period of risk associated with study treatments). The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the subject. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception

d. Males with pregnant or non-pregnant female partners of child-bearing potential agree to using a condom during treatment and for 90 days following treatment

4. Body mass index 18.0 to 40.0 kg/m^2, inclusive
5. Willing to participate in the study and provide written informed consent

Exclusion Criteria:

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

1. Active digital ulcer(s), recent history (within 3 months of Screening) of digital ulcers, or history of recurrent digital ulcerations that in the opinion of the Investigator increase the likelihood of developing a digital ulcer during the course of the study. Any history of gangrene, amputations, or other critical digital ischemic event
2. Presence of severe contractures (advanced fixed flexion) of the digits, which in the opinion of the Investigator could prevent accurate assessment of digital perfusion of the dorsal fingers
3. Raynaud's phenomenon due to any cause other than SSc (eg, peripheral or central vasculopathy other than SSc, past exposure to vasculopathic agents, past frostbite injury)
4. Severe gastrointestinal complications related to SSc that in the opinion of the Investigator could significantly affect study drug absorption
5. History of gastrointestinal bleeding or active gastric or duodenal ulcers

6. Subject's digits do not reach a temperature of ≥ 27°C after 20 minutes of acclimatization at room temperature (23 [± 1]°C) at Screening
7. Any change in dosage of the following medications within 30 days of Day 1 or planned change in dosage during study participation: Calcium channel blockers (CCBs), phosphodiesterase type 5 inhibitors (PDE5i), alpha-blockers, or angiotensin II receptor blockers (ARBs)
8. Use of nitrates within 30 days of Day 1
9. Use of endothelin-1 receptor antagonists (ERAs) and therapies targeting the prostacyclin receptor within 3 months of Day 1
10. Local treatment (of digits) with botulinum toxin within 30 days of Day 1
11. Surgical sympathectomy of digit within 3 months of Day 1
12. Use of vasoconstrictive drugs (eg, ergot derivatives, triptans) within 7 days of Day 1
13. Use of antiplatelet therapy with the exception of aspirin (eg, adenosine diphosphate receptor [$P2Y_{12}$] inhibitors, glycoprotein IIb/IIIa inhibitors), or anti-coagulants (eg, warfarin or direct oral anti-coagulants [DOACs], including oral thrombin inhibitors) within 7 days of Day 1
14. Use of any medications affecting the serotonin system (eg, selective serotonin reuptake inhibitors [SSRI], serotonin and norepinephrine reuptake inhibitors [SNRIs], atypical [second generation] antipsychotics possessing 5-HT_{2A} pharmacology, or any other serotonergic agents possessing 5-HT_{2A} pharmacology [eg, naftidrofuryl and the triazolopyridine antidepressant trazodone]) within 14 days of Day 1
15. Use of prescription medications/products or herbal preparations that are strong inhibitors or inducers of cytochrome P450 (CYP)3A4, or are strong inhibitors of P-glycoprotein within 14 days of Day 1 or 5 half-lives of the medication/product, whichever is longer. Refer to Section 5.4 Restricted Medications for details.
16. Use of prescription medications/products that are strong inhibitors of multidrug and toxin extrusion transporter-1 (MATE1) or organic cation transporter-2 (OCT2) within 14 days of Day 1 or 5 half-lives of the medication/product, whichever is longer. Refer to Section 5.4 Restricted Medications for details.
17. Use of prescription medications/products that are sensitive or moderately sensitive substrates of CYP2C8 within 14 days of Day 1 or 5 half-lives of the medication/product, whichever is longer. Refer to Section 5.4 Restricted Medications for details.
18. Use of prescription medications/products that are sensitive substrates of CYP3A4/5 within 14 days of Day 1 or 5 half-lives of the medication/product, whichever is longer. Exceptions are PDE5i (allowed per Exclusion Criterion #7) and atorvastatin. Refer to Section 5.4 Restricted Medications for details.
19. Consumption of grapefruit or grapefruit juice within 3 days of Check-in

20. Diabetes mellitus diagnosed more than 5 years ago or with known history of end-organ damage (diabetic retinopathy, nephropathy, neuropathy)
21. History of advanced heart failure (New York Heart Association [NYHA] Class 3 or 4) or myocardial infarction within 1 month prior to Screening
22. Any history of stroke, seizure disorder, intracranial bleeding, or intracranial aneurysm; significant head injury requiring hospital assessment within 30 days prior to Screening
23. Transient ischemic attack within the 6 months prior to Screening
24. History of major trauma, major surgery, and/or clinically significant hemorrhage within the 6 months prior to Screening
25. Active hepatitis C
26. At the discretion of the Investigator, any history or clinical manifestation of any endocrine, allergic, dermatological, hepatic, renal, hematological, pulmonary, gastrointestinal, neurological or psychiatric disorder, or any malignancy treated within 1 year of Screening (with the exception of basal cell carcinoma of skin which is not advanced) that would prevent the individual from participating in the study due to risk to the scientific validity of study assessments or to personal well being
27. Any abnormal clinical chemistry, hematology, electrocardiogram (ECG), urinalysis, or physical finding at Screening that in the opinion of the Investigator is deemed 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
28. Hepatic dysfunction (history of cirrhosis with diagnosed portal hypertension, or alanine aminotransferase [ALT] or aspartate aminotransferase [AST] > 3 × upper limit of normal [ULN]) at Screening)
29. 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 Screening
30. Impaired hemostasis (eg, thrombocytopenia [platelet count < 100,000/μL] at Screening; abnormal coagulation test defined as prothrombin time [PT] or partial thromboplastin time [PTT] > 1.5 × ULN, or international normalized ratio [INR] > 2 at Screening; past or present bleeding disorder, sickle cell or other platelet disorders, or carcinoid disorder)
31. Any surgeries or interventional procedures planned or anticipated during study participation
32. Positive urine test for amphetamines, barbiturates, benzodiazepines, cocaine, marijuana, methadone, methamphetamine, methylenedioxymethamphetamine, opiate, oxycodone, or phencyclidine. Exception is a test that is positive due to a prescription drug or medication.

33. 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 well being
34. Use of tobacco or nicotine-containing products (including but not limited to cigarettes, e-cigarettes, pipes, cigars, chewing tobacco, nicotine patches, nicotine lozenges, or nicotine gum) for at least 90 days prior to Screening
35. Previous participation in a study with temanogrel
36. Subjects who have received any investigational device or investigational drug within 30 days of Day 1, or 5 half-lives of the investigational drug (whichever is greater) prior to Screening
37. Hypersensitivity to temanogrel or placebo compounds
38. Inability to swallow capsules as required per the protocol
39. In the opinion of the Investigator, subject is not a candidate for blood sampling as required per the protocol

Test Product, Dose, and Mode of Administration:

The oral formulation of temanogrel contains 20 mg of active pharmaceutical ingredient in a Swedish orange hard-gelatin capsule.

Duration of Treatment:

Subjects will receive a single oral dose of study treatment on each of the 3 Treatment Visits in a randomized 3-period crossover treatment sequence.

Reference Therapy, Dose, and Mode of Administration:

Placebo will contain microcrystalline cellulose in a Swedish orange hard-gelatin capsule. Visual appearance and mode of administration of placebo will match that of the temanogrel drug product to maintain the blind.

Endpoints:

Primary Endpoint:

- Change in digital blood flow based on:
  - Rewarming area under the curve (AUC; °C, assessed with IR thermography) during the 30 minutes following a cold challenge
  - Reperfusion AUC (perfusion units [pu], assessed with LSCI) during the 30 minutes following a cold challenge

Secondary Endpoints:

- Change in the following temperature (°C, assessed with IR thermography) and perfusion (pu, assessed with LSCI) parameters:
  - Maximum reduction following a cold challenge
  - Maximum recovery during the 30 minutes following a cold challenge
  - AUC during the initial 2 minutes following a cold challenge
  - Slope during the initial 2 minutes following a cold challenge

- Time to achieve 50% recovery from the cold challenge-induced reduction
- Time to achieve 70% recovery from the cold challenge-induced reduction

- Change from Predose to Postdose in the following temperature (°C, assessed with IR thermography) and perfusion (pu, assessed with LSCI) parameters:
  - Room temperature values
  - Distal dorsal difference (DDD) (defined as the difference in measurements between the dorsum and the finger) at room temperature

Safety Endpoint:

- Safety and tolerability of temanogrel

Pharmacodynamic Assessments:

Pharmacodynamic (PD) assessments of digital blood flow based on both temperature and perfusion will be conducted simultaneously using IR thermography and LSCI, respectively. Digital blood flow will be assessed at each Treatment Visit at Predose for 5 minutes at room temperature, and at Postdose prior to cold challenge for 5 minutes at room temperature and for 30 minutes following a cold challenge. Region(s) of interest (ROIs) on both hands will be predefined and the same ROIs will be used for analysis during all digital blood flow measurements for all subjects. Data will be presented in temperature (°C) for IR thermography or in arbitrary pu for LSCI and averaged for all ROIs.

Biomarker Assessments:

Plasma serotonin concentration as well as markers of vascular injury and endothelial dysfunction (endothelin-1, factor VIII activity, intracellular adhesion molecule 1 [ICAM-1], tissue-type plasminogen activator antigen [t-PA], plasminogen activator inhibitor-1 [PAI-1] activity, PAI-1 antigen, vascular adhesion molecule 1 [VCAM-1], vascular endothelial growth factor [VEGF], and von Willebrand factor [VWF]) will be assessed at each Treatment Visit at Check-in and following the post-cold challenge digital blood flow assessments.

The relationships between selected PD measures and biomarker concentrations may be explored.

Pharmacokinetic Assessments:

Blood samples for plasma PK analysis of temanogrel and its metabolites will be collected at each Treatment Visit at Check-in and after the post-cold challenge digital blood flow assessments are completed.

The relationships between plasma concentration of selected analytes (temanogrel, its active metabolites, and/or all analytes combined) and selected PD measures may be explored.

Safety Assessments:

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

Statistical Methods:

Determination of Sample Size:

Approximately 24 subjects are planned to be randomized in Stage A, which is sufficient to achieve at least 80% power to detect a treatment effect of 16.6% from placebo for change in digital blood flow based on rewarming AUC (°C, assessed with IR thermography) during the 30 minutes following a cold challenge for each of the 2 temanogrel treatments based on a difference of means test for a 3-period, 3-treatment crossover design with a significance level 0.05 (2-sided). The test assumes the temanogrel treatment group mean of 365, placebo group mean of 313, and a standard deviation of the difference in temanogrel treatment and placebo group means of 86. In addition, with 24 subjects there is at least 80% power to detect a treatment effect of 23.5% from placebo for change in digital blood flow based on reperfusion AUC (pu, assessed with LSCI) during the 30 minutes following a cold challenge for each of the 2 temanogrel treatments (temanogrel treatment group mean of 24.7, placebo group mean of 20, and a standard deviation of the difference in temanogrel treatment and placebo group means of 7.8). Assumptions are based on previous studies in SSc-RP utilizing these or similar methods (Herrick 2014, Wilkinson 2018, Wise 2004). Subjects will be equally randomized (1:1:1:1:1:1 ratio) to 1 of the 6 treatment sequences (4 subjects per sequence).

Approximately 24 subjects are planned to be randomized in Stage B using the same 3-period, 3-treatment crossover design. Based on Stage A results, Stage B sample size may be modified, but not limited to, Stage A dose levels will be enriched or 2 additional temanogrel doses will be evaluated.

Stratification:

No randomization stratification factors will be employed.

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 95% 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 and sensitivity analyses, will be described in the Statistical Analysis Plan (SAP).

The primary endpoints of the study are the change in digital blood flow based on rewarming/reperfusion AUC (assessed with IR thermography and LSCI, respectively) during the 30 minutes following a cold challenge. The primary analyses will be analyzed using analysis of variance (ANOVA; Williams' design) with a model that includes treatment group, sequence, and period as factors. 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 ANOVA (Williams' design) with a model that includes treatment group, sequence, and period as factors. Least square means, SEs, and 95% CIs for the treatments and their difference will be presented together with their p-values.

Given subjects will receive all 3 treatments in 1 of 6 possible sequences, first-order carryover effects will be evaluated to assess the extent to which the order of treatments affected primary and secondary endpoints.

The primary safety endpoint of the study is the assessment of treatment-emergent adverse events (TEAEs) and will be performed using the Safety Set. All bleeding-related adverse events will be classified using the Bleeding Academic Research Consortium (BARC) criteria.

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, first-order carry effects) are not met, alternative approaches will be evaluated (eg, nonparametric analysis, log transformation). All statistical tests for efficacy parameters will be performed at the 0.05 significance level (2-sided).

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

Pharmacokinetic Analysis:

The PK analysis will be conducted using plasma concentrations of temanogrel and its metabolites from subjects who have received temanogrel and have evaluable plasma concentrations. Further details will be provided in the SAP.

Safety Analysis:

Adverse events will be listed and summarized by system organ class and preferred term, as well as according to severity and relationship to study treatment. TEAEs will be summarized by study stage and treatment group. Similarly, bleeding events will be summarized by BARC classification by study stage and treatment group. Observed values for clinical chemistry and hematology tests and vital signs will be summarized by study stage, treatment group, and study day. Individual data listings of clinical chemistry and hematology tests results will be presented for each subject. Observed values and changes from Baseline will be summarized descriptively. Observed values will be classified for normal, abnormality that is not clinically significant, and clinically significant abnormality by study stage, 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.

Interim Analysis:

Following Stage A, unblinded analyses will be conducted to review the safety, PK, and efficacy (eg, observed treatment effect, variability of digital blood flow measures) data. Based on Stage A results, Stage B sample size may be modified, such as, but not limited to, Stage A dose levels will be enriched or 2 additional doses will be evaluated. Full details of the safety, PK, and efficacy data interim analyses will be provided in the SAP.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Explanation
β-hCG	beta-human chorionic gonadotropin
ACR	American College of Rheumatology
ADL	activities of daily living
ADP	adenosine diphosphate
ADR	adverse drug reaction
ALT	alanine aminotransferase
APD791	temanogrel
ANOVA	analysis of variance
ARB	angiotensin II receptor blocker
Arena	Arena Pharmaceuticals, Inc.
AST	aspartate aminotransferase
AUC	area under the curve
BARC	Bleeding Academic Research Consortium
CABG	coronary artery bypass graft
CCB	calcium channel blocker
CFR	Code of Federal Regulations
CI	confidence interval
CK	creatine kinase
CKD Epi	Chronic Kidney Disease Epidemiology Collaboration
CMP	Clinical Monitoring Plan
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DAPT	dual antiplatelet therapy
DDD	distal dorsal difference
DOAC	direct oral anti-coagulant
DNA	deoxyribonucleic acid
ECG	electrocardiogram
EC	European Commission
eCRF	electronic case report form
eDiary	electronic diary

Abbreviation	Explanation
eGFR	estimated glomerular filtration rate
ERA	endothelin-1 receptor antagonist
EULAR	European League Against Rheumatism
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practices
5-HT	5-hydroxytryptamine; serotonin
IB	Investigator's Brochure
ICAM-1	intracellular adhesion molecule 1
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	international normalized ratio
IR	infrared
IRB	Institutional Review Board
IRT	interactive response technology
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
K_i	inhibition constant
LAM	lactational amenorrhoea method
LSCI	laser speckle contrast imaging
MATE1	multidrug and toxin extrusion transporter-1
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	modified Full Analysis Set
NYHA	New York Heart Association
OCT2	organic cation transporter-2
$P2Y_{12}$	adenosine diphosphate receptor
PAI-1	plasminogen activator inhibitor-1
PD	pharmacodynamic
PDE	phosphodiesterase

Abbreviation	Explanation
PDE5i	phosphodiesterase type 5 inhibitors
PK	pharmacokinetic(s)
POM	proof-of-mechanism
PRO	patient-reported outcome
PRP	platelet-rich plasma
PT	prothrombin time
PTT	partial thromboplastin time
pu	perfusion units
QTc	corrected QT interval
QTcB	corrected QT interval using Bazett's formula
QTcF	corrected QT interval using Fridericia's formula
RNA	ribonucleic acid
ROI	region of interest
RSI	Reference Safety Information
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SE	standard error
SOP	standard operating procedure
SNRI	serotonin and norepinephrine reuptake inhibitors
SSc	systemic sclerosis
SSc-RP	Raynaud's phenomenon secondary to systemic sclerosis
SSRI	selective serotonin reuptake inhibitor
TBL	total bilirubin
TEAE	treatment-emergent adverse event
TMF	Trial Master File
t-PA	tissue-type plasminogen activator antigen
ULN	upper limit of normal
US	United States
VAS	visual analogue scale
VCAM-1	vascular adhesion molecule 1
VEDOSS	Very Early Diagnosis of Systemic Sclerosis

Abbreviation	Explanation
VEGF	vascular endothelial growth factor
VWF	von Willebrand factor
WOCBP	women of child-bearing potential

1. INTRODUCTION

Raynaud's phenomenon is an exaggerated vascular response to cold temperature or emotional stress, which leads to vasoconstriction and reduced blood flow to the extremities (Herrick 2005). It can be idiopathic (primary Raynaud's phenomenon) or associated with other conditions such as connective tissue diseases (secondary Raynaud's phenomenon) (Bakst 2008, Herrick 2017, Pauling 2019). Systemic sclerosis (SSc) is an autoimmune disease resulting in hardening of the connective tissue, characterized by vasculopathy, endothelial dysfunction, and excessive deposition of extracellular matrix that leads to fibrosis of the skin and internal organs (Varga 2017). Raynaud's phenomenon is present in ~95% of patients with SSc and is often an initial manifestation of this disease (Herrick 2019, Meier 2012). In both primary and secondary Raynaud's phenomenon, attacks are characterized by skin color changes as a result of ischemia (white), followed by deoxygenation (blue), and reperfusion/hyperemia (red), and are usually accompanied by substantial numbness and pain (Herrick 2005, Pauling 2019). However, in patients with Raynaud's phenomenon secondary to systemic sclerosis (SSc-RP), more severe Raynaud's phenomenon manifestation is commonly observed, with reports of progression to digital ulcers or critical ischemia leading to gangrene and amputation in up to 60% of cases (Maundrell 2015).

Management of symptoms in primary Raynaud's phenomenon is usually focused on conservative approaches including avoidance of triggering conditions by limiting the exposure of extremities to cold conditions, cessation of smoking, and discontinuation of vasoconstrictive drugs (Bakst 2008, Herrick 2017). Considering the severity of Raynaud's phenomenon in SSc and subsequent complications, management based on lifestyle modifications is often insufficient for these patients and pharmacological treatment is typically initiated (Bakst 2008, Herrick 2017, Herrick 2019, Pauling 2019). There are, however, no currently approved treatments that reduce the frequency, duration, or severity of Raynaud's attacks in SSc-RP, and physicians are guided based on the limited evidence from agents approved in other indications. Recommended treatment options include vasodilating agents such as calcium channel blockers (CCBs), phosphodiesterase (PDE) 5 inhibitors, angiotensin II receptor blockers (ARBs), and topical nitrates; in more severe cases intravenous (IV) prostanoids or endothelin-1 receptor antagonists (ERAs) can be used (Herrick 2017, Herrick 2019, Linnemann 2016, Pauling 2019). The limited available evidence for most of these agents, particularly those often initiated early in the treatment of SSc-RP, suggests modest efficacy in SSc-RP (Herrick 2017, Linnemann 2016). Furthermore, CCBs and nitrates, often initiated early in treatment, increase the risk for hypotension, and IV prostanoids and ERAs, usually initiated in more advanced stages, often require more stringent monitoring owing to a more serious adverse effect profile (Linnemann 2016). Thus, there is an unmet need for an agent with demonstrated efficacy and acceptable safety profile that can be used early in treatment of SSc-RP.

Study APD791-204 is a Phase 2, multicenter, randomized, double-blind, placebo-controlled, crossover study to assess the effect of oral temanogrel on digital blood flow in subjects with SSc-RP. 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 SSc-RP. As a potent inverse agonist of the serotonin $(5\text{-HT})_{2A}$ 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. Temanogrel has a high binding affinity for the human 5-HT_{2A} receptor CCI and minimal affinity for 5-HT_{2B} CCI receptors, with no significant binding to any of the tested common receptors and transporters.

CCI

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, pharmacokinetics (PK), and pharmacodynamics (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, temanogrel was well-tolerated and there were no safety concerns associated with doses planned to be used in this 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. 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. The most common adverse events in subjects treated with single doses of IV temanogrel were mild pain and redness at the treatment administration site.

Subjects are not expected to receive any significant health benefit from participating in the study beyond that of an assessment of their medical status. However, assessments included in this study may afford additional insight into the individual disease pathophysiology. Findings from this study may also offer valuable insight into a new therapeutic approach for treatment of SSc-RP.

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 of the 5-HT_{2A} receptors present on the surface of platelets. 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 DAPT consisting of aspirin and clopidogrel. 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. 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. The risks of participation 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 such as conducting the hand cold challenges. 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 digital blood flow following a cold challenge in subjects with SSc-RP

Secondary Objectives

- To assess the effect of temanogrel on additional measures related to digital blood flow at room temperature and following a cold challenge in subjects with SSc-RP
- To assess the safety and tolerability of temanogrel in subjects with SSc-RP

Exploratory Objectives

- To explore relationships between select PD endpoints and the concentration of temanogrel/active metabolites and/or select biomarkers
- To assess pain following a cold challenge in subjects with SSc-RP

3. STUDY DESIGN

This is a Phase 2, multicenter, randomized, placebo-controlled, crossover study assessing the effect of oral temanogrel on digital blood flow in subjects with SSc-RP. The study will be conducted in 2 stages (Stage A and Stage B). Separate cohorts of subjects will participate in each stage. Subjects who participate in Stage A may not participate in Stage B. A study schematic is provided in Figure 1.

In Stage A, subjects will be equally randomized in a double-blind manner to a 3-period crossover treatment sequence. The Screening Period will last for up to 28 days prior to Day 1 (Treatment Visit 1). Each subject will participate in 3 Treatment Visits, which will each be separated by a Washout Period of at least 72 hours and up to approximately 7 days between study treatment administrations. During each Treatment Visit, subjects will receive a single dose of study treatment (placebo, 60 mg temanogrel, or 120 mg temanogrel) according to their crossover treatment sequence assignment.

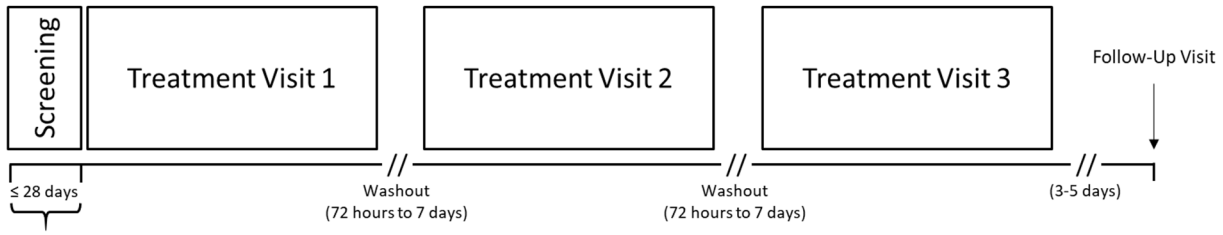
On Day 1, subjects will be admitted to the clinic for Treatment Visit 1. After Check-in assessments including blood sampling for clinical laboratory assessments, PK, and biomarkers, subjects will acclimatize for at least 20 minutes in a temperature-controlled room (23 [± 1]°C) followed by Predose digital blood flow assessments for 5 minutes at room temperature based on simultaneous collection of temperature and perfusion data using infrared (IR) thermography and laser speckle contrast imaging (LSCI), respectively. After study treatment administration, subjects will undergo re-acclimatization for at least 20 minutes, followed by Postdose assessments. Postdose assessments will start 45 (± 5) minutes after dosing with digital blood flow assessments performed once again for 5 minutes at room temperature. A cold challenge will then be conducted by immersing the hands in a temperature-controlled water bath (15 [± 1]°C) for 1 minute, followed by post-cold challenge digital blood flow assessments that will start 30 (± 10) seconds after the end of the cold challenge and last for 30 minutes. Blood samples for clinical laboratory assessments, PK, and biomarkers will be collected again after post-cold challenge digital blood flow assessments are complete. Subjects will be discharged from the study unit once all planned Postdose assessments have been completed. For Treatment Visit 2 and Treatment Visit 3, subjects will return to the clinic at approximately the same time of the day as for Treatment Visit 1 (between 0800 and 1200 hours) and will undergo the same assessments as for Treatment Visit 1. A schematic of Treatment Day assessments and procedures is provided in Appendix 2. Refer to the Schedule of Assessments (Appendix 1) for additional details on study assessments and procedures. A Follow-Up Visit will occur 4 (± 1) days after administration of final study treatment for a total study duration of 10 to 47 days.

Following the double-blinded conduct of Stage A, the Sponsor will conduct an unblinded evaluation of the efficacy and safety results prior to proceeding to Stage B. In Stage B, 2 single doses of temanogrel (doses to be determined after review of Stage A data, but not exceeding 240 mg) and placebo are planned to be evaluated with a study design identical to Stage A.

3.1. Overall Design

A schematic diagram of the study design is shown in Figure 1.

Figure 1: Schematic Diagram of Study Design



The study schematic is identical for Stage A and Stage B. In both stages, subjects will be equally randomized in a double-blind manner to a 3-period crossover treatment sequence. Separate cohorts of subjects will participate in each stage. In Stage A subjects will be treated with 60 mg temanogrel, 120 mg temanogrel, and placebo. Doses in Stage B will be determined based on the results of Stage A. Approximately 24 subjects are planned to be enrolled in Stage A. The number of subjects planned to be enrolled in Stage B is approximately 24; however, sample size may be adjusted based on the results of Stage A.

3.2. Discussion and Scientific Rationale for Study Design

3.2.1. Scientific Rationale for Temanogrel in SSc-RP

The purpose of this Phase 2 proof-of-mechanism (POM) study is to assess the effect of oral temanogrel on digital blood flow in subjects with SSc-RP. Temanogrel is a potent inverse agonist of the 5-HT_{2A} receptor that inhibits 5-HT-mediated amplification of platelet aggregation and blocks 5-HT-mediated vasoconstriction through its action on 5-HT_{2A} receptors at the surface of platelets and smooth muscle cells, respectively. Based on its mode of action, temanogrel is expected to improve microvascular digital blood flow and provide benefit to SSc patients at risk of Raynaud's attacks.

Raynaud's phenomenon in SSc is associated with more severe disease manifestation owing to a complex underlying pathophysiology, including vasculopathy and endothelial dysfunction (Herrick 2019, Pauling 2019), which detrimentally affect the microcirculation (Abraham 2007, Trojanowska 2010). Intravascular factors, including platelet activation and 5-HT release, likely also contribute to SSc-RP (Bakst 2008, Herrick 2005, Ntelis 2019, Postlethwaite 2007). Evidence suggests an important role of the 5-HT_{2A} pathway in platelets and smooth muscle cells, resulting in dual mechanism-of-action (amplification of platelet aggregation and vasoconstriction) by which 5-HT potentially impacts the pathophysiology of Raynaud's phenomenon in SSc. Raynaud's phenomenon in SSc is commonly triggered by cold temperature, which is known to enhance activation of platelets (Faraday 1998, Maurer-Spurej 2001). In addition, platelets from SSc patients have an increased aggregation response to collagen or 5-HT compared to platelets from healthy individuals (Friedhoff 1984, Goodfield 1988), suggesting hypersensitivity of platelets in patients with SSc may contribute to the elevated levels of 5-HT observed in patients with SSc-RP (Biondi 1988). It has been reported that 5-HT induces arterial vasoconstriction and reduces blood flow in human hands to a similar extent as observed with exposure to cold, and 5-HT_{2A} blockade attenuates the 5-HT-induced effects (Arneklo-Nobin 1985, Coffman 1988). In addition, enhanced vasoconstriction response to 5-HT has been observed in SSc patients compared to healthy individuals (Winkelmann 1976).

Importantly, the relevance of 5-HT and the 5-HT_{2A} pathway in SSc-RP has been validated in clinical studies evaluating the effects of 5-HT_{2A} antagonism using ketanserin and sarpogrelate, which have shown benefits on both digital blood flow and improvement of Raynaud's symptoms (Baart de la Faille 1986, Coffman 1989, Dormandy 1988, Igarashi 2000, Kato 2000, Klimiuk 1989, Kunnen 1988, Lukac 1985, Marasini 1990, Meloni 1987, Roald 1984, Seibold 1984, Stranden 1982, Tatnall 1985, Tooke 1990, Yoshimasu 2012).

3.2.2. Study Population

The study population consisting of subjects with SSc-RP was chosen as representative of the target population. However, subjects with active (or recurrent) skin ulcerations were excluded to avoid the additional burden associated with performing cold challenges, as well as potentially confounding the blood flow assessments. Subjects with advanced multiorgan disease, in particular gastrointestinal dysfunction, have been excluded due to the potential for delayed and/or poor absorption of temanogrel. Although embryo-fetal development studies have not been completed for the temanogrel program, women of child-bearing potential (WOCBP) will be included in the study population. Considering SSc occurs in women approximately 5 to 10 times more frequently than in men (Bergamasco 2019, Lo Monaco 2011), it would be difficult to effectively meet study objectives and perform a representative assessment without the inclusion of WOCBP in this population. In accordance with FDA Guidance for Industry, *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* (FDA 2010), inclusion of WOCBP is acceptable because the study is of short treatment duration (less than 2 weeks). In addition, participants who are of child-bearing potential will practice effective control of pregnancy risk and will undergo urine pregnancy testing prior to treatment administration on each Treatment Visit day and a home urine pregnancy test will be administered as part of the final Follow-Up Visit. Serum pregnancy testing will be performed prior to study enrollment and at each Treatment Visit.

3.2.3. Study Design and Methodology

This study has been designed as a randomized, double-blind, placebo-controlled, crossover study to reduce patient selection and assessment bias, and account for placebo effect and inter-subject differences in digital blood flow. Non-invasive assessment of the effect on digital blood flow following a single dose of study treatment was chosen as the primary objective for this POM study to ensure a reliable and objective initial evaluation of pharmacodynamic effects in the setting of SSc-RP (Wilkinson 2018). Patient-reported outcomes (PROs) designed to evaluate the frequency, duration, and severity of Raynaud's attacks, commonly used to evaluate real-world efficacy of pharmacotherapies in this setting, have not been included as primary efficacy assessment in this study due to short treatment duration.

Exposure to cold challenge was incorporated in the study design to allow for a dynamic assessment of digital blood flow under conditions similar to a common physiological trigger responsible for Raynaud's attacks in SSc (Pauling 2012). Digital blood flow will be assessed each Treatment Visit at Predose for 5 minutes at room temperature, and at Postdose prior to cold challenge for 5 minutes at room temperature and for 30 minutes following a cold challenge. Washout Periods between Treatment Visits are defined as a minimum of 72 hours, which is a sufficient period to ensure elimination of temanogrel, and up to approximately 7 days, to accommodate feasibility of multiple study visits for the study participants. Biomarkers related to

the mechanism of action of temanogrel (plasma serotonin concentration) as well as vascular injury and endothelial dysfunction will be evaluated to explore their relationship with digital blood flow and the PD effects of temanogrel, in order to provide additional mechanistic insights.

Assessments of digital blood flow will be performed using state-of-the-art noninvasive methods (ie, IR thermography and LSCI). IR thermography is an indirect method for evaluation of blood flow based on imaging skin temperature, while LSCI is based on differences in the speckle pattern (occurring when laser light illuminates a tissue) due to movement of blood cells (Ruaro 2019). While both mechanisms provide real-time dynamic assessment of perfusion, LSCI potentially allows for increased spatial and temporal resolution compared to IR thermography (Pauling 2015) but it is also more technically challenging due to its sensitivity to movement/vibrations and lighting (Wilkinson 2018). Imaging software for IR thermography and LSCI provide quantitative measures of blood flow within predefined regions of interest (ROIs) as mean temperature (°C) and arbitrary perfusion units (pu), respectively. Although based on different principles, LSCI and IR thermography have been demonstrated to have a comparable high test-retest reliability as well as a high latent correlation when measuring the rewarming/reperfusion area under the curve (AUC) following a cold challenge (Wilkinson 2018). These methods can be performed simultaneously and have been chosen to offer complementary results. These results will inform the further development of temanogrel for the treatment of SSc-RP, including appropriate selection of temanogrel dose(s) for evaluation of the effect on symptoms associated with Raynaud's attacks (ie, frequency, duration, severity).

3.2.4. Rationale for Dose Selection

Temanogrel doses selected for evaluation in Stage A are 60 mg and 120 mg, each administered as single oral dose. The 60 mg dose was chosen because the plasma concentrations anticipated to be achieved have exhibited near-maximal inhibition of 5-HT-mediated amplification of platelet aggregation, based on results from Study APD791-001 (Roupe 2008) and Study APD791-002 (Roupe 2009), and have demonstrated anti-vasoconstriction effects, based on data with ketanserin (a 5-HT_{2A} antagonist with similar affinity and potency at the 5-HT_{2A} receptor) in which concentrations of ~150 to 200 nM were associated with increased blood flow in SSc-RP patients (Klimiuk 1989) and anti-vasoconstrictive effects in the coronary microcirculation (Golino 1994). Temanogrel 120 mg was chosen as the second dose in Stage A to evaluate the dose-response of temanogrel in this study. Both doses are well below the highest tested single oral dose of temanogrel (320 mg), which demonstrated no tolerability or safety concerns in Study APD791-001. Choosing a range of doses to be tested in Stage A of this study will facilitate the evaluation of the dose response and selection of doses to potentially be tested in Stage B of the study. Dose selection in Stage B will be limited to doses that are not anticipated to exceed previously observed C_{max} values obtained from single oral dosing of temanogrel (ie, maximum concentration of 1610 ng/mL).

Doses in Stage B are not planned to exceed 240 mg, which is 25% lower than the highest tested single dose of oral temanogrel (320 mg) and demonstrated no tolerability or safety concerns in Study APD791-001.

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. Raynaud's phenomenon (defined as a history of digital cold sensitivity associated with color changes of cyanosis and pallor, with on average at least 5 attacks per week during the winter period) secondary to SSc based on either:
    a. Diagnosis of SSc (using the American College of Rheumatology/European League Against Rheumatism [ACR/EULAR 2013] and/or LeRoy and Medsger classification) (LeRoy 2001, van den Hoogen 2013)
    b. Diagnosis of very early SSc (using the Very Early Diagnosis of Systemic Sclerosis [VEDOSS] criteria) (Avouac 2011)
2. 18 to 75 years of age, inclusive
3. Females must meet a and c or b and males must meet d to qualify for the study:
    a. Female and not pregnant or breastfeeding
    b. Female and not of child-bearing 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
    c. Female of child-bearing potential and using a highly effective contraception method during treatment and for 30 days following treatment that can achieve a failure rate of less than 1% per year when used consistently and correctly. The following methods are considered highly effective birth control methods:
        - Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation, which may be oral, intravaginal, or transdermal
        - Progestogen-only hormonal contraception associated with inhibition of ovulation, which may be oral, injected, or implanted
        - Intrauterine device (IUD)
        - Intrauterine hormone-releasing system (IUS)
        - Bilateral tubal occlusion
        - Vasectomized partner
        - Sexual abstinence (complete sexual abstinence defined as refraining from heterosexual intercourse for the entire period of risk associated with study treatments). The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual

lifestyle of the subject. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception.

d. Males with pregnant or non-pregnant female partners of child-bearing potential agree to using a condom during treatment and for 90 days following treatment

4. Body mass index 18.0 to 40.0 kg/m^2, inclusive
5. 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. Active digital ulcer(s), recent history (within 3 months of Screening) of digital ulcers, or history of recurrent digital ulcerations that in the opinion of the Investigator increase the likelihood of developing a digital ulcer during the course of the study. Any history of gangrene, amputations, or other critical digital ischemic event.
2. Presence of severe contractures (advanced fixed flexion) of the digits, which in the opinion of the Investigator could prevent accurate assessment of digital perfusion of the dorsal fingers
3. Raynaud's phenomenon due to any cause other than SSc (eg, peripheral or central vasculopathy other than SSc, past exposure to vasculopathic agents, past frostbite injury)
4. Severe gastrointestinal complications related to SSc that in the opinion of the Investigator could significantly affect study drug absorption
5. History of gastrointestinal bleeding or active gastric or duodenal ulcers
6. Subject's digits do not reach a temperature of ≥ 27°C after 20 minutes of acclimatization at room temperature (23 [± 1]°C) at Screening
7. Any change in dosage of the following medications within 30 days of Day 1 or planned change in dosage during study participation: Calcium channel blockers (CCBs), phosphodiesterase type 5 inhibitors (PDE5i), alpha-blockers, or angiotensin II receptor blockers (ARBs).
8. Use of nitrates within 30 days of Day 1
9. Use of endothelin-1 receptor antagonists (ERAs) and therapies targeting the prostacyclin receptor within 3 months of Day 1
10. Local treatment (of digits) with botulinum toxin within 30 days of Day 1
11. Surgical sympathectomy of digit within 3 months of Day 1
12. Use of vasoconstrictive drugs (eg, ergot derivatives, triptans) within 7 days of Day 1
13. Use of antiplatelet therapy with the exception of aspirin (eg, adenosine diphosphate receptor [$P2Y_{12}$] inhibitors, glycoprotein IIb/IIIa inhibitors), or anti-coagulants (eg,

warfarin or direct oral anti-coagulants [DOACs], including oral thrombin inhibitors) within 7 days of Day 1

14. Use of any medications affecting the serotonin system (eg, selective serotonin reuptake inhibitors [SSRI], serotonin and norepinephrine reuptake inhibitors [SNRIs], atypical [second generation] antipsychotics possessing 5-HT_{2A} pharmacology, or any other serotonergic agents possessing 5-HT_{2A} pharmacology [eg, naftidrofuryl and the triazolopyridine antidepressant trazodone]) within 14 days of Day 1
15. Use of prescription medications/products or herbal preparations that are strong inhibitors or inducers of cytochrome P450 (CYP)3A4 or are strong inhibitors of P-glycoprotein within 14 days of Day 1 or 5 half-lives of the medication/product, whichever is longer. See Section 5.4 Restricted Medications for details.
16. Use of prescription medications/products that are strong inhibitors of multidrug and toxin extrusion transporter-1 (MATE1) or organic cation transporter-2 (OCT2) within 14 days of Day 1 or 5 half-lives of the medication/product, whichever is longer. See Section 5.4 Restricted Medications for details.
17. Use of prescription medications/products that are sensitive or moderately sensitive substrates of CYP2C8 within 14 days of Day 1 or 5 half-lives of the medication/product, whichever is longer. See Section 5.4 Restricted Medications for details.
18. Use of prescription medications/products that are sensitive substrates of CYP3A4/5 within 14 days of Day 1 or 5 half-lives of the medication/product, whichever is longer. Exceptions are PDE5i (allowed per Exclusion Criterion #7) and atorvastatin. See Section 5.4 Restricted Medications for details.
19. Consumption of grapefruit or grapefruit juice within 3 days of Check-in
20. Diabetes mellitus diagnosed more than 5 years ago or with known history of end-organ damage (diabetic retinopathy, nephropathy, neuropathy)
21. History of advanced heart failure (New York Heart Association [NYHA] Class 3 or 4) or myocardial infarction within 1 month prior to Screening.
22. Any history of stroke, seizure disorder, intracranial bleeding, or intracranial aneurysm; significant head injury requiring hospital assessment within 30 days prior to Screening
23. Transient ischemic attack within the 6 months prior to Screening
24. History of major trauma, major surgery, and/or clinically significant hemorrhage within the 6 months prior to Screening
25. Active hepatitis C
26. At the discretion of the Investigator, any history or clinical manifestation of any endocrine, allergic, dermatological, hepatic, renal, hematological, pulmonary, gastrointestinal, neurological, or psychiatric disorder, or any malignancy treated within 1 year of Screening (with the exception of basal cell carcinoma of skin which is not advanced) that would prevent the individual from participating in the study due to risk to the scientific validity of study assessments or to personal well being

27. Any abnormal clinical chemistry, hematology, electrocardiogram (ECG), urinalysis, or physical finding at Screening that in the opinion of the Investigator is deemed 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
28. Hepatic dysfunction (history of cirrhosis with diagnosed portal hypertension, or alanine aminotransferase [ALT] or aspartate aminotransferase [AST] > 3 × upper limit of normal [ULN]) at Screening
29. 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 Screening
30. Impaired hemostasis (eg, thrombocytopenia [platelet count < 100,000/µL] at Screening; abnormal coagulation test defined as prothrombin time [PT] or partial thromboplastin time [PTT] > 1.5 × ULN, or international normalized ratio [INR] > 2 at Screening); past or present bleeding disorder, sickle cell or other platelet disorders, or carcinoid disorder)
31. Any surgeries or interventional procedures planned or anticipated during study participation
32. Positive urine test for amphetamines, barbiturates, benzodiazepines, cocaine, marijuana, methadone, methamphetamine, methylenedioxymethamphetamine, opiate, oxycodone, or phencyclidine. Exception is a test that is positive due to a prescription drug or medication.
33. 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 well being
34. Use of tobacco or nicotine-containing products (including but not limited to cigarettes, e-cigarettes, pipes, cigars, chewing tobacco, nicotine patches, nicotine lozenges, or nicotine gum) for at least 90 days prior to Screening
35. Previous participation in a study with temanogrel
36. Subjects who have received any investigational device or investigational drug within 30 days of Day 1, or 5 half-lives of the investigational drug (whichever is greater) prior to Screening
37. Hypersensitivity to temanogrel or placebo compounds
38. Inability to swallow capsules as required per the protocol
39. In the opinion of the Investigator, subject is not a candidate for blood sampling as required per the protocol

5. SUBJECT RESTRICTIONS

5.1. Meals and Dietary Restrictions

Subjects must not consume grapefruit or grapefruit juice within 3 days of each Treatment Visit as described in Section 4.2 and through the completion of scheduled blood draws.

Subjects will be instructed to consume a breakfast of approximately 400 to 500 calories at least 2 hours prior to Check-in on Treatment Visit days. The breakfast should have a fat content of less than 25% (11 to 14 g). Examples of this type of breakfast may include 8 oz of 2% milk, 1 boiled egg, a large orange, and 1 packet of instant oatmeal/porridge made with water (containing approximately 415 calories and 10 g of fat) or two slices of toast, 2 tablespoons of marmalade, 1 tablespoon of butter, and 8 oz of orange juice (approximately 450 calories and 12 g of fat). However, a breakfast with similar fat content and total calories can be consumed. After breakfast, subjects should refrain from eating or drinking for at least 1.5 hours before or after dosing. On each Treatment Visit at Check-in, all subjects will be asked if dietary restrictions were adhered to, and their response will be noted in the source and electronic case report for (eCRF).

Subjects will be advised to avoid consuming alcohol, caffeine, and food high in indoles (eg, avocado, banana, tomato, plum, walnut, pineapple, and eggplant [aubergine]) for a minimum of 24 hours, and ideally 3 days, prior to each Treatment Visit and through the completion of scheduled blood draws to increase the accuracy of serotonin concentration assessments. On each Treatment Visit at Check-in, all subjects will be asked if they consumed alcohol, caffeine, or foods high in indoles, in the preceding 24 hours and/or 3 days and their response should be documented. If alcohol, caffeine, or foods high in indoles were consumed in the preceding 24 hours and/or 3 days, it should be noted in the eCRF. Blood samples for serotonin concentration assessment will be taken for all subjects, even if dietary restrictions are not adhered to.

5.2. Activity Restrictions

Subjects will be instructed to refrain from vigorous exercise for at least 4 hours prior to the start of digital blood flow assessments at each Treatment Visit. On each Treatment Visit at Check-in, all subjects will be asked if activity restrictions were adhered to, and their response will be noted in the source and eCRF.

Subjects will be instructed to stay indoors for the duration of each Treatment Visit.

5.3. Clothing Restrictions

Subjects will be instructed to wear light clothing that exposes the forearms and hands, and to remove jewelry, nail polish, and/or nail coverings from the hands-on Treatment Visit days.

5.4. 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 Visit). Additional details regarding prohibited drugs will be provided in a separate Prohibited Medications list.

The following are restricted medications:

- Change in dosage of CCBs, PDE5i, alpha-blockers, or ARBs
- Antiplatelet therapy with the exception of aspirin (eg, $P2Y_{12}$ inhibitors, glycoprotein IIb/IIIa inhibitors), or anti-coagulants (eg, warfarin or DOACs, including oral thrombin inhibitors)
- Nitrates
- ERAs and therapies targeting the prostacyclin receptor
- Vasoconstrictive drugs (eg, ergot derivatives, triptans)
- SSRIs, SNRIs, atypical (second generation) antipsychotics possessing $5\text{-}HT_{2A}$ pharmacology, or any other serotonergic agents possessing $5\text{-}HT_{2A}$ pharmacology (eg, naftidrofuryl and the triazolopyridine antidepressant trazodone)
- Local treatment (of digits) with botulinum toxin
- Strong inhibitors or inducers of CYP3A4 or P-glycoprotein (details provided in a separate Prohibited Medications list)
- Strong inhibitors of MATE1 or OCT2 (details provided in a separate Prohibited Medications list)
- Sensitive or moderately sensitive substrates of CYP2C8 (details provided in a separate Prohibited Medications list)
- Sensitive substrates of CYP3A4/5. Exceptions are PDE5i (allowed per Exclusion Criterion #7) and atorvastatin (details provided in a separate Prohibited Medications list)

If such medications are required, consider switching to another medication in the class that is not restricted, or refrain from dosing during Treatment Visit days. If a restricted medication is required, seek approval of the Medical Monitor and use with caution per approved product label.

5.5. Additional Restrictions

Tobacco or nicotine-containing products are prohibited for at least the 90 days prior to Screening as outlined in the exclusion criterion (Section 4.2) throughout study participation (until the Follow-Up Visit).

Subjects must refrain from the use of drugs of abuse listed in Table 2 for the duration of study participation. Prescription drugs and medications are allowed.

6. STUDY TREATMENT

6.1. Study Treatment(s) Administered

Study treatments in this study include the investigational medicinal product, defined as a pharmaceutical form of the active substance being tested (temanogrel) and the placebo being used as a reference (reference therapy). Study treatments are listed in Table 1.

Table 1: Study Treatment(s)

Study Treatment	Strength	Mode of Administration	Frequency	Formulation
Temanogrel	20 mg	Oral	Once per Treatment Visit	Capsule
Placebo	Not applicable	Oral	Once per Treatment Visit	Capsule

6.2. Identity of Study Treatments

6.2.1. Temanogrel

The oral formulation of temanogrel contains 20 mg of active pharmaceutical ingredient in a Swedish orange hard-gelatin capsule.

6.2.2. Placebo

Placebo will contain microcrystalline cellulose in a Swedish orange hard-gelatin capsule. Visual appearance and mode of administration of placebo will match that of the temanogrel drug product to maintain the blind.

6.3. Dosage and Administration

All enrolled subjects will receive a single oral dose of study treatment at each Treatment Visit, for a total of 3 doses of study treatment. Each subject will receive a single administration of each dose strength. Temanogrel doses to be administered in Stage A will be 60 mg (3 temanogrel capsules and 3 placebo capsules) or 120 mg (6 temanogrel capsules). Placebo doses will be administered as 6 placebo capsules. Selection of doses for Stage B will be based on the results from Stage A. Refer to Section 6.4 for further details related to treatment assignment.

Study treatment will be administered in a blinded fashion to the subjects. Study treatment administration will be performed by the Investigator or a qualified designee (eg, nurse). Study treatment will be administered orally with water (a maximum of 250 mL should be targeted; however, additional water may be ingested if required to administer the full dose of medication). A mouth check will be performed by the qualified designee to ensure that the subject has swallowed the study treatment. The date and exact clock time of each dosing will be recorded.

Study treatment requirements, dispensation, administration, destruction, and study staff roles will be further defined in a pharmacy manual.

6.3.1. Instructions for Missed Dose(s)

Subjects will be administered a single dose of study treatment at each Treatment Visit under the supervision of qualified study personnel. No missed doses are expected. Any deviation from expected dosing must be documented in the eCRF.

6.3.2. Dose Interruptions

Subjects will be administered a single dose of study treatment at each Treatment Visit. 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 equally randomized (1:1:1:1:1:1 ratio) to 1 of 6 crossover treatment sequences (ie, ABC, ACB, BAC, BCA, CAB, CBA; where A = the higher dose of temanogrel, B = the lower dose of temanogrel, and C = placebo). In each stage, 4 subjects are planned to be randomized to each treatment sequence. Subjects will receive the corresponding study treatment at each Treatment Visit according to their crossover treatment sequence assignment.

Subject identification numbers will be 12 characters in length, including dashes, 204-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 (XXX). Subject numbers will be assigned strictly sequentially at every site as subjects become eligible for enrollment, starting from 001. If a subject withdraws their participation in the study, then their unique subject number cannot be reused.

Subjects who discontinue from the study may be replaced at the discretion of the Sponsor. A replacement subject will be allocated to the same treatment sequence as the replaced subject.

6.5. Selection and Timing of Dose for Each Subject

Subjects will receive a single dose of study treatment at each Treatment Visit (with water, without food) based on their crossover treatment sequence assignment. Dosing should occur at approximately the same time of day at each Treatment Visit.

6.6. Blinding

The Investigator, subjects, and personnel directly involved with the conduct of the study will be blinded to the identity of study treatment and all randomization assignments during the conduct of each study stage. Individuals who are unblinded (eg, representatives from the bioanalytical lab responsible for analyzing PK samples, representatives from the Sponsor responsible for drug supply, and representatives from the Sponsor's safety team responsible for regulatory reporting and not involved in the assessment of adverse events) will not be involved in the management of the study and will not have access to other subject data beyond what is needed to perform their assigned function. The identity of specific treatments is not to be disclosed to subjects or to any other study personnel during conduct of each study stage. At the end of Stage A, an unblinded review of the data will be conducted by the Sponsor.

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.

6.7. Treatment Compliance

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.

6.8. 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 the Follow-Up Visit must be recorded along with:

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

Investigators should carefully evaluate local prescribing information of concomitant therapy for interactions described in Section 5.4. The Medical Monitor should be contacted if there are any questions regarding concomitant therapy.

6.8.1. Required Concomitant Therapy

None

6.8.2. Allowed Concomitant Therapy

Medications deemed by the Investigator to be appropriate and unlikely to interfere with the scientific validity of the study or personal well being of the subject, and which are not prohibited as indicated in inclusion and exclusion criteria and/or in Section 5, are permitted.

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

7. STUDY TREATMENT MATERIALS MANAGEMENT

7.1. Packaging and Labeling

Study treatment will be provided in induction-sealed, high-density polyethylene bottles with child-resistant screw caps. Each bottle will be labeled as required per country requirement.

7.2. Storage and Handling

Study treatment must be stored in an appropriate, restricted-access, secure location that is not accessed by unauthorized study personnel. Study treatment should be stored within a temperature range between 15°C to 25°C (59°F to 77°F).

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.

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

Used and/or partially used bottles should be stored in an appropriate, restricted-access, secure location that is not accessed by unauthorized study personnel.

7.3. Study Treatment Accountability

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

7.4. 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

Subjects who do not complete all 3 Treatment Visits may be replaced at the discretion of the Sponsor.

8.1. Discontinuation of Study Treatment

A subject's study treatment may be discontinued for any of the following reasons:

- Adverse event
- Death
- Lost to follow-up
- Physician decision
- Pregnancy (Section 10.8.6)
- Protocol deviation
- Study terminated by Sponsor
- Withdrawal by subject

8.2. Other Discontinuation from the Study

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

- Adverse event
- Death
- Lost to follow-up
- Physician decision
- Pregnancy (Section 10.8.6)
- Protocol deviation
- Study terminated by Sponsor
- Withdrawal by subject
- 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. When possible, all Follow-Up procedures specified in Section 9.3 and Section 9.4 should be performed. If a subject withdraws consent, no further evaluation should be performed, and no additional data should be collected. 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

A subject will be considered lost to Follow-Up if the subject repeatedly fails to return for scheduled visits or participate in the Follow-Up Visit and cannot be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject, reschedule the missed visit as soon as possible, counsel the subject on the importance of maintaining the assigned visit schedule, and ascertain whether or not the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to Follow-Up, the Investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and if necessary, a certified letter to the subject's last know mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.

Should the subject continue to be unreachable, he/she will be considered lost to follow-up.

8.4. Premature Termination of the Study or a 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 Committees (IECs)/ Institutional Review Boards (IRBs) will be informed about the termination of the study in accordance with applicable regulations.

The Sponsor has the right to replace a study site at any time. Reasons for 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

The Screening period is to occur up to 28 days prior to Treatment Visit 1 (Day –28 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 Visits

Randomization can occur after confirmation of all inclusion and exclusion criteria at Check-in prior to the planned administration of study treatment on Treatment Visit 1.

Each subject will participate in 3 Treatment Visits, which will each be separated by a Washout Period of at least 72 hours and up to approximately 7 days between study treatment administrations. When possible, it is preferred to schedule Treatment Visits with the minimum possible Washout Period between visits. For each Treatment Visit, subjects will be admitted to the clinic at approximately the same time of the day (between 0800 and 1200 hours). A schematic of Treatment Day assessments and procedures is provided in Appendix 2. Refer to the Schedule of Assessments (Appendix 1) for additional details on study assessments and procedures.

Venipuncture is the preferred blood collection method; however, if warranted, an indwelling catheter may be placed at the beginning of each Treatment Visit for collection of blood samples (the same blood collection method should be used at all Treatment Visits for a given subject; refer to Section 10.5 for guidelines regarding blood collection and catheter placement). After Check-in assessments including blood sampling for clinical laboratory assessments, PK, and biomarkers; subjects will acclimatize for at least 20 minutes in a temperature-controlled room (23 [± 1]°C), followed by Predose digital blood flow assessments. Digital blood flow assessments will be performed for 5 minutes at room temperature based on simultaneous collection of temperature and perfusion data using IR thermography (Section 10.3.1.1) and LSCI (Section 10.3.1.2), respectively. After study treatment administration, subjects will undergo re-acclimatization for at least 20 minutes, followed by Postdose assessments. Postdose digital blood flow assessments will start 45 (± 5) minutes after dosing and will again be performed for 5 minutes at room temperature. A cold challenge will then be conducted by immersing the hands in a temperature-controlled water bath (15 [± 1]°C) for 1 minute (± 3 seconds). The post-cold challenge digital blood flow assessments must begin 30 (± 10) seconds after the completion of the cold challenge and will last for 30 minutes. Blood samples for clinical laboratory assessments, PK and biomarkers will be collected after the post-cold challenge digital blood flow assessments are complete, followed by visual analogue scale (VAS) for pain assessment. Subjects will be discharged from the study unit once all planned assessments have been completed.

9.3. Follow-Up/End of Study

Subjects will have one Follow-Up Visit via phone call, and preferably via teleconference, 4 (± 1) days after the completion of Treatment Visit 3 to assess for adverse events, update concomitant medications, and if applicable, communicate the results of the home pregnancy test (Section 10.2.8). For each subject, study participation is completed once the Follow-Up Visit has been conducted. The End of Study Date is the date when the last subject completes his/her final Follow-Up Visit.

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 who has been randomized become unwilling or unable to complete a study Visit (individual missing data points do not count as early discontinuation), the Follow-Up Visit should be performed. 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. All screening evaluations must be completed and reviewed to confirm potential subjects meet all eligibility criteria prior to receiving the first dose of study treatment on Treatment Visit 1 (Appendix 1).

Individuals may qualify for study enrollment following an abnormal laboratory test, ECG, or vital signs 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 Sponsor's 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 reconsented and rescreened with a new screening number if the Investigator assesses that the subject is an appropriate candidate for rescreening. 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 at screening.

10.2.3. Prior and Ongoing Therapies

All medications and procedures conducted within 30 days prior to Screening will be recorded at Screening. Updates to medications or procedures prior to dosing on Treatment Visit 1 should be made as needed.

10.2.4. Medical History/Disease Specific History

A complete medical history of each subject will be collected and documented during screening to determine subject eligibility. The history should include recent blood donations (within 30 days), illnesses, and participation in other investigational drug or device studies.

Disease-specific history to be collected includes date of onset of Raynaud's phenomenon symptoms and first non-RP symptoms relevant to SSc, date of SSc diagnosis, frequency of Raynaud's phenomenon attacks, history of digital ulcers or critical ischemia/gangrene/amputations, and other relevant SSc-RP disease characteristics and history (eg, presence of SSc-specific autoantibodies, nailfold capillaroscopy findings, gastrointestinal dysfunction, other organ involvement).

10.2.4.1. Substance Use

At screening, the amount and duration of tobacco, nicotine, alcohol, and caffeine usage will be collected.

10.2.5. Urinalysis

Urinalysis parameters are identified in Table 2. Results of urinalysis assessments are required for eligibility purposes prior to randomization (Appendix 1).

10.2.6. Clinical Laboratory Assessments

Clinical laboratory assessments are identified in Table 2. Results of clinical laboratory assessments are required for eligibility purposes prior to randomization (Appendix 1).

10.2.7. Urine Drug Screen

A standard urine drug screen will be performed to determine eligibility prior to randomization (Appendix 1). Subjects who test positive for any drug included in Table 2 will not be eligible for study participation.

10.2.8. Pregnancy Testing

A serum pregnancy test for beta-human chorionic gonadotropin (β-hCG) will be performed on WOCBP at screening to determine eligibility and at each Treatment Visit. At each treatment visit, urine pregnancy tests (β-hCG) will be performed, and a negative result is required to be documented, prior to administration of study treatment. The results of the serum pregnancy test

at each Treatment Visit are not required prior to dosing. If at any point there is a case of a positive urine β-hCG test, the subject will have study treatment interrupted. If the serum test confirms positive, the subject will be discontinued from the study treatment and all the necessary follow up will be conducted as per Section 10.8.6. If the serum test is negative, the subject may resume study treatment.

At Treatment Visit 1, WOCBP will also be provided with a urine pregnancy test that is to be taken at home prior to the subject's Follow-Up visit on the same day of the Follow-Up visit. During the first Treatment Visit subjects will receive adequate training on the use of the home pregnancy test and will be informed on how to properly communicate the results of their test. If the result of the home pregnancy test is positive, subjects will be required to undergo a serum pregnancy test. If the serum test confirms positive, all necessary follow-up will be conducted as per Section 10.8.6. If the serum test is negative, no further follow-up is required.

Women who are surgically sterile or who are postmenopausal are not considered to be of child-bearing potential. Postmenopausal is defined as 12 consecutive months with no menses without an alternative medical cause.

10.2.9. Virology Screening

As defined in Table 2, hepatitis C screening will be performed to determine eligibility prior to randomization (Appendix 1).

10.2.10. Acclimatization Test

Subjects will be required to undergo acclimatization for at least 20 minutes in a temperature-controlled room (23 [± 1]°C). IR thermography will be used to assess digit temperature to determine eligibility. If a subject's digits do not reach a temperature of at least 27°C, the subject will not be eligible for study participation.

10.3. Pharmacodynamic Assessments

10.3.1. Digital Blood Flow Assessments and Cold Challenges

Assessments of digital blood flow based on both temperature and perfusion and will be conducted simultaneously using IR thermography (Section 10.3.1.1) and LSCI (Section 10.3.1.2), respectively. Digital blood flow data will be analyzed by a central core lab. Details on the applicable instructions regarding the collection, transfer, and analysis of blood flow data will be provided in a separate operation manual. Digital blood flow will be assessed at each Treatment Visit at Predose for 5 minutes at room temperature, and at Postdose prior to cold challenge for 5 minutes at room temperature and for 30 minutes following a cold challenge.

Digital blood flow will be assessed and analyzed as previously described (Wilkinson 2018) and details on the applicable methods can be found in separate operation manuals. Briefly, imaging should be performed at each Treatment Visit at approximately the same time of the day in a temperature-controlled (23 [± 1]°C), low-lit room, and any vibrations (included those caused by walking or talking) should be minimized during the digital blood flow assessments. The room temperature should be assessed at least during the acclimatization and re-acclimatization periods, and after the post-cold challenge digital blood flow assessments have been completed. Subjects should be in a seated position during the digital blood flow assessments; standing up and walking

for a minimum of 5 minutes before the start of imaging should be avoided. Hands should be placed at a fixed distance and angle from the thermal camera and LSCI and secured to avoid movement during imaging. Both hands will be used for digital blood flow assessments and cold challenges. Room temperature digital blood flow assessment will be performed following acclimatization for at least 20 minutes. For the cold challenge, hands will be placed in nitrile gloves (to prevent evaporative cooling) and immersed in a temperature-controlled water bath (15 [± 1]°C) up to the radiocarpal joints for 1 minute (± 3 seconds). The water temperature should be recorded at the beginning and at the end of the cold challenge. Immediately after the cold challenge, the gloves will be removed, the hands will be dried and returned to their original position on the insulating surface, and the post-cold challenge digital blood flow assessment will start 30 (± 10) seconds after the end of the cold challenge.

ROIs on both hands will be predefined and the same ROIs will be used for analysis during all digital blood flow measurements for all subjects. Data will be presented in temperature (°C) for IR thermography or in arbitrary pu for LSCI and averaged for all ROIs. Absolute measurements (eg, room temperature values, maximum reduction/recovery) as well as dynamic assessments dependent on the characteristics of the rewarming/reperfusion curve (eg, AUC, time to 50% and 70% recovery [minimum value + (baseline value – minimum value) × 0.5 and minimum value + (baseline value – minimum value) × 0.7]) will be assessed.

10.3.1.1. Infrared Thermography

Skin temperature will be assessed using a thermal camera. Imaging software for IR thermography provides quantitative measures of blood flow within predefined ROIs as mean temperature (°C). Additional details regarding the procedures for collection, transfer, and analysis of IR thermography data will be provided in a separate operation manual.

Planned timepoints for IR thermography assessments are provided in the Schedule of Assessments (Appendix 1).

10.3.1.2. Laser Speckle Contrast Imaging

Skin perfusion will be assessed using LSCI. Imaging software for LSCI provides quantitative measures of blood flow within predefined ROIs as mean arbitrary pu. Additional details regarding the procedures for collection, transfer, and analysis of LSCI data will be provided in a separate operation manual.

Planned timepoints for LSCI assessments are provided in the Schedule of Assessments (Appendix 1).

10.3.2. Visual Analogue Scale for Pain

Subjects will complete a 0 to 100 mm VAS assessment in response to the question "How much pain did you have in your hands after the cold challenge?". The VAS for pain will be completed as specified in the Schedule of Assessments (Appendix 1).

10.4. Urine Drug Screen

A standard urine drug screen for the presence of non-prescribed drugs of interest will be performed at each Treatment Visit as specified in the Schedule of Assessments (Appendix 1).

The results of the urine drug screen are not required prior to initiating study conduct of each Treatment Visit. However, if at any time a subject tests positive for any drug included in Table 2, the subject may be discontinued from study treatment at the discretion of the Sponsor.

10.5. Procedures for Blood Draws

Standard venipuncture may be used for blood collection at Screening. Blood sample collection at Treatment Visits should be performed preferably via venipuncture; however, an indwelling catheter may be used if warranted. If a catheter is used, it should be used consistently for all Treatment Visits for a given subject. The preferred placement of the indwelling catheter is in the antecubital region of the subject's non-dominant arm. The catheter should be placed in the same arm and region of the arm for each Treatment Visit. The method used and the location of the blood draws must be documented at each Treatment Visit.

10.6. Pharmacokinetic Assessments

Blood samples for plasma PK analysis of temanogrel, AR295980, and AR295981 will be collected for all subjects. Blood samples will be obtained as specified in the Schedule of Assessments (Appendix 1). Clock time will be documented for each PK blood sample. Detailed instructions regarding sample collection, processing, and shipping will be provided in a separate laboratory manual.

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.

During conduct of each study stage, drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel.

10.7. Biomarker Assessments

Blood samples for assessment of plasma serotonin concentration and markers of vascular injury and endothelial dysfunction (specified in Table 2) will be collected as specified in the Schedule of Assessments (Appendix 1). Detailed instructions regarding sample collection, processing, and shipping will be provided in a separate laboratory manual.

10.7.1. Future Biomarker Research

Where allowed by the regulatory authorities and if the subject has granted consent, residual plasma from samples collected to measure biomarkers may be stored for up to 10 years after the closing of the study. Samples will be stored according to local regulations for the study at a facility selected by the Sponsor to enable potential future analysis of analytes and 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, deoxyribonucleic acid (DNA), or ribonucleic acid (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. By signing the informed consent form

(ICF), subjects agree to the possible future analysis of these samples. At any time, the subjects can contact the clinical staff to request destruction of their residual samples after the required assessments are completed.

10.8. Safety Assessments

Safety assessments will include adverse events, vital signs (Section 10.8.1), physical examinations (Section 10.8.2), ECGs (Section 10.8.3), and clinical laboratory tests (Section 10.8.4). Planned timepoints for all safety assessments are indicated in the Schedule of Assessments (Appendix 1).

10.8.1. Vital Signs

Vital signs measurements will be made in the sitting position and include heart rate, blood pressure, body temperature, and respiratory rate. Subjects should be seated for at least 5 minutes prior to the collection of vital signs. Vital signs will be measured prior to any blood draws that occur at the same study visit or overlapping timepoint, with the exception of the Postdose blood draw for biomarkers and PK (Appendix 2). Planned timepoints for vital signs assessments are provided in the Schedule of Assessments (Appendix 1).

10.8.2. Physical Examinations

The Investigator will complete the physical exam at Screening. A full physical examination will include the following assessments:

- General inspection
- Head/ears/eyes/nose/throat examination
- Neck
- Cardiac examination
- Auscultation of lungs
- Abdominal examination (liver, spleen, and lower abdomen)
- Neurological assessment
- Musculoskeletal assessment to include lower extremity edema evaluation

A symptom-based physical exam will be performed at the end of the final Treatment Visit.

Focused physical examination of the hands (hand examination) will be performed by the Investigator (or designee) at Screening and at each Treatment Visit for inspection of any active skin ulcerations. If a subject develops an ulcer on their hand during the study, the subject will be discontinued from study treatment and from the study and will follow Early Termination (Section 9.4) procedures.

At each Treatment Visit, the first day of the most recent menstrual cycle will be documented for all women.

Planned timepoints for physical examinations, hand examinations, and menstrual cycle monitoring are provided in the Schedule of Assessments (Appendix 1). In addition, a

symptom-directed physical examination may be performed at the Investigator's discretion at any time during the study.

10.8.3. Electrocardiography

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, 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). All ECGs will be recorded with subjects in supine position. Supine rest time prior to ECGs will be at least 5 minutes. It is recommended to collect ECGs at least 30 minutes after the end of the subject's most recent meal.

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 obtained during Treatment Visits will also be analyzed by the core lab. Both local and central reports must be filed with the source documents.

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

10.8.4. Clinical Laboratory Assessments

Details regarding clinical laboratory sample collection, preparation, and shipment are provided in the laboratory manual. Unless otherwise specified, all laboratory assessments required by the protocol will be performed by a central laboratory. Refer to Table 2 for the list of clinical laboratory tests to be performed and the Schedules of Assessments (Appendix 1) for timing and frequency for each test.

The Investigator must review the laboratory reports, document the review, and record any clinically relevant changes on the adverse event section of the eCRF. The laboratory reports must be filed with the source documents. 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 nonprotocol-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 study treatment discontinuation), then the details must be documented in the appropriate eCRF.

Table 2: Clinical Laboratory Tests

Pregnancy Testing[a]	**Coagulation**	**Virology Screening**
Serum pregnancy test beta-human chorionic gonadotropin (β-hCG) Urine β-hCG	Activated partial thromboplastin time (PTT) Fibrinogen International Normalized Ratio (INR) Prothrombin time (PT) Thrombin time (TT)	Hepatitis C virus

Urinalysis	**Hematology**
Appearance Bilirubin Color Glucose Ketones Leukocyte esterase Microscopic examination of sediment Nitrite Occult blood pH Protein Specific gravity Urobilinogen	Hematocrit Hemoglobin Mean corpuscular hemoglobin (MCH) Mean corpuscular hemoglobin concentration (MCHC) Mean corpuscular volume (MCV) Platelet count Red blood cell (RBC) count White blood cell (WBC) count with differential

Serum Chemistry		**Endocrinology**
Alanine aminotransferase (ALT) Albumin Alkaline phosphatase (ALP) Aspartate aminotransferase (AST) Bicarbonate Blood urea nitrogen (BUN) Calcium Chloride Creatinine Direct bilirubin Creatine kinase (CK) Glucose Lactate dehydrogenase (LDH)	Phosphorus Potassium Sodium Total bilirubin Total cholesterol Total protein Triglycerides Uric acid	Thyroid-stimulating hormone (TSH) Thyroxine (T4) free Triiodothyronine (T3) free

Biomarkers
Endothelin-1
Factor VIII activity
Intracellular adhesion molecule 1 [ICAM-1]
Plasminogen activator inhibitor-1 [PAI-1] activity
PAI-1 antigen
Serotonin
Tissue-type plasminogen activator antigen [t-PA]
Vascular adhesion molecule 1 (VCAM-1)
Vascular endothelial growth factor (VEGF)
Von Willebrand factor [VWF]
Urine Drug Screen
Amphetamines, barbiturates, benzodiazepines, cocaine, marijuana, methadone, methamphetamine, methylenedioxymethamphetamine, opiate, oxycodone, phencyclidine

[a] Required only for women of child-bearing potential.

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 and planned timepoints for blood collection are provided in the Schedule of Assessments (Appendix 1).

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 will be collected from the time of consent.

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. Severity

The severity of each adverse event will be assessed at the onset by the Investigator. 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 (CTCAE), 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 (ADL).
Grade 3:	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self-care ADL (eg, preparing meals, shopping for groceries or clothes, using the telephone, managing money).

Grade 4:	Life-threatening consequences, urgent intervention indicated.
Grade 5:	Death related to adverse event.

10.8.5.1.5. 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 (eg, 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 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 or not further follow-up is necessary.

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

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

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 an 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 to determine whether an adverse event/ADR is expected:

- For a medicinal product not yet approved for marketing in a country, the Reference Safety Information (RSI) section of a company's IB will serve as the source document in that country.
- 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".

10.8.6. Pregnancy

If at any point any pregnancy test is positive, the subject will be withdrawn from the study treatment.

Details of all pregnancies in female subjects and female partners of male subjects will be collected after the start of study treatment and until 90 days after the last dose.

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 (IQVIA) **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. Safety-Related Stopping Criteria

10.9.1. Bleeding Events

Any bleeding event reported as Bleeding Academic Research Consortium (BARC) 3 or greater will pause enrollment and the event will be reviewed by the Investigator and Medical Monitor. Following review, the event may trigger unblinding, study stop, or the study may resume (following approval by health authorities and IECs/IRBs in accordance with applicable country-specific regulations).

10.9.2. Drug-Induced Liver Injury

Discontinuation of study treatment for an individual subject should be considered if any of the following occur:

- ALT or AST > 8 × ULN
- ALT or AST > 5 × ULN for more than 2 weeks
- ALT or AST > 3 × ULN **and** total bilirubin (TBL) > 2 × ULN **or** International Normalized Ratio (INR) > 1.5
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)

10.10. Maximum Blood Volume

The maximum amount of blood collected from each subject over the duration of the study, including planned pharmacokinetic, biomarkers, and clinical laboratory samples will not exceed 240 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

10.11. 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. Overdoses must be documented as protocol deviations.

11. PLANNED STATISTICAL METHODS

11.1. General Considerations

Details regarding the statistical analyses will be provided in the Statistical Analysis Plan (SAP), which will be finalized prior to breaking the blind for the Stage A interim analysis.

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

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, first-order carry effects) are not met, alternative approaches will be evaluated (eg, nonparametric analysis, log transformation). All statistical tests for efficacy parameters will be performed at the 0.05 significance level (2-sided).

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

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

11.2. Determination of Sample Size

Approximately 24 subjects are planned to be randomized in Stage A, which is sufficient to achieve at least 80% power to detect a treatment effect of 16.6% from placebo for change in digital blood flow based on rewarming AUC (°C, assessed with IR thermography) during the 30 minutes following a cold challenge for each of the 2 temanogrel treatments based on a difference of means test for a 3-period, 3-treatment crossover design with a significance level 0.05 (2-sided). The test assumes the temanogrel treatment group mean of 365, placebo group mean of 313, and an SD of the difference in temanogrel treatment and placebo group means of 86. In addition, with 24 subjects there is at least 80% power to detect a treatment effect of 23.5% from placebo for change in digital blood flow based on reperfusion AUC (pu, assessed with LSCI) during the 30 minutes following a cold challenge for each of the 2 temanogrel treatments (temanogrel treatment group mean of 24.7, placebo group mean of 20, and an SD of the difference in temanogrel treatment and placebo group means of 7.8). Assumptions are based on previous studies in SSc-RP utilizing these or similar methods (Herrick 2014, Wilkinson 2018,

Wise 2004). Subjects will be equally randomized (1:1:1:1:1:1 ratio) to 1 of the 6 treatment sequences (4 subjects per sequence).

Approximately 24 subjects are planned to be randomized in Stage B using the same 3-period, 3-treatment crossover design. Based on Stage A results, Stage B sample size may be modified, but not limited to, Stage A dose levels will be enriched or 2 additional temanogrel doses will be evaluated.

11.3. Analysis Sets

For purposes of analysis, the following populations are defined (Table 3).

Table 3: 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 randomized subjects who receive at least one dose of study treatment and have at least one baseline and post-baseline measurement.
Per Protocol Set	The Per Protocol Set will include all subjects from the FAS who receive the full dose of all 3 study treatments and are without major protocol violations that might affect the evaluation of the effect of study treatment on the primary endpoints. The violations will be predefined in the SAP and the Per Protocol Set will be specified prior to unblinding.
Pharmacokinetic Set	The Pharmacokinetic Set will include all subjects in the Safety Set with a Postdose PK measurement.
Safety Set	The Safety Set will include all randomized subjects who received at least one dose of study treatment.

11.4. Missing Data

If required, imputation of missing data will be performed and details will be given in the SAP.

11.5. Efficacy Analyses

The primary and secondary endpoints will be analyzed using the FAS. Other important statistical considerations and sensitivity analyses will be described in the SAP.

The primary endpoints of the study are the change in digital blood flow based on rewarming/reperfusion AUC (assessed with IR thermography and LSCI, respectively) during the 30 minutes following a cold challenge. The primary analyses will be analyzed using analysis of variance (ANOVA; Williams' design) with a model that includes treatment group, sequence, and period as factors. Least square means, standard errors (SEs), and 95% confidence intervals (CIs) for the treatments and their difference will be presented together with their p-values.

Unless otherwise specified, continuous secondary endpoints will be analyzed using ANOVA (Williams' design) with a model that includes treatment group, sequence, and period as factors. Least square means, SEs, and 95% CIs for the treatments and their difference will be presented together with their p-values.

Time-to-event secondary endpoints will be displayed using Kaplan-Meier plots and analyzed with Cox regression with a model that includes treatment group, sequence, and period as factors. The hazard ratio will be presented together with 95% CIs and the p-value.

Given subjects will receive all 3 treatments in 1 of 6 possible sequences, first-order carryover effects will be evaluated to assess the extent to which the order of treatments affected primary and secondary endpoints.

Details of the analysis methods for exploratory endpoints will be described in the SAP.

11.5.1. Primary Endpoint

- Change in digital blood flow based on:
  - Rewarming AUC (°C, assessed with IR thermography) during the 30 minutes following a cold challenge
  - Reperfusion AUC (pu, assessed with LSCI) during the 30 minutes following a cold challenge

11.5.2. Secondary Endpoints

- Change in the following temperature (°C, assessed with IR thermography) and perfusion (pu, assessed with LSCI) parameters:
  - Maximum reduction following a cold challenge
  - Maximum recovery during the 30 minutes following a cold challenge
  - AUC during the initial 2 minutes following a cold challenge
  - Slope during the initial 2 minutes following a cold challenge
  - Time to achieve 50% recovery from the cold challenge-induced reduction
  - Time to achieve 70% recovery from the cold challenge-induced reduction
- Change from Predose to Postdose in the following temperature (°C, assessed with IR thermography) and perfusion (pu, assessed with LSCI) parameters:
  - Room temperature values
  - Distal dorsal difference (DDD) (defined as the difference in measurements between the dorsum and the finger) at room temperature

11.5.3. Exploratory Endpoints

- The relationship between selected PD endpoints and select biomarkers may be explored
- The relationship between selected PD endpoints and the concentration of temanogrel and/or active metabolites may be explored
- VAS for pain

11.6. 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 95% CI for treatment groups and from pairwise comparisons will be reported in an exploratory manner.

11.7. Interim Analysis

Following Stage A, unblinded analyses will be conducted to review the safety, PK, and efficacy (eg, observed treatment effect, variability of digital blood flow measures) data. Based on Stage A results, Stage B sample size may be modified, such as, but not limited to, Stage A dose levels will be enriched, or 2 additional doses will be evaluated. Full details of the safety, PK, and efficacy data interim analyses will be provided in the SAP.

11.8. Safety Analyses

Observed values for clinical chemistry and hematology tests and vital signs will be summarized by study stage, treatment group, and study day. Individual data listings of clinical chemistry and hematology tests results will be presented for each subject. Observed values and changes from Baseline will be summarized descriptively. Observed values will be classified for normal, abnormality that is not clinically significant, and clinically significant abnormality by study stage, 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.

11.8.1. Safety Endpoints

- Safety and tolerability of temanogrel

11.8.2. Adverse Events

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be listed and summarized by system organ class and preferred term, as well as according to severity and relationship to study treatment. Treatment-emergent adverse events (TEAEs) will be summarized by study stage and treatment group. Similarly, bleeding events will be summarized by BARC classification by study stage and treatment group.

For each treatment group, the proportion of subjects with TEAEs will be summarized overall, by severity, and by relationship to study treatment. SAEs will also be summarized by treatment group. A TEAE 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 study treatment, 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.

11.8.2.1. BARC Bleeding Criteria Assessment

Based on mild bleeding events observed with escalating doses of oral temanogrel when co-administered with aspirin and clopidogrel in healthy adult subjects during completed Phase 1 studies, administration of single doses of oral temanogrel in this study may potentially increase the tendency of bleeding; therefore, the assessment of bleeding-related adverse events will be categorized by the Investigator (or qualified designee) using the BARC definition for bleeding (Mehran 2011) (Table 4). For any bleeding events that occur after the final Treatment Visit and before the Follow-Up Visit, applicable corresponding medical records should be requested for review by the Investigator (or qualified designee).

Table 4: BARC Definitions for Bleeding

Type	Definition
0	No bleeding
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
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: • Requiring nonsurgical, medical intervention by a healthcare professional. • Leading to hospitalization or increased level of care. • Prompting evaluation.
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.
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.
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.
BARC, Bleeding Academic Research Consortium; CABG, coronary artery bypass graft; U, unit
Source: (Mehran 2011).

11.8.3. Extent of Exposure

The number of treatments received by each subject and the number of subjects exposed to each treatment will be summarized.

11.8.4. Clinical Laboratory Parameters

Observed values for clinical chemistry and hematology tests and vital signs will be summarized by study stage, treatment group, and study day. Individual data listings of clinical chemistry and hematology tests results will be presented for each subject. Observed values and changes from Baseline at each Treatment Visit will be summarized descriptively. Observed values will be classified for normal, abnormality that is not clinically significant, and clinically significant abnormality by study stage, treatment group, and timepoint of collection.

11.8.5. Vital Signs

Descriptive statistics for vital signs (blood pressure, heart rate, respiratory rate, and body temperature) will be presented by treatment group.

11.8.6. Physical Examination

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

11.8.7. Electrocardiography

Individual ECG values will be listed by visit and summarized using descriptive statistics. Parameters to be provided for each ECG are heart rate, RR, PR, QRS, QT, QTc, QTcB, and QTcF. Post-Baseline ECGs for each subject will be compared with the Baseline ECG at each Treatment Visit. 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).

11.9. Pharmacokinetic Analysis

The PK analysis will be conducted using plasma concentrations of temanogrel and its metabolites from subjects who have received temanogrel and have evaluable plasma concentrations. Further details will be provided in the SAP.

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 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.

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. 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 telephone number).

When an important deviation from the protocol is deemed necessary for an individual subject, the Investigator must contact the Sponsor's Clinical Lead 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 efficacy 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 will be documented.

Note: 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. 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 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 CRO and 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, endoscopy reports, laboratory data/information, subject electronic diaries (eDiaries) or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, ECGs, X-rays, ultrasounds, right heart catheterization reports, 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. The Sponsor will provide written notification when it is appropriate for the Investigator to discard the study-specific documents referenced above.

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 custody of documentation will be transferred or moved to another location
- 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 (CFR) 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 CFR 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 CFR 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 CFR 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). 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

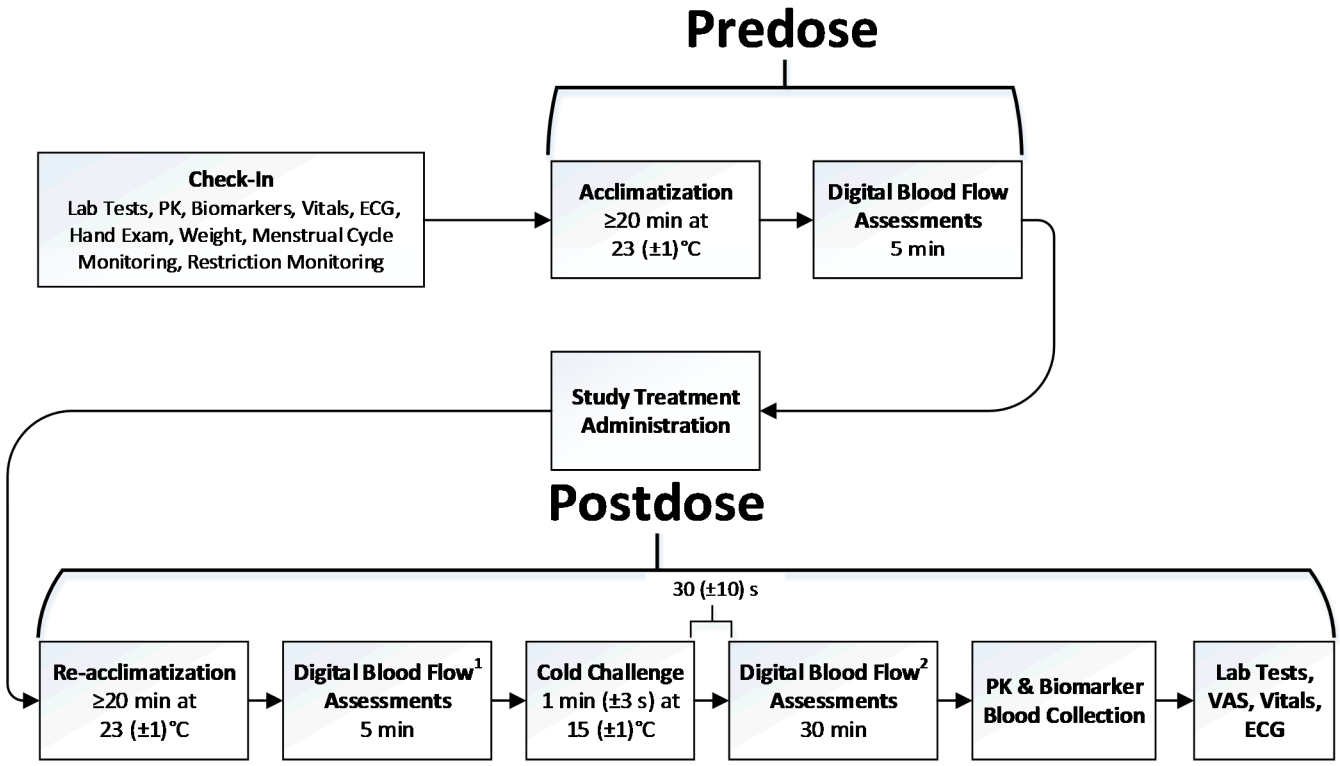
Visit[a]	**Screening**	**Treatment Visit 1**			**Treatment Visit 2**			**Treatment Visit 3**			**Follow-Up Visit**[b]
Timepoint	**Screen**[c]	**Check-in**	**Predose**[d]	**Postdose**[e]	**Check-in**	**Predose**[d]	**Postdose**[e]	**Check-in**	**Predose**[d]	**Postdose**[e]	
Informed consent	X										
Inclusion/exclusion	X										
Demographics	X										
Medical history	X										
Acclimatization test[f]	X										
Virology screening	X										
Physical examination[g]	X									X	
Hand examination[h]	X	X			X			X			
Prior/concomitant medication	→										
Height	X										
Body weight	X	X			X			X			
Urinalysis	X										
Endocrinology	X										
Serum chemistry/hematology/ coagulation	X	X		X	X		X	X		X	
Plasma serotonin blood draw[i]		X		X	X		X	X		X	
Markers of vascular injury and endothelial dysfunction[i]		X		X	X		X	X		X	
PK blood draw[i]		X		X	X		X	X		X	
Pregnancy test[j]	X	X			X			X			X
Urine drug screen[k]	X	X			X			X			
Vital signs	X	X		X	X		X	X		X	
ECG	X	X		X	X		X	X		X	
Adverse event reporting	→										

Visit[a]	Screening	Treatment Visit 1			Treatment Visit 2			Treatment Visit 3			Follow-Up Visit[b]
Timepoint	**Screen[c]**	**Check-in**	**Predose[d]**	**Postdose[e]**	**Check-in**	**Predose[d]**	**Postdose[e]**	**Check-in**	**Predose[d]**	**Postdose[e]**	
Randomization		X									
Menstrual cycle monitoring[l]		X			X			X			
Dietary and activity restriction monitoring[m]		X			X			X			
Room temperature digital blood flow assessments[n]			X	X		X	X		X	X	
Cold challenge and post-cold challenge digital blood flow assessments[o]				X			X			X	
Study treatment administration[p]			X			X			X		
Visual analogue scale for pain[q]				X			X			X	

[a] Treatment visits will be separated by a Washout period of at least 72 hours and a up to approximately 7 days between study treatment administrations. When possible, it is preferred to schedule Treatment Visits with the minimum possible Washout period between visits.
[b] The Follow-Up Visit will occur via phone call 4 (± 1) days after the final Treatment Visit (Treatment Visit 3) to assess for adverse events and any changes to concomitant medications. Site staff will work with subjects who withdraw early to obtain as much follow-up data as possible.
[c] The Screening Period will last for up to 28 days prior to Treatment Visit 1 (Day -28 to 1).
[d] Predose assessments are to occur on each Treatment Visit at approximately the same time of the day after the subject has acclimatized for at least 20 minutes in a temperature-controlled room (23 [± 1]°C).
[e] Postdose assessments are to occur at each Treatment Visit at 45 (± 5) minutes after study treatment administration and re-acclimatization for at least 20 minutes in a temperature-controlled room (23 [± 1]°C).
[f] Subjects are required to undergo acclimatization for at least 20 minutes in a temperature-controlled room (23 [± 1]°C) and IR thermography is used to assess digit temperature to determine eligibility.
[g] A full physical examination is performed per the site's standard of care at Screening. A symptom-based physical exam is performed at the end of final Treatment Visit (Treatment Visit 3).
[h] An exam of the hands for digital ulcers is performed at each Treatment Visit at Check-in.
[i] Postdose PK and biomarkers blood samples will be collected after the post-cold challenge digital blood flow assessment are completed. Refer to Section 10.5 for further information on blood sample collection.
[j] Pregnancy tests are required for all women of child-bearing potential. A serum pregnancy test is performed at Screening to determine eligibility and at each Treatment Visit. Urine pregnancy tests with a negative result are required prior to dosing at each Treatment Visit. Results of the serum pregnancy test at each Treatment Visit are not required prior to dosing. A home pregnancy test will be performed as part of the Follow-Up Visit.
[k] Urine drug screen at Screening is performed to determine eligibility. The results of subsequent urine drug screens are not required prior to initiating study conduct of each Treatment Visit. However, if at any time a subject test positive for any drug included in the urine drug screen, the subject may be discontinued from study treatment at the discretion of the Sponsor.
[l] The first day of the most recent menstrual cycle is documented at each Treatment Visit at Check-in.
[m] Subjects will be asked about their adherence to restrictions described in Section 5. Responses will be documented in the eCRF.
[n] Room temperature digital blood flow is assessed at each Treatment Visit at Predose for 5 minutes and at Postdose for 5 minutes prior to the cold challenge.
[o] The cold challenge is conducted at each Treatment Visit at after Postdose room temperature (pre-cold challenge) digital blood flow assessments by immersing the hands in temperature-controlled water bath (15 [± 1]°C) for 1 minute (± 3 seconds). The post-cold challenge digital blood flow assessments will begin 30 (± 10) seconds after the completion of the cold challenge and last for 30 minutes.
[p] Dosing is to occur at each Treatment Visit after completion of the Predose assessments.
[q] To be completed at each Treatment Visit at Postdose after completion of post-cold challenge digital blood flow assessments and blood draws.

ECG, electrocardiogram; eCRF, electronic case report form; IR, infrared; PK, pharmacokinetic

APPENDIX 2: TREATMENT VISIT FLOW OF ASSESSMENTS



DBF, Digital Blood Flow; ECG, electrocardiogram; PK, pharmacokinetic; VAS, visual analogue scale
[1] DBF Assessment – pre-cold challenge DBF
[2] DBF Assessment – post-cold challenge DBF

Note: Postdose assessments should begin 45 minutes (± 5) after study drug administration and re-acclimatization for at least 20 minutes in a temperature-controlled room (23°C [± 1°C]).

APPENDIX 3: INVESTIGATOR SIGNATURE

Study title: A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Crossover Study to Assess the Effect of Oral Temanogrel on Digital Blood Flow in Subjects with Raynaud's Phenomenon Secondary to Systemic Sclerosis

Study number: APD791-204

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

Note to File, Addendum

Date: 28 December 2022

To: TMF

From: PPD

PPD

Protocol No.: APD791-204

Subject: Document the status of documents and outline plans for select post-database lock pharmacokinetic analyses

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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 13 October 2022. The document here serves as the addendum to APD791-204 NTF (approved on 28 October 2022) to outline the plans for select post-database lock pharmacokinetic analyses.

Final Status:

Pharmacokinetic Analysis

- As per draft statistical analysis plan (SAP) v0.5
- Final pharmacokinetic parameters received from Medpace on December 16, 2022
- Revised TFLs with updated numbering for Listings 16.2 were received from Medpace on December 28, 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

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Deliverables & Analyses: Pharmacokinetic(PK) parameters were estimated as per stated in SAP (v0.5) 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.

30 Dec 2022 12:40:037-0500

PPD

PPD

REASON: I approve this document.

30 Dec 2022 11:46:059-0500

PPD

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Appendix A – Table of Contents of APD791-204 Plasma Concentration Summary

14.4.4.1.1 Summary of Plasma Temanogrel Concentrations (ng/mL) by Treatment and Visit
14.4.4.1.2 Summary of Plasma AR295980 (M1) Concentrations (ng/mL) by Treatment and Timepoint
14.4.4.1.3 Summary of Plasma AR295981 (M2) Concentrations (ng/mL) by Treatment and Timepoint
16.2.8.3 Plasma Temanogrel Pharmacokinetic Sample Collection
16.2.8.4 Plasma AR295980 (M1) Pharmacokinetic Sample Collection
16.2.8.5 Plasma AR295981 (M2) Pharmacokinetic Sample Collection

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Note to File (Amendment 1)

Date: 28 October 2022

To: TMF

From: PPD

Protocol No.: APD791-204

Subject: Document the status of biometrics-related documents/processes and outline plan for select post-database lock safety and efficacy analyses

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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 APD791-204 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) which occurred on 13 October 2022.

Final Status:

Statistical Analysis Plan

- Draft SAP (v0.5)

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 04 November 2022
- ADaM: Draft specifications (development not yet begun)

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

- Based on Programming Specifications (v1.0 dated 11 October 2022), the listings described in "Deliverables & Analyses" section will be produced.

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 development, 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.

Following DBL, Medpace Biostatistics will produce the outputs based on raw datasets, both eCRF (EDC) and external non-CRF. The table of contents of the final outputs is contained in Appendix A. Upon approval of the Note to File Amendment 1, any updates on TFL shells, including but not limited to titles, footnotes, headings, table re-numbering, and additional TFLs, are allowed without amendment.

Efficacy analyses from laser speckle contrast imaging (LSCI) and infrared thermography (IR) data obtained from the Medpace core lab will not be included in outputs described in this Note to File. Instead, efficacy analyses and reporting will be conducted separately and are not planned to be included in the clinical study report.

Signatures:

PPD

PPD

PPD

PPD

Distribution:

☒ TMF or applicable document repository

Appendix A – Table of Contents of Final Report

- Table 1 Stage A. Subject Disposition (All screened Subjects)
- Table 2 Stage A. Subject Disposition (Full Analysis Set)
- Table 3 Stage A. Demographic and Baseline Characteristics (Full Analysis Set)
- Table 4 Stage A. Overview Summary of Treatment Emergent Adverse Events (TEAE) (Safety Set)
- Table 5 Stage A. Treatment Emergent Adverse Events (TEAE) by System Organ Class and Preferred Term (Safety Set)
- Table 6 Stage A. Summary of Selected Laboratory Parameters – Chemistry, hematology, coagulation (Safety Set)
- Table 7 Stage A. Summary of 12-Lead Electrocardiogram (Safety Set)

- Figure 1.1 Stage A. Plots of Vital Signs – SBP (mmHg) (Safety Set)
- Figure 1.2 Stage A. Plots of Vital Signs – DBP (mmHg) (Safety Set)
- Figure 1.3 Stage A. Plots of Vital Signs – Heart Rate (bpm) (Safety Set)
- Figure 1.4 Stage A. Plots of Vital Signs – Respiratory Rate (resp/min) (Safety Set)
- Figure 1.5 Stage A. Plots of Vital Signs – Body Temperature (°C) (Safety Set)
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- Listing 1 Stage A. Subject Disposition (Full Analysis Set)
- Listing 2 Stage A. Demographic and Baseline Characteristics (Full Analysis Set)
- Listing 3 Stage A. Disease History (Full Analysis Set)
- Listing 4 Stage A. Study Drug Administration (Safety Set)
- Listing 5 Stage A. Treatment-Emergent Adverse Events (Safety Set)
- Listing 6 Stage A. Abnormal 12-Lead Electrocardiogram (Safety Set)
- Listing 7 Stage A. Significant Abnormal Physical Exam Findings (Safety Set)